

# EVALUATION OF SHINGRIX VACCINE AGAINST HERPES ZOSTER





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DOMINIQUE ROBERFROID, RENATE ZEEVAERT, CHARLINE MAERTENS DE NOORDHOUT, NANCY THIRY



|                                    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
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Reported interests:

All experts and stakeholders consulted within this report were selected because of their involvement in the topic of Herpes Zoster. Therefore, by definition, each of them might have a certain degree of conflict of interest to the main topic of this report.

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- **The external experts were consulted about a (preliminary) version of the scientific report. Their comments were discussed during meetings. They did not co-author the scientific report and did not necessarily agree with its content.**
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## LIST OF ABBREVIATIONS

| ABBREVIATION | DEFINITION                                                                                                |
|--------------|-----------------------------------------------------------------------------------------------------------|
| 95% CrI      | 95% credibility interval                                                                                  |
| ADL          | Activities of daily living                                                                                |
| AE           | Adverse event                                                                                             |
| BPI          | Brief pain inventory                                                                                      |
| BAPCOC       | Belgian commission coordinating the antibiotic policy                                                     |
| CBIP/BCFI    | Centre belge d'information pharmacothérapeutique / Belgisch centrum voor farmacotherapeutische informatie |
| CFR          | Case-fatality rate                                                                                        |
| CHO          | Chinese Hamster Ovarian                                                                                   |
| CI           | Confidence interval                                                                                       |
| CMI          | Cell-mediated immunity                                                                                    |
| COPD         | Chronic Obstructive Pulmonary Disease                                                                     |
| CORTDS       | Corticosteroids exposure                                                                                  |
| COVID        | Coronavirus disease                                                                                       |
| CPRD         | Clinical practice research datalink                                                                       |
| CRM/CTG      | Commission de remboursement des médicaments / Commissie Tegemoetkoming Geneesmiddelen                     |
| EMA          | European Medicine Agency                                                                                  |
| ELISA        | Enzyme-linked immunosorbant assay                                                                         |
| EQ-5D        | EuroQoL 5 dimensions                                                                                      |
| ESRD         | End stage renal disease                                                                                   |
| EUnetHTA     | European network for health technology assessment                                                         |
| FACH         | Flemish agency for care and health                                                                        |
| FDA          | Food and drug administration                                                                              |



|        |                                                                   |
|--------|-------------------------------------------------------------------|
| FU     | Follow-up                                                         |
| GBS    | Guillain-Barré syndrome                                           |
| GCP    | Good clinical practice                                            |
| GePaRD | German pharmaco-epidemiological research database                 |
| GMC    | geometric mean concentration                                      |
| gE     | Glycoprotein E                                                    |
| GP     | General practitioner                                              |
| GPRD   | General practice research database                                |
| GRADE  | Grading of recommendations assessment, development and evaluation |
| HES    | Hospital episode statistics                                       |
| HFR    | Hospital fatality rate                                            |
| HIV    | Human immunodeficiency virus                                      |
| HM     | Haematological malignancy                                         |
| HRQoL  | Health-related quality of life                                    |
| HSCT   | Hematopoietic stem cell transplant                                |
| HTA    | Health Technology Assessment                                      |
| HZ     | Herpes zoster                                                     |
| HZO    | Herpes zoster ophtalmicus                                         |
| IBD    | Inflammatory Bowel Disease                                        |
| ICD    | International classification of diseases                          |
| ICER   | Incremental cost-effectiveness ratios                             |
| ICH    | International conference on harmonization                         |
| ICTRP  | International clinical trials registry platform                   |
| INATHA | International network of agencies for health technology           |



|         |                                                                                                                                                                        |
|---------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| IR      | Incidence rate                                                                                                                                                         |
| IM      | intramuscular                                                                                                                                                          |
| JCVI    | Joint committee on vaccination and immunisation                                                                                                                        |
| KHP     | Kaiser Permanente Hawaii                                                                                                                                               |
| LOS     | Length of stay                                                                                                                                                         |
| LTFU    | Long-term follow-up                                                                                                                                                    |
| MCD     | Minimal Clinical Data (RHM/MZG)                                                                                                                                        |
| mBPI-SF | Modified brief pain inventory short form                                                                                                                               |
| MD      | Mean difference                                                                                                                                                        |
| mTVC    | Modified vaccinated cohort                                                                                                                                             |
| NCSF    | National Christian Sickness Fund                                                                                                                                       |
| NIAC    | National immunisation advisory committee                                                                                                                               |
| NIHDI   | National Institute for Health and Disability (Institut National d'Assurance Maladie-Invalidite / Rijksinstituut voor Ziekte- en Invaliditeitsverzekering, INAMI/RIZIV) |
| NIVEL   | Netherlands institute for health services research                                                                                                                     |
| NNV     | Number needed to vaccinate                                                                                                                                             |
| NMA     | Network meta-analysis                                                                                                                                                  |
| NRS     | Numerical rating scale                                                                                                                                                 |
| OIT     | Other immunosuppressive therapy                                                                                                                                        |
| OLDW    | OptimumLabs data warehouse                                                                                                                                             |
| OR      | Odds ratio                                                                                                                                                             |
| PCR     | Polymerase chain reaction                                                                                                                                              |
| PCV13   | 13-valent pneumococcal conjugate vaccine                                                                                                                               |
| PD      | Principal diagnosis                                                                                                                                                    |



|          |                                                                                 |
|----------|---------------------------------------------------------------------------------|
| PHN      | Postherpetic neuralgia                                                          |
| pIMD     | Potential immune-mediated disorders                                             |
| PRISMA-P | Preferred reporting items for systematic review and meta-analysis for protocols |
| PRO      | Patient-reported outcome                                                        |
| PROSPERO | Prospective register of systematic reviews                                      |
| PSA      | Probabilistic sensitivity analysis                                              |
| PY       | Person-years                                                                    |
| QoL      | Quality of life                                                                 |
| QALY     | Quality-adjusted life-years                                                     |
| RCT      | Randomised Control Trial                                                        |
| RoB      | Risk of bias                                                                    |
| ROBINS-I | Risk of bias in non-randomized studies of interventions                         |
| RR       | Risk ratio's                                                                    |
| RZV      | Adjuvant recombinant subunit vaccine, Shingrix                                  |
| SAE      | Serious adverse event                                                           |
| sc       | Subcutaneous                                                                    |
| SD       | Standard deviation                                                              |
| SF-12    | Medical outcomes study 12-items short form health survey                        |
| SF-36    | Medical outcomes study 36-items short form health survey                        |
| SGP      | Sentinel General Practice                                                       |
| SIQ      | Short Italian questionnaire                                                     |
| S2k      | European consensus based                                                        |
| SOM      | Solid organ malignancy                                                          |
| SOT      | Solid organ transplant                                                          |



|       |                                                                        |
|-------|------------------------------------------------------------------------|
| SPMA  | Standardized mortality rates                                           |
| SPS   | Shingles prevention study                                              |
| STIKO | Standing committee on vaccination                                      |
| TDaP  | Tetanus toxoid, reduced diphtheria toxoid, acellular pertussis vaccine |
| TVC   | Total vaccinated cohort                                                |
| VAERS | Vaccine adverse event reporting system                                 |
| VAHS  | Veterans affairs healthcare system                                     |
| VE    | Vaccine effectiveness                                                  |
| VRR   | Vaccine response rate                                                  |
| VZV   | Varicella-zoster virus                                                 |
| WHO   | World health organisation                                              |
| WTP   | Willingness to pay                                                     |
| YCG   | Yearly contact group                                                   |
| ZOE   | Zoster Efficacy                                                        |
| ZVL   | Live attenuated varicella-zoster virus vaccine, Zostavax               |



## ■ SUMMARY

This Health Technology Assessment aims at evaluating the efficacy, safety, cost-effectiveness and budget impact of a non-live adjuvanted recombinant subunit vaccine (Shingrix, GSK) against herpes zoster (HZ). Shingrix is administered intramuscularly 2 months apart. Shingrix received a market authorisation granted by the European Medicine Agency (EMA) in March 2018. Shingrix is indicated in adults 50 years of age or older and in adults 18 years of age or older at increased risk of HZ.

### **Burden of disease in Belgium**

Herpes zoster, or shingles, results from the reactivation of latent varicella-zoster virus (VZV) in the dorsal-root or cranial-nerve ganglia. This neurocutaneous disease is characterized by a vesicular rash with an unilateral and dermatomal distribution and is almost always (90%) accompanied by pain. In Belgium, there are around 48 000 cases per year with an overall incidence rate of 39.7 per 10 000 person-years. The incidence of HZ increases with age, which is the most influential risk factor. Two thirds of the cases occur in individuals  $\geq 50$  years with an incidence rate of 70.1 per 10 000 person-years. The incidence of herpes zoster is almost 3 times higher in individuals older than 90 years than in those aged between 50 and 59 years. Immunosuppressive conditions and therapies are also an important risk factor of HZ and its complications. Other risk factors are female sex, a personal or family history of HZ, asthma, diabetes, chronic renal disease and chronic obstructive pulmonary disease.

Zoster is typically mild and self-limiting, but complications can occur, the most frequent one being postherpetic neuralgia (PHN), a dermatomal pain of clinically significant intensity persisting at least 90 days after the appearance of the acute herpes zoster. The incidence of PHN in Belgium is unknown but based on international studies, it is fair to assume that 10% to 20% of HZ patients  $\geq 50$  years are concerned. Other complications are much more rare but can be serious. They include ocular complications, secondary bacterial infection and sepsis, central nervous system complications, cerebrovascular disease, and Guillain–Barré syndrome.

Around 2500 patients are hospitalized every year in our country with a primary or secondary diagnosis of HZ, resulting in an annual hospitalisation incidence of 2.3 per 10 000 person-years. The incidence of hospitalisation



truly attributable to HZ is lower as HZ is considered principal diagnosis in 42% of cases, i.e. 1092 hospitalisations in 2019. Zoster with complications accounted for 68% of these hospitalisations with HZ as principal diagnosis (20% for ocular disease and 10% for PHN). The incidence of hospitalisation increased sharply with age, from 0.58 per 10 000 person-years in 50-59y to 6.3 in ≥80 years.

On average, 12 deaths are attributed to HZ every year, with a crude mortality rate of 0.011 (95%CI: 0.010-0.013) per 10 000 person-years.

Burden of HZ in Belgium in terms of QALY's lost has been estimated between 880 (95 CrI: 631-1162) and 1306 (95 CrI: 920-1743) in immunocompetent individuals ≥ 50 years.

### **Vaccine efficacy and safety**

We carried out a systematic literature review compliant with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) requirements. The protocol was registered in PROSPERO (REF CRD42022311749).

#### ***Immunocompetent individuals***

In the 2 pivotal trials ZOE-50 and ZOE-70, Shingrix efficacy to prevent HZ was estimated at 97.2% (95%CI: 93.7-99.0;  $p<0.001$ ) in individuals ≥50 years and 91.3% (95%CI: 86.8-94.5;  $p<0.001$ ) in individuals ≥70 years over a follow-up period between 3.2 and 3.8 years (high quality data). The Number Needed to Vaccinate (NNV) was 36.4 (95%CI: 31.9-42.2) in individuals ≥50y and 32.3 (95%CI: 28.5-37.1) in individuals ≥70y. There was no significant difference in vaccine efficacy among different age groups.

An open-labelled follow-up study (Zoster-049 or ZOE-LTFU) of the pooled ZOE-50/70 population included a sub-sample (50.6%) of the ZOE-50/70 participants and reported an overall vaccine efficacy against HZ of 90.9% (95%CI: 88.2-93.2) during a mean follow-up of 7.1 years after vaccination (moderate quality evidence). The authors suggest a trend toward a plateau with vaccine efficacy of 84.9% in year 6, 85.3% in year 7 and 84.1% in year 8. However further follow-up data will be necessary to confirm this. The NNV over 7 years was 23.4 (95%CI: 21.6-25.7). Applied to Belgium, these results

would translate in 64 and 77 cases of HZ avoided per 10 000 person-years vaccinated ≥50 years and ≥60 years, respectively. The monitoring of participants of the two trials is still ongoing.

The vaccine efficacy to prevent PHN was 88.8% (95%CI: 68.7-97.1;  $p<0.001$ ) among adults ≥70 years and 91.2% (95%CI: 75.9-97.7;  $p<0.001$ ) among adults ≥50 years over a follow-up period between 3.2 and 3.8 years (high quality data). The NNV for prevention of PHN over 3.8 years was high at 334.5 (95%CI: 251.5-499.4) for individuals ≥50 years and 261.2 (95%CI: 188.2-426.5) for individuals ≥70 years. Applied to Belgium, these results would translate in 8-10 and 10-12 cases of PHN avoided per 10 000 person-years vaccinated ≥50 years and ≥60 years, respectively. Protection against PHN on a longer duration is unknown.

No major safety signal was identified in these 2 trials. Around 9% of vaccine recipients reported grade 3 (severe) local reactions. Systemic reactions (myalgia, fatigue, fever, shivering, headache, gastro-intestinal symptoms) presented in around 55%-65% of vaccinees (vs. around 25% in placebo group), of which 6% to 11% were severe. The incidence of serious adverse events was balanced between RZV and placebo groups. Despite high rates of local and general symptoms after vaccination, second dose compliance was high.

Good vaccine efficacy against HZ was confirmed in 3 post-marketing in-population studies, although lower than in the pivotal trials (between 70% and 85%) and the evaluation was on a shorter duration (7 to 24 months) (moderate quality evidence). One of these studies also reported a vaccine efficacy against PHN of 76.0% (95%CI: 68.4–81.8) in patients aged ≥65 years over a 7 months follow-up. Two other studies reported a risk of Guillain-Barré syndrome 2.3 to 2.8 higher in vaccinated people, resulting in an attributable risk of 3 per million RZV doses (95%CI: 0.62-5.64). Three reports on post-licensure safety surveillance in the United States did not confirm that excess risk. No other safety signal was detected.



### *Immunocompromised individuals*

There is good quality data that Shingrix is effective in reducing the risk of HZ also in immunocompromised individuals  $\geq 18$  years with haematopoietic stem cell transplantation (HSCT) or haematological malignancies. Although the relative reduction was smaller than in immunocompetent persons (VE 70%; 95%CI: 53-81), the number of cases prevented for a given number of vaccinations was much higher because of the higher baseline risk (618 HZ cases avoided per 10 000 person-years vs. 86 per 10 000 person-years in immunocompetent individuals  $\geq 50$  years). There is also some evidence that the vaccine would reduce significantly hospitalisation rate in these patients (moderate quality evidence). Vaccine efficacy in the presence of other immunosuppressive conditions is not well known as only immunogenicity studies are available, and the threshold of cell-mediated immunity ensuring protection is unknown. However, 2 post-marketing in-population studies in immunocompromised individuals (with various conditions) reported a vaccine efficacy similar to the one observed for HSCT patients (around 65%). All the studies carried out in immunocompromised individuals were of short duration (maximum 2 years) and protection on a longer period is unknown. No major safety signal was reported.

KCE shared a preliminary version of the present clinical review with the Superior Health Council of Belgium to inform its deliberations in mid-2022. The latter very recently issued an advice supporting the use of RZV in immunocompetent adults  $\geq 60$  years and in immunocompromised patients  $\geq 16$  years. The Council however also emphasized the need to account for upcoming cost-effectiveness analysis in the decision-making concerning this vaccine.

### **Cost-effectiveness**

A 2021 Belgian economic evaluation of Shingrix in immunocompetent adults estimated that, compared to Zostavax, Shingrix was more clinically effective (in terms of QALYs gained and avoided clinical outcomes) in all age groups. Administering Shingrix at a younger age (50 years) was more cost-effective assuming a long duration of protection of the vaccine (providing on average 40-50 years of protection), while vaccination at a later age (80 years) was more cost-effective assuming a short duration of protection of the vaccine (providing around 7 to 10 years of protection).

However, with incremental cost-effectiveness ratios (ICER) above € 87 000 per QALY gained, RZV vaccination was not found to be cost-effective at any of the explored vaccination ages (at 50, 60, 70, 80 or 85 years) or at any of the assumed duration of protection (long or short) when the US private sector price of RZV was used (€ 140.26 per dose). Meantime the Belgian list price of RZV was set up at € 170.26 per dose. Hence strong decreases in the price of RZV vaccine were advocated for a better balance between the health gains and the costs. For example, assuming a long duration of vaccine protection, the price for 1 dose of Shingrix should drop to € 37.49 per dose such that vaccination at 50 years would cost € 30 000 per QALY gained. As a comparison, the ICER for influenza vaccination in  $\geq 65$ -year-olds, a strategy recommended and funded in Belgium, was previously estimated at € 19 125 per QALY at most.

The assumed duration of protection of Shingrix had a strong impact on the cost-effectiveness results. This duration of protection was estimated based on the 4-year data from the two pivotal ZOE trials. Our extrapolations based on the 8-year data of the ZOE-LTFU trial showed that the assumption of a short duration of vaccine protection can clearly be discarded. They also showed that the assumption of a long duration of vaccine protection is plausible though too optimistic. The lowest ICER in Pieters et al. is thus likely underestimated. The incidence of HZ cases also had a strong impact on the cost-effectiveness results. This incidence was derived from the medically attended cases and was limited to the immunocompetent population, providing a lower estimate of the number of individuals who can benefit from vaccination. Consideration of the whole population (including the immunocompromised) would likely improve the ICERs.



The results of recent economic evaluations performed in settings similar to Belgium (Europe and North America) were explored. The bulk of those evaluations (both sponsored and non-sponsored) reported more favourable results about the cost-effectiveness of RZV vaccination in the overall or immunocompetent population, with ICERs not exceeding € 47 000 per QALY (see section 6.4 for a full description of those results). Only two studies reported less favourable results. A Dutch economic evaluation estimated that RZV prices should decrease to be cost-effective at the € 20 000 per QALY gained, while, in a Swedish study, RZV was not found to be cost-effective as it costed € 170 000 per QALY. The cost-effectiveness of RZV vaccination in specific populations such as the immunocompromised still needs to be explored, as only one GSK-sponsored conference abstract on this topic was published so far.<sup>1</sup>

The budget required to fund the vaccination strategies recently recommended by the Superior Health Council would be substantial. Vaccination of the immunocompetent population aged ≥60 years, at a 46.2% uptake and at the official vaccine price (€ 170.26 per dose) would cost € 493.77 million the first year and € 24.37 million annually afterwards to vaccinate each new cohort of immunocompetent individual turning 60 years. The vaccine price identified in the Belgian economic evaluation to make this strategy cost-effective (€ 30 000 per QALY threshold) is around € 30 per dose. At this reduced price, the budget required to vaccinate the immunocompetents ≥60 years would be € 124.51 million the first year, and € 6.15 million annually afterwards. Vaccination of the immunocompromised ≥18 years<sup>a</sup> at a 90% uptake would be high at the official vaccine price, with € 108.12 million required the first year and € 0.78 million each subsequent year. At the negotiated price of € 30 per dose, the budget would decrease to € 27.26 million the first year and € 0.20 million each following year.

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<sup>a</sup> The Superior Health Council recommends vaccination of immunocompromised ≥16 years. In our simulations however, the age of 18 years will be considered as the EMA market authorisation of Shingrix is for adults only.



## ■ SCIENTIFIC REPORT

### 1 BACKGROUND

#### 1.1 Herpes zoster

Herpes zoster (HZ), or shingles, results from the reactivation of latent varicella-zoster virus (VZV) in the dorsal-root or cranial-nerve ganglia, usually decades after primary infection by VZV (Figure 1).<sup>2</sup> Anyone who has had varicella (chickenpox) is at risk of HZ. In Europe varicella affects over 90% of children before the age of 15.<sup>3</sup> Among individuals who have suffered from varicella, one over five will develop HZ.<sup>4,5</sup> This reactivation of the virus results of an age-related decline in immunity and/or an immunodeficiency or immunosuppression caused by disease or therapy<sup>a,2,7</sup> The overall incidence rate is internationally estimated between 20 and 50 per 10 000 person-years (more details are provided in section 3.2).<sup>8,9</sup> HZ incidence increases markedly after 50 years of age and two thirds of the cases occurred in individual aged 50 years or older.<sup>5,7,10</sup>

This neurocutaneous disease is characterized by a vesicular rash with an unilateral and dermatomal distribution and is almost always (90%) accompanied by pain. HZ diagnosis is mostly determined clinically. HZ complaints are highly specific and accompanied by typical lesions, with a positive predictive value of clinical judgment estimated at 90.8% (95%CI: 87.3-94.3).<sup>11</sup> The prodromal phase is typically 3-4 days in duration, but longer durations of  $\geq 1$  week are not uncommon. Fever, malaise and headache may be present. The rash typically heals in 2-4 weeks but may leave scarring and pigmentation changes.

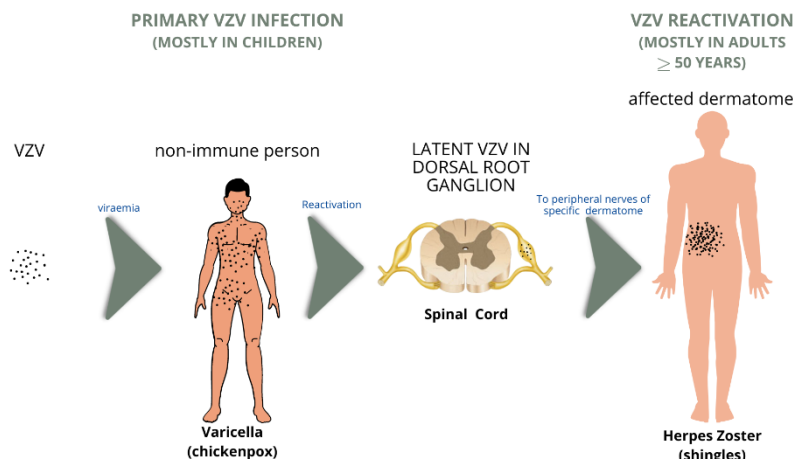
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<sup>a</sup> HZ is not transmitted directly as it is reactivation of VZV. Therefore, HZ does not occur in epidemics and periodicity is not described. However, the herpes lesions are contagious for non-immune persons and can lead to varicella (primary infection).<sup>6</sup> Due to the fact that HZ is most common in older adults

and HZ lesions occur very locally, this mode of transmission is expected to be very limited. HZ, originally not thought to occur more than once in an individual, is now estimated to recur in approximately 6.4% of immunocompetent people. The recurrence rate is higher among the immunocompromised population.<sup>2</sup>



**Figure 1 – Natural history of VZV infection**



Source: KCE.

The median duration of acute pain is 2 weeks, but 60-70% of patients continue to have persistent pain 1 month after the episode, 40% of those considering it severe.<sup>12, 13</sup>

Zoster is typically mild and self-limiting, but complications can occur, the most frequent one being postherpetic neuralgia (PHN). PHN is a complex neuropathic pain condition which is a consequence of the nerve damage caused by the reactivation of VZV in the ganglia. The more conventional definition of PHN is dermatomal pain of clinically significant intensity, persisting at least 90 days after the appearance of the acute herpes zoster rash affecting the same dermatome. The pain has been described as a constant burning or stabbing sensation, and some individuals experience allodynia (pain triggered from light contact with nonpainful stimuli).<sup>14</sup> PHN causes physical disability, emotional distress and interference with daily activities and sleep.<sup>15</sup> PHN would occur in 5% to 30% of HZ cases,<sup>8</sup> and can lead to several months of treatment and profoundly affect a patient's quality

of life (for more details on PHN incidence see section 3.3).<sup>3, 8, 14, 16</sup> PHN progressively improves and after 1 year only 1-2% of the patients still experience pain.<sup>12, 13</sup> However longer durations in a higher proportion of patients have been reported.<sup>8</sup>

Other complications are more rare but can be serious. In particular, Herpes Zoster Ophthalmicus (HZO), i.e. a reactivation of VZV in the fifth cranial nerve (trigeminal nerve), is associated with a high rate of complications, especially when the nasociliary division of the ophthalmic nerve is involved, as evidenced by Hutchinson's sign, namely papulovesicular lesions on the side and top of the nose.<sup>12, 13</sup> Significant complications include acute or delayed keratitis, uveitis, conjunctivitis, scleritis, eyelid retraction, oculomotor palsies, paralytic ptosis, secondary glaucoma, optic neuritis or even acute retinal necrosis with the risk of bilateral blindness.<sup>12, 13</sup> Other complications include secondary bacterial infection and sepsis, encephalitis, meningoencephalitis, myelitis, cerebellitis, cerebrovascular disease, radiculitis and Guillan-Barré syndrome (for more details on complications incidence see section 3.4).<sup>12, 13</sup>

Patients at higher risk of PHN and other complications can be identified by a series of risk factors, such as increasing age (the most influential factor), immunosuppressive conditions (including cancer, haemopathies, HIV infected, solid organ and bone marrow transplant recipients), and immunosuppressive therapies.<sup>12, 13</sup> Certain clinical findings at an early stage of HZ also identify patients at higher risk of complications. These include prodromal dermatomal pain, acute severe pain in the herpes stage, the presence of satellite lesions (aberrant vesicles), severe rash and/or involvement of multiple dermatomes or multisegmental HZ, number of lesions >50, cranial/sacral localization, haemorrhagic lesions, simultaneous presence of lesions in different developmental stages, altered general status, and meningeal or other neurological signs and symptoms.<sup>12-14, 16</sup>

The incidence of HZ and its complications is expected to increase as the population is aging, the prevalence of malignancies and autoimmune diseases, as well as the use of immunosuppressant therapies, increases.<sup>7, 17</sup>

HZ and associated complications can result in a significant reduction of patients' quality of life and in a significant economic burden (for more details on economic burden see chapter 6).<sup>15, 18-21</sup>



## 1.2 Treatment

In the absence of risk factors for complicated courses, HZ usually is a self-limiting disease.<sup>12, 13</sup> Since PHN is the most frequent sequela of HZ, reducing its incidence is a major secondary treatment goal. In immunosuppressed or otherwise susceptible patients, treatment goals extend to reducing the incidence and intensity of accompanying complications. Antiviral therapies, such as Acyclovir, Famcyclovir and Valacyclovir are used in the acute phase of infection with the main aims of reducing and/or stopping viral replication, which is thought to play a role in relieving pain and shortening duration of symptoms. In Belgium, Farmaka (<https://farmaka.cbip.be/fr/formulaire-p-a/148>; accessed 29/08/2022), in agreement with the Belgian commission coordinating the antibiotic policy (BAPCOC), recommends considering using Acyclovir (500 mg x 8 per day, 7 days), particularly in patients > 60 years (higher risk of PHN), in patients with extended lesions and when pain precedes the eruption. In all cases, treatment must be started between 48h-72h after the start of the eruption. EBPracticeNet (<https://ebpnet.be/fr/ebsources/209?searchTerm=zona>; accessed 29/08/2022) provides globally the same recommendations.

Antiviral drugs **should** be provided:

a. in patients with immunodeficiency, the prime consideration being to prevent morbidity and mortality associated with visceral dissemination of VZV:

- Medullary depression (leukemia, granulocytopenia)
- Primary immunodeficiency
- HIV carriers
- Any serious systemic illness
- Poorly controlled diabetes
- Antineoplastic chemotherapy
- Continuous use of oral corticosteroid medications

b. in patients with HZ in the trigeminal nerve area.

Antiviral drugs **can** be provided in:

- Patients older than 60 years because the clinical course is usually more severe.
- Young patients when the disease is particularly severe.

Recommendations in the European consensus-based (S2k) Guideline on the Management of Herpes Zoster are grossly similar, but also include patients ≥50 years of age, severe HZ (severe pain, haemorrhagic or necrotizing lesions, extended lesions).<sup>13</sup> EBPracticeNet recommends the molecules and dosage displayed in Table 1.

**Table 1 – Antiviral treatments recommended by EBPracticeNet**

| Drugs                             | Dosage                                                                                                |
|-----------------------------------|-------------------------------------------------------------------------------------------------------|
| <b>Acyclovir</b>                  | 800 mg × 5 times a day × 7 days per os<br>10 mg/kg × 3 times intra-venous in immunosuppressed patient |
| <b>Valacyclovir</b>               | 1 g × 3 times a day × 7 days per os                                                                   |
| <b>Famcyclovir</b>                | 250 mg × 3 times a day × 7 days per os                                                                |
| <b>(not available in Belgium)</b> | 500 mg × 2 times a day × 7 days per os                                                                |

There is no evidence for the application of local antiviral preparations for cutaneous HZ.<sup>13</sup> Intravenous acyclovir may be used in patients who present with complicated HZ or who are at risk of a complicated course.<sup>13</sup> Intravenous acyclovir is recommended in patients with acute retinal necrosis.<sup>13</sup> In cases with involvement of cranial nerves, systemic corticosteroids may be added to acyclovir.<sup>13</sup>

Management of chronic pain associated with herpes zoster is complex. According to a Cochrane review published in 2014, there is high quality evidence that oral acyclovir does not significantly reduce the incidence of PHN, while there is insufficient evidence to determine the effect of other antiviral treatments.<sup>22</sup> Other therapeutic approaches include acetaminophen, non-steroidal anti-inflammatory agents, tricyclic antidepressants, opiates, anticonvulsants, capsaicin, topical anaesthetics, and opioids, with varying degrees of efficacy. The topical application of local



anaesthetics or capsaicin cream is not advocated.<sup>13</sup> If pain severity at baseline is moderate-to-severe or other risk factors for PHN are present, use of a tricyclic anti-depressant (e.g. amitriptyline) or antiepileptic (e.g. gabapentin, pregabalin) drug may be considered.<sup>13, 23</sup>

### 1.3 Vaccine

Varicella-zoster virus (VZV)-specific T-cell-mediated immunity (CMI) is considered important in preventing the reactivation of latent VZV and preventing the propagation of the reactivated virus.<sup>24</sup> HZ vaccines are believed to boost VZV-specific memory T-cells, preventing their decline below the presently unknown threshold required for protection against HZ.<sup>24</sup>

A live attenuated VZV vaccine (Zostavax, Merck Sharpe & Dohme Corp) is available to prevent HZ in individuals  $\geq 50$  years of age. However, Zostavax (ZVL) has some limitations. Clinical trials indicate that vaccine efficacy against HZ is 70% in adults 50–59 years of age, and declines with age from 64% in persons 60–69 years to 18% in those  $\geq 80$  years.<sup>25, 26</sup> Moreover, efficacy of ZVL against HZ decreases over time, from 62% in the first year after vaccination to approximately 40% by the fifth year postvaccination.<sup>27</sup> Subsequently, this vaccine was not judged to be cost-effective in a former KCE publication.<sup>28</sup> Besides its relatively low efficacy, the risk of disease resulting from replication of the vaccine virus in immunosuppressed individuals is a concern explaining why ZVL is contra-indicated in immunocompromised individuals.<sup>29</sup> The use of Zostavax was discontinued in the US in November 2020.<sup>30</sup>

A new adjuvant recombinant subunit vaccine (Shingrix, GSK) containing VZV glycoprotein E (gE) and the AS01<sub>B</sub> adjuvant system (GSK) has been developed (also named RZV for Recombinant Zoster Vaccine). VZV gE was selected as a candidate vaccine antigen because it is essential for viral replication and cell-to-cell spread and is a primary target of VZV-specific immune responses. VZV gE is produced by recombinant DNA technology in

Chinese Hamster Ovarian (CHO) cells. The antigen was combined with AS01<sub>B</sub> because this adjuvant system promotes strong CD4+ T-cell and humoral immune responses against recombinant proteins.<sup>31</sup> Although the immunologic basis for protection against herpes zoster is not known, VZV-specific CD4+ T-cells are believed to play a central role. Accordingly, HZ/su induces strong gE-specific immune responses, including CD4+ T-cell responses, that are preserved with age. Moreover, the robustness of the immune responses to gE are attributable to the action of the AS01<sub>B</sub> adjuvant system, which has also been shown to enhance CD4+ T-cell and humoral immune responses to subunit antigens from other pathogens. The finished product is presented as a powder and suspension for injection containing 50 µg of glycoprotein E (gE) antigen (powder) adjuvanted with AS01B (suspension).<sup>32</sup>

Shingrix is administered intramuscularly 2 months apart. Shingrix received a market authorisation granted by the European Medicine Agency (EMA) in March 2018 on the basis of two pivotal phase III RCTs showing high efficacy against HZ and PHN without notification of major safety alerts.<sup>32</sup> Shingrix is indicated for prevention of HZ and postherpetic neuralgia PHN in adults 50 years of age or older and in adults 18 years of age or older at increased risk of HZ. Very recently (August 2022), the Superior Health Council of Belgium, which offers guidance to public health policy-makers, recommended the vaccine in immunocompetent adults  $\geq 60$  years and in immunocompromised patients  $\geq 16$  years.<sup>a</sup> The Council however also emphasized the need to account for upcoming cost-effectiveness analysis in the decision-making concerning this vaccine.

<sup>a</sup> The advice of the Superior Health Council of Belgium can be found at (accessed 09/09/2022): [20220906\\_css-9684\\_herpes\\_zoster\\_vweb.pdf](https://20220906_css-9684_herpes_zoster_vweb.pdf) ([belgium.be](https://belgium.be)).



## 2 RESEARCH QUESTIONS

Shingrix (or RZV) is a new vaccine with a market authorisation granted by EMA in March 2018. A reimbursement request is soon to be submitted by the producer (GSK) to the National Institute for Health and Disability Insurance (NIHDI, Institut National d'Assurance Maladie-Invalidite / Rijksinstituut voor Ziekte- en Invaliditeitsverzekering INAMI/RIZIV). Therefore, the time is ripe to evaluate clinical efficacy, safety, and cost-effectiveness of the vaccine on the basis of a comprehensive appraisal of up-to-date evidence. The aim is to provide the Drug Reimbursement Commission (Commission de remboursement des médicaments (CRM)/ Commissie Tegemoetkoming Geneesmiddelen (CTG)) with independent information and evidence-based recommendations. The Communities, as competent authorities in terms of vaccination, also need information for decision making, in particular for vaccine promotion campaigns and vaccination programmes in nursing homes.

The research questions are thus as followed:

1. What is the clinical efficacy and safety of Shingrix
  - a. in the general population
  - b. in individuals at risk of complicated HZ, e.g. immunosuppressed patients
2. What would be the comparative cost-effectiveness and the budget impact of introducing Shingrix in Belgium
  - a. in the overall population  $\geq 50$  years
  - b. in targeted age-groups, e.g. individuals turning 60 years vs individuals turning 70
  - c. in targeted patient groups, e.g. immunosuppressed patients

## 3 BURDEN OF DISEASE OF HZ IN BELGIUM

### 3.1 Methods

For each dimension of the burden of disease, we first retrieved and analysed recent Belgian data from various sources, which are described in the relevant chapters. A previous Belgian Health Technology Assessment (HTA) of Zostavax also provided valuable data on the burden of disease relating to HZ infection,<sup>20, 28</sup> and a consistency check was applied. As a second step, we retrieved international population-based studies to allow for comparison with or completion of Belgian data. This was based on a pragmatic literature review, i.e. for each outcome we used the results of a recent high-quality systematic review. When appropriate, we searched for more recent primary population-based studies published after the search date of the reference systematic review. As much as possible, results were stratified by age range and level of immune competency (immunocompetent vs. immunocompromised). The pragmatic search strategy is presented in Appendix 1.1 and 1.2.

### 3.2 Incidence of HZ

#### Main findings

- Based on data collected through the Belgian Network of Sentinel General Practices, the overall incidence rate of HZ in the period 2006-2012 was 39.7 per 10 000 person-years. In total, there are around 48 000 cases per year.
- The incidence of HZ increases with age. Two thirds of the cases occur in individuals  $\geq 50$  years (incidence rate of 70.1 per 10 000 person-years; 95%CI: 54.7-88.6). In the period 2006-2012, the incidence of herpes zoster was almost 3 times higher in individuals older than 90 years (130 cases per 10 000 person-years) than in those aged between 50 and 59 years (45 cases per 10 000 person-years).



- These results are congruent with those of other European studies, although some variations in incidence rates can be observed across and within countries likely due to various case registration methods (GP surveillance vs. claim data). Incidence rates based on GP surveillance are fairly similar across Europe, but are systematically lower than incidence rates derived from electronic searches in GP records or from claim data.

### 3.2.1 Belgian data

#### 3.2.1.1 Belgian Network of Sentinel General Practices

The Belgian network of Sentinel General Practices (SGP) registered HZ cases from year 2006 to 2012 and in 2021. In 2012, this network included 172 GPs (in 146 SGPs) covering around 175 000 citizens (1.6% of the Belgian population; 1.8% of the Flemish region, 1.1% of the Walloon region and 1.5% of the population in Brussels).<sup>33</sup> In 2021, the network included 96 GPs grouped in 73 practices covering 0.85% of the Belgian population (1.23% of Brussels, 0.89% of Flanders and 0.69% of Wallonia).<sup>34</sup> The population covered, which serves as the denominator in computing incidence rates, is estimated by dividing the sum of all patient encounters in the participating SGP by the mean number of patient encounters in Belgian general practice per inhabitant, provided by the NIHDI.<sup>33</sup> The SGPs are fairly similar to non-sentinel GPs according to age-gender distribution and the population covered is representative of the general population. The validity of the disease registration has been assessed.<sup>35-37</sup> HZ was defined as groups of vesicles which are localized on the area of one dermatome (International Classification of Primary Care, ICPC-2, code S70).<sup>38</sup> In

addition to age and sex, other variables were also registered: being vaccinated against chickenpox, a history of chickenpox, duration of symptoms before consulting, treatment with antiviral drugs (yes/no question), hospitalisation (yes/no question) (personal communication: Dieter Van Caeteren<sup>a</sup>). Since 2021, being vaccinated against Herpes Zoster (yes/no question), ophthalmic HZ (yes/no question), Postherpetic neuralgia (PHN) and existence of other complications following HZ (yes/no question) are also registered. The Sentinel Network registered the first consultation of a new episode of HZ, which, in combination with catchment population estimates, enabled estimates of the annual incidence rate of patients with HZ who visit a GP at least once. This system did not cover cases seen only by a specialist (e.g. dermatologists, geriatrists) or in emergency rooms. However, it is unlikely that this would have resulted in an underestimation of registered cases as a previous Belgian survey reported that 99% of ambulatory cases of HZ visited a GP.<sup>20</sup> Moreover, it seems reasonable to think that people not seeking any medical care for their HZ were likely to experience a very small burden, and therefore their contribution to the analysis is considered negligible. The data collected in 2021 have been impacted by the COVID-19 crisis (decrease of GP contacts and SGPs' participation). Although presented in this report, they should be interpreted with caution and in light of the results for the years 2006-2012. Data from year 2006 to 2012, incidence estimates and 95%CI were provided to us by Sciensano. There were 4 843 cases registered between 2006 and 2012 (Table 2, Table 3, and Table 4). There were 665 cases registered in 2012, which can be extrapolated to 41 562 cases in the general population (1.6% of the Belgian population is covered) and in 2021, there were 185 cases registered of HZ, which can be extrapolated to 21 765 cases in the population (0.85% of the Belgian population is covered).

<sup>a</sup> Epidemiologist at Sciensano.

**Table 2 – Number and incidence rate (by 10 000 population) of reported herpes zoster cases, 2006-2008**

| Age-group (years) | 2006       |             |                  | 2007       |             |                  | 2008       |             |              |
|-------------------|------------|-------------|------------------|------------|-------------|------------------|------------|-------------|--------------|
|                   | N          | IR.         | 95% CI           | N          | IR.         | 95% CI           | N          | IR.         | 95% CI       |
| <50               | 182        | 15.3        | 13.2-17.7        | 272        | 24.7        | 21.9-27.9        | 295        | 24.3        | 21.6-27.2    |
| ≥50               | 420        | 64.5        | 58.5-71.0        | 446        | 73.5        | 66.9-80.7        | 502        | 73.9        | 67.5-80.6    |
| 50-59             | 92         | 37.7        | 30.4-46.2        | 112        | 49.6        | 40.9-59.7        | 111        | 44.1        | 36.3-53.1    |
| 60-69             | 100        | 57          | 46.4-69.4        | 108        | 65.4        | 53.7-79          | 145        | 77.7        | 65.5-91.4    |
| 70-79             | 128        | 85.1        | 71-101.2         | 123        | 89.3        | 74.2-106.6       | 133        | 87.4        | 73.2-103.6   |
| 80-89             | 86         | 122.5       | 98-151.3         | 93         | 136.8       | 110.4-167.5      | 97         | 123.4       | 100.1-150.5  |
| ≥90               | 14         | 125.6       | 68.7-210.7       | 10         | 100.7       | 48.3-185.3       | 16         | 153.3       | 87.6-249     |
| <b>Total</b>      | <b>602</b> | <b>33.5</b> | <b>30.9-36.3</b> | <b>718</b> | <b>43.2</b> | <b>40.2-46.4</b> | <b>797</b> | <b>42.9</b> | <b>40-46</b> |

Data source & calculation: Sciensano, GP sentinel network. IR. = Incidence rate (number of reported cases per 10 000 inhabitants), CI=Confidence Interval, age unknown for 88 cases.

**Table 3 – Number and incidence rate (by 10 000 population) of reported herpes zoster cases, by age-group, 2009-2012 and 2021**

| Age-group (years) | 2009       |             |                  | 2010       |             |                  | 2011       |             |                  | 2012       |             |                  | Age-group (years) | 2021       |             |                  |
|-------------------|------------|-------------|------------------|------------|-------------|------------------|------------|-------------|------------------|------------|-------------|------------------|-------------------|------------|-------------|------------------|
|                   | N          | IR.         | 95% CI           | N          | IR.         | 95% CI           | N          | IR.         | 95% CI           | N          | IR.         | 95% CI           |                   | N          | IR.         | 95% CI           |
| <50               | 233        | 19.5        | 17.1-22.2        | 215        | 20.4        | 17.8-23.3        | 237        | 24.7        | 21.7-28.1        | 237        | 21.5        | 18.8-24.4        | <50               | 55         | 8.3         | 6.9-9.1          |
| ≥50               | 496        | 75.3        | 68.8-82.2        | 409        | 68.6        | 62.1-75.6        | 383        | 69.1        | 62.3-76.4        | 428        | 66.1        | 60.0-72.7        |                   |            |             |                  |
| 50-59             | 114        | 46.5        | 38.3-55.8        | 97         | 44.1        | 35.8-41.3        | 96         | 46.9        | 38-57.3          | 113        | 47.3        | 39-56.8          | 50-59             | 38         | 25          | 20.8-27.6        |
| 60-69             | 118        | 65.8        | 54.4-78.8        | 102        | 61.9        | 50.5-75.1        | 101        | 64.7        | 52.7-78.6        | 95         | 51.2        | 41.4-62.5        | 60-74             | 45         | 24.4        | 20.3-27          |
| 70-79             | 150        | 100.2       | 84.8-117.6       | 131        | 99.3        | 83-117.8         | 99         | 84.4        | 68.6-102.7       | 115        | 87.3        | 72.1-104.8       | ≥75               | 47         | 47.5        | 39.5-52.5        |
| 80-89             | 97         | 131.2       | 106.4-160.1      | 71         | 100.4       | 78.5-126.7       | 77         | 114.9       | 90.7-143.6       | 84         | 106.6       | 85.1-132         |                   |            |             |                  |
| ≥90               | 17         | 157.6       | 91.8-252.3       | 8          | 93          | 40.1-183.2       | 10         | 106.9       | 51.3-196.6       | 21         | 173.8       | 107.6-265.7      |                   |            |             |                  |
| <b>Total</b>      | <b>729</b> | <b>40.2</b> | <b>37.4-43.2</b> | <b>624</b> | <b>38.2</b> | <b>35.3-41.3</b> | <b>620</b> | <b>41.4</b> | <b>38.2-44.8</b> | <b>665</b> | <b>38.5</b> | <b>35.6-41.5</b> | <b>Total</b>      | <b>185</b> | <b>16.8</b> | <b>13.9-18.6</b> |

Data source & calculation: Sciensano, GP sentinel network. IR. = Incidence rate (number of reported cases per 10 000 inhabitants), CI=Confidence Interval, \* age unknown for 88 cases.

**Table 4 – Total number and incidence rate (by 10 000 population) of reported herpes zoster, by age-group, 2006-2012**

| Age-group<br>(years) | 2006-2012 |       |             |
|----------------------|-----------|-------|-------------|
|                      | N         | IR    | 95% CI      |
| <50                  | 1671      | 21.5  | 21-21.9     |
| ≥50                  | 3 084     | 70.1  | 54.7-88.6   |
| 50-59                | 735       | 45.2  | 44.4-45.9   |
| 60-69                | 769       | 63.4  | 61.8-65     |
| 70-79                | 879       | 90.4  | 89.3-91.6   |
| 80-89                | 605       | 119.4 | 116.8-122   |
| ≥90                  | 96        | 130.1 | 113.6-146.7 |
| Total                | 4843*     | 39.7  | 28.3-54.1   |

*Data source & calculation: Sciensano, GP sentinel network. IR. = Incidence rate (number of reported cases per 10 000 inhabitants), CI=Confidence Interval, \* age unknown for 88 cases*

The annual incidence of HZ was stable during the period 2006-2012, varying from 33.5 per 10 000 person-years (95%CI: 30.9-36.3) in 2006 to 38.5 cases per 10 000 person-years (95%CI: 35.6-41.5) in 2012 and to 16.8 cases per 10 000 person years (95%CI: 13.9-18.6) in 2021 (Table 2, Table 3, and Table 4). The overall incidence rate was 39.7 per 10 000 person-years through 2006-2012 period. Applying the incidence rates calculated over the period 2006-2012 (Table 4) to the Belgian population at 01/01/2022 results in 47 682 cases overall, among whom 32 669 are ≥50yr and 25 500 are ≥60yr (see Table 44). Figure 2 indicates no seasonality in the number of herpes zoster cases despite of two downward shifts observed in week 24 (71 cases) and week 30 (69 cases) that correspond to the summer time

period (June-July). There is also an important upward shift in week 36 in September (121 cases). The incidence of HZ increases with age and in 2012, the incidence of herpes zoster was 8 times higher in individuals older than 90 years (173.8 cases per 10 000 person-years<sup>a</sup>) than in those below 50 years (21.5 cases per 10 000 person-year) (Figure 3 and Table 3). Of note, because of relatively low number of cases in the highest age ranges, the annual incidence was much more variable in these age groups. Fifty-eight percent of the cases occurred in women but incidence rates standardized for age were not available.

The majority of the patients who suffered from herpes zoster received an antiviral treatment (73.2%;95%CI:71.9-74.4)<sup>b</sup> of the total reported herpes zoster cases). This figure amounted to 81% in patients aged >50 years (see Appendix 1.3). Type of treatment given was not described.

A negative skewed distribution of the proportion of treated patient by age-group is observed in Figure 4. This means that patients are increasingly treated to the extent that they become older. This phenomenon is observed in both women and men.

Among the 1 931 herpes zoster cases reported from 2010 to 2012, a very small proportion was hospitalised (1.6%;95%CI 1.1-2.3) of the total reported cases (31/1931), and the majority of the patients who were hospitalised were female older than 50 years (n=17, 54.8% of the total hospitalised) (see Appendix 1.4).

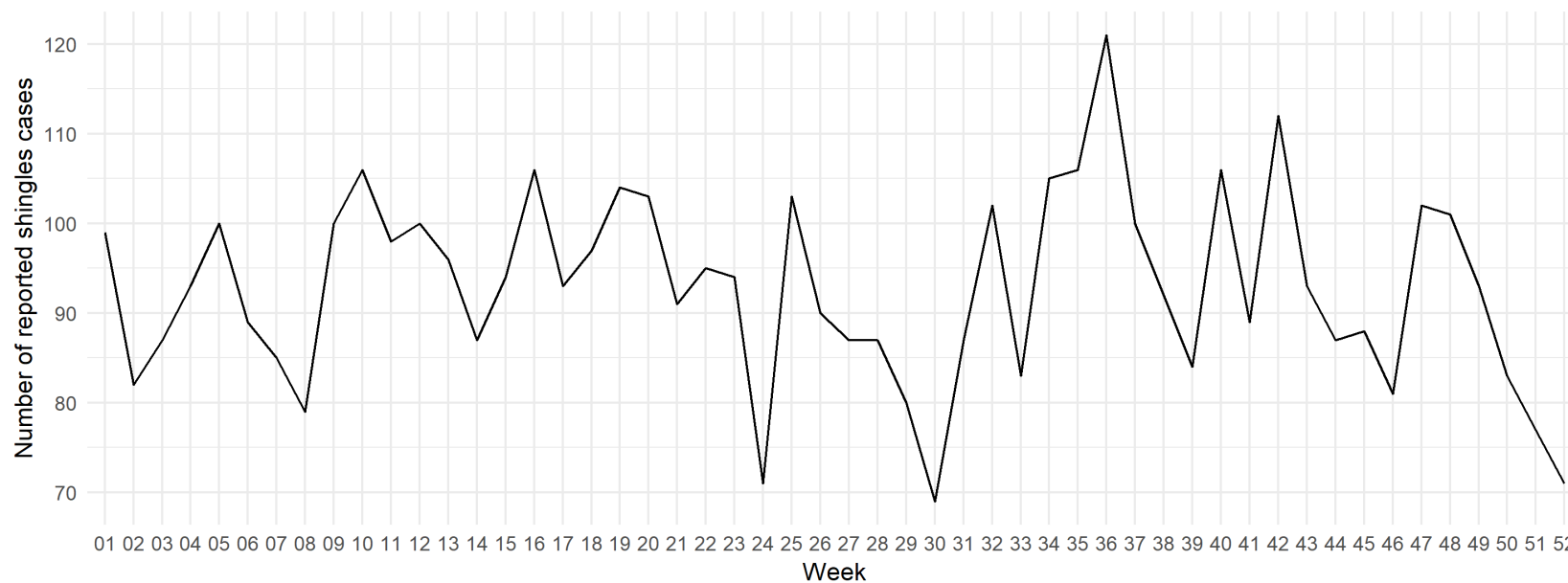
In 2021, among the 185 registered HZ cases, 10 were immunosuppressed patients (18.5%). No patients were vaccinated against varicella or herpes zoster. Majority had a history of varicella, 72.4% in case of consultation for shingles and 55.6% in case of PHN.

<sup>a</sup> The incidence in patients >90 years was substantially lower in 2010 and 2011.

<sup>b</sup> Information on treatment was missing in 1% of cases.



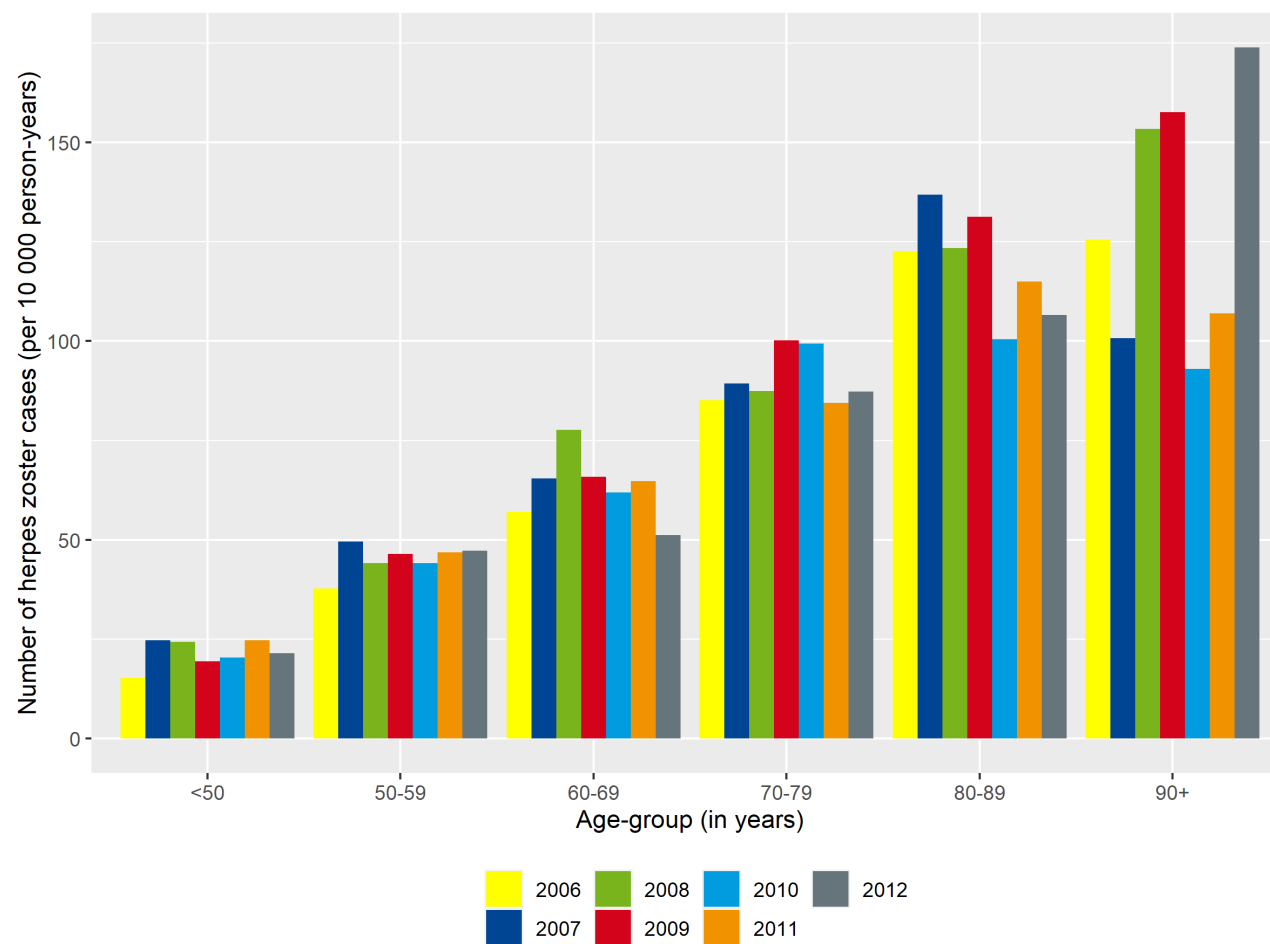
**Figure 2 – Number of reported shingles cases per week, 2006-2012\***



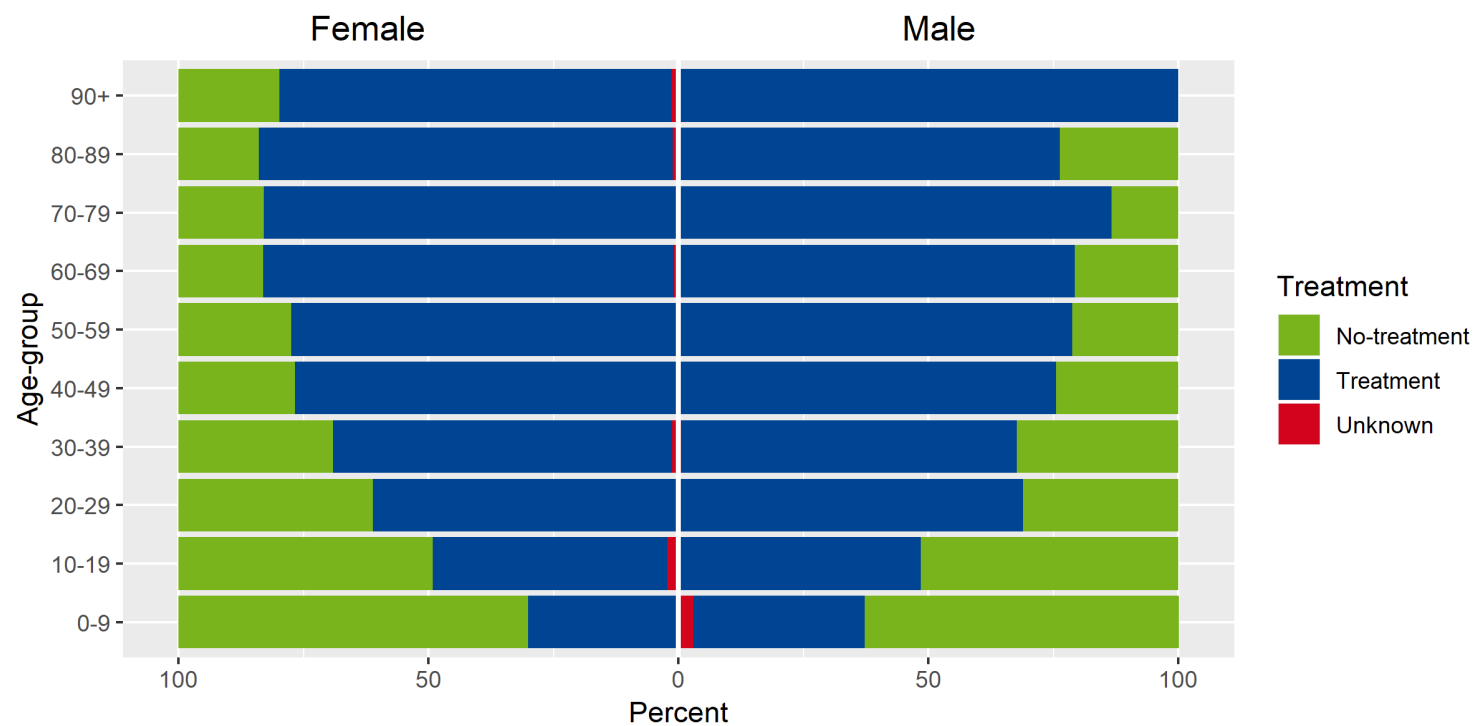
Data source: Sciensano, GP sentinel network. \* 2021 was excluded from the figure because the impact of COVID-19 crisis to 2021 data will create misleading interpretation of trends.



**Figure 3 – Incidence rate (per 10 000 person-years) of reported herpes zoster, by age-group, Belgium, 2006-2012**



Data source & calculation: GP sentinel network, Sciensano.

**Figure 4 – Proportion of antiviral treatment for herpes zoster infection, by sex and age-group, 2006-2012**

Data source: Sciensano, GP sentinel network.



### 3.2.1.2 INTEGO

Intego is a computerized morbidity registration network in Belgium based on general practice data from over 90 general practitioners based in Flanders and currently covering 285 000 individual patients and over two million patient-years.<sup>39</sup> External validation of the Intego database has been examined by means of national and international comparisons.<sup>35</sup> Its initial aim is to collect incidence rates of diagnoses presented to the general practitioner. Only new diagnoses are counted. The dataset now also includes year of birth, gender, the years that the patient contacted the practice, diagnoses, drug prescriptions, laboratory results, some biomedical parameters such as blood pressure, height, weight, smoking status and mortality. Other lifestyle information, such as nutrition, is not recorded. Incidence is calculated as the number of new cases of disease divided by the person-time magnitude. Incidence rates can be provided for the total population, or stratified by age group and/or gender or some other ad hoc defined subgroup and can be standardized for the Flemish, Belgian, European or World population. The denominator is the yearly contact group (YCG), patients which visit the practice at least once in a given year or the practice population, all patients in a practice, consisting of the YCG plus the group which does not visit their general practitioner in a given period. This last group is estimated from all non-profit health insurance agencies, which includes complete data on all reimbursed medical and paramedical acts, age, gender and residence as well as the total insured population. A yearly correction factor is calculated, to estimate the percentage of patients consulting a general practitioner by age group, gender and region and hence the practice population.<sup>35</sup>

Data were directly downloaded from the Intego website<sup>a</sup> or provided by the Intego team. The registration period covers years 2006-2021. Standardized incidence estimates can be extracted compared to practice population (per 1000 patients) or annual contact group (per 1000 patients). We decided to retain incidence rate compared to contact group because we thought it better reflected the incidence of HZ among in Belgium.

**Table 5 – Number and incidence rate (per 10 000 population) of reported HZ, Flanders, 2006-2021**

| Year | Number of reported HZ cases | Annual population | Incidence HZ (per 10 000 ) | LB 95% CI | UB 95% CI |
|------|-----------------------------|-------------------|----------------------------|-----------|-----------|
| 2006 | 596                         | 133 931           | 44.5                       | 40.93     | 48.07     |
| 2007 | 587                         | 132 322           | 44.36                      | 40.77     | 47.95     |
| 2008 | 597                         | 134 733           | 44.31                      | 40.76     | 47.86     |
| 2009 | 620                         | 140 259           | 44.2                       | 40.72     | 47.68     |
| 2010 | 592                         | 140 119           | 42.25                      | 38.85     | 45.65     |
| 2011 | 656                         | 151 963           | 43.17                      | 39.86     | 46.47     |
| 2012 | 542                         | 120 747           | 44.89                      | 41.11     | 48.67     |
| 2013 | 616                         | 130 391           | 47.24                      | 43.51     | 50.97     |
| 2014 | 576                         | 131 575           | 43.78                      | 40.2      | 47.35     |
| 2015 | 616                         | 123 229           | 49.99                      | 46.04     | 53.94     |
| 2016 | 453                         | 112 446           | 40.29                      | 35.77     | 44.80     |
| 2017 | 427                         | 102 976           | 41.47                      | 36.79     | 46.14     |
| 2018 | 871                         | 241 909           | 36.01                      | 32.82     | 39.19     |
| 2019 | 1005                        | 252 534           | 39.80                      | 36.77     | 42.82     |
| 2020 | 1092                        | 262 289           | 41.63                      | 38.71     | 44.56     |
| 2021 | 1032                        | 278 214           | 37.09                      | 34.15     | 40.04     |

Data Intego. LB=Lower bound, UB=Upper bound, CI=Confidence Interval.

<sup>a</sup> Intego website: [https://intego.gbiomed.kuleuven.be/intego-apps/inc\\_prev\\_v0/](https://intego.gbiomed.kuleuven.be/intego-apps/inc_prev_v0/) (last access: 4 April 2019).



The yearly incidence of HZ was 44.89 cases per 10 000 person-years in 2012 (95%CI: 41.11-48.67) and 37.09 cases per 10 000 person-year (95%CI: 34.15-40.04) in 2021. That incidence was somehow higher than the 42 per 10 000 person-years (95%CI: 35.6-41.5) observed in the network of SGPs in Flanders in 2012. The same patterns as in the SGPs were observed: higher incidence in women and in the older ages. However the peak incidence was in the age range 70-79 years (101.5 cases per 10 000

person-years in 2012), and not in the patients aged  $\geq 90$  years (around 30.00 per 10 000 person-years in 2012 in Flanders) as observed in the Sentinel Network of General Practitioners (200.6 cases per 10 000 person-years in 2012 in Flanders). The reasons for such differences are unclear, and may relate to a different case definition or the different way of computing the denominator. Also, the numbers were very small in the age range  $\geq 90$  years in the Intego database resulting in high variability of annual incidence.

**Table 6 – Number and incidence rate (per 10 000 contacts population) of reported HZ, by age-group, Flanders, 2006-2015**

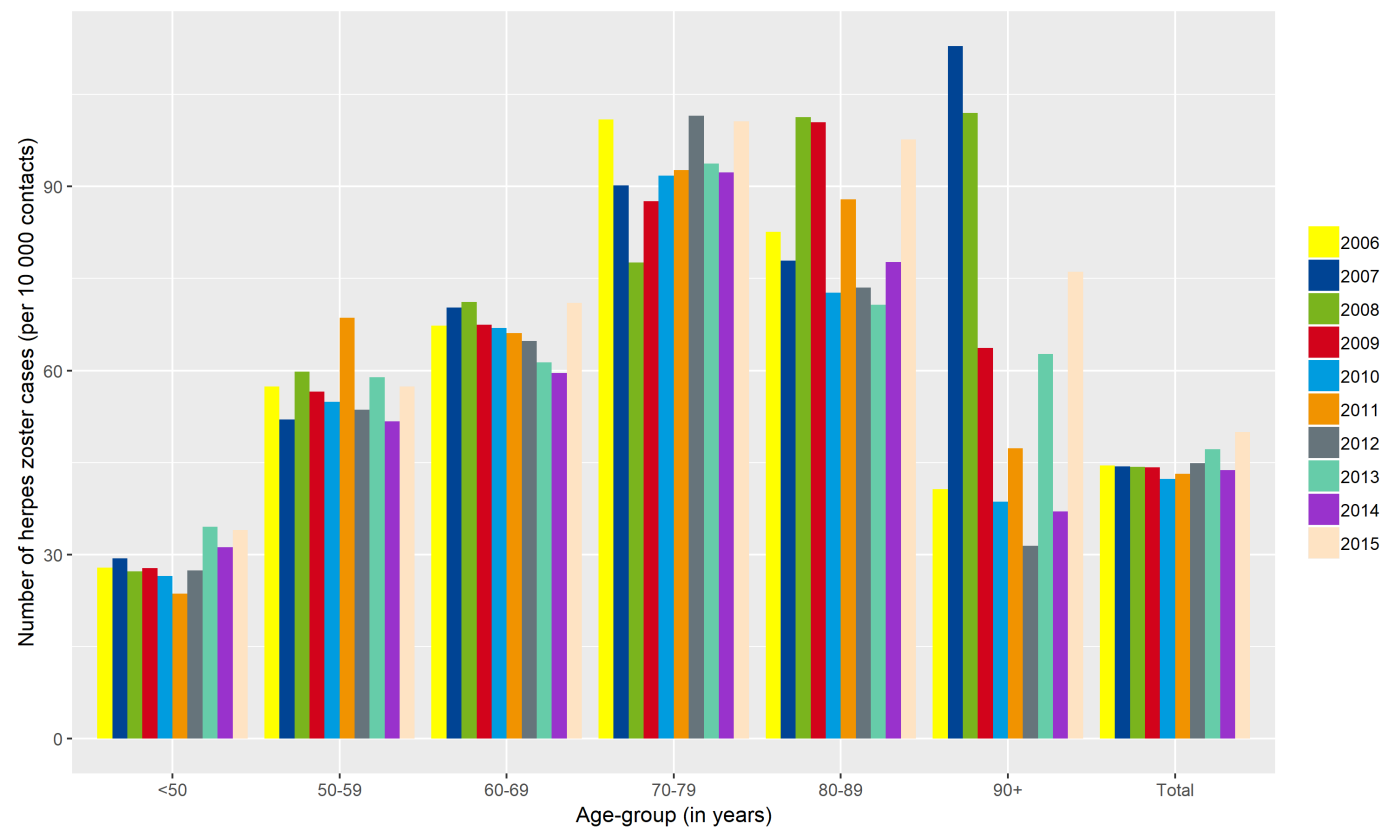
| Age-group (years) | 2006<br>(n, inc) |       | 2007<br>(n, inc) |       | 2008<br>(n, inc) |       | 2009<br>(n, inc) |       | 2010<br>(n, inc) |      | 2011<br>(n, inc) |      | 2012<br>(n, inc) |              | 2013<br>(n, inc) |      | 2014<br>(n, inc) |      | 2015<br>(n, inc) |       |
|-------------------|------------------|-------|------------------|-------|------------------|-------|------------------|-------|------------------|------|------------------|------|------------------|--------------|------------------|------|------------------|------|------------------|-------|
| <50               | 235              | 27.9  | 243              | 29.4  | 229              | 27.3  | 245              | 27.8  | 231              | 26.5 | 221              | 23.6 | 194              | 27.4         | 276              | 34.5 | 254              | 31.2 | 257              | 34.0  |
| 50-59             | 101              | 57.4  | 91               | 52.0  | 107              | 59.8  | 104              | 56.6  | 102              | 54.9 | 142              | 68.6 | 94               | 53.6         | 105              | 58.9 | 93               | 51.7 | 98               | 57.4  |
| 60-69             | 91               | 67.3  | 95               | 70.3  | 98               | 71.2  | 96               | 67.5  | 97               | 66.9 | 108              | 66.1 | 88               | 64.8         | 85               | 61.3 | 83               | 59.6 | 96               | 71.0  |
| 70-79             | 114              | 101.0 | 101              | 90.2  | 88               | 77.7  | 101              | 87.6  | 105              | 91.8 | 112              | 92.7 | 103              | <b>101.5</b> | 94               | 93.7 | 90               | 92.3 | 93               | 100.6 |
| 80-89             | 50               | 82.6  | 48               | 77.9  | 67               | 101.3 | 69               | 100.5 | 52               | 72.7 | 66               | 87.9 | 51               | 73.5         | 48               | 70.7 | 51               | 77.7 | 61               | 97.7  |
| 90-94°            | 5                | 40.7  | 9                | 112.9 | 8                | 102.0 | 5                | 63.7  | 5                | 38.6 | 7                | 47.3 | 5                | 31.4         | 8                | 62.7 | 5                | 37.0 | 11               | 76.1  |

Data Intego. Inc=incidence rate (per 10 000 contacts). ° 90-99 years in 2006, 2010-2012 and 2015.

**Table 7 – Number and incidence rate (per 10 000 contacts population) of reported HZ, by age-group, Flanders, 2016-2021**

| Age-group (years) | 2016<br>(n, inc*) |      | 2017<br>(n, inc) |      | 2018<br>(n, inc) |      | 2019<br>(n, inc) |      | 2020<br>(n, inc) |      | 2021<br>(n, inc) |      |
|-------------------|-------------------|------|------------------|------|------------------|------|------------------|------|------------------|------|------------------|------|
| <50               | 177               | 24.8 | 181              | 28.4 | 382              | 25.1 | 447              | 28.2 | 457              | 28.1 | 461              | 26.4 |
| 50-59             | 76                | 56.8 | 59               | 46.9 | 110              | 37.5 | 127              | 42.4 | 156              | 50.4 | 147              | 45.3 |
| 60-69             | 72                | 59.3 | 80               | 69.7 | 158              | 58.8 | 165              | 58.1 | 186              | 62.3 | 178              | 56.5 |
| 70-79             | 73                | 87.9 | 56               | 66.1 | 122              | 64.9 | 147              | 73.8 | 167              | 79.2 | 137              | 62.1 |
| 80-89             | 42                | 73.1 | 45               | 82.1 | 79               | 66.4 | 96               | 76.0 | 106              | 77.7 | 91               | 68.3 |
| 90-94             | 6                 | 51.4 | 4                | 43.1 | 16               | 75.4 | 21               | 86.0 | 15               | 47.8 | 16               | 50.4 |

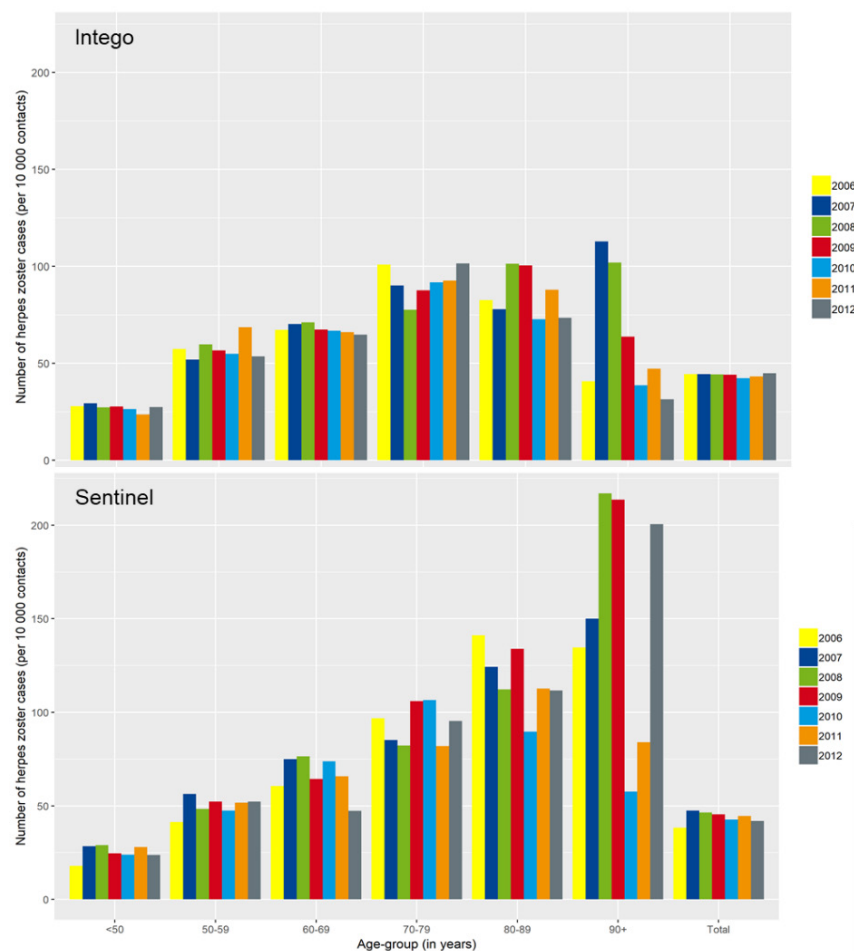
Data Intego. Inc=incidence rate (per 10 000 contacts).

**Figure 5 – Annual incidence of HZ (per 10 000 contacts), by age-group, Flanders 2006-2015**

Data source: Intego.



Figure 6 – Incidence rate of Herpes Zoster (per 10 000 contacts), by age-group, by data source (Intego vs. Sentinel), Flanders, 2006-2012



Data source: GP sentinel network, Sciensano, Intego.



### 3.2.1.3 PERMANENT SAMPLE

The Permanent Sample database (Echantillon Permanent – Permanente Steekproef (EPS)) follows the reimbursed health expenditures for a group of people over the years. This group is composed of randomly drawn members of the Sickness Funds, approximately 1 in 40 for members younger than 65, and 1 in 20 for members aged 65 and older. This sample contains approximately 300 000 individuals that are followed since 2002. The sample is updated yearly to compensate for mortality and aging and new members are added according to the same sample size rules. For all individuals in the sample, demographic and socio-economic information is collected in addition to detailed information on health care expenditures. Observations with ATC code J05AB01 (i.e. antiviral treatment) were selected from the permanent sample (PS) for 2003 to 2017. Patient identification number, CNK code, age group ( $\geq 65$  years or not) and number of boxes were extracted from the database. The main objective of the analysis was to cross-check the incidence rate of HZ reported in the Sentinel and/or Intego databases (see 3.2.1.2 and 3.2.1.1) by identifying patients who have bought aciclovir and/or valaciclovir in a posology that corresponds to the recommended treatment of HZ (i.e. aciclovir 800 mg  $\times$  5 times a day  $\times$  7 days per os OR aciclovir 10 mg/kg  $\times$  3 times intra-venous in immunosuppressed patient OR valaciclovir 1 g  $\times$  3 times a day  $\times$  7 days per os- see 1.2). We started by investigating consumption data in the ambulatory sector in 2012, i.e. antiviral treatment bought in an open to the public pharmacy, with an extrapolation for the entire Belgian population<sup>a</sup>. However, only 5160 patients were identified in the PS database. This is significantly lower than what is reported by the Sentinel and Intego network ( $\sim 40\,000$  HZ cases/year). Possible reasons for such discrepancy may be no treatment (for example when the patient consults more than 72 hours after the rash appeared) or use of treatments not captured (for example the use of topical

antivirals). It seems therefore impossible to identify patients with HZ infection through the PS database. Computations can be found in Appendix 1.3.

### 3.2.1.4 Literature

Four publications reported the incidence of HZ in Belgium,<sup>20, 21, 38, 40</sup> each being based on the data collected through the Belgian Network of Sentinel General Practices (see section 3.2.1.1)<sup>b</sup>. Their results are thus fully similar to our analysis. Between 2006 and 2012, 4843 cases of HZ were registered.<sup>38</sup> The annual incidence of consultations for HZ varied between 33.5 and 43.2 cases per 10 000 person-years. The majority of cases were women (58%). Mean age was 59 years and 64% of cases were older than 50 years.<sup>38</sup> The highest incidence was observed in individuals  $>90$  years (173.8 per 10 000 person-years).<sup>38</sup> The vast majority of the cases (99%) was not vaccinated against chickenpox. In 73% of patients, an antiviral treatment was started (81% in patients  $>50$  years). The incidence was lower in Wallonia than in Flanders (34.1 per 10 000 person-years vs. 42.0 per 10 000 person-years in 2012, respectively).<sup>38</sup> The three other publications also based their estimates on sentinel GPs and reported very similar estimates. In Bilcke et al. 2012, the rate at which people visit a GP at least once for HZ in Belgium was 37.8 per 10 000 person-years over the period 2006–2008.<sup>20</sup>

<sup>a</sup> To extrapolate permanent sample results to the entire Belgian population, older than 65 years are weighted for 20 people and younger than 65 years are weighted for 40 people.

<sup>b</sup> Because it was based on ancient data, we did not consider the following publication: Truyers C, Bartholomeeusen S, Buntinx F, De Loof J: Incidentie van herpes zoster. Huisarts Onderzoek 2005, 34:260–262.



### 3.2.2 International data

A recent good-quality systematic literature review (search strategy up to December 2018) assessed HZ incidence in individuals  $\geq 50$  years.<sup>7, 10</sup> Sixty-nine studies published between January 2002 and December 2018 were included.<sup>a</sup> Most studies ( $n = 51$ ) were passive surveillance studies, with either a retrospective ( $n = 50$ ) or prospective ( $n = 1$ ) design. Furthermore, 15 active surveillance studies (10 prospective and 5 retrospective), and 3 unmatched retrospective cohort studies were retrieved.<sup>7, 10</sup> Incidence rates in individuals  $\geq 50$  years ranged 66-90.3 per 10 000 person-years for North America, 52.3-109 per 10 000 person-years for Europe and 109 per 10 000 person-years in the Asia-Pacific region.<sup>10</sup> Incidence rates (60.5-128 versus 43.0-85 cases per 10 000 person-years) were higher in females than males. In the majority of the studies ( $n=35$ ), the incidence increased with increasing age. However, in 14 studies a drop in incidence was reported for the highest age groups (i.e.  $>80$  years). In 17/23 studies reporting for different years, an increasing trend of HZ incidence was observed over the years.<sup>10</sup>

These results are consistent with those of two previous systematic reviews which used slightly different approach.<sup>8, 9</sup> Kawai et al. 2014 (search strategy up to December 2013) including 63 studies (prospective cohort, health insurance claims database, RCT) reported on the incidence of HZ from 22 countries: North America ( $N=18$ ), Europe ( $N=33$ ), Asia ( $N=7$ ), South America ( $N=3$ ) and the Middle East ( $N=2$ ).<sup>8</sup> Overall, the incidence rate of HZ ranged between 30 and 50 per 10 000 person-years in all ages. The age-specific incidence rates of HZ were similar across countries, with a steep rise after 50 years of age. The incidence rate was about 60-80 per 10 000 person-years at age 60 and 80-120 per 10 000 person-years at age 80.

<sup>a</sup> USA ( $n = 14$ ), Canada ( $n = 6$ ), UK ( $n = 6$ ), Germany ( $n = 5$ ), Japan ( $n = 5$ ), the Netherlands ( $n = 5$ ), Spain ( $n=5$ ), Taiwan ( $n = 4$ ), Australia ( $n = 3$ ), China ( $n = 3$ ), Italy ( $n = 3$ ), France ( $n = 2$ ), New Zealand ( $n = 2$ ), Sweden ( $n = 2$ ), Denmark ( $n = 1$ ), Israel ( $n = 1$ ), Norway ( $n = 1$ ), Poland ( $n = 1$ ), and South Korea ( $n = 1$ ).

<sup>b</sup> Papers with a quality score of less than 15 out of the 30 maximum possible points were excluded from the literature review. Points were attributed to

Twenty-five studies on trends of HZ incidence from 7 countries showed that incidence rates within countries appeared to increase over time.<sup>8</sup> There was however no convincing evidence to link the increase in HZ incidence with the roll out of varicella vaccination programmes.

The second previous systematic review by Pinchinat et al. (search strategy limited up to 2010) was restricted to population-based studies carried out in Europe.<sup>9</sup> Studies limited to immunocompromised populations were excluded. Papers with a low quality score<sup>b</sup> were also excluded. The authors reported a similar annual HZ incidence in the 21 studies included<sup>c</sup> ranging from 20 to 45.7 per 10 000 person-years. The HZ incidence rates in the studies excluded because of a low quality score were in the same range. The overall incidence was lower in Iceland, Germany and Switzerland (around 20 per 10 000 person-years), medium in the UK, the Netherlands and France (around 30 per 10 000 person-years), and higher in Belgium, Spain and Italy (around 40 per 10 000 person-years). However, no geographic trend of overall incidence was clearly observed. There was a rapid increase after age 50 years to around 70-80 per 10 000 person-years and up to 110 per 10 000 person-years after 80 years of age. Incidence rates were consistently higher among women than men (male/female ratio range: 1.13-1.56), and this difference also increased with age. Studies performed among immunocompetent people and among the general population (including both immunocompetent and immunocompromised people), showed that the risk of HZ was slightly higher in the general population (98.0 per 10 000 person-years in Germany and 43.1 per 10 000 person-years in Italy) than among immunocompetent people (95.0 per 10 000 person-years in Germany and 40.7 per 10 000 person-years in Italy).<sup>9</sup>

representativeness of the sample detection, incidence calculation, study design, and discussion of limitations.

<sup>c</sup> One from Belgium, four from France, two from Germany, two from Iceland, two from Italy, three from the Netherlands, two from Spain, one from Switzerland, and four from the UK.



From the 2 systematic reviews cited above,<sup>8, 9</sup> we extracted data from primary studies conducted in Europe to document further the split of HZ incidence rate by age categories in the various countries and compare it to Belgian data.<sup>a</sup> The selection criteria for such studies were: included at least 400 HZ cases (to avoid too big imprecision around the estimates)- reported incidence by age-range- reported on data collected after 2000 (to avoid historical distortion). Ten studies were identified.<sup>9, 41-49</sup> Our search yielded 31 primary studies published after 2013 and carried out in Western countries, among which 14 reported on HZ incidence.<sup>6, 50-61</sup> The final count was thus 24 studies, of which seven had been carried out in Germany and five in the UK, were included. Studies characteristics and results are presented in (Table 8).

In Table 8, the incidence rate of HZ displayed some variation across European countries. For example, the overall HZ incidence rate went from 38 per 10 000 person-years in France,<sup>42</sup> an estimate very close to the Belgian one, to 62.1 per 10 000 in the UK (immunocompetent individuals)<sup>60</sup> and 64.2 per 10 000 in Italy.<sup>55</sup> Variations could be observed also within countries, as already observed in Belgium (section 3.2.1). For example in Germany, the incidence in individuals  $\geq 50$  years went from 67 per 10 000 person-years<sup>54</sup> to 98 per 10 000 person-years.<sup>43</sup> Studies stratifying results by immunocompetency status reported higher incidence rate in immunocompromised vs. immunocompetent individuals, as in Germany<sup>53</sup> or the UK.<sup>60</sup> However, the gradient was much greater (around 2) in Germany than in the UK.

In comparison, the 2 pivotal studies on the evaluation of Shingrix efficacy reported an incidence of HZ in the placebo group of 93 per 10 000 person-years in individuals  $\geq 50$  years<sup>31</sup> to 110 per 10 000 person-years in individuals  $\geq 80$  years.<sup>63</sup> RCTs assessing the efficacy of Zostavax vaccine reported a rate of HZ in the placebo group of 65.7 per 10 000 person-years in individuals 50-59 years,<sup>26</sup> 107.9 per 10 000 person-years in patients 60-69 years and 115 per 10 000 person-years in patients  $\geq 70$  years.<sup>25</sup> Incidence rates were thus fairly similar to those observed in in-population studies.

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<sup>a</sup> At the time we did this review (July 2019), no Belgian cost-effectiveness analysis was foreseen. The objective was thus to cross-check Belgian and foreign incidence rates distribution to evaluate the applicability of foreign CEA findings. Our research project was put on hold between September 2019 and December 2021 because availability of Shingrix for the Belgian market was

reduced. When we restarted the research in early 2022, no attempt was made to update our pragmatic review as we considered unlikely that new contradictory evidence would emerge on incidence, risk factors and complications of HZ. However, results from more recent systematic reviews were included, as it is the case here for paper from Van Oorschot et al. 2021.<sup>7</sup>

**Table 8 – Incidence of HZ in European population-based studies**

| Country              | Data collection                                                                                                                 | N cases | Incidence per 10 000 person-years (95%CI), per age-groups |                             |                     |                     |                      |                       |                       |                      |                       |                                   |                       | Source                              |
|----------------------|---------------------------------------------------------------------------------------------------------------------------------|---------|-----------------------------------------------------------|-----------------------------|---------------------|---------------------|----------------------|-----------------------|-----------------------|----------------------|-----------------------|-----------------------------------|-----------------------|-------------------------------------|
|                      |                                                                                                                                 |         | Overall<br>(95%CI)                                        | ≥50                         | 50<br>54            | 55<br>59            | 60<br>64             | 65<br>69              | 70<br>74              | 75<br>79             | 80<br>84              | 85<br>89                          | 90<br>94              |                                     |
| France<br>2005       | - Retrospective survey in a random selection of 231 GPs, 41 dermatologists, 15 neurologists<br>-Patients ≥50y                   | 777     | -                                                         | 89.9<br>(83.4-96.4)         | 58.4<br>(50.1-66.7) |                     | 83.9<br>(71.6-96.2)  |                       | 124.3<br>(108-140)    |                      | 134.7<br>(113-157)    |                                   |                       | Mick 2010 <sup>41</sup>             |
| France<br>2005-08    | -GP surveillance (1200 GPs)<br>-All patients                                                                                    | 2375    | 38.2<br>(36.4-40.5)                                       | 45-54y: 41.6<br>(38.5-45.4) |                     | 57.7<br>(49.7-69.6) |                      | 86.8<br>(68.9- 105.1) |                       | 98.5<br>(86.2-104.6) |                       | 57-94y:<br>107.7<br>(89.5- 135.0) |                       | Gonzales-Chiappe 2010 <sup>42</sup> |
| France<br>2017       | -GP surveillance<br>-All patients                                                                                               | 1139    | 41.3<br>( 38.5-44.1)                                      |                             | 41.7<br>(34.1-49.3) |                     | 69.3<br>(58.9-79.7)  |                       | 100.3<br>(84.8-115.8) |                      | 117.0<br>(95.8-138.2] |                                   | 113.3<br>(71.8-154.8) | Sentinelles 2018 <sup>50</sup>      |
| Germany<br>2004      | -Searches in computerized records<br>-120 399 Patients ≥50y                                                                     | 1176    | -                                                         | 98.0                        | 68.0                | 68.0                | 96.0                 | 85.0                  | 123.0                 | 124.0                | 125                   |                                   |                       | Schiffner-Rohe 2010 <sup>43</sup>   |
| Germany<br>2005-2009 | -Retrospective cohort with claim data from 3 insurance companies (SHI) (in- and out-patient with ICD-10) and drug prescriptions | 215 959 | 60<br>(59-60)                                             | 104 to 109                  |                     |                     | 100<br>(DSA: 63-103) | 114<br>(DSA: 72-118)  | 134<br>(DSA: 85- 138) |                      | 139<br>(DSA: 94- 148) |                                   |                       | Hillebrand 2015 <sup>51a</sup>      |

<sup>a</sup> Data by age groups are extracted from the paper by Van Oorschot et al. 2018.<sup>18</sup>



| Country                               | Data collection                                                                                                                                         | N cases | Incidence per 10 000 person-years (95%CI), per age-groups                                                                                             |                         |                         |                         |                         |                            |                            |                            |                            |                            |                            | Source                             |
|---------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------|---------|-------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|-------------------------|-------------------------|-------------------------|----------------------------|----------------------------|----------------------------|----------------------------|----------------------------|----------------------------|------------------------------------|
|                                       |                                                                                                                                                         |         | Overall<br>(95%CI)                                                                                                                                    | ≥50                     | 50<br>54                | 55<br>59                | 60<br>64                | 65<br>69                   | 70<br>74                   | 75<br>79                   | 80<br>84                   | 85<br>89                   | 90<br>94                   |                                    |
|                                       | -All patients                                                                                                                                           |         |                                                                                                                                                       |                         |                         |                         |                         |                            |                            |                            |                            |                            |                            |                                    |
| Germany<br>2005-<br>2016 <sup>a</sup> | -GP surveillance +<br>inpatient data<br>-All patients                                                                                                   | 2784    | 42.5<br>(42.4-42.7)                                                                                                                                   |                         | ±40 <sup>b</sup>        |                         | ±60                     |                            | ±70                        |                            | ±85                        |                            |                            | Zoch-Lesniak<br>2018 <sup>52</sup> |
| Germany<br>2006-<br>2012              | -Claims data from<br>4 statutory<br>health insurances<br>(GePaRD)<br>including<br>outpatient and<br>inpatient - based<br>on ICD-10-GM<br>-Patients ≥18y | 442 979 | Overall:<br>75.2 (74.7- 75.8) <sup>c</sup><br>Immunocompr<br>omised <sup>d</sup> : 115<br>(113.8- 116.3)<br>Immunocomp<br>etent: 56.2<br>(55.6- 56.7) |                         |                         |                         |                         |                            |                            |                            |                            |                            |                            | Schröder 2017 <sup>53</sup>        |
| Germany<br>2007-<br>2008 <sup>e</sup> | -Searches in claim<br>database<br>outpatient ICD-10<br>in 17 regions<br>-Patients≥50y                                                                   | 164 335 | -                                                                                                                                                     | 98.5<br>(98.0-<br>99.0) | 63.8<br>(62.9-<br>64.8) | 77.3<br>(76.3-<br>78.4) | 90.0<br>(88.7-<br>91.3) | 108.5<br>(107.3-<br>109.8) | 115.0<br>(113.6-<br>116.3) | 123.2<br>(121.5-<br>124.9) | 126.5<br>(124.5-<br>128.5) | 128.2<br>(125.6-<br>130.8) | 137.7<br>(133.3-<br>142.2) | Ultsch 2011 <sup>44</sup>          |

<sup>a</sup> We present here results for year 2012.

<sup>b</sup> Derived from the graphic p 1810.

<sup>c</sup> Figures in 2012.

<sup>d</sup> Patients were considered IC if they had at least one IC condition or a prescription of an IC drug. The IC conditions were: infection with human immunodeficiency virus (HIV), malignant neoplasms, chronic kidney disease, organ transplantation, stem cell transplantation, and autoimmune diseases. IC drugs included corticosteroids for systemic use, antineoplastic drugs, immunosuppressants, and disease modifying antirheumatic drugs.

<sup>e</sup> We present here results from 2008.



| Country                           | Data collection                                                                               | N cases | Incidence per 10 000 person-years (95%CI), per age-groups |                     |               |               |               |               |               |                |             |          |          |     | Source                         |
|-----------------------------------|-----------------------------------------------------------------------------------------------|---------|-----------------------------------------------------------|---------------------|---------------|---------------|---------------|---------------|---------------|----------------|-------------|----------|----------|-----|--------------------------------|
|                                   |                                                                                               |         | Overall<br>(95%CI)                                        | ≥50                 | 50<br>54      | 55<br>59      | 60<br>64      | 65<br>69      | 70<br>74      | 75<br>79       | 80<br>84    | 85<br>89 | 90<br>94 | ≥95 |                                |
| <b>Germany<br/>2005-<br/>2008</b> | -Searches in claim database<br>-outpatient and in-patient ICD-10 in 1 region<br>-All patients | 5384    | 57.9<br>(56.4-59.3)                                       | 93.3<br>(90.5-96.0) | 65.6          |               | 91.9          |               | 112.4         |                | 127.6       |          |          |     | Ultsch 2013 <sup>45</sup>      |
| <b>Germany<br/>2010-<br/>2014</b> | - Notified by 125GP+6 dermatologists+6 ophthalmologists<br>-Patients≥50y                      | 1551    | -                                                         | 67<br>(64-71)       | 36<br>(30-42) | 55<br>(47-63) | 63<br>(55-73) | 72<br>(62-82) | 72<br>(63-81) | 97<br>(85-110) | 94 (84-106) |          |          |     | Schmidt-Ott 2018 <sup>54</sup> |
| <b>Italy<br/>2003-05</b>          | Searches in computerized Records<br>-450 000 patients ≥15y                                    | 5675    | 43.1<br>(41.1-45.2)                                       |                     | 41.5          | 56.3          | 69.0          | 71.1          | 82.2          | 85.6           | 79.7        | 61.3     |          |     | Giallorete 2010 <sup>46</sup>  |
| <b>Italy<br/>2013-<br/>2015</b>   | -Searches in computerized records <sup>a</sup> - 56 GP<br>-All patients                       | 598     | 64.2 <sup>b</sup><br>(59.3- 69.5)                         |                     | 39.5          | 55.5          | 64.5          | 60.7          | 90.6          | 81.9           | 88.5        | 55.9     |          |     | Alicino 2017 <sup>55</sup>     |
| <b>Netherlands 1998-<br/>2001</b> | -GP surveillance (NIVEL) <sup>c</sup><br>-All patients                                        | NR      | 32.5                                                      |                     | 39.0          | 54.7          | 65.7          | 64.5          | 74.5          | 72.0           | 77.5        | 83.5     |          |     | De Melker 2006 <sup>47</sup>   |

<sup>a</sup> A case of HZ was defined as a patient with a diagnosis of HZ registered in the clinical chart or a patient with the prescription of antiviral drugs for the treatment of HZ.

<sup>b</sup> In 2012.

<sup>c</sup> All cases based on GP surveillance network NIVEL were identified by ICPC-code S70.



| Country                      | Data collection                                                                                                       | N cases | Incidence per 10 000 person-years (95%CI), per age-groups |      |                           |                        |                                |                        |               |               |            |          |          |     | Source                                                             |
|------------------------------|-----------------------------------------------------------------------------------------------------------------------|---------|-----------------------------------------------------------|------|---------------------------|------------------------|--------------------------------|------------------------|---------------|---------------|------------|----------|----------|-----|--------------------------------------------------------------------|
|                              |                                                                                                                       |         | Overall<br>(95%CI)                                        | ≥50  | 50<br>54                  | 55<br>59               | 60<br>64                       | 65<br>69               | 70<br>74      | 75<br>79      | 80<br>84   | 85<br>89 | 90<br>94 | ≥95 |                                                                    |
| <b>Netherlands 2002-2011</b> | -GP surveillance (NIVEL)<br>-All patients                                                                             | NR      | 34.0                                                      |      |                           |                        |                                |                        |               |               |            |          |          |     | Van Lier 2019 <sup>6</sup>                                         |
| <b>Netherlands 2012-2016</b> | -GP surveillance (NIVEL) <sup>a</sup><br>-All patients                                                                | -       | 52.0                                                      |      | 59.1<br>(DSA:<br>57.5-61) | 85.7<br>(DSA: 83.5-88) | 119.0<br>(DSA:<br>115.7-122.2) | 148.1<br>(143.5-152.7) |               |               |            |          |          |     | De Boer 2018 <sup>56</sup><br>Van Lier 2019 <sup>6</sup>           |
| <b>Spain 2005-2006</b>       | -Searches in computerized records of GPs<br>-All patients                                                             | 4959    |                                                           |      | 58.6                      | 66.4                   | 84.1                           | 90.5                   | 96.0          |               | 89.9       |          |          |     | Cenoz 2011<br>(figures extracted from Pinchinat2013 <sup>9</sup> ) |
| <b>Spain 2005-2012</b>       | -Data drawn from electronic clinical records in primary care                                                          | 211 650 | 44.5<br>(44.0- 45.0)                                      |      | 45-64y: 47.5              |                        |                                | 105.3                  |               |               |            | 112.8    |          |     | Esteban-Vasallo 2014 <sup>57</sup>                                 |
| <b>Sweden 2008-2010</b>      | -Data extracted from 2 registers (GP and hospital) in 1 county - no HZ in previous year- ICD-10: B02<br>-All patients | 13 296  | 26 (25-27) -<br>33 (32-33)                                |      | 28<br>(26-30)             | 36<br>(34-39)          | 45<br>(43-48)                  | 60<br>(57-63)          | 77<br>(73-81) | 83<br>(79-88) | 92 (88-96) |          |          |     | Sundstrom 2015 <sup>58</sup>                                       |
| <b>Sweden 2011</b>           | - Incidence of HZ was estimated from the number of prescriptions of antiviral drugs<br>-Patients ≥50y                 | 29 900  | -                                                         | 57.7 | 37.9                      | 45.6                   | 55.0                           | 61.0                   | 71.2          | 72.8          | 76.7       | 112.7    |          |     | Nilsson 2015 <sup>59</sup>                                         |

<sup>a</sup> Rates adjusted for possible misdiagnoses by setting the proportion of false-positive diagnoses at 10.0% (95%CI 7.9–12.4%). Rate adjusted for immunocompetent.<sup>53</sup>



| Country      | Data collection                                                                                                                      | N cases | Incidence per 10 000 person-years (95%CI), per age-groups |                     |                      |          |                      |                       |                         |                 |                           |          |          |                                  | Source |
|--------------|--------------------------------------------------------------------------------------------------------------------------------------|---------|-----------------------------------------------------------|---------------------|----------------------|----------|----------------------|-----------------------|-------------------------|-----------------|---------------------------|----------|----------|----------------------------------|--------|
|              |                                                                                                                                      |         | Overall<br>(95%CI)                                        | ≥50                 | 50<br>54             | 55<br>59 | 60<br>64             | 65<br>69              | 70<br>74                | 75<br>79        | 80<br>84                  | 85<br>89 | 90<br>94 | ≥95                              |        |
| UK 1994-01   | -GP surveillance<br>-All patients                                                                                                    | 14 532  | 32.0                                                      |                     | M:39.9 F: 59.1       |          |                      | M:77.5 F:98.4         |                         | M: 95.8 F:110.4 |                           |          |          | Fleming 2004 <sup>48</sup>       |        |
| UK 2000-2006 | -Electronic records primary care (GPRD) + Hospital Episode Statistics (HES)<br>-Patients ≥50y                                        | 25 002  | -                                                         | 52.3<br>(51.7-52.9) | 34.4                 | 40.8     | 49.0                 | 59.6                  | 63.4                    | 70.9            | 72.9                      | 62.2     |          | Gauthier 2009 <sup>49</sup>      |        |
| UK 2000-2012 | -Electronic records primary care (GPRD) + Hospital Episode Statistics (HES)- ICD-10-first episode<br>- Immunocompetent patients ≥18y | -       | 62.1<br>(61.2- 63.0)                                      |                     | 49.0<br>(47.2- 50.8) |          | 69.2<br>(66.4- 72.0) | 86.2<br>(83.0- 89.5)  | 110.4<br>(107.5- 113.4) |                 | 110.2<br>(106.4- 114.1)   |          |          | Yanni 2018 <sup>60</sup>         |        |
|              | Immunocompromised patients ≥18y <sup>a</sup>                                                                                         |         | 77.7<br>(76.7-78.8)                                       |                     | 68.5<br>(66.2-70.8)  |          | 88.0<br>(84.6- 9.14) | 99.3<br>(95.6- 103.0) | 113.2<br>(110.3-116.3)  |                 | 126.1<br>(122.2 to 130.2) |          |          |                                  |        |
| UK 2005-2016 | -Sentinel GP (Royal College of General Practitioners (RCGP)                                                                          | 26 257  | -                                                         |                     |                      |          |                      | 81.8                  |                         |                 |                           |          |          | Amirthalingam 2018 <sup>61</sup> |        |

<sup>a</sup> Immunocompromised patients suffered from at least one of the following conditions: haematopoietic stem cell transplant (HSCT); solid organ transplantation (SOT); solid organ malignancy (SOM); haematological malignancy (HM); HIV; end-stage renal disease (ESRD); corticosteroids exposure (CORTDS); other immunosuppressive therapy (OIT) exposures including biological treatments; other immunodeficiency conditions (OIC); and autoimmune diseases (AID). The AIDs comprised: RA, systemic lupus erythematosus (SLE), IBDs, PSOR, multiple sclerosis (MS), polymyalgia rheumatica and autoimmune thyroiditis (AT).



| Country        | Data collection                                                                                                                              | N cases | Incidence per 10 000 person-years (95%CI), per age-groups |     |          |          |          |          |          |          |          |          |          |     | Source                    |
|----------------|----------------------------------------------------------------------------------------------------------------------------------------------|---------|-----------------------------------------------------------|-----|----------|----------|----------|----------|----------|----------|----------|----------|----------|-----|---------------------------|
|                |                                                                                                                                              |         | Overall<br>(95%CI)                                        | ≥50 | 50<br>54 | 55<br>59 | 60<br>64 | 65<br>69 | 70<br>74 | 75<br>79 | 80<br>84 | 85<br>89 | 90<br>94 | ≥95 |                           |
|                | Research and Surveillance Centre (RSC) - 164 practices - extraction of electronic data -Patients 60-89y - not vaccinated                     |         |                                                           |     |          |          |          |          |          |          |          |          |          |     |                           |
| <b>UK 2013</b> | -Data from the Clinical Practice Research Datalink (CPRD), (7% sample of the UK population)<br>-Patients ≥70y- immunocompetent- unvaccinated | 8006    | -                                                         |     |          |          |          |          |          |          | 88.0     |          |          |     | Walker 2018 <sup>62</sup> |

CI: Confidence Interval, DSA: Deterministic Sensitivity Analysis, GePaRD: German Pharmacoepidemiological Research Database, GPRD: General Practice Research Database, HES: Hospital Episode Statistics.



### 3.2.3 Risk of recurrence

In their systematic review of the literature, Kawai et al. included 9 studies on HZ recurrence from 5 countries.<sup>8</sup> Obviously risk of recurrence depends upon length of follow-up, and included studies were heterogeneous on that aspect. The risk of recurrence of HZ ranged from 1% to 6%, with long-term follow-up studies (from 8 years to 20 years according to studies) showing higher risk (5–6%).<sup>8</sup>

More recent studies reported consistent findings. In Italy the proportion of patients aged  $\geq 50$  years ( $n=598$ ) who reported a previous episode of HZ in the year before the current episode was 2.2%, raising to 4.2% and 5.7% in the previous 5 and 10 years, respectively.<sup>55</sup> Considering the entire lifetime, 14.1% of subjects reported a previous HZ, with 58.2% of these subjects reporting 2 or more episodes.<sup>55</sup> In Japan, the proportion of recurrence was estimated at 6.4% (1076/16 784).<sup>64</sup> In an UK study ( $n=621\,588$ ), HZ recurrence (defined as any HZ episode occurring after a 180-day disease-free period of HZ or HZ complications, except PHN) within 2 years of the incident HZ was 2.26% (95%CI: 2.01-2.52) in the immune-compromised patients and 1.54% (95%CI: 1.33-1.77) in the immune-competent ones.<sup>60</sup>

### 3.2.4 Discussion

Previous systematic reviews reported that overall HZ incidence rates in the general population were fairly similar across countries, varying from 20.0 to 46 per 10 000 person-years in Europe<sup>9</sup> or from 30 to 50 per 10 000 person-years worldwide.<sup>8</sup> In individuals  $\geq 50$  years, the HZ incidence rates ranged between 52.3 and 109 cases per 10 000 person-years in Europe.<sup>10</sup> Incidence increased with age and was consistently higher in females than in males.

Although incidence rates were globally in the same range across Europe, some variations were observed between and within countries. Such differences most probably came from differences in case registration. For example, in Germany the fact that incidence rates by age intervals were much higher in Hillebrand et al.<sup>51</sup> than in other studies was likely due the use of claim data, and thus to a more comprehensive registration of cases (not only clinical codes but also codes for drug prescriptions were used to identify

cases, whereas other studies were based on GP surveillance.<sup>52, 54</sup> The incidence in  $\geq 50$  year individuals in Hillebrand et al.<sup>51</sup> (104 to 109 per 10 000 person-years) was close to figures reported in the same age group in RCTs on Shingrix<sup>31</sup> and to figures in 60-69 years old in RCT on Zostavax.<sup>25</sup> However, in the Netherlands, the incidence rates were also similar to those observed in Hillebrand and RCTs, although they were calculated from data generated from GP surveillance.<sup>56</sup>

In Belgium, incidence rates were comparable with those from studies in Germany,<sup>52, 54</sup> in Italy,<sup>55</sup> in France<sup>42, 50</sup> and in Spain,<sup>57</sup> all based on GP surveillance. In the Netherlands, the overall incidence rate was also similar until 2012 when NIVEL adopted a new method to estimate incidence rate.<sup>6</sup> There were also within-country variations: the incidence was lower in Wallonia than in Flanders in the Sentinel Network of GPs, and in Flanders the incidence was slightly higher in the Intego database than in the Sentinel Network of GPs. Therefore, incidence rates based on GP surveillance are fairly similar across Europe, but are systematically lower than incidence rates derived from electronic searches in GP records or from claim data.

There are various elements that could contribute to a possible under-estimation of the incidence rates based on GP surveillance:

- Based on a survey among patients who suffered HZ, Bilcke et al. reported that 99% of ambulatory HZ patients consulted a GP at least once,<sup>20</sup> implying that the validity of estimates of HZ incidence based on GP visits was likely high. However, the sample on which the authors based their estimate might have been biased towards more compliant patients (only 130 participants responded to an open call for participation into the survey on the internet and magazines) or more severe cases and this bias might have led to an under- or over-estimation.
- Another contributing factor to a sub-optimal registration would be that the population visiting a GP for HZ presented itself a selection bias, i.e. older patients living in nursing home could have been less covered by sentinel GPs. The elderly population in institutions is probably underrepresented influencing the numerator (personal communication: Marine Sabbe, Nathalie Bossuyt, Sciensano). Multi-comorbid patients



might also be less captured through the SGP. A proportion of patients may consult directly a medical specialist, e.g. geriatrist.<sup>a</sup>

- Only ambulatory cases are covered by sentinel GP. Bilcke, on the basis of a second survey, reported that 89.5% of hospitalized HZ patients visited a GP at some point.<sup>20</sup> Therefore, a better estimation of overall HZ cases should account not only for cases registered by sentinel GPs but also for the 10% of hospitalized cases with no GP consultations. However, this would not modify significantly the HZ incidence. For example, in 2012, there were 665 cases reported by SGP for a reference population estimated at 1.8% of the total population, i.e. by extrapolation there were 41 562 cases overall. In the same year, the number of hospitalisations for HZ was 2567. Therefore, 257 cases could be added to the 41 562 cases registered by SGP.
- Another explanation would be an over-estimated reference population, resulting in lower incidence rates. For example in the Netherlands, incidence rates increased dramatically when the definition of reference population was modified.<sup>6</sup>

### 3.3 Incidence of Postherpetic Neuralgia (PHN)

#### Main findings

- There is no reliable data of PHN incidence in Belgium
- International studies reported a risk of developing PHN ranging from 5% to 30%, depending on the type of study design, age distribution of study population, and pathology definition. The risk of PHN increases with age, as does the severity and duration of related pain.

- In about half of the European primary studies included, the risk of PHN was less than 10% in individuals 50-59 years and between 10% and 20% in individuals 70-79 years.

#### 3.3.1 Belgian data

##### 3.3.1.1 Sentinel General Practice

PHN was registered only since year 2021. The incidence of PHN in 2021 was 0.8 cases per 10 000 person-years (95%CI: 0.7-0.9), respectively 0.5 (95%CI 0.4-0.6) and 0.3 (95%CI 0.2-0.3) cases per 10 000 person-years for women and men. But as explained above, the registration was sub-optimal during that year and these figures should be considered with caution.

##### 3.3.1.2 Intego

No registration of PHN.

##### 3.3.1.3 Minimal Clinical Data (RHM/MZG)

This database includes only hospitalised patients and is inappropriate to evaluate the frequency of PHN as many patients with PHN are likely not to be hospitalised.

##### 3.3.1.4 Literature

In Belgium, a survey by questionnaire among patients who had experienced an episode of HZ estimated the risk of PHN (defined as having a pain score of  $\geq 3$  on the 'worst pain' question from the Zoster Brief Pain Inventory,<sup>65</sup> and being sick for >90 days) at 39% for hospitalized HZ cases (among 153 interviewees representative of the National Christian Sickness Fund (NCSF)) and at 26% for ambulatory cases (among 130 interviewees of the

<sup>a</sup> Almost 100 % of HZ-cases had at least one outpatient physician contact in Germany, among whom 90% visited a GP.<sup>45</sup>



NCSF who responded to an open appeal).<sup>20</sup> In hospitalized patients, PHN ranged from 30% in patients aged <60 years up to 53% in patients aged >80 years. However, these results should be considered with caution as the sample size was small and the risk of selection bias was high. First 56% of hospitalized HZ patients and 38% of the ambulatory patients were declared immunocompromised<sup>a</sup> or having other conditions<sup>b</sup> (e.g., chronic pain syndromes, cognitive impairment, severe hearing loss) that would interfere with the evaluation of herpes zoster or compliance with protocol requirements.<sup>20</sup> Second, NCSF questionnaires were completed by only 59% of the hospitalised persons receiving the questionnaire (this proportion is not reported for ambulatory patients).

### 3.3.2 International data

Figures of PHN incidence are reportedly imprecise in link with various definitions of PHN, the varying methodology and quality of studies, and the age distribution of the study population.<sup>17</sup> Two systematic reviews reported on PHN incidence. The good quality systematic review of cohorts (n=19-search date up to February 2014) by Forbes et al.<sup>14</sup> reported that the percentage of patients with zoster developing PHN ranged from 2.6% to 67.3%. Most of the time PHN was either assessed using a standard scale of pain or by simple report of the patient. However, definition of PHN, % of loss-to-follow up, settings and sample size were highly variable. For example, one study reporting 67.3% PHN analysed only 104 of the 280 patients included, jeopardizing the validity of this estimate.<sup>66</sup> Another systematic review by Kawai et al.,<sup>8</sup> including 49 studies (search strategy up to 2013) with diverse designs (prospective cohort, health insurance claims database, RCT) reported a risk of developing PHN ranging from 5% to 30%,

depending on the type of study design, age distribution of study population, and pathology definition.

The age at which HZ appears is the principal risk factor for the development of PHN. The risk of PHN increases dramatically with age, as does the severity and duration of related pain.<sup>17</sup> It was reported that the relative risk estimates per 10-year increase ranged from 1.22 to 3.11.<sup>14</sup> Aside from age-associated risks, evidence regarding risk factors of PHN is currently limited. A meta-analysis including 19 prospective studies showed significant increases in the risk of PHN with clinical features of acute zoster including prodromal pain (summary rate ratio=2.29, 95%CI: 1.42-3.69), severe acute pain (rate ratio=2.23, 95%CI: 1.71-2.92), severe rash (rate ratio=2.63, 95%CI: 1.89-3.66), and ophthalmic involvement (rate ratio=2.51, 95%CI: 1.29-4.86).<sup>14</sup> The same findings were reported in a more recent systematic literature review.<sup>16</sup> Evidence for differences by gender was conflicting, with considerable between-study heterogeneity.<sup>14</sup> A proportion of studies reported an increased risk of postherpetic neuralgia with severe immunosuppression (n=3/5) and diabetes mellitus (n=1/4). Systemic lupus erythematosus, recent trauma, and personality disorder symptoms were associated with postherpetic neuralgia in single studies. No evidence of higher postherpetic neuralgia risk was found with depression (n=54) or cancer (n=55).<sup>14</sup>

To get a more precise estimate of risk of PHN in Europe, we extracted from these two systematic reviews<sup>8, 14</sup> the results from European studies with the following characteristics: studies with less than 10% of patients lost-to-follow up- PHN defined as (neuropathic) pain persisting ≥90 days after the onset of herpetic rash- a sample size arbitrarily set at >400 HZ patients (with an estimated average PHN incidence around 15%, lower numbers would not allow age stratification with enough precision)- and a publication after year

<sup>a</sup> In the Shingles Prevention Study,<sup>25</sup> immunosuppression was defined as resulting from 1. disease (e.g., malignancy; HIV infection), corticosteroids (except intermittent topical or inhaled corticosteroid [ $<800$  mcg/day beclomethasone dipropionate or equivalent]), or other immunosuppressive/cytotoxic therapy (cancer chemotherapy or organ

transplantation); 2. active neoplastic disease (except local skin cancer or other malignancies [e.g., prostate cancer] that are stable in the absence of immunosuppressive/cytotoxic therapy).

<sup>b</sup> As defined in the Shingles Prevention Study.<sup>25</sup>



2000. Eight studies fulfilled these criteria.<sup>41, 44, 45, 46, 49, 67, 68, 69</sup> Moreover, the search for more recent primary studies (published after December 2013) yielded 12 hits. Therefore, 20 studies were included in total, among which 5 were carried out in Germany and 5 in the UK. Study design, case definition and results are presented in Table 9.

In the age range 50-59 years, the proportion of PHN went from a low 2% in Iceland or the Netherlands<sup>67, 69</sup> to 15.5% in a prospective study in Italy<sup>70</sup> or 19.3% in France (Table 9).<sup>41</sup> Eleven studies reported a risk below 10%. The very high risk reported in France by Mick et al.<sup>41</sup> may possibly be linked with the involvement of neurologists and pain clinics in case ascertainment, i.e. there might have been a selection bias towards more severe cases. Variations can be observed within countries. For example, in the UK, the proportion of PHN in that age range went from 5.5%<sup>60</sup> to 9%.<sup>49</sup> In Italy, the risk of PHN in that age range went from 3.9% (primary-care database and

national hospital-discharge records)<sup>46</sup> to 15.5% (prospective study in 108 general practices).<sup>70</sup> The proportion of HZ cases suffering from PHN increased with age, although the figures in 80+ were very similar to those observed in individuals aged 70-79 years, with the exception of an Italian study displaying a sharp increase in individuals  $\geq 85$  years.<sup>55</sup> In the age range 70-79 years, the risk of PHN was between 7.8% in a study in Germany<sup>45</sup> and 37.3% in a study in France.<sup>41</sup> Twelve studies over 20 reported a risk of PHN between 10% and 20% in individuals aged 70-79 years. In the UK, the PHN risk in individuals  $\geq 70$  years was 4.6% in study by Walker et al.<sup>62</sup> and 10.9% in study by Forbes et al.<sup>71</sup> The same database was used (Clinical Practice Research Datalink (CPRD)) but Forbes et al.<sup>71</sup> also used Hospital Episode Statistics. This said there was also a difference in PHN risk between studies from Gauthier et al.<sup>49</sup> (19% PHN risk in individuals  $\geq 80$  years) and Yanni et al.<sup>60</sup> (12% PHN risk in individuals  $\geq 80$  years) although combining both primary care and hospital data.

**Table 9 – Proportion of PHN in HZ patients in European Countries**

|   | Country | Author                        | Study design                                                                                                                                  | Case definition                                                            | Nbr of HZ cases | % of PHN (95%CI) by age    |            |                      |                             |                              |                           |
|---|---------|-------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------|-----------------|----------------------------|------------|----------------------|-----------------------------|------------------------------|---------------------------|
|   |         |                               |                                                                                                                                               |                                                                            |                 | Overall                    | $\geq 50y$ | 50-59                | 60-69                       | 70-79                        | 80+                       |
| 1 | France  | Mick 2010 <sup>41</sup>       | -Random selection of 231 GPs, 41 dermatologists, 15 neurologists, + pain clinics<br>-Patients $\geq 50y$ -immunocompetent                     | Pain persisted for $\geq 90$ days                                          | 777             |                            |            | 19.3<br>(12.9- 25.6) | 28.7<br>(20.8- 36.7)        | 37.3<br>(29.3- 45.2)         | 40.5<br>(30.0- 51.0)      |
| 2 | France  | Duracinsky 2014 <sup>72</sup> | - Random sample of 644 GPs with consecutive inclusion of all patients with acute HZ - patients contacted by telephone<br>-Patients $\geq 70y$ | Persistence of pain of any intensity 3 months or more after the rash onset | 462             |                            |            |                      |                             | 70-74y: 13.3<br>75-79y: 15.3 | 80-84y: 11.6<br>85+: 19.0 |
| 3 | Germany | Hillebrand 2015 <sup>51</sup> | -Retrospective cohort with claim data (in- and out-patient with ICD-10)                                                                       | Code (B02.-) and either additionally a                                     | 215 959         | 11.5 (2005) to 14.9 (2009) |            | 12.5                 | 60-64y: 15.4<br>65-69: 17.5 | 20.0                         | 20.4                      |



| Country | Author                                                                   | Study design                | Case definition                                                                                                                                                                                    | Nbr of HZ cases                                                   | % of PHN (95%CI) by age |                       |                             |                             |                             |                             |
|---------|--------------------------------------------------------------------------|-----------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------|-------------------------|-----------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
|         |                                                                          |                             |                                                                                                                                                                                                    |                                                                   | Overall                 | ≥50y                  | 50-59                       | 60-69                       | 70-79                       | 80+                         |
|         | Results by age are extracted from Van Oorschot et al. 2018 <sup>18</sup> | -All patients               | code of PHN (G53.0) or a prescription of pain medication during the quarter of the HZ episode or the following quarter                                                                             |                                                                   |                         |                       |                             |                             |                             |                             |
| 4       | Germany 2006-2012                                                        | Schröder 2017 <sup>53</sup> | -Claims data from 4 statutory health insurances (GePaRD) <sup>a</sup> - including outpatient and inpatient- based on ICD-10-GM and/or pain medication in the 2 quarters after HZ<br>-Patients ≥18y | ICD-10 codes or pain medications in the 2 first quarters after HZ | 442 979                 | 27                    |                             |                             |                             |                             |
| 5       | Germany 2007-2008                                                        | Ultsch 2011 <sup>44</sup>   | -Searches in claim database outpatient ICD-10 in 17 regions<br>-Patients ≥50y                                                                                                                      | Pain persisted for ≥90 days                                       | 374 645                 | 0.43*<br>(0.43- 0.44) | 55-59: 0.22*<br>(0.21-0.23) | 65-69: 0.35*<br>(0.34-0.37) | 75-79: 0.78*<br>(0.75-0.81) | 85-89: 0.97*<br>(0.92-1.03) |
| 6       | Germany 2005-2008                                                        | Ultsch 2013 <sup>45</sup>   | -Searches in claim database outpatient and in-patient ICD-10 in 1 region. HZ hospitalized or sick-leave 3-6 mo after HZ-diagnosis or initiation of a PHN related pain therapy                      | PHN as pain persisting for at least 3 months after HZ-onset       | 5 384                   | 4.5                   | 3.4                         | 4.9                         | 7.8                         | 7.8                         |

<sup>a</sup> GePaRD: German Pharmacoepidemiological Research Database.



|    | Country                  | Author                            | Study design                                                                                            | Case definition                                                                                  | Nbr of HZ cases | % of PHN (95%CI) by age |                     |                                                         |                                                          |                                                         |                          |
|----|--------------------------|-----------------------------------|---------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|-----------------|-------------------------|---------------------|---------------------------------------------------------|----------------------------------------------------------|---------------------------------------------------------|--------------------------|
|    |                          |                                   |                                                                                                         |                                                                                                  |                 | Overall                 | ≥50y                | 50-59                                                   | 60-69                                                    | 70-79                                                   | 80+                      |
|    |                          |                                   | -All ages                                                                                               |                                                                                                  |                 |                         |                     |                                                         |                                                          |                                                         |                          |
| 7  | Germany<br>2010-<br>2014 | Schmidt-Ott<br>2018 <sup>54</sup> | -Notified by 125GP+6<br>dermatologists+6<br>ophthalmologists<br>-Patients≥50y                           | Pain (≥3 on the<br>ZBPI scale) for<br>≥90 days                                                   | 513             |                         | 11.9<br>(9.2- 15.0) | 50-54: 13.2<br>(5.9- 24.6)<br>55-59: 8.5<br>(3.5- 16.8) | 60-64: 11.9<br>(4.9- 22.9)<br>65-69: 14.9<br>(7.4- 25.7) | 70-74: 13.0<br>(6.9- 21.7)<br>75-79: 8.9<br>(3.9- 16.8) | 14.3<br>(6.8-25.4)       |
| 8  | Iceland<br>1990-95       | Helgason<br>2000 <sup>69</sup>    | -Patients presenting to<br>participating GPs with first<br>ever zoster diagnosis - any<br>age           | PHN at 3<br>months after<br>zoster                                                               | 421             | 7.2                     |                     | 2                                                       | 13.7                                                     | 28                                                      |                          |
| 9  | Italy<br>2003-<br>2005   | Gialloreti<br>2010 <sup>46</sup>  | -Primary-care database<br>and national hospital-<br>discharge records,<br>-aged ≥50-<br>immunocompetent | PHN at 3<br>months                                                                               | 5675            |                         | 6.2                 | 3.9                                                     | 5.3                                                      | 10.1                                                    | 11.7                     |
| 10 | Italy<br>2009-<br>2010   | Bricout<br>2014 <sup>70</sup>     | -Prospective study in 108<br>general practices<br>-Patients≥50y-<br>immunocompetent                     | Pain persisted<br>for ≥90 days                                                                   | 413             |                         | 20.6<br>(16.5-25.2) | 15.5                                                    | 18.8                                                     | 28.4                                                    |                          |
| 11 | Italy<br>2013-<br>2015   | Alicino 2017 <sup>55</sup>        | -Searches in computerized<br>records - 56 GPs<br>-Patients ≥50y                                         | Neuropathic pain<br>or prescription of<br>neuropathic pain<br>medication at 3<br>months after HZ | 598             |                         |                     | 50-54: 7.3<br>55-59: 8.7                                | 60-64: 8.2<br>65-69: 14.9                                | 70-74: 11.3<br>75-79: 15.3                              | 80-84: 14.3<br>≥85: 28.6 |



|    | Country                          | Author                       | Study design                                                                                                                            | Case definition              | Nbr of HZ cases | % of PHN (95%CI) by age |      |                              |                              |                              |                              |
|----|----------------------------------|------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------|------------------------------|-----------------|-------------------------|------|------------------------------|------------------------------|------------------------------|------------------------------|
|    |                                  |                              |                                                                                                                                         |                              |                 | Overall                 | ≥50y | 50-59                        | 60-69                        | 70-79                        | 80+                          |
| 12 | Netherlands<br>1944-1999         | Opstelten 2002 <sup>67</sup> | -Patients with zoster identified from EHRs <sup>a</sup> from primary care- any age                                                      | PHN at 3 months after zoster | 837             | 2.6                     |      | 55-64: 2.9<br>(0.8–7.2)      | 65-74: 3.3<br>(0.9–8.3)      | 75+: 9.0<br>(4.8–15.2)       |                              |
| 13 | Netherlands<br>2001-2004         | Opstelten 2007 <sup>68</sup> | -Immunocompetent patients presenting to GPs with acute zoster and recruited into a trial                                                | PHN at 3 months              | 598             | 7.7                     |      | -                            | -                            | -                            | -                            |
| 14 | Spain (Valencia)<br>2009-2014    | Munoz 2018 <sup>73</sup>     | -Electronic diagnosis in primary care and hospitals <sup>b</sup><br>-Patients ≥50y-immunocompetent                                      | Pain persisted for ≥90 days  | 87 086          |                         | 15.7 | 9.6<br>0.53*<br>(0.50- 0.55) | 14.0<br>1.13*<br>(1.10-1.17) | 19.1<br>1.77*<br>(1.71-1.83) | 21.3<br>2.12*<br>(2.04-2.20) |
| 15 | Sweden<br>2008-2010 <sup>c</sup> | Sundstrom 2015 <sup>58</sup> | -Data extracted from 2 registers (GP and hospital) in 1 county- ICD-10 code B02.2 and G53.3 OR analgesics prescription<br>-All patients | Pain persisted for ≥90 days  | 13 296          | 6.4                     |      | 50-54:5.2<br>55-59: 4.9      | 60-64: 5.7<br>65-69: 6.8     | 70-74: 9.2<br>75-79: 9.7     | 11.3                         |

<sup>a</sup> electronic health care record.

<sup>b</sup> PHN cases were defined using the following criteria: (1) the presence of an ICD-9 code for HZ followed by an ICD- 9 code indicative of PHN (053.12, 053.13 or 053.19) within the defined periods (30–180, 90–180 and 150–180 days post HZ), or (2) the presence of an ICD-9 code for HZ followed by a prescription consistent with PHN during the defined periods, or (3) the presence of an ICD-9 code for HZ followed by an ICD-9 code for chronic pain (338.2) during the defined periods.

<sup>c</sup> Results from 2010.



| Country | Author       | Study design                     | Case definition                                                                                                                                                                                             | Nbr of HZ cases                                                                           | % of PHN (95%CI) by age |                     |                         |                                                     |                          |                      |
|---------|--------------|----------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|-------------------------|---------------------|-------------------------|-----------------------------------------------------|--------------------------|----------------------|
|         |              |                                  |                                                                                                                                                                                                             |                                                                                           | Overall                 | ≥50y                | 50-59                   | 60-69                                               | 70-79                    | 80+                  |
| 16      | UK 2000-2006 | Gauthier 2009 <sup>49</sup>      | -Large primary-care dataset and official hospital episode statistics <sup>a</sup><br>-aged ≥50 y- immunocompetent                                                                                           | PHN ≥3 months<br>25 002 <sup>b</sup>                                                      |                         | 13.7<br>(13.2-14.1) | 50-54y: 8<br>55-59y: 10 | 60-64y: 11<br>65-69y: 13                            | 70-74y: 15<br>75-79y: 18 | 19                   |
| 17      | UK 2000-2012 | Yanni 2018 <sup>60</sup>         | -Data drawn from electronic records primary care (Clinical Practice Research Datalink (CPRD)) and from Hospital Episode Statistics database (HES)- ICD-10- first episode<br>-Patients ≥18y- immunocompetent | Within 90 days<br>18 583                                                                  | 9.1<br>(8.68 - 9.52)    |                     | 5.5<br>(4.7- 6.5)       | 60-64y: 6.7 (5.7-7.8)<br>65-69y: 8.9 (7.8- 10)      | 12.5<br>(11.6- 13.4)     | 12.4<br>(11.3- 13.6) |
|         |              |                                  | -Patients ≥18y- Immunocompromised                                                                                                                                                                           | Within 90 days<br>21 146                                                                  | 10.6<br>(10.2-11.1)     |                     | 6.8<br>(6.0- 7.7)       | 60-64y: 8.9 (7.8-10.1)<br>65-69y: 12.2 (11.0- 13.4) | 14.2<br>(13.3- 15.1)     | 15.0<br>(13.9-16.2)  |
| 18      | UK 2005-2016 | Amirthalingam 2018 <sup>61</sup> | -Sentinel GP (Royal College of General Practitioners (RCGP). Research and Surveillance Centre (RSC)- 164 practices- extraction of electronic data<br>-Patients 60-89y- not vaccinated                       | Pain persisting beyond 90 days from rash onset- based on Read codes (thesaurus)<br>26 257 |                         |                     |                         |                                                     | 13.8                     |                      |

<sup>a</sup> Severity of PHN was assessed on the basis of prescribed medications.

<sup>b</sup> After excluding patients with diabetic neuropathy, epilepsy and recurrent HZ.



|    | Country      | Author                    | Study design                                                                           | Case definition             | Nbr of HZ cases | % of PHN (95%CI) by age |      |       |                                        |       |      |
|----|--------------|---------------------------|----------------------------------------------------------------------------------------|-----------------------------|-----------------|-------------------------|------|-------|----------------------------------------|-------|------|
|    |              |                           |                                                                                        |                             |                 | Overall                 | ≥50y | 50-59 | 60-69                                  | 70-79 | 80+  |
| 19 | UK 2010-2011 | Forbes 2016 <sup>71</sup> | - Electronic records primary care (GPRD) and from hospital (HES)<br>-All patients      | Pain persisted for ≥90 days | 119 413         | 5.8                     |      |       | 50-79y: 6.4<br><70y: 3.6<br>≥70y: 10.9 |       | 12.8 |
| 20 | UK 2013      | Walker 2018 <sup>62</sup> | - Electronic records primary care (GPRD)<br>-Patients≥70y-immunocompetent-unvaccinated | Pain persisting ≥3 months   | 8 006           |                         |      | -     | -                                      | 4.6   |      |

\* Incidence per 1000 person-years. CI: Confidence Interval, GPRD: General Practice Research Database, HES: Hospital Episode Statistics.

In comparison, in the 2 recent pivotal trials on Shingrix combined,<sup>31, 62</sup> the % of HZ cases developing PHN (defined as a worst pain score of 3 or higher for pain that persisted or developed more than 90 days after the onset of herpes zoster rash) in the placebo group was 9.6% (36/284) in individuals ≥70 years, with an incidence of PHN of 12 per 10 000 person-years. The incidence rate was 9 per 10 000 person-years in individuals ≥50 years. In the trial by Oxman on Zostavax,<sup>25</sup> the % of HZ cases developing PHN (defined as pain rated as 3 or more on a scale ranging from 0 ("no pain") to 10 ("pain as bad as you can imagine"), persisting or appearing more than 90 days after the onset of rash) was 13.8% (80/642) in individuals ≥60 years. Results on PHN risk were not reported as such in the second RCT on Zostavax.<sup>26</sup>

### 3.3.3 Discussion

The 20 population-based European studies reported varying proportions of HZ cases suffering from PHN. Such variation in the overall figures was not unexpected as there was a lot of variation in the definition of patients included (all patients vs. patients ≥18 vs. patients ≥50 years), study design (prospective vs. retrospective- claim data vs. prospective cohort vs. survey), assessors (only GP vs. a range of health professionals, e.g. neurologists),

setting (general practice with or without hospital care), and pain (any pain vs. pain ≥3 on the ZBPI scale). Estimates based on primary care may be biased downwards, as severe cases and immunocompromised patients could be treated exclusively in secondary care, although probably representing a minority of cases. Therefore, case ascertainment based on both primary care and hospital care databases might yield a more complete data collection and thus higher incidence rates. Also patients with mild pain might use over-the-counter medications for pain relief, and this can also result in a downwards bias.<sup>62, 71</sup> In some studies, cases could also be ascertained on the basis of prescription of pain killers, e.g. in Alicino 2017.<sup>55</sup>

In contrast, the Belgian estimates of PHN risk seem quite high as 26% of ambulatory cases suffered PHN.<sup>20</sup> This study has the merit of reporting unique data for Belgium. However, information was collected through surveys in which HZ patients were asked a posteriori to give a score to the worst, least and average pain they experienced during their HZ episode. This might have introduced a recall bias. Moreover, there might also be a selection bias, as explained above, as questionnaires were completed by 59% of the hospitalised persons receiving the questionnaire. The 39% PHN risk in hospitalized cases may reflect a bias selection towards most severe



cases. Moreover, the proportion of declared immunocompromised patients was high.

We have searched for incidence data of PHN defined as pain persisting  $\geq 90$  days after the onset of herpetic rash. In their systematic review, Kawai et al. also analysed duration of PHN. They included 6 prospective cohort studies which reported that approximately 30–50% of patients with PHN experienced pain lasting for more than 1 year, and sometimes several years.<sup>8</sup> However, these studies had small sample size (from 14 to 158) and were ancient, and the author of the review did not report on the selection process, characteristics of patients nor provide quality appraisal of the studies. Therefore these figures should be considered with caution.

### 3.4 Other complications

Rare but serious cutaneous, visceral, neurological (including encephalitis, meningitis, Ramsay Hunt syndrome, cerebellitis, myelitis and stroke-related syndromes) and ocular (including keratitis, conjunctivitis, iritis, blepharitis, retinitis, optic neuritis, orbital myositis, and scleritis) complications can occur. Some of these complications lead to severe illness, high healthcare costs and mortality, while others can seriously affect quality of life.<sup>74</sup> Ocular complications are the most frequent ones.

#### 3.4.1 Ocular complications

HZ ophthalmicus (HZO) occurs when VZV reactivation affects the ophthalmic branch of the fifth cranial nerve and can involve eye structures. HZO with eye complications is the second most common HZ complication.<sup>75</sup> A systematic review by Kawai et al., 2014<sup>8</sup> reported a risk of HZO ranging between 10% and 15% of HZ cases on the basis of 4 old population-based studies in the USA (data 1945–59),<sup>76</sup> France (data 1997–1998),<sup>77</sup> The Netherlands (data 1994–1999),<sup>67</sup> and Saudi Arabia (data 1988–2006).<sup>78</sup> A wide range of eyes complications, such as keratitis, uveitis and conjunctivitis can result from HZO, i.e. HZO occurs with or without eye involvement.<sup>a</sup> Risk of ocular complications among HZ patients in recent large population-based European studies<sup>51, 53, 58, 60, 74</sup> is between 1.6 and 4.8% (Table 10) In the pivotal RCTs on Shingrix, this proportion was 1.5%.<sup>b79</sup> In the UK study by Yanni et al., the risk did not appear increased in the immunocompromised patients compared to immunocompetent ones.<sup>60</sup> Incidence rates are presented in Table 11.

#### 3.4.2 Cerebrovascular and cardiac complications

Five systematic reviews reported on the risk of zoster-associated cardiac events and/or cerebrovascular events.<sup>80–84</sup> Zoster was associated with a 1.5-fold increased stroke risk four weeks following onset (summary estimate: 1.55- 95%CI: 1.46-1.65), which resolved after one year. Subgroup analyses suggested post-zoster stroke risk was greater among ophthalmic zoster patients, and younger patients.<sup>80, 82</sup> In another review, relative risk for stroke

<sup>a</sup> ICD-10 code B02.3 corresponds to zoster with blepharitis, conjunctivitis, iridocyclitis, iritis, keratitis, keratoconjunctivitis, or scleritis.

<sup>b</sup> In the pooled pivotal trials ZOE-50 and ZOE-70<sup>31, 63</sup> (for more details see Chapter 4), secondary and exploratory analyses focused on the occurrence of complications other than PHN,<sup>79</sup> including disseminated disease, ophthalmic disease, neurologic disease, visceral disease, HZ vasculitis and stroke. The risk of developing such complications in the placebo recipients with HZ was 3.4% (16/477). The most frequently reported complication in the placebo group was ophthalmic disease (seven participants, 1.5%), followed

by disseminated disease (six participants, 1.2%), neurologic disease (three participants, 0.6%), and one case of vasculitis presumed to be due to HZ (0.2%). One participant had both ophthalmic and neurologic (meningitis) disease. Most HZ-related complications occurred in participants  $\geq 70$  years.<sup>79</sup> Excluding PHN, the HZ complication rate for placebo recipients  $\geq 50$  years was 3 per 10 000 person-years overall and increased with age. When PHN was included in the numerator, HZ complication rate summed up to 12.2% (58/477).



after zoster was 1.78 (95%CI: 1.70-1.88) for the first month following herpes zoster, dropping progressively to 1.43 (95%CI: 1.38-1.47) after 3 months, to 1.20 (95%CI: 1.14-1.26) after 1 year.<sup>83</sup> There are several plausible mechanisms to an elevated risk of cardiovascular events.<sup>81</sup> The development of herpes zoster may lead to migration of VZV from the neurons to the cerebral and coronary vasculature. This may lead to a local inflammatory response, causing vessel occlusion and ultimately ischemia, increasing the risk for cerebrovascular and cardiac complications.<sup>81</sup> Patients with herpes zoster ophthalmicus could be susceptible to a cerebrovascular event due to the proximity of the trigeminal ganglion to the cerebral arteries. Herpes zoster could also produce systemic inflammation, autoimmune responses, or hemodynamic changes leading to cardiovascular events. However, the association between herpes zoster and cardiovascular events could result from both diseases sharing similar precipitating factors, e.g. illness or stress. The role of residual confounding is difficult to assess. Future studies in this area would benefit from the assessment of, and accounting for, common causes and/or triggers of herpes zoster and acute cardiac events.<sup>81</sup> More importantly, it should be noted that the risk of stroke associated with HZ is small, going from 0.8% of HZ cases to 4%, with considerable variations between studies. It was only 0.6% (95%CI: 0.5-0.7) in the more recent UK cohort by Yanni et al.,<sup>60</sup> and risk of neurological complications (including stroke) was 0.48% (95%CI: 0.44-0.51) in another recent large UK cohort study.<sup>74</sup>


**Table 10 – Proportion of HZ cases with complications other than PHN in population-based European studies**

| Country                             | Author                        | Study design                                                                                                                                                                            | Nb HZ cases | % of HZ cases with complications (95%CI) |                   |                   |            |                     |                   |
|-------------------------------------|-------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|------------------------------------------|-------------------|-------------------|------------|---------------------|-------------------|
|                                     |                               |                                                                                                                                                                                         |             | Overall                                  | Ocular            | Other nervous     | Meningitis | Other complications | Stroke            |
| <b>Germany 2005-2009</b>            | Hillebrand 2015 <sup>51</sup> | -Retrospective cohort with claim data (in- and out-patient with ICD-10)<br>-All patients                                                                                                | 215 959     | -                                        | 4.8               | -                 | 0.1        | 4.0                 | -                 |
| <b>Sweden 2008-2010<sup>a</sup></b> | Sundstrom 2015 <sup>58</sup>  | -Data extracted from 2 registers (GP and hospital) in 1 county- ICD-10 codes)<br>-All patients                                                                                          | 13 296      | -                                        | 4.08              | -                 | 0.14       | 1.19                | -                 |
| <b>UK 2001-18</b>                   | Forbes 2016 <sup>74</sup>     | -Data drawn from electronic records primary care (Clinical Practice Research Datalink (CPRD))<br>-Immunocompetent                                                                       | 178 964     | -                                        | 1.3*<br>(1.3-1.4) | 0.5*<br>(0.4-0.5) | -          | -                   | -                 |
| <b>UK 2000-2012</b>                 | Yanni 2018 <sup>60</sup>      | -Data drawn from electronic records primary care (Clinical Practice Research Datalink (CPRD)) and from Hospital Episode Statistics database (HES)<br>-Patients ≥18y-<br>immunocompetent | 18 583      | 2.3<br>(2.1- 2.6)                        | 1.6<br>(1.4- 1.8) | 0.5<br>(0.4- 0.6) | -          | 0.3<br>(0.2- 0.4)   | 0.6<br>(0.5- 0.7) |
|                                     |                               | -Patients ≥18y-<br>Immunocompromised                                                                                                                                                    | 21 146      | 2.9<br>(2.7- 3.2)                        | 1.9<br>(1.8- 2.1) | 0.6<br>(0.5- 0.8) | -          | 0.3<br>(0.2- 0.4)   | 0.4<br>(0.3- 0.5) |

\* Risk of complications attributable to zoster, i.e. the difference in risk between patients with- and without HZ. CI: confidence interval, HZ: Herpes Zoster.

<sup>a</sup> Results from 2010.

**Table 11 – Incidence rates of complications other than PHN in population-based European studies**

| Country                  | Author                        | Study design                                                                                                                                                                        | Nb HZ cases | Incidence of HZ with complications (95%CI) per 10 000 person-years |                                                     |                                                       |                                                           |                                                    |                      |
|--------------------------|-------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|--------------------------------------------------------------------|-----------------------------------------------------|-------------------------------------------------------|-----------------------------------------------------------|----------------------------------------------------|----------------------|
|                          |                               |                                                                                                                                                                                     |             | Overall                                                            | Ocular                                              | Other nervous                                         | Meningitis                                                | Other complications                                | Stroke               |
| <b>Germany 2005-2009</b> | Hillebrand 2015 <sup>51</sup> | - Retrospective cohort with claim data (in- and out-patient with ICD-10)<br>-All patients                                                                                           | 215 959     | -                                                                  | 3.5<br>(3.4- 3.7)                                   | 11.3<br>(11.1- 11.6)                                  | 0.1<br>(0- 0.1)                                           | 2.9<br>(2.8-3.1)                                   | -                    |
| <b>Germany 2006-2012</b> | Schröder 2017 <sup>53</sup>   | -Claims data from 4 statutory health insurances (GePaRD) including outpatient and inpatient- based on ICD-10-GM and/or pain medication in the 2 quarters after HZ<br>-Patients ≥18y | 442 979     | -                                                                  | IC: 6.5<br>(6.2- 6.8)<br>IC-free:<br>3.1 (2.9- 3.2) | IC: 17.9<br>(17.4-18.4)<br>IC-free:<br>7.3 (7.1- 7.5) | IC: 0.1<br>(0- 0.1)<br>IC-free:<br>0.1 (0- 0.1)           | IC: 5.6<br>(6.2-6.8)<br>IC-free:<br>2.5 (2.4- 2.6) | -                    |
| <b>UK 2000-2012</b>      | Yanni 2018 <sup>60</sup>      | -Data drawn from electronic records primary care CPRD and from hospital HES-ICD-10- complications within 90 days<br>-Patients ≥18y- immunocompetent                                 | 18 583      | 9.1<br>(8.68 - 9.52)                                               | 5.5<br>(4.7- 6.5)                                   | -                                                     | 60-64y:<br>6.7 (5.7-7.8)<br>65-69y:<br>8.9 (7.8- 10)      | 12.5<br>(11.6- 13.4)                               | 12.4<br>(11.3- 13.6) |
|                          |                               | -Patients ≥18y- Immunocompromised                                                                                                                                                   | 21 146      | 10.6<br>(10.2-11.1)                                                | 6.8<br>(6.0- 7.7)                                   | -                                                     | 60-64y:<br>8.9 (7.8-10.1)<br>65-69y:<br>12.2 (11.0- 13.4) | 14.2<br>(13.3- 15.1)                               | 15.0<br>(13.9- 16.2) |

95%CI: 95% confidence interval, CI: Confidence Interval, CPRD: General Practice Research Database, GePaRD: German Pharmacoepidemiological Research Database, HES: Hospital Episode Statistics, IC: immune-compromised, IC-free: immunocompetent.



### 3.4.3 Other complications

In a recent large cohort study among unvaccinated immunocompetent adults with incident HZ in the UK (years 2001 to 2018- n=178 964) the risks of zoster-specific complications within 3 months of zoster diagnosis were 0.37% (95%CI: 0.34-0.39) for Ramsay Hunt syndrome and 0.01% (95%CI: 0.0-0.01) for disseminated zoster.<sup>74</sup> For complications not specific to HZ, the risk attributable to zoster were 0.48% (95%CI: 0.44-0.51) for neurological complications<sup>a</sup>, 0.29% (95%CI: 0.26-0.32) for cutaneous complications<sup>b</sup> and 0.078% (95%CI: 0.73-0.84) for visceral complications.<sup>c74</sup> Of note, these are risk attributable to HZ, i.e. the risk difference between HZ patients and control individuals not having suffered of HZ.

## 3.5 Hospitalisation

### Main findings

- The annual incidence of hospitalisation with HZ as primary or secondary diagnosis is 2.3 per 10 000 person-years (2.2 inpatients-0.1 daycare) in the period 2008-2020. This corresponds to an average around 2500 inpatient hospitalisations per year. The incidence of hospitalisation truly attributable to HZ is probably lower as HZ is principal diagnosis in 42% of cases in 2019, with around 900 hospitalisations in individuals  $\geq 50$  years.

<sup>a</sup> Cranial and peripheral nerve palsies (excluding Ramsay Hunt syndrome), encephalitis, transverse myelitis, meningitis, Guillain-Barré syndrome and stroke.

<sup>b</sup> Secondary bacterial skin infection (cellulitis, necrotizing fasciitis and erysipelas).

<sup>c</sup> Pneumonia, hepatitis, pancreatitis, sepsis, pulmonary embolism, osteomyelitis, pleuritis, peritonitis, myocardial infarction, myositis, myocarditis, pericarditis and endocarditis.

- Incidence of hospitalisations increased sharply with age. Most of the inpatients were older than 70 years (63.2%). The incidence rate adjusted for age was similar between male and female.
- In 2019, 55% of the hospitalisations with HZ as primary diagnosis and 68% with HZ as principal diagnosis were zoster with complications. Zoster ocular disease accounted for around 20% of the principal diagnosis and PHN for 10%.

### 3.5.1 Belgian data

#### 3.5.1.1 Literature

A previous Belgian study used the Minimal Clinical Data (MCD- Minimale Ziekenhuisgegevens MZG- Résumé Hospitalier Minimum RHM) to assess hospitalisation rates for the period 2000-2007.<sup>20, 28</sup> MCD is a mandatory registration of hospitalised patient information for every hospital in Belgium. Patients with HZ receive an ICD-9-CM code '053' in primary or secondary diagnostic fields. HZ hospitalisation rates were calculated by dividing the yearly number of HZ hospitalisations from the MCD by the Belgian population from the same year. The results were cross-validated by retrieving in the Carenet<sup>d</sup> database members of the National Christian Sickness Fund (NCSF) who were hospitalised for HZ in the period 2006-2009<sup>e</sup>. In this database, a medical clinician searched the diagnostic fields of

<sup>d</sup> Carenet is designed for the exchange of information about hospital admissions, end of hospitalisation and costs of hospitalisations between hospitals and health insurance companies through an electronic system.

<sup>e</sup> Rates were obtained by dividing the number of NCSF hospitalisations in 2006–2009 by the age- and gender-specific Belgian population over the same years, the latter divided by 0.422 (since NCSF covers 42.2% of the Belgian population) and adjusted according to the number of Belgian hospital beds covered by Carenet.



the retrieved records manually and removed all hospitalisations that were unlikely to be due to VZV, or for which this was unclear.<sup>20</sup>

In this study, the hospitalisation rate for primary cause of HZ in Belgium was on average 14.2 per 100 000 person-years, and increased with increasing age.<sup>20</sup> High variation in the hospitalisation rates for very old ages was due to the very small number of persons of such age.

### 3.5.1.2 Minimal Clinical Data

MCD data were analyzed to estimate the number of patients hospitalised for HZ from 2008 to 2020 (excluding 2015<sup>a</sup>) and to describe the characteristics of the patients hospitalised for HZ for the same period of time and with more details for 2019. Stays with an ICD-9 CM code of 053\* (from 2008 to 2014) or an ICD-10 CM code of B02\* (for 2016-2020) in principal, primary or secondary diagnosis were extracted from the database. The principal diagnosis is based on an algorithm that defines the principal diagnosis as the first valid primary diagnosis code of the first specialism. Information on year, principal diagnosis, presence of HZ at admission, primary and secondary diagnosis, birth date, sex, type of stay (inpatient or daycare patient), date of admission and date of discharge were extracted as well. Patients who came to the emergency room without being hospitalised were mostly excluded from the analysis because their extent diagnoses are usually not coded. Those who had a diagnosis code were included in daycare patients. Daycare patients included day care hospitalisation (for medical and/or surgical treatment) while inpatients included patients who counted at least one night of hospitalisation. Analyses were performed at a patient level. Stays that are not reimbursed<sup>b</sup> by INAMI-RIZIV were excluded from the analysis (19.7% of losses for daycare; 2.7% for inpatients).

A patient counts for a unique HZ episode whatever the number of re-hospitalisations during the year. If the patient is re-hospitalised the next year,

he was counted as a new HZ episode. As the yearly rate of re-hospitalisation is low (7.8% in 2008-2020), also in the patients with a HZ as principal diagnosis (3.4% in 2008-2020), and the average duration between two hospitalisations is short (53.7 days between first and second hospitalization in 2019), i.e. not suggesting a new HZ episode- we considered this approximation acceptable. Belgian population on 1 January was used to calculate the number of HZ cases per 100 000 inhabitants. Population data for 2008-2020 were provided by Statbel, the Belgian statistical office.

Length of stay was calculated by doing the difference of days between discharge and admission dates and age was calculated by doing the difference of days between admission and birth dates. Six age-groups were defined <50, 50-59, 60-64, 65-69, 70-79 and 80+ years.

From 2008 to 2020, there were 29 691 inpatients and 1594 daycare patients included in the MCD database who had a diagnosis of HZ in primary and/or secondary diagnosis. This corresponds to an annual incidence of 22.16 cases and 1.19 cases per 100 000 inhabitants for the inpatients and daycare patients, respectively (Table 12). Despite a slight decrease of the number of inpatients from 2008 to 2011 and from 2019 to 2020 (-17.0% likely due to changes in hospital management and/or registration system relating to covid-19 pandemic), we did not observe big variations of the incidence of inpatients across the years (see Figure 7, Figure 8 & Table 12). There is decrease of the number of daycare patients with HZ diagnosis from 2008 to 2020 (-41.6%) (Figure 7 & Table 12).

HZ was flagged as primary diagnosis in 39% of the cases over the period 2017-2020). A very small proportion of patients had a HZ in both primary and secondary diagnosis (inpatients: 3.7%- daycare: 0.3%) from 2008 to 2020. The proportion of patients with HZ as primary, secondary or both are presented in Figure 7.

<sup>a</sup> RHM-MZG data for 2015 are of poor quality because of the change of classification of diseases from ICD-9 CM to ICD-10 CM during that year.

<sup>b</sup> Stays of foreign patients and patients depending on a Public Centre for Social Action (CPAS-OCMW) are not supported by compulsory insurance.

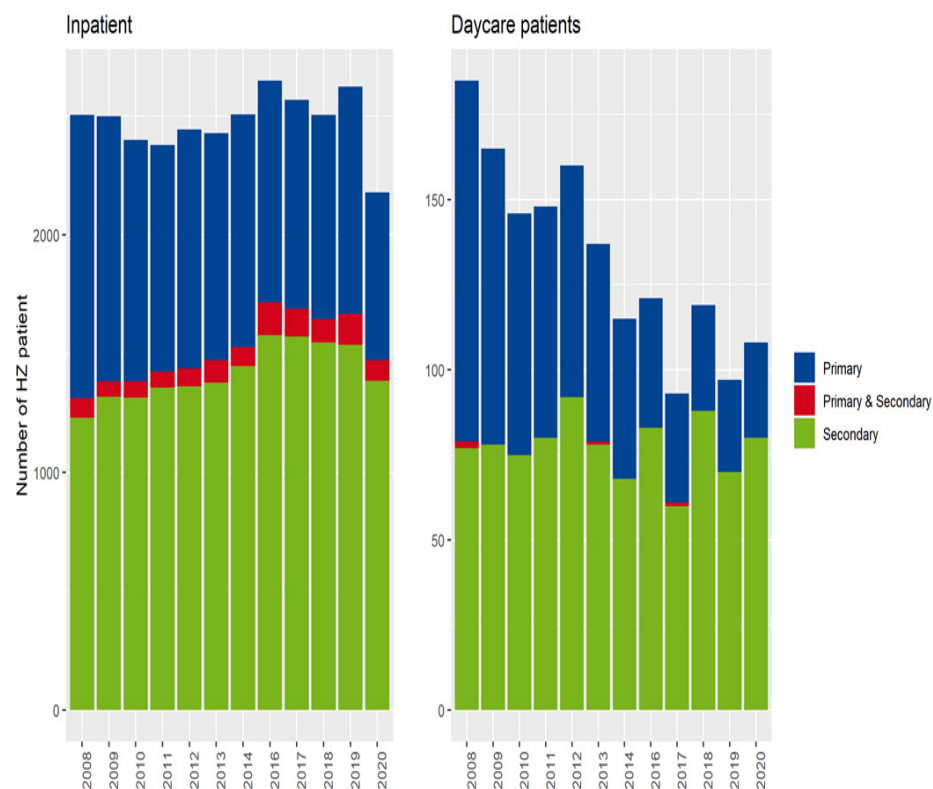

**Table 12 – Number of patients with HZ as primary, secondary, primary and secondary diagnosis, by type of hospitalization, by year**

| Year         | Inpatient     | Inpatient<br><u>adjusted*</u> | Daycare<br>patients | Daycare<br>patients<br><u>adjusted*</u> | Total<br>inpatient<br>OR daycare<br>patients | Number of<br>inpatients<br>with HZ<br>diagnosis<br>per 100 000<br>inhabitants** | Number of<br><u>adjusted*</u><br>inpatients<br>with HZ<br>diagnosis<br>per 100 000<br>inhabitants** | Number of<br>daycare<br>patients<br>with HZ<br>diagnosis<br>per 100 000<br>inhabitants** | Number of<br><u>adjusted*</u><br>daycare<br>patients<br>with HZ<br>diagnosis<br>per 100 000<br>inhabitants** | Number of<br>inpatient OR<br>daycare patients<br>per 100 000<br>inhabitants** |
|--------------|---------------|-------------------------------|---------------------|-----------------------------------------|----------------------------------------------|---------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------|
| <b>2008</b>  | 2 506         | 2 595                         | 185                 | 208                                     | 2 649                                        | 23.30                                                                           | 24.13                                                                                               | 1.72                                                                                     | 1.94                                                                                                         | 24.63                                                                         |
| <b>2009</b>  | 2 500         | 2 578                         | 165                 | 178                                     | 2 621                                        | 23.06                                                                           | 23.78                                                                                               | 1.52                                                                                     | 1.64                                                                                                         | 24.18                                                                         |
| <b>2010</b>  | 2 399         | 2 486                         | 146                 | 167                                     | 2 511                                        | 21.91                                                                           | 22.70                                                                                               | 1.33                                                                                     | 1.53                                                                                                         | 22.93                                                                         |
| <b>2011</b>  | 2 379         | 2 450                         | 148                 | 181                                     | 2 501                                        | 21.56                                                                           | 22.20                                                                                               | 1.34                                                                                     | 1.64                                                                                                         | 22.66                                                                         |
| <b>2012</b>  | 2 444         | 2 523                         | 160                 | 182                                     | 2 567                                        | 22.02                                                                           | 22.73                                                                                               | 1.44                                                                                     | 1.64                                                                                                         | 23.13                                                                         |
| <b>2013</b>  | 2 429         | 2 478                         | 137                 | 159                                     | 2 536                                        | 21.78                                                                           | 22.22                                                                                               | 1.23                                                                                     | 1.43                                                                                                         | 22.74                                                                         |
| <b>2014</b>  | 2 508         | 2 577                         | 115                 | 152                                     | 2 593                                        | 22.37                                                                           | 22.99                                                                                               | 1.03                                                                                     | 1.36                                                                                                         | 23.13                                                                         |
| <b>2016</b>  | 2 650         | 2 703                         | 121                 | 173                                     | 2 744                                        | 23.41                                                                           | 23.87                                                                                               | 1.07                                                                                     | 1.53                                                                                                         | 24.24                                                                         |
| <b>2017</b>  | 2 568         | 2 650                         | 93                  | 129                                     | 2 642                                        | 22.68                                                                           | 23.41                                                                                               | 0.82                                                                                     | 1.14                                                                                                         | 23.34                                                                         |
| <b>2018</b>  | 2 505         | 2 558                         | 119                 | 173                                     | 2 596                                        | 22.02                                                                           | 22.49                                                                                               | 1.05                                                                                     | 1.52                                                                                                         | 22.82                                                                         |
| <b>2019</b>  | 2 624         | 2 709                         | 97                  | 140                                     | 2 695                                        | 22.96                                                                           | 23.70                                                                                               | 0.85                                                                                     | 1.23                                                                                                         | 23.58                                                                         |
| <b>2020</b>  | 2 179         | 2 234                         | 108                 | 145                                     | 2 262                                        | 18.96                                                                           | 19.44                                                                                               | 0.94                                                                                     | 1.26                                                                                                         | 19.68                                                                         |
| <b>TOTAL</b> | <b>29 691</b> | <b>30 540</b>                 | <b>1 594</b>        | <b>1 988</b>                            | <b>30 917</b>                                | <b>22.16</b>                                                                    | <b>22.79</b>                                                                                        | <b>1.19</b>                                                                              | <b>1.48</b>                                                                                                  | <b>23.08</b>                                                                  |

Data source: MCD, Statbel. \* Adjusted for the loss of stays. To adjust the incidence rate, we weighted the number of cases of HZ on the proportion of stays before and after database coupling. For instance, in 2008, we counted 2823 stays before database coupling and 2726 after database coupling, i.e. a ratio of 1.0356- we therefore adjusted the number of HZ cases by multiplying 2506 by 1.0356 which corresponds to an adjusted number of HZ cases of 2595 in 2008. \*\* Population at 1<sup>st</sup> January.

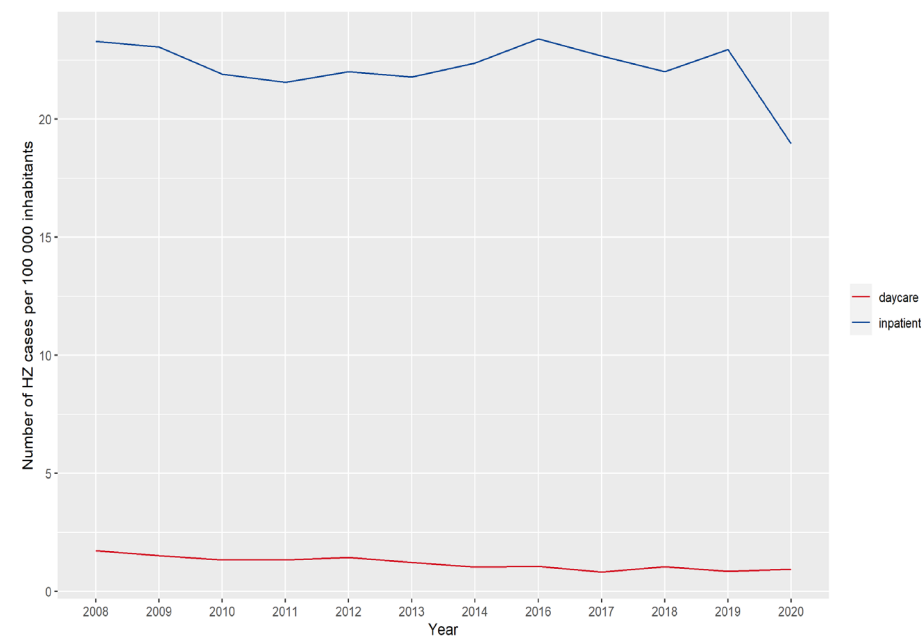


**Figure 7 – Proportion of patients with HZ as primary, secondary, primary and secondary diagnosis, by type of stay, by year**



Data source: RHM-MZG.

**Figure 8 – Annual incidence of hospitalisation for HZ per 100 000 inhabitants, by type of stay 2008-2020**



Data source: MCD. Primary, secondary, and both primary and secondary HZ diagnosis were included.



The proportions of inpatients and daycare patients with a secondary diagnosis of HZ increased from 2008 (inpatients: 2008: 49.1%- 2020: 63.6%- daycare patients: 2008: 41.6%- 2020: 74.1%) (see Table 14-16 and Figure 3 in Appendix 1.6 for more details). In year 2019, 36.4%, 58.6% and 5.0% of inpatients had a primary, secondary, or both primary and secondary diagnosis of HZ (Table 16 in Appendix 1.6). The incidence rate of HZ primary diagnosis was 8.41 per 100 000 person-years, and 13.52 per 100 000 person-years for secondary diagnosis. For both type of diagnoses the incidence rate increased with age and incidence rates were similar between males and females in each age range.

From 2008 to 2020, around half of the patients (43.0%) had HZ as principal diagnosis and, as for the primary diagnosis of HZ, we observed that this proportion decreased across the years (2008: 50.8%- 2019: 41.6%) (see Table 14-15 in Appendix 1.6 for more details). Thus the incidence of hospitalisation truly attributable to HZ is probably lower than the overall incidence base on primary/secondary diagnosis. In 2019, the overall incidence rate of hospitalisation with HZ as principal diagnosis was 1.0 (95%CI: 0.8-1.1) per 10 000 person-years; it was 1.9 (1.8-2.1) in individuals  $\geq 50$  years and 2.7 (2.5-2.8) in those  $\geq 60$  years.

In 2016 and 2019, HZ without complications (ICD-10 B029) was the most frequent primary or secondary diagnosis in inpatient or daycare (around 45%), i.e. cases were complicated in 55%. The proportion of patients with various complications is presented in Table 13.


**Table 13 – Number of patients admitted for HZ, by diagnosis (primary or secondary) and by type of stay, 2016 and 2019**

| Diagnosis combination                                 | Label                                                                              | N<br>2016 | prop  | N<br>2019 | prop  |
|-------------------------------------------------------|------------------------------------------------------------------------------------|-----------|-------|-----------|-------|
| <b>Daycare (2016: n= 121- 2019: n=97)</b>             |                                                                                    |           |       |           |       |
| B029                                                  | Zoster without complications                                                       | 53        | 43.8% | 44        | 45.4% |
| B0229                                                 | Other postherpetic nervous system involvement                                      | 36        | 29.8% | 25        | 25.8% |
| Other diagnosis combination with less than 4 patients |                                                                                    | 13        | 10.7% | 16        | 16.5% |
| B0230                                                 | Zoster ocular disease, unspecified                                                 | 10        | 8.3%  | 6         | 6.2%  |
| B028                                                  | Zoster with other complications                                                    | 9         | 7.4%  | 6         | 6.2%  |
| <b>Inpatient (2016: n=2 650- 2019: n= 2 624)</b>      |                                                                                    |           |       |           |       |
| B029                                                  | Zoster without complications                                                       | 1 226     | 46.3% | 1 185     | 45.2% |
| B0229                                                 | Other postherpetic nervous system involvement                                      | 352       | 13.3% | 349       | 13.3% |
| B028                                                  | Zoster with other complications                                                    | 323       | 12.2% | 317       | 12.1% |
| B0230                                                 | Zoster ocular disease, unspecified                                                 | 284       | 10.7% | 325       | 12.4% |
| Diagnose combinations with less than 10 patients      |                                                                                    | 104       | 3.9%  | 104       | 4.0%  |
| B0221                                                 | Postherpetic geniculate ganglionitis                                               | 89        | 3.4%  | 71        | 2.7%  |
| B0222                                                 | Postherpetic trigeminal neuralgia                                                  | 44        | 1.7%  | 49        | 1.9%  |
| B0239                                                 | Other herpes zoster eye disease                                                    | 36        | 1.4%  | 33        | 1.3%  |
| B020                                                  | Zoster encephalitis                                                                | 34        | 1.3%  | 28        | 1.1%  |
| B0233                                                 | Zoster keratitis                                                                   | 33        | 1.2%  | 32        | 1.2%  |
| B021                                                  | Zoster meningitis                                                                  | 23        | 0.9%  | 42        | 1.6%  |
| B029+B0229                                            | Zoster without complications + Other postherpetic nervous system involvement       | 19        | 0.7%  | 11        | 0.4%  |
| B0230+ B0229                                          | Zoster ocular disease, unspecified + Other postherpetic nervous system involvement | 16        | 0.6%  | 5         | 0.2%  |
| B0231                                                 | Zoster conjunctivitis                                                              | 15        | 0.6%  | 18        | 0.7%  |
| B027                                                  | Disseminated zoster                                                                | 15        | 0.6%  | 17        | 0.6%  |
| B0223                                                 | Postherpetic polyneuropathy                                                        | 13        | 0.5%  | 15        | 0.6%  |
| B0232                                                 | Zoster iridocyclitis                                                               | 12        | 0.5%  | 11        | 0.4%  |
| B0229+ B028                                           | Zoster with other complications + Other postherpetic nervous system involvement    | 13        | 0.5%  | 12        | 0.5%  |

Data source: MCD. For patients with multiple hospitalisation/admission this is the first hospitalisation/admission that is taken into account- primary and secondary diagnosis are included.



In 2016 and 2019, the most frequent principal diagnosis was zoster without complications (ICD-10 B029: 32.1% in 2016 and 31.6% in 2019), followed by zoster ocular disease, unspecified (B0230: 19.7% in 2016 and 21.1% in 2019) and zoster with other complications (B028: 14.6% in 2016 and 15.4% in 2019) (see Table 14). PHN (B0229 other postherpetic nervous system

involvement) accounted for 10.1% of the principal diagnoses in 2019. In 2019, the median length of stay was the highest for postherpetic myelitis (B0224: Median 38 days, Min 3 – Max 73), zoster encephalitis (B020: Median 14 days, Min 4 – Max 94), and disseminated zoster (B027: Median 12 days, Min 2 – Max 30).

**Table 14 – Length of stay inpatient hospitalized for HZ as principal diagnosis (n=1 072), by type of diagnosis, 2016 and 2019**

| Inpatient                                           | N patients*  | p           | Mean LOS (in days) | SD LOS (in days) | Median (LOS) | Min (LOS) | Max (LOS)  | N patients*  | p           | Mean LOS (in days) | SD LOS (in days) | Median (LOS) | Min (LOS) | Max (LOS) |
|-----------------------------------------------------|--------------|-------------|--------------------|------------------|--------------|-----------|------------|--------------|-------------|--------------------|------------------|--------------|-----------|-----------|
|                                                     | 2016         |             |                    |                  |              |           |            | 2019         |             |                    |                  |              |           |           |
| B029 Zoster without complications                   | 344          | 32.1%       | 8.97               | 10.5             | 6.0          | 1.0       | 106.0      | 345          | 31.6%       | 8.6                | 8.8              | 6            | 1         | 87        |
| B0230 Zoster ocular disease, unspecified            | 211          | 19.7%       | 9.26               | 10.2             | 6.0          | 1.0       | 93.0       | 230          | 21.1%       | 8.7                | 7.9              | 7            | 1         | 65        |
| B028 Zoster with other complications                | 156          | 14.6%       | 11.41              | 11.5             | 8.0          | 1.0       | 97.0       | 168          | 15.4%       | 9.8                | 10.6             | 6            | 1         | 59        |
| B0229 Other postherpetic nervous system involvement | 120          | 11.2%       | 12.87              | 8.02             | 9.0          | 1.0       | 92.0       | 110          | 10.1%       | 10.2               | 10.4             | 7            | 1         | 73        |
| B0221 Postherpetic geniculate ganglionitis          | 69           | 6.4%        | 8.06               | 11.1             | 6.0          | 1.0       | 88.0       | 51           | 4.7%        | 9.2                | 7.6              | 7            | 1         | 35        |
| B0222 Postherpetic trigeminal neuralgia             | 32           | 3.0%        | 7.59               | 6.23             | 6.0          | 1.0       | 31.0       | 31           | 2.8%        | 8.1                | 10.0             | 7            | 1         | 58        |
| B0239 Other herpes zoster eye disease               | 25           | 2.3%        | 8.88               | 9.31             | 6.0          | 1.0       | 41.0       | 14           | 1.3%        | 12.3               | 18.0             | 6.5          | 3         | 73        |
| B021 Zoster meningitis                              | 25           | 2.3%        | 14.6               | 16.2             | 12.0         | 1.0       | 89.0       | 49           | 4.5%        | 13.6               | 13.2             | 10           | 3         | 75        |
| B020 Zoster encephalitis                            | 24           | 2.2%        | 20.63              | 17.8             | 14.5         | 1.0       | 89.0       | 25           | 2.3%        | 21.2               | 19.6             | 14           | 4         | 94        |
| B0233 Zoster keratitis                              | 24           | 2.2%        | 12.17              | 9.84             | 8.0          | 5.0       | 20.0       | 22           | 2.0%        | 12.1               | 14.9             | 7.5          | 2         | 72        |
| B0231 Zoster conjunctivitis                         | 13           | 1.2%        | 6.00               | 2.83             | 5.0          | 2.0       | 10.0       | 19           | 1.7%        | 9.4                | 9.6              | 6            | 1         | 40        |
| B0232 Zoster iridocyclitis                          | 12           | 1.1%        | 10.83              | 8.02             | 9.0          | 4.0       | 32.0       | 7            | 0.6%        | 12.7               | 14.7             | 7            | 3         | 45        |
| B0223 Postherpetic polyneuropathy                   | 8            | 0.7%        | 11.13              | 6.45             | 8.0          | 5.0       | 20.0       | 8            | 0.7%        | 11.0               | 10.2             | 9.5          | 2         | 32        |
| B027 Disseminated zoster                            | 5            | 0.5%        | 9.4                | 4.83             | 7.0          | 5.0       | 16.0       | 11           | 1.0%        | 11.8               | 8.2              | 12           | 3         | 30        |
| B0224 Postherpetic myelitis                         | 3            | 0.3%        | 14.67              | 16.2             | 14.0         | 9.0       | 21.0       | 2            | 0.2%        | 38.0               | 49.5             | 38           | 3         | 73        |
| B0234 Zoster scleritis                              | 1            | 0.1%        | 1.0                | NR               | 1.0          | NR        | NR         | 0            | 0.00%       | -                  | -                | -            | -         | -         |
| <b>Total</b>                                        | <b>1 072</b> | <b>100%</b> | <b>10.19</b>       | <b>11.19</b>     | <b>7.0</b>   | <b>1</b>  | <b>106</b> | <b>1 092</b> | <b>100%</b> | <b>9.75</b>        | <b>10.38</b>     | <b>7</b>     | <b>1</b>  | <b>94</b> |

Data source: MCD. \* For patient with re-hospitalisation with HZ in principal diagnosis, this is the first admission that is presented.



The median length of stay (LOS) was 9 days (min 1 - max 229 days) and was lower among patients with a principal diagnosis of HZ (PD median LOS: 7 days- Not PD median LOS: 12 days) (Table 15 & Figure 9).

Not surprisingly, the incidence of HZ increases with age, regardless of the type of hospitalisation (inpatient, daycare, inpatient or daycare). In 2019, there was 22.02 inpatients per 100 000 inhabitants in the older than 50 years and 5.3 inpatient cases per 100 000 in the younger than 50 years for HZ as principal diagnosis. In Belgium in 2019, the annual number of inpatients went from 12.43 per 100 000 inhabitants aged 50-59 years to 173 per 100 000 inhabitants aged 80 years and over. Most of the inpatients were older than 70 years (63.2%) and female (56.4%) (Figure 10 and Table 16). However, the rate of hospitalisation per 100 000 person-years stratified for age was similar between sex. Corresponding figures by primary/secondary diagnosis can be found in Table 14-16 and Figure 3 in Appendix 1.6.

In 2019, patients with a diagnostic principal of HZ were younger than patients without a diagnostic principal of HZ (20.1% vs. 9.8% <50yr), Table 16. They also presented more often with a complicated form of HZ (68% vs. 55% overall), particularly HZO.

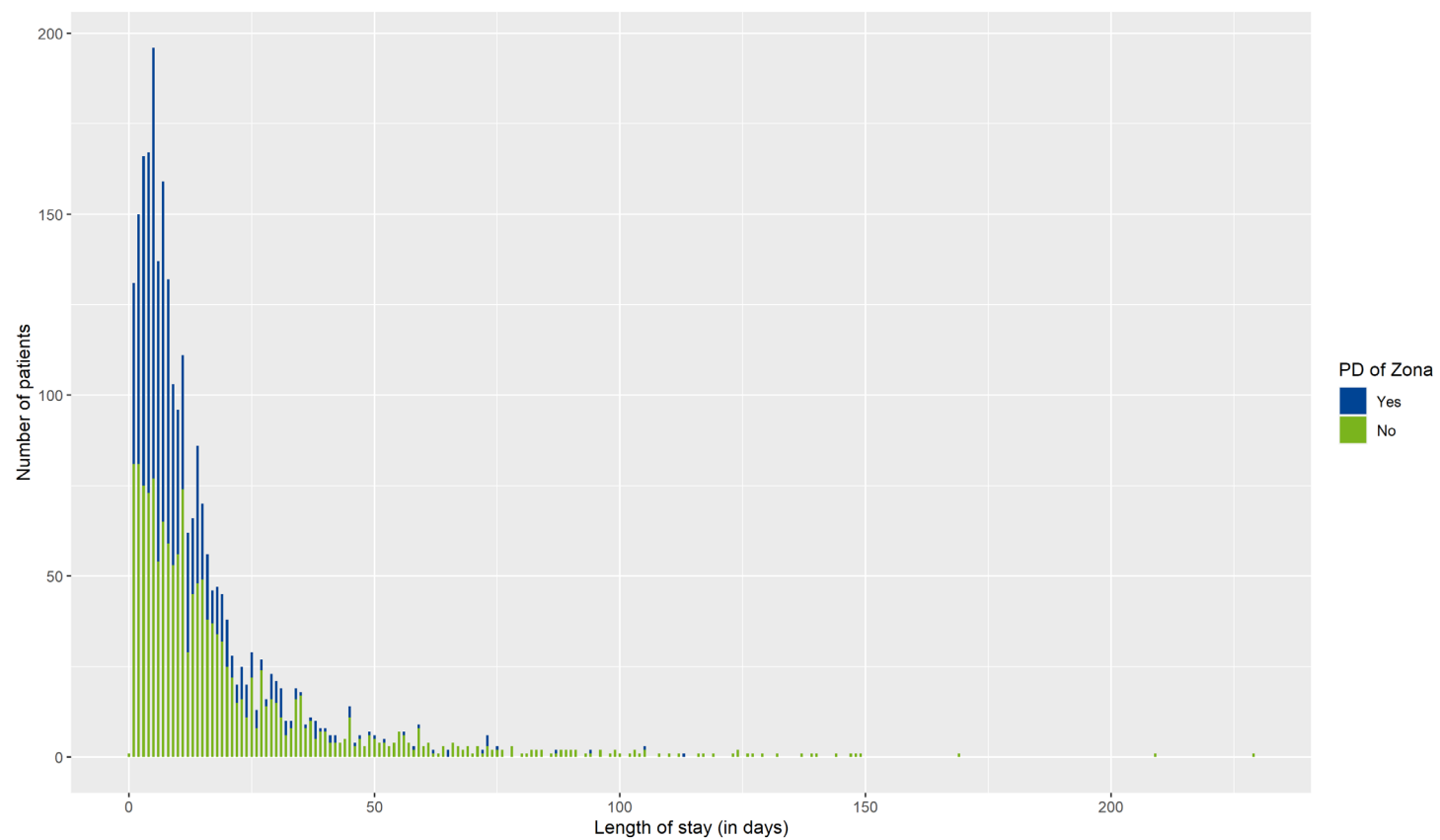
**Table 15 – Mean (SD) and median (Min-Max) length of stay, by type of diagnosis, 2019**

|                                                              | Median<br>(in days) | Min-Max<br>(in days) | Mean<br>(in days) | SD<br>(in days) |
|--------------------------------------------------------------|---------------------|----------------------|-------------------|-----------------|
| <b>Patient with HZ as principal diagnosis (n=1092 )*</b>     | 7                   | 1-113                | 10.3              | 11.4            |
| <b>Patient without HZ as principal diagnosis (n=1532 )**</b> | 12                  | 1-229                | 23.1              | 24.1            |
| <b>TOTAL</b>                                                 | 9                   | 9-229                | 15.9              | 20.4            |

*Data source: MCD. \* For patients with multiple hospitalizations we added up the days of all hospitalizations with a HZ as principal diagnosis. \*\* For patients with multiple hospitalization we added up all the days of hospitalization with primary and/or secondary diagnosis of HZ.*



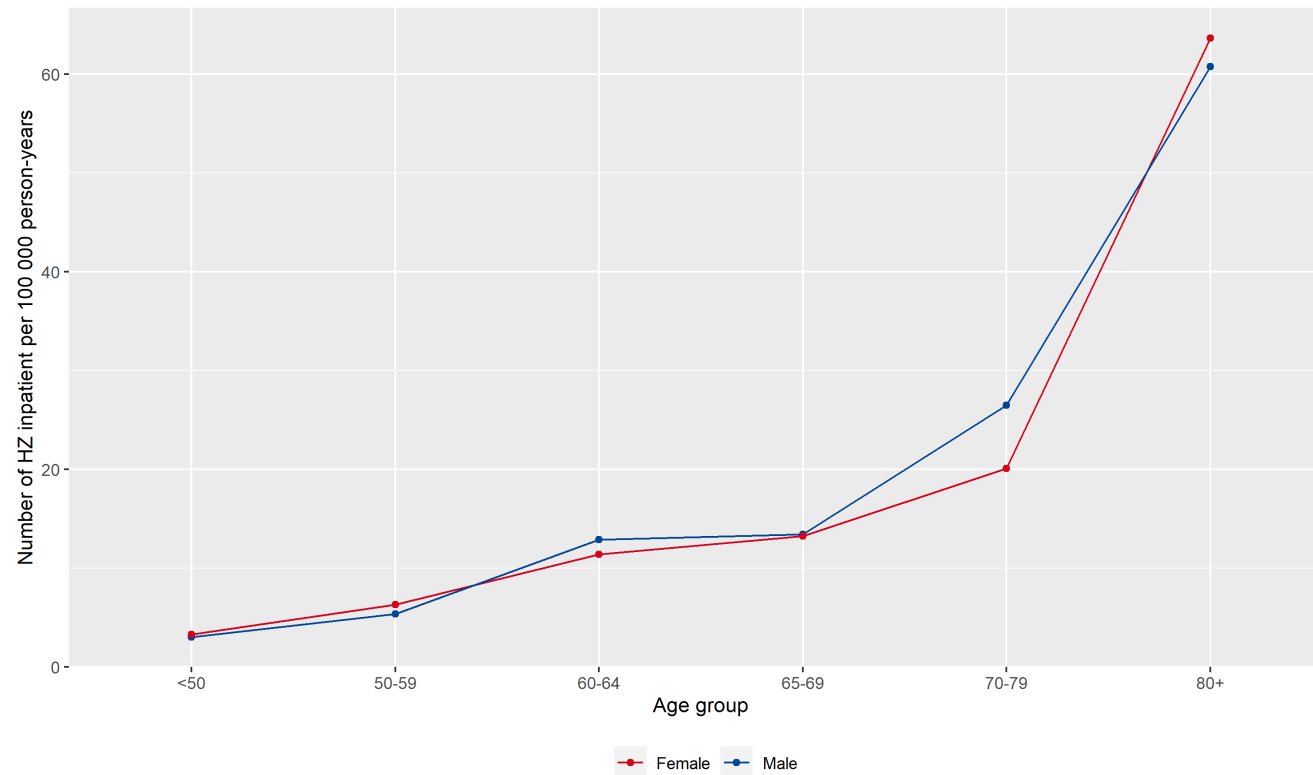
**Figure 9 – Length of stay, by type of HZ diagnosis (principal vs not principal), 2019**



Data source: MCD, PD=Principal diagnosis.



**Figure 10 – Incidence of HZ inpatients (principal diagnosis), by sex, by age-group, 2019**



Data source: MCD.


**Table 16 – Number of patients hospitalized with HZ as principal diagnosis vs. not principal diagnosis, by sex and age-group, 2019**

| Table 10. Number of patients hospitalized with HZ as principal diagnosis vs. not principal diagnosis, by sex and age group, 2010 |     |       |                                              |                          |       |                                              |                                |              |                                                    |
|----------------------------------------------------------------------------------------------------------------------------------|-----|-------|----------------------------------------------|--------------------------|-------|----------------------------------------------|--------------------------------|--------------|----------------------------------------------------|
| Number of inpatients (%)                                                                                                         |     |       | Number of inpatients per 100 000 inhabitants | Number of inpatients (%) |       | Number of inpatients per 100 000 inhabitants | Total number of inpatients (%) |              | Total number of inpatients per 100 000 inhabitants |
| Male                                                                                                                             |     |       | Male                                         | Female                   |       | Female                                       | Total                          | Total        |                                                    |
| <b>Total (n=2 624)</b>                                                                                                           |     |       |                                              |                          |       |                                              |                                |              |                                                    |
| <50                                                                                                                              | 160 | 14.0% | 4.54                                         | 209                      | 14.1% | 6.08                                         | 369                            | <b>14.1%</b> | 5.30                                               |
| 50-59                                                                                                                            | 99  | 8.7%  | 12.35                                        | 99                       | 6.7%  | 12.50                                        | 198                            | <b>7.5%</b>  | 12.43                                              |
| 60-64                                                                                                                            | 97  | 8.5%  | 27.72                                        | 82                       | 5.5%  | 22.76                                        | 179                            | <b>6.8%</b>  | 25.20                                              |
| 65-69                                                                                                                            | 104 | 9.1%  | 34.84                                        | 117                      | 7.9%  | 36.91                                        | 221                            | <b>8.4%</b>  | 35.91                                              |
| 70-79                                                                                                                            | 274 | 24.0% | 65.99                                        | 266                      | 18.0% | 54.55                                        | 540                            | <b>20.6%</b> | 59.81                                              |
| 80+                                                                                                                              | 410 | 35.8% | 171.85                                       | 707                      | 47.8% | 173.75                                       | 1 117                          | <b>42.6%</b> | 173.04                                             |
| <b>HZ principal diagnosis (n= 1 092)</b>                                                                                         |     |       |                                              |                          |       |                                              |                                |              |                                                    |
| <50                                                                                                                              | 106 | 21.7% | 3.01                                         | 113                      | 18.7% | 3.29                                         | 219                            | 20.1%        | 3.15                                               |
| 50-59                                                                                                                            | 43  | 8.8%  | 5.36                                         | 50                       | 8.3%  | 6.32                                         | 93                             | 8.5%         | 5.84                                               |
| 60-64                                                                                                                            | 45  | 9.2%  | 12.86                                        | 41                       | 6.8%  | 11.38                                        | 86                             | 7.9%         | 12.11                                              |
| 65-69                                                                                                                            | 40  | 8.2%  | 13.40                                        | 42                       | 7.0%  | 13.25                                        | 82                             | 7.5%         | 13.32                                              |
| 70-79                                                                                                                            | 110 | 22.5% | 26.49                                        | 98                       | 16.3% | 20.10                                        | 208                            | 19.0%        | 23.04                                              |
| 80+                                                                                                                              | 145 | 29.7% | 60.77                                        | 259                      | 43.0% | 63.65                                        | 404                            | 37.0%        | 62.59                                              |
| <b>HZ not principal diagnosis (n= 1 532)</b>                                                                                     |     |       |                                              |                          |       |                                              |                                |              |                                                    |
| <50                                                                                                                              | 54  | 8.2%  | 1.53                                         | 96                       | 10.9% | 2.79                                         | 150                            | 9.8%         | 2.15                                               |
| 50-59                                                                                                                            | 56  | 8.5%  | 6.98                                         | 49                       | 5.6%  | 6.19                                         | 105                            | 6.9%         | 6.59                                               |
| 60-64                                                                                                                            | 52  | 7.9%  | 14.86                                        | 41                       | 4.7%  | 11.38                                        | 93                             | 6.1%         | 13.09                                              |
| 65-69                                                                                                                            | 64  | 9.8%  | 21.44                                        | 75                       | 8.6%  | 23.66                                        | 139                            | 9.1%         | 22.58                                              |
| 70-79                                                                                                                            | 164 | 25.0% | 39.50                                        | 168                      | 19.2% | 34.45                                        | 332                            | 21.7%        | 36.77                                              |
| 80+                                                                                                                              | 265 | 40.5% | 111.07                                       | 448                      | 51.1% | 110.10                                       | 713                            | 46.5%        | 110.46                                             |

Data source: MCD. Denominator was population at 1<sup>st</sup> January, for patient with multiple hospitalisation, this is the age of the first hospitalisation who is presented.



### 3.5.2 International data

A systematic review including 28 studies on hospitalisation rates from 14 countries (including the Belgian study by Bilcke et al.<sup>20</sup>) reported rates of HZ-related hospitalisation ranging widely from 2 to 25 per 100 000 person-years in studies examining all ages.<sup>8</sup> The authors mentioned that the variation in the estimates might reflect the differing admission criteria in the different settings. Hospitalisations with a primary diagnosis of HZ accounted for about 29-42% of HZ-related hospitalisations. Studies that included hospitalisations with non-primary diagnosis codes (e.g. secondary) may have overestimated the hospitalisation rate because they may represent prior or incidental HZ. Hospitalisation rates increased steeply with age, with the majority of the cases occurring in adults  $\geq 50$  years of age. For example, in the USA, HZ-associated hospitalisation rates (confirmed with medical records) ranging from 10 per 100 000 in adults 60-69 years of age to 65 per 100 000 in adults  $\geq 80$  years of age were reported.<sup>85</sup> Similarly, the rate of hospitalisation with primary diagnosis of HZ ranged from 13 per 100 000 in adults 60-64 years of age to 96 per 100 000 in adults  $\geq 80$  years of age in Australia.<sup>86</sup> The rates ranged from 31 per 100 000 in adults 60-64 years of age to 100 per 100 000 in adults  $\geq 80$  years of age in Germany.<sup>44</sup>

The proportion of all HZ cases being hospitalized was between 1.3% in the UK<sup>74</sup> and 3.7% in Germany.<sup>45, 51</sup>

### 3.5.3 Discussion

HZ-related hospitalisation rates vary internationally from 2 to 25 per 100 000 person-years in studies examining all ages.<sup>8</sup> In Belgium, from 2008 to 2020, an incidence of 23.08 cases per 100 000 inhabitants was observed. These variations across countries might reflect different hospital admission practices, health-seeking behaviour, or selection criteria in studies. Whether secondary diagnoses are considered along primary diagnoses, or not, also contributed to the variation of incidence rates across countries. For example,

in France, the mean annual HZ hospitalisation rate was  $14 \pm 0.7$  hospitalisations per 100 000 inhabitants between 2000 and 2006 (based on 61 429 hospital discharges with a primary or associated HZ code).<sup>42</sup> This annual hospitalisation rate was  $4.1 \pm 0.3$  per 100 000 inhabitants when only discharges with a HZ main code were considered. Internationally, hospitalisations with HZ as principal diagnosis accounted for about 29-42% of HZ-related hospitalisations.<sup>8</sup> In Belgium, that proportion was 42.0% in 2019. This may also explain why a previous Belgian study where hospitalisations attributable to HZ were ascertained manually by a clinical expert reported a lower overall hospital incidence than the one computed by us.<sup>20</sup>

Trend of hospitalisation rate over time was also varying across countries, either decreasing,<sup>87</sup> increasing<sup>52</sup> or being stable.<sup>88</sup> In Belgium, no important variation of the incidence of inpatients across the years was observed.

Because hospital-based treatment is likely linked to presence of complications or underlying diseases, studies likely comprise the most severe cases of HZ. Complicated cases accounted for 30%<sup>89</sup> to 53%<sup>90</sup> of cases in previous studies, with neurological complications being the most frequent ones, followed by ophthalmic complications. Moreover, patient frailty was likely a risk factor for hospitalisation. The same observations applied to Belgium where HZ with complications account for around 55% of the hospitalisations with HZ as primary diagnosis.

Independently from the geographical area investigated, hospitalisations proportionally increase with increasing age and the majority of HZ-related admissions occurred in adults aged  $\geq 50$  years. The increase in incidence rate with age was observed for all subtypes of HZ. Another constant factor was a higher incidence rate in females. This is consistent with Belgian data.

In Belgium in 2019 there were 1092 hospitalisations overall, among which 873 in individuals  $\geq 50$  years. As a comparison, the average number of hospitalisations due to influenza<sup>a</sup> was estimated between 2140 and 3256

<sup>a</sup> Considering an uptake of 28% in those aged 50-64 years, 50% in 65-74 years and 71% in those 75+ years.



(with 244 to 356 deaths)<sup>a</sup> and the average number of hospitalisations due to pneumococcus in unvaccinated adults ≥50 years was estimated to be 5800 (440 deaths).<sup>b</sup>

## 3.6 Mortality rates

### Main findings

- Crude HZ mortality rate was previously estimated between 0.17 and 0.68 per 1 000 000 person-years in Flemish inhabitants over the years 1997-2008. This rate was 1.1 (95%CI: 0.96-1.26) per 1 000 000 person-years in Belgium over the years 1998-2016, based only on death certificates. This represents on average 11-12 deaths per year.
- HZ mortality rate increased with age (10.9 and 72.6 per 1 000 000 person-years for 80-89 and 90+ years, respectively).
- Meaningful international comparisons of crude mortality rate, case-fatality rate or hospital-fatality rates are hampered by variations of study methodologies, case definition, coding practices, healthcare seeking behaviors, comorbidity rates and severity in each country.

### 3.6.1 Belgian data

#### 3.6.1.1 SPMA & Statbel

To appraise the specific mortality rates, we used the standardized mortality rates (SPMA <https://spma.wiv-isp.be/SitePages/About.aspx>) provided by Sciensano (ISP-WIV)<sup>c</sup>. Since 1991, the FPS Economy ([Directorate general Statistics and Economic Information](#), ex NIS) centralises the mortality information coded by the Flemish and French Communities (International Classification of Disease-9 (ICD-9)). From the year 1998, ICD-10 is used. These data are grouped in SPMA by age, sex, nationality and district. The mortality information is registered on the basis of residency (*de jure* information) instead of place of death (*de facto* information). As far as mortality is concerned, only the initial cause of death is taken into account. The initial cause of death is defined in accordance with the encoding rules of the World Health Organization (WHO), as:

1. the diseases or the injuries which are at the base of a reaction chain of morbidities that finally lead to death or
2. the circumstances of the accident or the act of violence which have caused the fatal injury.

We searched the database with the ICD-10 code “B02” for HZ. No more than 3 digits are possible, so deaths associated with complicated HZ could not be differentiated. The results for 2012 were as follows:

<sup>a</sup> [Rapport KCE 204 : Vaccination contre la grippe saisonnière : priorité aux enfants ou à d'autres groupes cibles ? \(2013\)](#)

<sup>b</sup> [Rapport KCE 274 : Quelle vaccination contre le pneumocoque chez les personnes âgées ? \(2016\)](#)

<sup>c</sup> In report KCE 151, the specific mortality rate was based on death certificates provided by the Flemish Agency for Health Care and Health (FACH; Vlaams

Agentschap Zorg & Gezondheid/L'Agence flamande Soins et Santé'). Causes of death were derived from the death certificates, which are filled in by the medical doctor and completed by the public services of the municipality of the deceased person. These death certificates were screened by expert clinicians, who indicated which of these deaths were likely avoidable through the avoidance of HZ episodes.

**Table 17 – Standardized Mortality Ratio (SMR) by regions, in 2012**

| SMR             | Absolute numbers of death | SMR per 100 000 person-years (95%CI) |
|-----------------|---------------------------|--------------------------------------|
| <b>Belgium</b>  | 11                        | 0.03 (0.01-0.05)                     |
| <b>Flanders</b> | 5                         | 0.04 (0.00-0.07)                     |
| <b>Wallonia</b> | 5                         | 0.02 (0.00-0.05)                     |
| <b>Brussels</b> | 1                         | 0.02 (0.03-0.06)                     |

Source: SPMA (Sciensano).

### 3.6.1.2 Statbel

Information on initial cause of death related to herpes zoster was provided by the Belgian statistical office (Statbel) (based on death certificates) for the years 1998-2016 and included information on age-group, sex and region of the patient. Total Belgian population by year, sex and region was also provided by Statbel and referred to the population on the first of January. The crude mortality rate for herpes zoster is low with about 1.10 deaths per 1 000 000 inhabitants (95%CI: 0.96-1.26) from 1998 to 2016, with a sharp increase after 80 years (Table 18). No difference is apparent between sex.

**Table 18 – Herpes zoster crude mortality rate, by sex and age-group, 1998-2016**

| Age-group     | Sex    | Deaths | Population 1998-2016* | Crude mortality rate (per 1 000 000 inhabitants) |
|---------------|--------|--------|-----------------------|--------------------------------------------------|
| <b>&lt;50</b> | Female | 1      | 64 708 176            | 0.02                                             |
| <b>50-59</b>  | Female | 0      | 13 359 117            | 0.00                                             |
| <b>60-69</b>  | Female | 4      | 10 806 618            | 0.37                                             |
| <b>70-79</b>  | Female | 15     | 9 043 179             | 1.66                                             |
| <b>80-89</b>  | Female | 58     | 5 245 894             | 11.06                                            |
| <b>90+</b>    | Female | 77     | 1 024 462             | 75.16                                            |
| <b>&lt;50</b> | Male   | 2      | 66 484 594            | 0.03                                             |
| <b>50-59</b>  | Male   | 0      | 13 373 369            | 0.00                                             |
| <b>60-69</b>  | Male   | 3      | 10 095 545            | 0.30                                             |
| <b>70-79</b>  | Male   | 13     | 6 999 918             | 1.86                                             |
| <b>80-89</b>  | Male   | 30     | 2 855 704             | 10.51                                            |
| <b>90+</b>    | Male   | 20     | 311 783               | 64.15                                            |
| <b>&lt;50</b> | Both   | 3      | 131 192 770           | 0.02                                             |
| <b>50-59</b>  | Both   | 0      | 26 732 486            | 0.00                                             |
| <b>60-69</b>  | Both   | 7      | 20 902 163            | 0.33                                             |
| <b>70-79</b>  | Both   | 28     | 16 043 097            | 1.75                                             |
| <b>80-89</b>  | Both   | 88     | 8 101 598             | 10.86                                            |
| <b>90+</b>    | Both   | 97     | 1 336 245             | 72.59                                            |

Data source: Statbel, \* Population 1 January 1999 – 1 January 2017.



### 3.6.1.3 Literature

The HZ-related mortality rates were evaluated for Belgium.<sup>20</sup> The Flemish Agency for Care and Health (FACH- Vlaams Agentschap Zorg & Gezondheid/L'Agence flamande Soins et Santé) registers the causes of death (ICD-10 code) by year, gender and age for Flemish habitants who died in the Flemish region ('het Vlaamse Gewest') or in the Brussels region ('Brussels Gewest'). FACH provided all death certificates from 1998 to 2007 for residents of the Flemish region (representing 60% of the Belgian population) that contained ICD-10 codes 'B01' and 'B02'. Causes of death were derived from the death certificates, which are filled in by the medical doctor and completed by the public services of the municipality of the deceased person. The death certificates related to HZ were screened by five HZ experts.<sup>20</sup> From the 186 adult deaths recorded, only those for which HZ appeared as a primary cause of death were evaluated by the five expert clinicians (n=59, age range 61–102 years). Considering all deaths for which at least four of the five experts believed were due to HZ (n=10) resulted in a HZ mortality rate of 0.017 per 100 000 person-years. Considering all 59 recorded deaths, but excluding the 17 deaths for which at least four of the five clinicians believed were not due to HZ, results in a HZ mortality rate of 0.068 per 100 000 person-years.<sup>20</sup> The mortality rate was thus lower than our estimate based only on death certificates.

### 3.6.2 International data

A systematic literature review of studies and databases providing data for HZ-associated mortality in adults aged ≥50 years in Europe was published in 2015 (with search strategy up to 31/10/2013).<sup>3</sup> Twelve studies from 7 countries (Belgium- France- Germany- the Netherlands- Portugal- Spain and England and Wales) were included. In addition, four databases that provided HZ-associated mortality data from Europe were identified<sup>a</sup>. Methods varied among countries. Three studies reported mortality data

specifically for patients with underlying conditions. Four studies presented mortality data for deaths with HZ as the primary cause, one with HZ as the primary diagnosis at hospital admission and three with HZ as primary or associated cause- the remaining four studies did not specify if HZ was the primary or associated cause.<sup>3</sup> Only in Spain was microbiological confirmation of infection used.

#### Mortality rates (8 studies)

The mortality rates ranged from 0 in those aged 55–59 years in Germany<sup>44</sup> to 19.5 per 100 000 person-years for those aged ≥95 years in France.<sup>42</sup> The median mortality rate was 0.039 per 100 000 person-years in the WHO-European database. Despite the between-countries differences in rates, there was a trend towards higher mortality rates in older age groups in all countries, with the increase occurring from the age of 70-74 years. The HZ mortality rate varied by gender and was generally higher in women, although in Spain, Italy, France and, particularly, Denmark, the mortality rate was higher in men.

#### Case-fatality rates (4 studies)

The overall case-fatality rate (CFR) went from 22 per 100 000 cases in Germany<sup>44</sup> to 75 per 100 000 in France.<sup>42</sup> The 2 studies from UK provided estimation of CFRs that were around 2 per 100 000 cases in those aged 45 to 65 years old, and 61 per 100 000 cases in those aged ≥65.<sup>4, 91</sup> The CFR varied from 0 in those aged 55-59 years in Germany<sup>44</sup> to 2018 per 100 000 cases in those aged ≥85 years in England and Wales.<sup>4, 91</sup>

#### Hospital-fatality rates (5 studies)

The hospital-fatality rate (HFR) varied from 400 per 100 000 hospitalized cases in those aged 60–69 years in Portugal<sup>92</sup> to 7100 per 100 000 hospitalized cases in those aged >80 years in Spain.<sup>93, 94</sup> The HFRs reported

<sup>a</sup> European Detailed Mortality Database (WHO-DMDDB), CépiDc database from INSERM in France, the Office for National Statistics for England and Wales and the German Federal Health Monitoring System.



in Spain were higher than in other countries where the HFR was generally under 1000 per 100 000 cases until the age of 75 to 85 years. Data from the two studies that provided fatality rates for sub-groups of patients with underlying conditions showed that there was a higher fatality rate in these populations.

A second systematic review by Kawai et al.<sup>8</sup> included 10 studies on mortality rates from 10 countries. There was a large overlap between countries included in the review by Bricout et al. and this one. We extracted the results of the 7 studies carried out in Europe (Table 19). Mortality rates associated with HZ ranged from 0.017 per 100 000 person-years in individuals of all ages in Belgium<sup>20</sup> to 0.465 per 100 000 person-years in individuals  $\geq 50$  years in Sweden (Table 19) adapted from Kawai et al.<sup>8</sup> Most studies reported that the majority of deaths occurred in adults  $\geq 60$  years of age.

More recent studies reported congruent results. In Sweden<sup>a</sup>, the mortality rate in 2011 in individuals  $\geq 50$  years was 0.12 per 100 000 person-years.<sup>59</sup> A recent UK retrospective cohort study based on the Clinical Practice Research Datalink reported higher figures, with HZ-associated mortality rate of 0.74 per 100 000 (95%CI: 0.45-1.15) in immuno-compromised patients and 0.37 per 100 000 person-years (95%CI: 0.19-0.66) in immunocompetent patients.<sup>60</sup>

### 3.6.3 Discussion

International comparisons are difficult given the differences in study methodologies and coding practices in each country.<sup>3</sup> Also, the data are presented for differing age groups, some of which are very large, making comparisons between studies difficult. In particular, some data are given for patients aged  $\geq 65$  years whereas HZ-associated mortality rates are very different between those aged 65 to 75 years and those aged  $\geq 85$  years. The differences in case definitions used could account for a substantial part of

the heterogeneity.<sup>3</sup> Most studies used clinical diagnosis for HZ, without requiring laboratory confirmation. In an elderly population, with many patients presenting underlying conditions or other comorbidities, it is difficult for a physician to be certain about the causal relationship between HZ and death, particularly if the certifying physician does not have access to all the patient's medical records and autopsy results.<sup>3</sup>

It is possible that the variations in the HZ-HFR are due to differences in the numerator since HZ hospitalisation rates may vary between countries due to different healthcare pathways, healthcare seeking behaviours, or perception of symptoms. In addition, differences in coding practices could contribute to this heterogeneity. Other factors such as differences in the prevalence of underlying risk factors for severe illness, differences in comorbidity rates or some other unidentified factors in different populations may also contribute to the observed heterogeneity.<sup>3</sup>

Although most studies used HZ codes on death certificates for the primary cause of death, some used the codes for either primary or associated causes of death. Some of the limitations of using death certificates for estimating mortality incidence include incompleteness and errors. In a previous Belgian study, the overall specific mortality rate ranged from 0.017 per 100 000 person-years to 0.068 per 100 000 person-years according to the way the cause of death was ascertained by clinical experts.<sup>20</sup> But these rates were based on data from Flanders and Brussels. For this evaluation, we computed the mortality rates for the period 1998-2016 for the whole country, and the result was substantially higher at 0.11 per 100 000 person-years. However, there was no ascertainment of the cases by a panel of clinicians to evaluate the plausibility of HZ being the true cause of death. The rate of 0.11 per 100 000 person-years is close to rates observed in UK<sup>4</sup> and Netherlands,<sup>47</sup> but far below other countries (Table 19).

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<sup>a</sup> Deaths related to HZ (ICD-10: B02) were collected from the Swedish Causes of Death Register covering all the people who died and were registered as living in Sweden until 2011.

**Table 19 – Mortality rates associated with herpes zoster in European countries**

| Country           | Author                              | Database                             | Case definition                  | Year      | Age      | Mortality (100 000 person-years) |
|-------------------|-------------------------------------|--------------------------------------|----------------------------------|-----------|----------|----------------------------------|
| <b>UK</b>         | Brisson 2001 <sup>4</sup>           | National statistics in England/Wales | Underlying cause                 | 1993-2000 | All ages | 0.094                            |
| <b>France</b>     | Gonzalez-Chiappe 2010 <sup>42</sup> | National mortality data              | Underlying or contributing cause | 2000-2007 | All ages | 0.286                            |
| <b>Germany</b>    | Ultsch 2011 <sup>44</sup>           | Federal health monitoring system     | Underlying cause                 | 2007-2008 | ≥ 50 yrs | 0.210                            |
| <b>Netherland</b> | de Melker 2006 <sup>47</sup>        | National statistics registry         | Underlying or contributing cause | 1996-2002 | All ages | 0.114                            |
| <b>Belgium</b>    | Bilcke 2012 <sup>20</sup>           | Flemish agency for care and health   | Underlying cause                 | 1998-2007 | All ages | 0.017                            |
| <b>Spain</b>      | Gil 2009 <sup>93</sup>              | National hospital data               | Underlying cause                 | 1998-2004 | ≥ 30 yrs | 0.060                            |
| <b>Sweden</b>     | Studahl 2013 <sup>95</sup>          | National hospital data               | Underlying cause                 | 2006-2010 | ≥ 50 yrs | 0.465                            |

*This table was adapted from results by Kawai et al.<sup>8</sup>*



### 3.7 Quality of life

#### Main findings

- HZ affects quality of life of patients as measured by various specific or generic instruments. Mean utility values were highly correlated with the mean pain scores over time.
- Burden of HZ in Belgium in terms of QALY's lost has been estimated between 880 (95% CrI: 631–1162) and 1306 (95% CrI: 920–1743) in immunocompetent individuals  $\geq 50$  years.

HZ-associated pain can occur during 3 distinct phases of the disease: in the prodromal phase (prior to rash onset), in the acute phase (together with the rash and usually disappearing within 2 to 4 weeks) and in the chronic phase (PHN).<sup>70</sup> The pain and resulting discomfort associated with herpes zoster and PHN can have substantial impact on patient's health related quality of life (HRQoL), affecting activities of daily living and mental health, especially among the elderly.<sup>19, 96</sup> Impact of acute HZ on QoL is equalling that seen with chronic conditions such as congestive heart failure, diabetes mellitus, myocardial infarction and clinical depression.<sup>15, 97</sup> Additionally, non-pain complications like herpes ophthalmicus, stroke and visceral complications, can impact the quality of life and increase the risk of permanent physical impairment.<sup>15</sup>

#### 3.7.1 Disease-specific instruments

To assess pain severity and interference in patients with HZ the Zoster Brief Pain Inventory (ZBPI) and the Modified Brief Pain Short Form (mBPI-SF) (both derivate measures of the Brief Pain Inventory (BPI), a validated patient reported outcome (PRO) measure applied in a broad spectrum of medical

conditions) have been used.<sup>98-103</sup> In this questionnaire pain severity is evaluated on 4 items: 'current pain' and 'worst', 'least' and 'average pain' over the previous 24 hours, and pain interference is evaluated by the impact of pain on seven health status domains including general activity, mood, walking ability, normal work, social relations, sleep and enjoyment of life. Each item is assessed on a 11-point numerical rating scale ranging from 0 (no pain/does not interfere) to 10 (pain as bad as you can imagine/completely interferes).<sup>19, 104</sup> Pain severity cut-points were set on 1-3 for mild pain, 4-6 for moderate pain and 7-10 for severe pain.<sup>104</sup> Investigators have also used other instruments to measure pain intensity and/or its interference like the McGill Pain Questionnaire Present Pain Intensity<sup>a</sup>, the Zoster Impact Questionnaire<sup>b</sup> or other not validated questionnaires.<sup>15, 19, 70, 105, 106</sup> An overview of the instruments used in HZ can be found in Table 20.

**Table 20 – Disease specific and generic instruments to measure QoL**

| Outcome                | Instrument                                         | References   |
|------------------------|----------------------------------------------------|--------------|
| Pain interference      | ZBPI (Zoster Brief Pain Inventory)                 | 98-103       |
|                        | mBPI-SF (modified short form brief pain inventory) | 104          |
| ADL (disease specific) | Zoster Impact Questionnaire (ZIQ)                  | 107          |
|                        | Short Italian Questionnaire (SIQ)                  | 96, 108      |
|                        | Bespoke questionnaires or surveys                  | 105, 106     |
| Generic HRQoL          | SF-12 (12-item short-form health survey)           | 70, 98, 109  |
|                        | SF-36 (36-item short-form health survey)           | 77, 101, 103 |
|                        | EQ-5D <sup>c</sup> (EuroQoL 5 dimensions)          | 99-104, 110  |
|                        | Short Italian Questionnaire (SIQ)                  | 96, 108      |

*ADL: activities of daily living, HRQoL: health related quality of life, SF: short form.*

Gater et al. reported in a critical review 21 European studies with a consistently significant negative impact of herpes zoster and PHN on

<sup>a</sup> The present pain intensity (PPI) scale from the McGill Pain Questionnaire uses the following responses: no pain and mild, discomforting, distressing, horrible, and excruciating pain.

<sup>b</sup> ZIQ assesses how pain and PHN affect functional aspects of life (bathing, grooming, dressing, concentration, preparing meals, eating meals,

housework, leisure activities, leaving house, shopping, travelling). The ZIQ was not evaluated against other validated pain questionnaires.

<sup>c</sup> The EQ-5D is a standardized generic questionnaire comprising 5 items used to provide a simple descriptive profile and a single index value for health status (ranging from 0–1). The EQ-5D also includes a visual analogue scale, which records the respondent's self-rated health.



HRQoL.<sup>19</sup> The pain reported in herpes zoster or PHN was generally moderate to severe, but average and worst pain levels reported by patients with PHN were higher compared to those with herpes zoster. The experienced pain was found to interfere with many aspects of patient's daily life and higher levels of pain were associated with greater interferences.<sup>104, 109</sup> Greater impact on all seven health status was found in patients with PHN compared to patients with herpes zoster (Table 21).<sup>98, 101, 103, 105, 106</sup> The aspect 'Sleep' was the most affected, whereas walking ability was the least affected in herpes zoster patients and enjoyment of life was the least affected in PHN patients. Some studies focused on specific aspects, for example mood and social relations. In studies by Weinke et al.<sup>106</sup> and Lukas et al.,<sup>105</sup> respectively 11 009 German individuals and 44 545 individuals from 6 other countries (Spain, Portugal, The Netherlands, Belgium, Sweden and Switzerland) were questioned whether they had a diagnosis of painful HZ in the past 5 years. All individuals were older than 50 years and were residing in private households. In total 1393 patients (288 and 1005) reported herpes zoster, of which 163 (32 and 131) with PHN. Up to 29% of patients with HZ and up to 43% of PHN patients reported feelings of moderate anxiety or depression, whereas extreme anxiety or depression was reported by up to 5% of HZ patients and up to 11% of PHN patients. Up to 78% of HZ patients and 91% of PHN patients reported stress some of the time, whereas 19% of HZ patients and 41% of PHN patients reported stress most of the time.<sup>105, 106</sup> Intense pain was associated with greater risk of anxiety and depression, compared to mild pain.<sup>15, 111, 112</sup> Impact on social and family life was described in up to 50% of patients with herpes zoster and 81% of patients with PHN.<sup>105, 106</sup> Feelings of isolation from family and friends and reduced communication were reported in about one fifth of patients with HZ.<sup>105</sup> An acute episode of herpes zoster can lead to permanent loss of independence in some elderly, leading to further isolation and withdrawal.<sup>15</sup>

**Table 21 – Pain interference on ADL assessed by ZBPI or similar**

| Health state domains | HZ (mean scores) | PHN (mean scores) |
|----------------------|------------------|-------------------|
| Enjoyment of life    | 3.6-4.0          | 3.8-5.2           |
| General activity     | 3.8-4.4          | 3.1-5.7           |
| Mood                 | 3.4-4.5          | 3.4-5.9           |
| Normal work          | 3.3-4.4          | 2.9-6.1           |
| Sleep                | 4.5-4.9          | 6.3-6.5           |
| Social relations     | 2.1-3.5          | 2.1-5.4           |
| Walking ability      | 1.7-4.0          | 1.7-5.8           |

Table adapted from <sup>19</sup>. ADL: activities of daily living, HZ: herpes zoster, PHN: post herpetic neuralgia, ZBPI: zoster brief pain inventory.

Three more recent prospective observational studies with similar methodology were performed in primary care settings in Germany, Italy and Spain and reported on the substantial impact of herpes zoster on the quality of life of individuals aged 50 years or older.<sup>99, 100, 102</sup> Patients consulting for a first HZ episode<sup>a</sup> were asked to fill in QoL and pain assessment questionnaires (EQ-5D and ZBPI) at initial consultation and 15, 30, 60 and 90 days after onset of the rash. Patients with PHN<sup>b</sup>, were assessed up until day 180 and those with PHN at day 180 were followed up until day 270. Results are summarized in Table 22. The mean worst pain scores for patients with HZ were highest at D0 (first day of HZ rash) and decreased monotonically over time. PHN patients had higher mean worst pain scores at presentation and remained higher for a longer period of time. At 90 days the mean worst pain of PHN patients was similar to that of HZ patients (all patients and the ones without PHN) at D0. In between, mean worst pain

<sup>a</sup> A case of HZ was defined as new unilateral pain accompanied with unilateral rash and without an alternative diagnosis.

<sup>b</sup> PHN was defined as a 'worst' pain score  $\geq 3$  on the ZBPI scale persisting or appearing 90 days or more after rash onset.



increased and decreased in the Spanish study or decreased monotonically in the others.<sup>99, 100, 102</sup>

Most patients with HZ who did not develop PHN, reported pain and impact on quality of life or ADL for about one month after onset of the rash. Similar to pain levels, the mean ZBPI ADL score was highest at D0 and diminished monotonically over time. Similar to previous data, the item of ZBPI ADL most affected was sleep, whereas walking ability was the least affected in both HZ and PHN patients

### 3.7.2 Generic Instruments

Generic HRQoL instruments have also been used in patients with herpes zoster, such as the EQ-5D, SF-12, SF-36<sup>a</sup>, and the Short Italian Questionnaire (SIQ)<sup>b</sup>. An overview of the different generic instruments used in herpes zoster, can be found in Table 20. HRQoL SF-12 scores were found to be lower in patients with pain compared to patients without pain.<sup>70, 98</sup> Increased levels of pain were also associated with lower generic HRQoL scores<sup>101, 103, 104, 109</sup> and lowest scores were reported by patients with PHN.<sup>77, 101, 103</sup> Serpel et al. and Gater et al. evaluated HRQoL both with SF-36 and EQ-5D in respectively PHN and HZ patients and found lower scores compared to age matched norms ( $p < 0.05$ ).<sup>101, 103</sup> Findings suggested higher

pain severity and greater deficits in HRQoL in females, but these differences were not always significant.<sup>70, 101, 108, 110</sup>

In the three recent and similar observational studies in Italy, Germany and Spain, EQ-5D scores were the lowest at D0 and gradually increased over 3 months by almost the same absolute amount (about 0.2), but PHN patients had lower utility scores throughout.<sup>99, 100, 102</sup> The results of these studies can be found in Table 22. The German and Italian scores of the whole group were practically the same, whereas the Spanish scores were slightly lower (0.085 at D0, 0.037 at D30 and 0.056 at D90). The calculated utility loss during the first month after herpes zoster diagnosis equated to 0.138 in the Spanish and 0.134 (0.131 without PHN) in the Italian study (loss of approximately 4.1 days of perfect health per month). Mean utility values were highly correlated with the mean pain scores over time.

The burden of HZ in Belgium in terms of quality adjusted life years (QALY) lost has been estimated between 880 (95% CrI: 631–1162) and 1306 (95% CrI: 920–1743) in immunocompetent individuals  $\geq 50$  years (see chapter 6).<sup>21</sup>

In comparison, the average number of QALYs lost due to influenza<sup>c</sup> was estimated to be 5814<sup>d</sup> and the average number of QALYs lost due to pneumococcus in adults  $\geq 50$  years was 4150.<sup>e</sup>

<sup>a</sup> The SF-36 is a standardized generic questionnaire that consists of 36 items evaluating HRQoL. The psychometric validity is well-established for use in HZ and PHN populations. Items explore eight dimensions: physical functioning, role functioning due to physical problems, role functioning due to emotional problems, bodily pain, general health perceptions, vitality, social function and mental health. Two summary scores can be calculated: the Physical Component Summary and Mental Component Summary.

<sup>b</sup> The Short Italian questionnaire is previously validated and evaluates intensity of pain, psychological profile and quality of life; information about anxiety or depression and the perceptions that an individual has about their pain and

quality of life (worst pain over last week, physical and social functioning, vitality, physical and emotional role, psychological distress and well-being). Each item is scored between 0 (negative) and 10 (maximum).

<sup>c</sup> Considering an uptake of 28% in those aged 50-64 years, 50% in 65-74 years and 71% in those 75+ years.

<sup>d</sup> [Rapport KCE 204 : Vaccination contre la grippe saisonnière : priorité aux enfants ou à d'autres groupes cibles ? \(2013\)](#)

<sup>e</sup> [Rapport KCE 274 : Quelle vaccination contre le pneumocoque chez les personnes âgées ? \(2016\)](#)


**Table 22 – Quality of life measures comparison HZ and PHN (in Germany, Italy and Spain)**

| Parameters          | Germany                         |                           |                        | Italy                           |                        | HZ all patients<br>Mean (SD) | Spain                  |                  |
|---------------------|---------------------------------|---------------------------|------------------------|---------------------------------|------------------------|------------------------------|------------------------|------------------|
|                     | HZ<br>all patients<br>Mean (SD) | HZ<br>No PHN<br>Mean (SD) | HZ<br>PHN<br>Mean (SD) | HZ<br>all patients<br>Mean (SD) | HZ<br>PHN<br>Mean (SD) |                              | HZ no PHN<br>Mean (SD) | PHN<br>Mean (SD) |
| Number of patients  | 513                             | 452                       | 61 (11.9 %)            | 391                             | 40 (10.2%)             | 545                          | 520                    | 25 (4.6%)        |
| Mean worst pain D0  | 5.1                             | 4.9 (2.8)                 | 6.7 (2.2)              | 5.7 (2.63)                      | 7.8 (2.18)             | 5.5 (2.96)                   | 5.4 (3.02)             | 6.9 (1.67)       |
| Mean worst pain D30 |                                 | 2.1 (2.6)                 | 5.7 (2.4)              | 2.6 (3.04)                      | 7.3 (1.95)             | 1.0                          | 0.6                    | 6.3              |
| Mean worst pain D90 | 0.7                             | 0.1 (0.8)                 | 4.4 (1.5)              | 0.7(1.94)                       | 5.7 (1.96)             | 0.6 (1.75)                   | 0.0 (0.37)             | 5.5 (1.93)       |
| ZBPI ADL D0         |                                 | 2.970 (0.12)              |                        | 3.48 (2.71)                     |                        |                              | 2.91 (0.16)            |                  |
| ZBPI ADL D30        |                                 |                           |                        | 1.82 (2.46)                     |                        |                              |                        |                  |
| ZBPI ADL D90        | 0.66 (0.07)                     |                           | 2.889 (0.25)           | 0.58 (1.47)                     |                        |                              | 0.55 (0.10)            |                  |
| EQ-5D D0            | 0.740 (0.012)                   | 0.760 (0.251)             | 0.614 (0.328)          | 0.746 (0.011)                   |                        | 0.661 (0.018)                | 0.671 (0.019)          |                  |
| EQ-5D D30           | 0.859 (0.009)                   | 0.892 (0.153)             | 0.654 (0.273)          | 0.848 (0.011)                   |                        | 0.811 (0.012)                | 0.823 (0.012)          |                  |
| EQ-5D D90           | 0.942 (0.006)                   | 0.960 (0.109)             | 0.825 (0.136)          | 0.932 (0.008)                   |                        | 0.876 (0.010)                | 0.888 (0.010)          |                  |

ADL: activities of daily living, D: day, EQ-5D: EuroQol 5 dimensions, HZ: herpes zoster, PHN: postherpetic neuralgia, ZBPI: zoster brief pain inventory.



### 3.8 Vaccine-targetable risk factors

The two main vaccine-targetable risk factors are increasing age and immunosuppression. We define immunocompromised patients as patients with congenital or acquired immunodeficiency, solid or hematological cancers treated in the previous 3 years, inflammatory or auto-immune conditions requiring immunosuppressor treatments (e.g. rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease), haematopoietic stem cell transplant, solid organ transplant, HIV with CD4 cells  $<200$  per  $\text{mm}^3$ , and chronic renal failure.

#### 3.8.1 Age

All studies displayed a sharp increase in incidence of HZ incidence, incidence of complications and incidence of hospitalisations with increasing age.<sup>7-9, 14, 113</sup> This association is also clearly demonstrated for HZ incidence, hospitalisation and mortality rates in Belgium as demonstrated in above sections. The correlation between age and HZ incidence may be related to a decreased cellular-mediated immune response to HZ as result of immunosenescence.<sup>9</sup> A likely complementary explanation would be the higher incidence of favouring co-morbidities (e.g., diabetes or COPD) or immunosuppressive conditions in older individuals. With an aging population, the yearly number of HZ cases is expected to raise in the coming years and to become a more important public health issue. An increase over time is indeed observed in many countries.<sup>7</sup>

Incidence rates were also reported as being systematically higher among women than men (male/female ratio around 1.4).<sup>7, 9, 113</sup> Evidence is contradictory as whether this difference decreased<sup>7</sup> or increased<sup>9</sup> with age. The reason for such a difference is not known. Women might simply be more likely to seek medical advice, thereby causing a higher reporting rate, or there may be some biological mechanism by which women are more susceptible to VZV reactivation.<sup>114</sup> The gender divide was less apparent as regards PHN incidence, as reported in a systematic review by Forbes et al.<sup>14</sup> Of 9 studies reporting the age-adjusted association between gender and PHN, some suggested an increased risk of PHN among females but others reported a decreased risk, whereas others found no evidence of an

association. Moreover, in Belgium the rate of hospitalisation stratified adjusted for age was found similar between males and females (see section 3.5.1).

#### 3.8.2 Immunosuppression

##### Main findings

- Immunocompromised patients have a higher risk of HZ and complications than immunocompetent individuals. The rate varies by immunocompromising conditions and is particularly high for hematopoietic stem cell transplant recipients and hematologic malignancies.
- The risk of HZ in patients with auto-immune diseases is also increased but to a lower degree.
- An exact summary measures of the risk increase is difficult given the large variation in study estimates for cumulative incidence and incidence of HZ across studies and within each immunocompromised category.
- There is imprecise and contradictory evidence on increased incidence of PHN and other complications.

##### 3.8.2.1 Incidence of HZ

A recent good quality systematic literature review by McKay et al. (search strategy up to January 2019) focused on 5 major immunocompromising conditions in adults: hematopoietic stem cell transplant (HSCT) recipients, hematologic malignancies (HM), solid organ transplant (SOT) recipients, solid tumor malignancies (STM), and human immunodeficiency virus (HIV).<sup>115</sup> It included 34 studies with low or moderate risk of bias. The incidence rate of HZ ranged from 90 to 950 per 10 000 person-years. Incidence rates that exceeded 400 per 10 000 person-years were reported for both HSCT and HM.<sup>115</sup> The highest cumulative incidence was in autologous HSCT recipients (median: 18.6%; IQR: 11%-23%), with a risk 6-



10 times that for US adult population.<sup>115</sup> Other populations of immunocompromised patients had median HZ incidence estimates <300/10 000 person-years. However, there was large variation in study estimates for HZ cumulative incidence and incidence rates within each immunocompromised category due to differences in patients characteristics, study design (RCTs and observational studies were included), case ascertainment, use of antiviral prophylaxis, and follow-up duration.

Another good quality systematic review of risk factors for HZ (search date up to 2017- 84 studies) also reported that the risk of HZ was increased in individuals suffering from auto-immune diseases including rheumatoid arthritis and systemic lupus erythematosus (Table 23).<sup>113</sup> However, the risk ratios were around 1.3, i.e. much lower than the immunocompromising conditions reported above, except for systemic lupus erythematosus (RR 2.10; 95%CI: 1.40-3.15). Here also a huge heterogeneity of results across studies was observed.<sup>113</sup>

Primary studies not included in the systematic reviews cited above (because not limited to specific immunosuppressive conditions or more recent) reported consistent results. In one German study, the incidence rate per 10 000 person-years of herpes zoster (in all manifestations) was almost twice as high in immunocompromised patients (IR=115; 95%CI: 114-116) compared to immunocompetent subjects (IR=59; 95%CI: 58-59).<sup>53</sup> The incidence rate was also higher in highly immunocompromised patients (IR=134; 95%CI: 132-136) than in patients with a low severity of immunosuppression (IR=100; 95%CI: 98-10.1). These differences were observed for both sexes and in all age groups.<sup>53</sup> In another large German study based on German health insurance data, Hillebrand et al. found an HZ incidence rate about 75% higher in immunocompromised patients than in immunocompetent ones.<sup>51</sup> In UK, Yanni et al. found in a retrospective cohort of 621 588 individuals with 16 selected immunocompromised conditions<sup>a</sup>

and a gender/age-matched cohort of immunocompetent individuals that the overall incidence rate of HZ in the immunocompromised cohort was 77.7 per 10 000 person-years (95%CI: 76.7-78.8) and 62.1 per 10 000 PY (95%CI: 61.2-63.0) in the immuno-competent individuals.<sup>60</sup> This was in line with a previous matched case-control study (114 959 HZ cases) which reported that patients with severely immunosuppressive conditions were at greatest risk of zoster, e.g. patients with lymphoma (adjusted odds ratio=3.90; 95%CI: 3.21-4.74) and myeloma (adjusted OR=2.16; 95%CI: 1.84-2.53).<sup>116</sup> In the same country, a case-control study (192 081 HZ cases) focusing on the link with cancers reported that malignancy overall was positively associated with zoster risk (adjusted OR=1.29; 95%CI: 1.27-1.32), and that the association was especially strong for haematological malignancies (adjusted OR=2.46; 95%CI: 2.33-2.60).<sup>117</sup>

### 3.8.2.2 Incidence of PHN

In the systematic review by McKay et al. the risk of developing PHN ranged from 6% to 45% across the immunocompromising conditions (HCT, HM, SOT, STM, HIV- 12 studies).<sup>115</sup> Within each of the immunocompromising categories, there was heterogeneity between PHN estimates: HCT (range, 6%-41%; n=6), SOT(range, 7%-45%; n=3), HM (range, 6%-40%; n=3), STM (9%; n=1), and HIV (6%; n=1). A systematic review by Forbes et al. reported that immunosuppression and autoimmune conditions were also a risk factor for developing PHN.<sup>14</sup> However, results were sometimes conflicting, likely due to the inclusion of small studies with limited methodological quality. More recent studies based on large samples provided relevant information. In UK in a retrospective cohort study based on the Clinical Practice Research Datalink (n=621 588) the proportion of PHN was 36% higher in immunocompromised than in immunocompetent HZ patients over all ages.<sup>60</sup> In UK, another cohort study including 119 413 HZ cases consistently reported that PHN risk was higher in those with severely

<sup>a</sup> haematopoietic stem cell transplant (HSCT); solid organ transplantation (SOT); solid organ malignancy; (SOM); haematological malignancy (HM); HIV; end-stage renal disease (ESRD); corticosteroids exposure (CORTDS); other immunosuppressive therapy (OIT) exposures including biological

treatments; other immunodeficiency conditions (OIC); and autoimmune diseases (AID). The AIDs comprised: rheumatoid arthritis, systemic lupus erythematosus (SLE), inflammatory bowel diseases, psoriasis, multiple sclerosis (MS), polymyalgia rheumatica and autoimmune thyroiditis (AT).



immunosuppressive conditions, including leukemia (13.7%; OR=2.07; 95%CI: 1.08–3.96) and lymphoma (12.7%; OR= 2.45; 95%CI: 1.53–3.92), or with autoimmune conditions, including rheumatoid arthritis (9.1%; OR=1.20; 95%CI: 0.99–1.46).<sup>71</sup> In contrast, in a retrospective cohort study on data from 7 million statutory health insurance carried out in Germany, immunocompromised persons suffered only slightly more complications (31%) than immunocompetent ones (27%).<sup>51</sup>

### 3.8.2.3 Incidence of other complications

As for HZ and PHN incidence, immunosuppression is considered a risk factor for complications other than PHN, although the evidence is contradicting. In Germany, Hillebrand et al. found that immunocompromised persons suffered only slightly more complications than immunocompetent ones and did not show higher proportions of severe complications such as zoster encephalitis, zoster meningitis or zoster ophthalmicus,<sup>51</sup> whereas in the study by Schröder et al. the difference in complications incidence between immunocompetent and immunocompromised patients was substantial (see Table 10).<sup>53</sup> In UK, the incidence of complications also was pretty similar between the two populations.<sup>60</sup> In the recent good quality systematic review by McKay et al. the risk of developing disseminated HZ among HSCT recipients ranged from 0% to 32% with a median of 3% (IQR: 0.2%–3.8%) (18 studies).<sup>115</sup> Studies reporting ocular complications (4 studies) and hospitalisation (2 studies) were infrequent, and risk estimates ranged from 0% to 1% and from 14% to 19%, respectively. Rare complications, such as HZ encephalitis, may be poorly captured in

administrative databases. The opposite is true for hospitalisation, which is common for many immunosuppressed populations. However, determining if hospitalisation was HZ-related or due to complications of the underlying condition can be difficult in retrospective cohort studies.<sup>115</sup>

### 3.8.3 Other risk factors

In a good quality systematic review of risk factors for HZ (search date up to 2017- 84 studies), Kawai et al., besides autoimmune diseases, listed the following factors as being associated with HZ infection: black race (half the risk of HZ as white individuals), a family history of HZ, asthma (RR=1.25; 95%CI: 1.13–1.39), diabetes (RR=1.30; 95%CI: 1.17–1.45), and COPD (RR=1.31; 95%CI: 1.22–1.41) (Table 23).<sup>113</sup> The association with asthma and COPD is linked with the use of corticosteroid, but it seemed that the association was still significant after adjustment for corticosteroid use. Asthma, COPD, and diabetes have also been reported as risk factors of PHN.<sup>71</sup> Regarding more particularly diabetes, a matched case-control study in UK (144 959 HZ cases), type 1, but not type 2, diabetes showed some association with zoster (adjusted OR=1.27; 95%CI: 1.07 to 1.50).<sup>116</sup> Similar figures were observed in Spain.<sup>118</sup>

However, results in Table 23 report a relatively small risk increase for these conditions (except family history and auto-immune diseases). Moreover, the results are highly heterogeneous across studies, and it is unclear how far the results of these studies were adjusted for the effect of confounding factors. Therefore their utility to identify priority target groups to vaccinate is unclear.



**Table 23 – Risk factors for HZ based on systematic literature review by Kawai et al.<sup>113</sup>**

|                                              | Number of studies | Pooled Risk ratio | 95% CI    | Heterogeneity (I <sup>2</sup> ) |
|----------------------------------------------|-------------------|-------------------|-----------|---------------------------------|
| <b>Female sex</b>                            | 27                | 1.31              | 1.27-1.34 | 97%                             |
| <b>Black individuals</b>                     | 5                 | 0.54              | 0.47-0.63 | 88%                             |
| <b>Family history</b>                        | 5                 | 3.59              | 2.39-5.40 | 78%                             |
| <b>Rheumatoid arthritis</b>                  | 5                 | 1.67              | 1.41-1.98 | 97%                             |
| <b>Systemic lupus erythematosus</b>          | 4                 | 2.10              | 1.40-3.15 | 92%                             |
| <b>Inflammatory bowel disease</b>            | 5                 | 1.35              | 1.28-1.42 | 0%                              |
| <b>Chronic kidney disease</b>                | 3                 | 1.28              | 1.14-1.42 | 93%                             |
| <b>Chronic obstructive pulmonary disease</b> | 5                 | 1.31              | 1.22-1.41 | 91%                             |
| <b>Asthma</b>                                | 6                 | 1.25              | 1.13-1.39 | 93%                             |
| <b>Diabetes mellitus</b>                     | 14                | 1.30              | 1.17-1.45 | 99%                             |
| <b>Depression</b>                            | 8                 | 1.36              | 1.15-1.61 | 96%                             |

## 4 VACCINE EFFICACY AND SAFETY

### 4.1 Methods

A systematic review of the literature was performed following a previously written protocol in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis for Protocols (PRISMA-P). The final version of this protocol was registered with The International Prospective Register of Systematic Reviews (PROSPERO, REF CRD42022311749). No significant deviations from the protocol occurred.

A literature search was conducted to identify RCTs and observational studies, evaluating the efficacy and safety of the recombinant zoster vaccine (RZV) compared to placebo, other herpes zoster vaccines or no vaccine in immunocompetent patients older than 50 years and immunocompromised individuals older than 18 years. While RCTs are the golden standard for clinical research and provide excellent efficacy data, observational studies are able to show effectiveness in the real world. Moreover, observational studies can be more suitable to study long term safety. Only publications in French and English were considered. Case reports, case series with less than 30 participants, in animal, in-vitro only studies, editorials and abstracts were excluded (Table 24).

**Table 24 – Inclusion and exclusion criteria for literature search based on PICOS**

|                      | Inclusion                                                                                                               | Exclusion                                                                                                                   |
|----------------------|-------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------|
| <b>Participants</b>  | Immunocompetent individuals<br>>50 years<br>Immunocompromised*<br>patients >18 years                                    |                                                                                                                             |
| <b>Intervention</b>  | Recombinant adjuvanted<br>zoster vaccine (Shingrix)                                                                     |                                                                                                                             |
| <b>Comparator(s)</b> | Placebo or live attenuated<br>vaccine (Zostavax) or no<br>vaccine                                                       |                                                                                                                             |
| <b>Outcome(s)</b>    | Efficacy: 1. HZ; 2. PHN; 3.<br>Other complications of HZ**;<br>4. Hospitalisation; 5. Burden of<br>disease<br>Safety*** |                                                                                                                             |
| <b>Design</b>        | RCT<br>Observational study with a<br>control group                                                                      | Case report, case series<br>(n<30), editorials, abstracts;<br>phase 1-2 trials; in-vitro only<br>studies; in-animal studies |
| <b>Time frame</b>    | Any                                                                                                                     |                                                                                                                             |
| <b>Languages</b>     | English, French                                                                                                         | Other languages                                                                                                             |

*HZ herpes zoster, PHN postherpetic neuralgia, \* Allo- and autogenic stem cell transplantation, solid organ transplantation, solid tumour and chemotherapy, haematological malignancies, HIV, immune mediated disease, inflammatory bowel disease. \*\* HZ vasculitis; disseminated HZ; ophthalmic, neurologic, or visceral disease; and stroke. \*\*\* Total discontinuations, serious adverse events, Guillain-Barré Syndrome, reactogenicity (injection site or local reactions (pain, redness, swelling) and systemic reactions (fatigue, fever, myalgia, gastro-intestinal symptoms and headache).*

#### 4.1.1 Information sources and literature search

Medline, Embase and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched from 1 January 2012 to 7 February 2022. The search strategy for each of the databases can be found in Appendix 2.1. Additional relevant studies were identified by checking the citations of the publications. Ongoing or recently completed trials were identified on the International Clinical Trials Registry Platform (ICTRP) Search Portal and ClinicalTrials.gov, and the same was done for systematic reviews on PROSPERO. The websites from EMA, FDA, INATHA and EUNATHA were checked for relevant information and prior HTA studies using the keyword 'zoster'. Experts in the fields were consulted.

#### 4.1.2 Screening process

Publications were initially screened using title and abstract. If publications were considered potentially relevant, full-text articles were obtained and evaluated for inclusion and exclusion criteria. The two first steps were achieved by one reviewer, and cross-checked with an independent group of experts for identification of any missing publications.

#### 4.1.3 Data items and abstraction process

Data extraction on each eligible publication was performed by one researcher and checked against the original study by a second independent researcher. Information extracted included information on study methodology, patient characteristics and all measures of relevant outcomes. For study method we included study design, funding, setting, sample size and duration of follow-up. Other data extracted were participant characteristics (mean age, age range, gender, inclusion and exclusion criteria), intervention and comparator, and primary and secondary outcomes.

The primary outcomes studied were outcomes concerning vaccine efficacy: the incidence rate of participants with confirmed herpes zoster (HZ), postherpetic neuralgia (PHN) or other HZ complications (for example vasculitis, disseminated HZ, visceral HZ, ophthalmic, cardiac or neurological



complications including stroke), hospitalisation rate and mean difference in burden of illness.

The secondary outcomes studied were measures of safety including the proportion of participants with one or more (serious) adverse event based on International Conference on Harmonization - Good Clinical Practice (ICH-GCP) definition including reactogenicity (symptoms of local or systemic reactions), Guillain-Barré syndrome (GBS), potential immune mediated disease (pIMD) and mortality.

#### 4.1.4 Quality appraisal and risk of bias assessment

Two researchers independently assessed the quality of evidence. For RCTs we used the version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2) (<https://methods.cochrane.org/bias/resources/rob-2-revised-cochrane-risk-bias-tool-randomized-trials>). For quality appraisal of systematic literature reviews the AMSTAR 2 tool (<https://amstar.ca/Amstar-2.php>) was used, and for primary observational studies the Cochrane Risk Of Bias In Non-Randomized Studies - of Interventions (ROBINS-I) (<https://methods.cochrane.org/bias/risk-bias-non-randomized-studies-interventions>). Quality assessment was performed following the Grading of recommendations, assessment, development and evaluation (GRADE) methods and evidence tables were made in GRADEpro GDT.

#### 4.1.5 Statistical approach

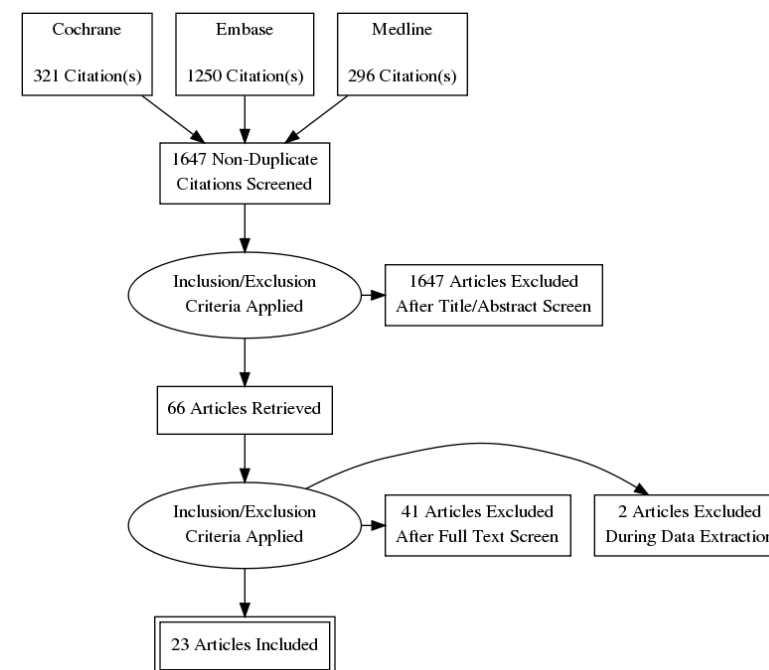
Meta-analysis and production of forest plots was performed in Review manager 5.3. For dichotomous primary and secondary outcomes, the pooled risk ratio's (RR) and 95% confidence Intervals (CI) were calculated. For continuous outcomes, we estimated difference in means (MD) with 95%CI. The Higgins I<sup>2</sup> statistics was used to estimate the proportion of total variation in study estimates that is due to heterogeneity.<sup>119</sup> Results were considered statistically significant when p-value <0.05. Subgroup analysis was done for different age ranges (18-49, 50-59, 60-69, 70-79, >80) and individuals with/without immunosuppression to assess the potential effect of these factors on RZV effectiveness.

## 4.2 Results

### 4.2.1 Literature search

A summary of the literature search can be found in Figure 11. The search in bibliographic databases yielded 1867 references, of which 54 were duplicates. Of the 1713 titles and abstracts screened 66 articles were sought for retrieval and assessed for eligibility based on full text. Eventually, 23 publications were withheld with data from 13 studies (6 RCTs and 7 observational studies) Study and patient characteristics can be found in Table 25. Papers excluded after in depth reading can be found in Appendix 2.2.

**Figure 11 – PRISMA flow diagram**





The prophylactic efficacy and safety of Shingrix in older, immunocompetent individuals was evaluated in two phase 3 RCTs (ZOE-50 and ZOE-70).<sup>31, 63</sup> Nine additional publications pertaining to these two trials were included in the evaluation of efficacy and safety of RZV.<sup>79, 120-127</sup> One of these publications reports the partial results of an extension study of ZOE-50 and ZOE-70, ZOE-LFTU.<sup>120</sup> One paper referring to ZOE-50/70 was excluded because of the non-relevant Asian subpopulation studied.<sup>128</sup>

Clinical efficacy and safety of RZV in immunocompromised patients was studied in 4 phase 3 RCTs. The four patient groups studied were patients who underwent a haematopoietic stem cell transplantation (ZOE-HSCT, Zoster-002),<sup>129-131</sup> patients with haematological malignancies (Zoster-039),<sup>132</sup> a renal transplant (Zoster-041),<sup>133</sup> or a solid tumour (Zoster-028).<sup>134</sup> The publication by Stadtmauer et al. was excluded because of non-relevant subgroup analysis (underlying disease for patients with haematopoietic stem cell transplantation (ZOE-HSCT)).<sup>131</sup> Data on reactogenicity and safety from 6 trials in immunocompromised patients (the previously mentioned phase 3 RCTs and 2 phase 1/2 studies in HSCT and HIV-infected patients) was found in an overview research article.<sup>135</sup>

Eight observational studies on RZV were identified in 7 papers. The outcome studied in the observational studies was mostly effectiveness, either against HZ,<sup>136-140</sup> against HZO<sup>136, 140-142</sup> and/or against PHN.<sup>136</sup> In two studies (a cohort and a self-controlled case study reported in the same paper), the outcome was Guillain Barré syndrome.<sup>143</sup> Four studies reported only about immunocompetent older patients,<sup>139, 140, 142</sup> while two included both immunocompetent and immunocompromised patients<sup>136, 143</sup> and 2 included patients with inflammatory bowel disease.<sup>138, 144</sup> During literature search more cohort studies were identified, but excluded because of a lack of control group (see Appendix 2.2).

Of note, the search also yielded a number of interesting publications pertaining to RZV:

- Four reports on co-administration with other vaccines: 23-valent pneumococcal polysaccharide<sup>145</sup> pneumococcal conjugate vaccine 13,<sup>146</sup> influenza<sup>147</sup> and tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine (TDaP).<sup>148</sup>

- Three reports of post-licensure safety surveillance in the United States.<sup>149-151</sup>
- A cohort study about the risk for COVID-19 diagnosis and the risk of hospitalisation after RZV vaccination.<sup>152</sup>

We identified 6 ongoing studies on ClinicalTrials.gov:

- NCT04748939, a phase 4, double blind, placebo controlled RCT in patients with rheumatic disease (safety and immunogenicity)
- NCT04839982, Zoster-076, a phase 4, quadruple blind, placebo controlled RCT in Chinese adults ≥ 50 years (vaccine efficacy, immunogenicity and safety)
- NCT05219253, Zoster-081, a phase 3, quadruple blind, placebo controlled RCT in Indian adults ≥ 50 years (humoral immunogenicity and safety)
- NCT05047770, Zoster-091, a phase 3, open label RCT of Shingrix and Influenza Vaccine when sequentially or co-administered with Moderna's mRNA-1273 booster vaccination against COVID-19 (immunogenicity and safety)
- NCT04091451, Zoster-062, a phase 3, quadruple blind, placebo controlled RCT in adults aged 50 years and above who have had a previous episode of shingles (immunogenicity and safety)
- NCT04516408, a quadruple blind, placebo controlled RCT in stable systemic lupus erythematosus (SLE) patients (efficacy and safety)

We retrieved the assessment reports of the EMA<sup>32</sup> and the FDA.<sup>153</sup> No relevant information was found on the websites of EUnetHTA and INATHA and no ongoing systematic review was found on PROSPERO.



#### 4.2.2 Quality appraisal/risk of bias

Included RCTs were judged overall high quality based on the Risk of Bias tool of the Cochrane collaboration (Table 19 in Appendix 2.3). They were all funded by GSK. The Risk of Bias according to the ROBINS-I tool for observational studies can be found in Table 20 in Appendix 2.3. Included observational studies were judged low to moderate quality.

#### 4.3 Clinical efficacy and safety in immunocompetent individuals (pivotal ZOE-50 and ZOE-70 trials)

The prophylactic efficacy and safety of RZV in older, immunocompetent individuals were evaluated in two pivotal phase 3, randomized (1:1), observer-blinded, placebo-controlled, multicentre trials.<sup>31, 63</sup> Zoster-006 (ZOE-50) was performed in adults 50 years of age or older,<sup>31</sup> whereas Zoster-022 (ZOE-70) included adults 70 years of age or older.<sup>63</sup> The RCTs were rated low risk of bias. The follow-up study of ZOE-50/70 (ZOE-LTFU)<sup>120</sup> was rated unclear risk of bias, mainly because of potential selection bias and reporting bias. Some of the analyses performed on pooled data from ZOE-50 and ZOE-70,<sup>121, 124, 126, 127</sup> were rated unclear risk of bias because of their post-hoc analysis. The other publication on pooled data from ZOE-50 and ZOE-70 was rated low risk of bias (Table 19 in Appendix 2.3).

ZOE-50 and ZOE-70 were run in parallel. Participants were randomly assigned in a 1:1 ratio to either the vaccine group (2 intramuscular doses of the vaccine 2 months apart) or the placebo group. Participants who were 70 years of age or older were first randomly assigned to either ZOE-50 or ZOE-70 and afterwards to either the vaccine group or the placebo group. Participants were stratified according to region (Asia and Australia, Europe, Latin America, and North America) and age group (50 to 59, 60 to 69, and ≥70 years in ZOE-50 and 70 to 79 years versus. ≥80 years in ZOE-70). They were followed up for a mean of 3.2 years in ZOE-50 and 3.7 years in ZOE-

70. Because the appearance of the reconstituted vaccine differed from the placebo solution, injections were done by study staff who did not participate in any study assessment. The investigators, participants, and assessors were unaware whether vaccine or placebo had been administered. The primary outcome was the reduction in herpes zoster risk. A suspected case of herpes zoster was defined as new unilateral rash with pain (broadly defined to include allodynia, pruritus, or other sensations) that had no alternative diagnosis. Participants were instructed on how to recognize signs and symptoms of herpes zoster and to contact their study site immediately if any developed. They were required to record their symptoms on a specific diary card. Investigators were to examine suspected cases of herpes zoster within 48 hours, if possible. For each suspected case, the rash was photographed and 3 lesions of each suspected case of herpes zoster were sampled for confirmation by polymerase chain reaction (PCR). If PCR was negative or samples not available, the final diagnosis was determined by unanimous agreement among the five members of an ascertainment committee unaware of PCR results. For assessing adverse events, a reactogenicity subgroup<sup>a</sup> (8926 participants (58%) of ZOE-50 and 1025 participants (7.4%) of ZOE-70) recorded solicited injection-site reactions (pain, redness, and swelling) and systemic reactions (fatigue, fever, gastrointestinal symptoms, headache, myalgia, and shivering) on diary cards for 7 days after each vaccination. The participants graded the intensity of the solicited reactions on a scale from 0 (absent) to 3 (severe, preventing normal everyday activities). Unsolicited adverse events were recorded for 30 days after each dose. Serious adverse events, defined as death, life-threatening events, hospitalisation (required or prolonged), disability or incapacity were recorded in all participants for up to 12 months after the second dose. Events potentially related to the study vaccine or study participation, deaths, and potentially immune-mediated diseases were evaluated in all participants over the entire study period.

<sup>a</sup> All participants who were 70 years of age or older and randomly selected participants in two other age groups (50 to 59 years and 60 to 69 years) (ZOE-50) and a randomly selected subgroup of age-stratified participants (ZOE-70).



The primary analysis (vaccine efficacy) was carried out in the modified vaccinated cohort (mTVC, excluded participants who did not receive the second dose of vaccine or who had HZ within 1 month after the second dose). The modified vaccinated cohort of ZOE-50 and ZOE-70 included about 95% of the total vaccinated cohort (TVC, i.e. at least one dose of the vaccine), both in RZV and placebo recipients. An overview of the

publications with safety and/or efficacy data on RZV in immunocompetent individuals (ZOE-50, ZOE-70, ZOE-LTFU and (post-hoc) analysis performed on pooled data from ZOE-50 and ZOE-70) can be found in Table 25. Demographic characteristics were similar in both study groups (RZV or placebo) of ZOE-50 and ZOE-70. Some small discrepancies in number of participants were noticed across the publications, but these were minimal.

**Table 25 – Included papers on immunocompetent individuals ≥50 years**

| Publication                                                   | Study design                                                                                                             | Patient characteristics                                                                                                                           | Mean Follow-up                                | Number of patients                                                     | Mean age (± SD)  | Gender (%) and White race (%)              | Intervention                                   | Outcome                                                                                    |
|---------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|------------------------------------------------------------------------|------------------|--------------------------------------------|------------------------------------------------|--------------------------------------------------------------------------------------------|
| <b>ZOE-50<sup>31</sup></b>                                    | Phase 3 RCT<br>1:1 randomized<br>Placebo-controlled<br>Triple blind<br>Multicentre<br>18 countries<br>Funded by industry | <b>Inclusion criteria:</b><br>≥ 50 years<br><b>Exclusion criteria:</b><br>History of HZ<br>HZ or varicella vaccine<br>Immunosuppressive condition | 3.2y                                          | 15 411 TVC<br>14 759 mTVC                                              | 62.3y<br>(±9.0)  | Female 61.2<br>Male 38.8<br><br>White 71.8 | RZV IM<br>versus<br>placebo<br>2 doses (0, 2m) | Efficacy against HZ<br><br>Secondary outcomes:<br>Efficacy by age group<br>Safety          |
| <b>ZOE-70<sup>63</sup></b>                                    | Phase 3 RCT<br>1:1 randomized<br>Placebo-controlled<br>Triple blind<br>Multicentre<br>18 countries<br>Funded by industry | <b>Inclusion criteria:</b><br>≥70 years<br><b>Exclusion criteria:</b><br>History of HZ<br>HZ or varicella vaccine<br>Immunosuppressive condition  | 3.7y                                          | 13 900 TVC<br>13 163 mTVC                                              | 75.5y<br>(±4.7)  | Female 54.9<br>Male 45.1<br><br>White 76.9 | RZV IM<br>versus<br>placebo<br>2 doses (0, 2m) | Efficacy against HZ<br>≥70y<br><br>Secondary outcome:<br>Safety                            |
| <b>ZOE-50/70<sup>63</sup><br/>HZ and PHN</b>                  | ZOE-50 and ZOE-70<br><br>Funded by industry                                                                              | ZOE-50 and ZOE-70<br>All patients ≥70y<br><br>Analysis against PHN<br>all patients ≥50y                                                           | 3.8y                                          | ≥70:<br>17 531 TVC<br>16 596 mTVC<br>≥50:<br>29 305 TVC<br>27 916 mTVC | Not<br>specified | Not specified                              | RZV IM<br>versus<br>placebo<br>2 doses (0, 2m) | Efficacy against HZ<br>and PHN ≥70y<br>Secondary outcomes:<br>Efficacy against PHN<br>≥50y |
| <b>ZOE-50/70<br/>Complications<br/>(not PHN)<sup>79</sup></b> | ZOE-50 and ZOE-70<br><br>Funded by industry                                                                              | ZOE-50 and ZOE-70<br>All patients ≥50y                                                                                                            | 3.9±0.7y<br>(ZOE-50)<br>3.7y±0.8y<br>(ZOE-70) | 27 916 mTVC                                                            | Not<br>specified | Not specified                              | RZV IM<br>versus<br>placebo<br>2 doses (0, 2m) | Secondary outcomes:<br>Efficacy against<br>HZ-complications (not-<br>PHN)                  |



|                                                      |                                                                             |                                                                                                           |               |                                                          |                                 |                                            |                                                |                                                                                                                                                               |
|------------------------------------------------------|-----------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------|---------------|----------------------------------------------------------|---------------------------------|--------------------------------------------|------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                      |                                                                             |                                                                                                           |               |                                                          |                                 |                                            |                                                | HZ-related mortality and HZ-related hospitalisation                                                                                                           |
| <b>ZOE-50/70 Safety<sup>125</sup></b>                | ZOE-50 and ZOE-70<br>Funded by industry                                     | ZOE-50 and ZOE-70<br>All patients ≥50y                                                                    | 4.4y          | 29 305 TVC                                               | 68.6 y                          | Male 41.8<br>Female 58.2<br>White 73.7     | RZV IM<br>versus<br>placebo<br>2 doses (0, 2m) | Safety                                                                                                                                                        |
| <b>ZOE-50/70 Underlying conditions<sup>126</sup></b> | ZOE-50<br>ZOE-50 and ZOE-70<br>Post hoc analysis<br>Funded by industry      | ZOE-50 and ZOE-70<br>Patients ≥50y with at least one specific medical condition at enrolment <sup>a</sup> | Not specified | 23 035 mTVC (82.5% of ZOE-50/70)                         | 68.5 y (±9,8)                   | Male 41.8<br>Female 58.2<br>White 73.7     | RZV IM<br>versus<br>placebo<br>2 doses (0, 2m) | Efficacy and safety according to number and type of selected medical conditions present at enrolment                                                          |
| <b>ZOE-50/70 Quality of life<sup>123</sup></b>       | ZOE-50 and ZOE-70<br>Funded by industry                                     | ZOE-50 and ZOE-70<br>All patients ≥50 from ZOE-50<br><br>All patients ≥70y from ZOE-50/70                 | Not specified | ZOE-50 :<br>14 753 mTVC<br>ZOE-50/70 ≥70y<br>16 596 mTVC | Not specified                   | Not specified                              | RZV IM<br>versus<br>placebo<br>2 doses (0, 2m) | Least, worst and average pain<br>HZ Burden of illness<br>HZ Burden of interference<br>Quality of life                                                         |
| <b>ZOE-frailty study<sup>122</sup></b>               | Observational retrospective study (international)<br><br>Funded by industry | Centres willing to participate<br><br>ZOE-50 and ZOE-70 patients ≥50y                                     | ±4y           | 26 976 (92% of TVC ZOE-50/70)                            | 68.8y                           | Male 41.9<br>Female 58.1<br><br>White 74.6 | RZV IM<br>versus<br>placebo<br>2 doses (0, 2m) | Frailty status<br>Secondary outcomes: efficacy against HZ, efficacy against HZ burden of illness, immunogenicity, reactogenicity and safety by frailty status |
| <b>ZOE-50/70 ≥pIMD<sup>124</sup></b>                 | ZOE-50 and ZOE-70<br>Post hoc analysis<br><br>Funded by industry            | ZOE-50 and ZOE-70 patients ≥50y with at least one pIMD, at                                                | 4.4y          | 1943 (6.6% of pooled ZOE-50/70)                          | RZV<br>68.8±9.6y<br><br>Placebo | Female 60.4<br>Male 39.6<br><br>White 85.4 | RZV IM<br>versus<br>placebo<br>2 doses (0, 2m) | Efficacy and safety                                                                                                                                           |

<sup>a</sup> Selected medical conditions at enrolment: hypertension, osteoarthritis and/or vertebral disorder, dyslipidemia, diabetes, osteoporosis/osteopenia, gastroesophageal reflux disease, sleep disorder, prostatic diseases, hypothyroidism, depression, coronary heart disease.



|                                                                                       |                                                                              | enrolment (not-immunocompromised)                                                                                                                                                               |               |                                                                    | 69.4y±9.5y                                                                                            |                                                                                              |                                                              |                                                                                                                                                                                                                  |
|---------------------------------------------------------------------------------------|------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------|--------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------|--------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>ZOE-50/70</b><br><b>Sex, geographic area and ethnicity/ancestry</b> <sup>127</sup> | ZOE-50 and ZOE-70<br>Post hoc analysis<br><br>Funded by industry             | ZOE-50 and ZOE-70<br><br>All patients ≥50 from ZOE-50<br><br>All patients ≥70y from ZOE-50/70                                                                                                   | Not specified | ZOE-50<br>14 753 mTVC<br><br>ZOE50/70<br>≥ 70 years<br>16 596 mTVC | ZOE 50<br>RZV 62.3 y<br>Placebo<br>62.2y<br><br>ZOE50/70<br>≥ 70 years<br>RZV 75.5<br>Placebo<br>75.5 | ZOE 50<br>Female 61.2<br>Male 38.8<br><br>ZOE50/70<br>≥ 70 years<br>Female 54.9<br>Male 45.1 | RZV IM<br>versus<br>placebo<br>2 doses (0, 2m)               | Efficacy against HZ and PHN according to sex, geographic area, ethnicity/ancestry                                                                                                                                |
| <b>ZOE-50/70</b><br><b>Reactogenicity trends</b> <sup>121</sup>                       | ZOE-50 and ZOE-70<br>Post hoc analysis<br><br>Funded by industry             | ZOE-50 and ZOE-70<br><br>All patients ≥50y                                                                                                                                                      | Not specified | 29 305 TVC                                                         | Not specified                                                                                         | Not specified                                                                                | RZV IM<br>versus<br>placebo<br>2 doses (0, 2m)               | Reactogenicity trends: the intensity of each solicited injection site and general event after dose 1 was compared to the intensity of the same event reported after dose 2.                                      |
| <b>Zoster-049</b><br><b>ZOE-LTFU</b> <sup>120</sup>                                   | Phase 3b open label<br>Extension ZOE-50 and ZOE-70<br><br>Funded by industry | <b>Inclusion criteria:</b><br>At least 1 RZV dose in ZOE-50 or ZOE-70<br><br><b>Exclusion criteria:</b><br>Use of immunosuppressive and immune modifying treatments<br>Other VZV or HZ vaccines | 7.1y          | 7413 TVC<br>7277 mTVC                                              | mTVC<br>67.2y±9.4                                                                                     | mTVC<br>Male 39.3<br>Female 60.7<br><br>White 76.5                                           | RZV IM<br>versus historic control/placebo group in ZOE-50/70 | Efficacy against HZ from 5.1 years to 7.1 years after vaccination (in total 2 years)<br>Secondary<br>Efficacy against HZ from 1 month post-dose 2 until 7.1 years (in total 7 years)<br>Immunogenicity<br>Safety |

HZ: Herpes Zoster, LTFU: long-term follow-up, mTVC: modified vaccinated cohort, PHN: postherpetic neuralgia, RZV: recombinant zoster vaccine, TVC: total vaccinated cohort.



#### 4.3.1 Prevention of Herpes Zoster

Main efficacy results on prevention of herpes zoster in immunocompetent individuals  $\geq 50$  years are presented in Table 26. We report high quality of evidence of the use of RZV (statistically superior) for the outcome herpes zoster in immunocompetent adults, although the included RCTs were all funded by industry (GSK) and a publication bias cannot be fully excluded (Table 37). In individuals  $\geq 50$ y (ZOE 50), the incidence rate of herpes zoster in the modified vaccinated cohort was 0.3 per 1000 person-years in the vaccination group and 9.1 per 1000 person-years in the placebo group, resulting in an estimated vaccine efficacy of 97.2% (95%CI: 93.7-99.0;  $p < 0.001$ ) over a 3.2 year follow-up period. The vaccine efficacy was 91.3% (95%CI: 86.8-94.5;  $p < 0.001$ ) in individuals  $\geq 70$ y (pooled ZOE-50/70). There was no significant difference in vaccine efficacy among different age groups of ZOE-50, ZOE-70 and the ZOE-50/70 pooled data (Table 26), and vaccine efficacy was very similar in the respective total vaccinated cohorts. In order to prevent one case of HZ over 3.2 years and 3.8 years, respectively, 36.4 participants (95%CI: 31.9-42.2) needed to be vaccinated in individuals  $\geq 50$ y (ZOE-50) and 32.3 (95%CI: 28.5-37.1) in individuals  $\geq 70$ y (pooled data ZOE-50/70) (Table 27).

The vaccine efficacy was also evaluated in different subgroups by post-hoc analysis using the pooled data from ZOE-50 and ZOE-70. Subgroups were defined by the presence of at least one selected medical condition at enrolment,<sup>a,126</sup> the presence of at least one potential immune mediated disorder (e.g. psoriasis, spondyloarthritis)<sup>124</sup> or the frailty status.<sup>b,122</sup> Overall the vaccine efficacy was high in all different subgroups, with only

small differences noticed between subgroups (Table 21 in Appendix 2.4). Vaccine efficacy was also similar in males and females.<sup>127</sup>

The protective effect against HZ decreased moderately over the years as the vaccine efficacy was 97.6% during year 1, 92.0% during year 2, 84.7% during year 3, and 87.9% during year 4 after the second vaccination, but confidence intervals overlapped (pooled ZOE-50/70; modified vaccinated cohort).<sup>63</sup> An open-labelled follow-up study (Zoster-049 or ZOE-LTFU) of the pooled ZOE-50/70 population included a sub-sample (50.6%) of the ZOE-50/70 participants and reported overall vaccine efficacy of 90.9% (95%CI: 88.2-93.2) in the modified vaccinated cohort during a mean follow-up of 7.1 years after vaccination.<sup>120</sup> The authors suggest a trend toward a plateau with vaccine efficacy of 84.9% (95%CI: 70.4-93.1) in year 6, 85.3% (95%CI: 71.3-93.3) in year 7 and 84.1% (95%CI: 64.4-94.0) in year 8 (available data on 6876 patients) (Table 28). However further follow-up data will be necessary to confirm this. The NNV (to prevent HZ) over 7 years was 23.4 (95%CI: 21.6-25.7) (Table 27). The monitoring of participants of the two trials is still ongoing. The risk of selection bias is unclear as in total 50.6% (7413 participants) of the 14 648 ZOE-50/70 participants who received at least 1 RZV dose were enrolled in ZOE-LTFU, but a sample size of 6000 participants would allow a lower limit for the annual vaccine efficacy estimate  $> 30\%$  to be achieved with a probability of  $\geq 99\%$ .<sup>120</sup> Selection criteria included: a. inclusion of individuals who, in the opinion of the investigator, could and would comply with the requirements of the protocol or individuals with a caregiver who, in the opinion of the investigator, could and would comply with the requirements of the protocol (e.g., completion of the diary cards, availability for follow-up contacts); b. exclusion of individuals who experienced a serious adverse event from first vaccination in the ZOE-50/70 studies to enrolment in this follow-up study that was considered related to

<sup>a</sup> Selected medical conditions at enrollment: hypertension, osteoarthritis and/or vertebral disorder, dyslipidemia, diabetes, osteoporosis/osteopenia, gastroesophageal reflux disease, sleep disorder, prostatic diseases, hypothyroidism, depression, coronary heart disease.

<sup>b</sup> Frailty status of individuals in ZOE-50 and ZOE-70 was measured using the accumulation of deficits approach using data from medical history, SF-36 and

EQ-5D questionnaires recorded before the first dose of RZV or placebo. According to the resulting Frailty index (FI), participants were assigned to 3 different subgroups:  $FI \leq 0.08$  non-frail,  $> 0.08$  and  $\leq 0.25$  pre-frail and  $> 0.25$  frail.<sup>154</sup> The participants with missing FI were classified as unknown.



study vaccine.<sup>120</sup> Participants in the vaccinated group were thus highly selected and it is not reported in the paper how much they differ from initial participants in the ZOE-50 and ZOE-70 studies.

Moreover, in the absence of an unvaccinated placebo group for the LTFU (placebo recipients from ZOE-50/70 were also vaccinated with RZV meanwhile), the efficacy analyses (overall and annual) for the period of this LTFU study used historical control estimates from the ZOE-50/70 placebo groups recorded during the trials, adjusted for age and region at randomization during the ZOE-50/70 studies. The impact of this approach on the estimates of vaccine efficacy is unclear.

**Table 26 – Vaccine efficacy against Herpes Zoster in immunocompetent individuals ≥50 years (modified total vaccinated cohort)**

| Study                                     | Patients     | FU          | Incidence rate of HZ per 1000 person-years |                         | Efficacy %  | 95%CI            |
|-------------------------------------------|--------------|-------------|--------------------------------------------|-------------------------|-------------|------------------|
|                                           |              |             | RZV (n/PY)                                 | Placebo (n/PY)          |             |                  |
| <b>ZOE-50<sup>155</sup></b>               | <b>≥50y</b>  | <b>3.2y</b> | <b>0.3 (6/23 297)</b>                      | <b>9.1 (210/23 171)</b> | <b>97.2</b> | <b>93.7-99.0</b> |
|                                           | 50-59y       | 3.2y        | 0.3 (3/11 161)                             | 7.8 (87/11 135)         | 96.6        | 89.6-99.3        |
|                                           | 60-69y       | 3.2y        | 0.3 (2/7008)                               | 10.8 (75/6953)          | 97.4        | 90.1-99.7        |
|                                           | ≥70y         | 3.2y        | 0.2 (1/5128)                               | 9.4 (48/5083)           | 97.9        | 87.9-100.0       |
| <b>ZOE-70<sup>63</sup></b>                | <b>≥70y</b>  | <b>3.7y</b> | <b>0.9 (23/6541)</b>                       | <b>9.2 (223/6622)</b>   | <b>89.8</b> | <b>84.2-93.7</b> |
|                                           | 70-79y       | 3.7y        | 0.9 (17/19 347)                            | 8.8 (169/19 248)        | 90.0        | 83.5-94.4        |
|                                           | ≥80y         | 3.7y        | 1.2 (6/5059)                               | 11.0 (54/4920)          | 89.1        | 74.6-96.2        |
| <b>ZOE-50/70<sup>63</sup></b>             | <b>≥70y</b>  | <b>3.8y</b> | <b>0.8 (25/30 726)</b>                     | <b>9.3 (284/30 415)</b> | <b>91.3</b> | <b>86.8-94.5</b> |
|                                           | 70-79y       | 3.8y        | 0.8 (19/24 411)                            | 8.9 (216/24 263)        | 91.3        | 86.0-94.9        |
|                                           | ≥80y         | 3.8y        | 1.0 (6/6315)                               | 11.1 (68/6152)          | 91.4        | 80.2-97.0        |
| <b>ZOE-LTFU, Zoster-049<sup>120</sup></b> | <b>≥50 y</b> | <b>7.1y</b> | <b>0.8 (59/72 745)</b>                     | <b>8.9 (651/72 745)</b> | <b>90.9</b> | <b>88.2-93.2</b> |

HZ: Herpes Zoster, RZV: recombinant zoster vaccine, n: number of HZ cases, PY: person-years, CI: confidence interval, LTFU: long-term follow-up.

**Table 27 – Number needed to vaccinate (NNV) for HZ and PHN in immunocompetent individuals ≥50y (modified vaccinated cohort)**

| Study                          | Patients | FU   | % RZV (n/N)     | % Placebo (n/N)  | ARR | 95%CI   | NNV          | 95% CI             |
|--------------------------------|----------|------|-----------------|------------------|-----|---------|--------------|--------------------|
| <b>HZ</b>                      |          |      |                 |                  |     |         |              |                    |
| <b>ZOE-50<sup>31</sup></b>     | ≥50y     | 3.2y | 0.1 (6/7344)    | 2.8 (210/7415)   | 2.7 | 2.4-3.1 | <b>36.4</b>  | <b>31.9-42.2</b>   |
|                                | 50-59y   | 3.2y | 0.1 (3/3492)    | 2.5 (87/3525)    | 2.4 | 1.9-2.9 | <b>42.0</b>  | <b>34.4-53.7</b>   |
|                                | 60-69y   | 3.2y | 0.1 (2/2141)    | 3.5 (75/2166)    | 3.4 | 1.9-2.9 | <b>29.7</b>  | <b>24.1-38.6</b>   |
|                                | ≥70y     | 3.2y | 0.1 (1/1711)    | 2.8 (48/1724)    | 2.7 | 1.9-3.5 | <b>36.7</b>  | <b>28.5-51.5</b>   |
| <b>ZOE-50/70<sup>63</sup></b>  | ≥70y     | 3.8y | 0.3 (25/8250)   | 3.3 (284/8346)   | 3.1 | 2.7-3.5 | <b>32.3</b>  | <b>28.5-37.1</b>   |
|                                | 70-79y   | 3.8y | 0.3 (19/6468)   | 3.3 (216/6554)   | 3.0 | 2.5-3.4 | <b>33.3</b>  | <b>28.9-39.2</b>   |
|                                | ≥80y     | 3.8y | 0.3 (6/1782)    | 3.8 (68/1795)    | 3.5 | 2.5-4.4 | <b>28.9</b>  | <b>22.8-39.5</b>   |
| <b>ZOE- LTFU<sup>120</sup></b> | ≥50y     | 7.1y | 0.4 (59/13 881) | 4.7 (651/13 881) | 4.3 | 3.9-4.6 | <b>23.4</b>  | <b>21.6-25.7</b>   |
| <b>PHN</b>                     |          |      |                 |                  |     |         |              |                    |
| <b>ZOE-50/70<sup>63</sup></b>  | ≥50y     | 3.8y | 0.03 (4/13 881) | 0.3 (46/14 035)  | 0.3 | 0.2-0.4 | <b>334.5</b> | <b>251.5-499.4</b> |
|                                | ≥70y     | 3.8y | 0.05 (4/8250)   | 0.4 (36/8346)    | 0.4 | 0.2-0.5 | <b>261.2</b> | <b>188.2-426.5</b> |

ARR: absolute risk reduction; CI: confidence interval; LTFU: long-term follow-up; n: number of HZ cases; N: number of participants; NNV: number needed to vaccinate.

**Table 28 – Vaccine efficacy (2 doses) reported in the ZOE-LTFU study**

| Follow-up     | Shingrix Efficacy (95% CI) |
|---------------|----------------------------|
| <b>Year 1</b> | 97.7 (93.1-99.5)           |
| <b>Year 2</b> | 92.7 (86.2-96.6)           |
| <b>Year 3</b> | 92.4 (85.0-96.6)           |
| <b>Year 4</b> | 89.8 (80.3-95.2)           |
| <b>Year 6</b> | 84.9% (70.4-93.1)          |
| <b>Year 7</b> | 85.3% (71.3-93.3)          |
| <b>Year 8</b> | 84.1% (64.4-94.0)          |

Source: Boutry et al. (2021)<sup>120</sup>

#### 4.3.2 Prevention of Post Herpetic Neuralgia (PHN)

We report high quality of evidence of the use of RZV (statistically superior) for the outcomes PHN in immunocompetent adults, although the included RCTs were all funded by industry (GSK) and a publication bias cannot be fully excluded (Table 37). In the pooled modified vaccinated cohort that included all participants of the ZOE-50 and ZOE-70 studies, the incidence of postherpetic neuralgia was 0.1 per 1000 person-years in the vaccination group and 1.2 per 1000 person-years in the placebo group, resulting in an estimated vaccine efficacy of 88.8% (95%CI: 68.7-97.1;  $p<0.001$ ) among adults 70 years of age or older and 91.2% (95%CI: 75.9-97.7;  $p<0.001$ ) among adults 50 years of age or older (Table 29).<sup>63</sup> Postherpetic neuralgia did not develop in any vaccine recipient younger than 70 years of age. The incidence of postherpetic neuralgia among vaccine recipients with breakthrough herpes zoster did not differ significantly from that among placebo recipients (12.5% and 9.6%, respectively;  $p=0.54$ ). Thus, the protection against PHN appeared to be driven by the lower incidence of HZ. The NNV for prevention of PHN over 3.8 years was 334.5 (95%CI: 251.5-



499.4) for individuals  $\geq 50$  years and 261.2 (95%CI: 188.2-426.5) for individuals  $\geq 70$  years. Prevention of PHN was not yet reported in the currently available publication from the follow-up study of ZOE-50/70 (ZOE-LTFU).<sup>120</sup>

**Table 29 – Vaccine efficacy against PHN (modified vaccinated cohort) ZOE-50/70 pooled<sup>63</sup>**

| Patients      | FU   | Incidence rate of PHN per 1000 person-years |                    | Efficacy % | 95%CI        |
|---------------|------|---------------------------------------------|--------------------|------------|--------------|
|               |      | RZV (n/PY)                                  | Placebo (n/PY)     |            |              |
| $\geq 50y$    | 3.8y | 0.1<br>(4/53 172)                           | 0.9<br>(46/53 545) | 91.2       | 75.9-97.7    |
| <b>50-59y</b> | 3.8y | 0.0<br>(0/13 790)                           | 0.6<br>(8/13 929)  | 100.0      | 40.8-100.0   |
| <b>60-69y</b> | 3.8y | 0.0 (0/8621)                                | 0.2 (2/8674)       | 100.0      | -442.9-100.0 |
| $\geq 70y$    | 3.8y | 0.1<br>(4/30 760)                           | 1.2<br>(36/30 942) | 88.8       | 68.7-97.1    |
| <b>70-79y</b> | 3.8y | 0.1<br>(2/24 439)                           | 1.2<br>(29/24 660) | 93.0       | 72.4-99.2    |
| $\geq 80y$    | 3.8y | 0.3 (2/6322)                                | 1.1 (7/6282)       | 71.2       | -51.6-97.1   |

CI: confidence interval, FU: follow-up, HZ: Herpes Zoster, RZV: recombinant zoster vaccine, n: number of HZ cases, PY: person-years.

In another study based on data from the ZOE-50 trial and data of individuals  $\geq 70$  years from ZOE-50 and ZOE-70 trials combined (referred to as pooled ZOE-70 data), Curran et al. evaluated the effect of vaccination on burden of illness and burden of interference with activities of daily living (ADL) of herpes zoster.<sup>123</sup> Patients with a suspected case of HZ were asked to fill in the Zoster Brief Pain Inventory (ZBPI) (section 3.9 Quality of Life) daily for 28 days after start of the rash and weekly afterwards until either the patients was pain free for four weeks or 90 days had passed after rash onset. Day 0 is defined as the first day of HZ rash. The ZBPI severity of illness score was calculated as the area under the curve (0-182d) of the ZBPI 'worst pain' score (Likert type scales- 0-10, with 10 signifying the worst imaginable pain).

A score of 0 was given to patients without confirmed HZ. After aggregation of the severity of illness scores over all patients in a group and dividing by the total follow-up in years, the resulting burden of illness score reflected incidence of HZ, and severity and duration of HZ pain. The ZBPI severity of interference score was calculated similarly as the area under the curve (0-182d) of the ZBPI ADL score (the degree to which the HZ pain interferes with seven ADL, rated on Likert-type scales 0-10 with 0 signifying 'does not interfere' and 10 'completely interferes'; a summary ADL score is calculated by averaging the scores for the seven activities). A score of 0 was given to patients without confirmed HZ. The burden of interference score was calculated as the ZBPI severity of interference score for all patients in a group divided by the total follow-up in years and reflected incidence of HZ, and duration and degree to which the HZ pain interferes with ADL. Quality of life was assessed by the EuroQol-5 Dimension (EQ-5D) and by the Short Form Survey (SF-36). Participants were asked to fill in both questionnaires before vaccination dose 1. Patients without an HZ episode were asked to fill in the questionnaires again at 14, 26 and 38 months, whilst patients with suspected HZ did this at the first visit for the suspected HZ and weekly together with the ZBPI. Analysis included only HZ cases confirmed by polymerase chain reaction or by the adjudication committee.

The vaccine efficacy, defined as 1 minus the relative reduction in the burden of illness score in the RZV group compared with the score in the placebo group, was estimated to be greater than 90% both in the ZOE-50 and the pooled ZOE-70 populations. Although vaccine efficacy against burden of illness was lower in patients of 80 years or older (82.2%, 95%CI: 77.2-87.2) compared to the 70-79 years age category (95.1%, 95%CI: 92.5-97.7) in the pooled ZOE-70 analysis, the absolute reduction in burden of illness score was higher in these patients ( $\pm 1.6$ ) compared to patients 50-69 years ( $\pm 1.0$ ). The authors provide us with no information whether this difference is statistically significant. Patients with breakthrough HZ infection after vaccination had a lower maximal individual ZBPI worst-pain score in the pooled ZOE-70 analysis ( $p=0.0032$ ) and a lower maximal individual ZBPI average-pain in ZOE-50 analysis ( $p=0.049$ ) and pooled ZOE-70 analysis ( $p=0.043$ ). On day 0 utility losses were the highest and difference between RZV and placebo was greatest (up to 0.14 in ZOE-50, not significantly different). Utility losses and differences decreased over time. A negative



impact on QoL remained until the end of week 4. Due to limited number of HZ cases in the RZV group, there was no significant difference in the duration of significant pain between the RZV and placebo groups.<sup>123</sup>

#### 4.3.3 Prevention of other complications and hospitalisations

Low quality of evidence was identified for the use of RZV for the outcomes herpes zoster ophthalmicus (HZO) and hospitalisation in immunocompetent adults, due to very serious imprecision. The use of RZV in immunocompetent adults was not found to be statistically superior than the use of placebo for the outcomes HZO and hospitalisations (Table 37).

The incidence of HZ-associated complications other than PHN was analysed in the pooled dataset of all individuals of 50 years or older (N=27 916 participants or 106 755 person-years in the modified vaccinated cohort).<sup>79</sup> Complications included HZ vasculitis, disseminated HZ, ophthalmic, neurologic, or visceral disease, and stroke if they were associated with a confirmed HZ case. Incidence rate was low in both groups (0.0 per 1000 person-year in the vaccinated group (only 1 case), and 0.4 per 1000 person-years in the placebo group). Only one HZ-related complication, ophthalmic disease, was observed among the 32 RZV recipients (3.1%) with confirmed HZ. At least one HZ-related complication other than PHN was reported in 16 out of 477 (3.4%) placebo recipients with a confirmed HZ episode. The most frequently reported complication in the placebo group was ophthalmic disease (seven participants, 1.5%), followed by disseminated disease (six participants, 1.2%), neurologic disease (three participants, 0.6%), and one case of vasculitis presumed to be due to HZ (0.2%). One participant had both ophthalmic and neurologic (meningitis) disease. Most HZ-related complications occurred in participants ≥70 years (13/17; 76.5%). No cases of HZ-associated visceral disease or stroke were reported neither in the RZV group nor in the placebo group. RZV reduced

the risk of HZ-related complications other than PHN by 93.7% (95%CI: 59.5-99.9; p= 0.0003) in participants ≥50 years and by 91.6% (95%CI: 43.3-99.8; p= 0.0035) in participants ≥70 years. When PHN and other complications were considered together, the vaccine efficacy was 91.3% (95%CI: 78.5-97.3; p< 0.0001) in participants ≥50 years and 88.6% (95%CI: 71.2-96.5; p< 0.0001) in those ≥70 years. There were too few hospitalisations for carrying out a meaningful assessment (5 in the placebo group).<sup>79</sup>

#### 4.3.4 Adverse events

We found high quality of evidence for the use of RZV for the outcomes serious adverse events (SAE), potential immune-mediated diseases (pIMD) and death. There was no statistical difference between patients vaccinated with RZV and placebo regarding these outcomes (Table 23 in Appendix 2.4).

Solicited and unsolicited adverse events (AE), serious adverse events and potential immune-mediated diseases were evaluated in ZOE-50, ZOE-70 and in pooled data from both trials.<sup>31, 63, 125</sup>

Solicited adverse events (local and systemic reactions) were collected in a reactogenicity subgroup<sup>a</sup> consisting of 8926 participants (58%) of the ZOE-50 study and 1010 (7.3%) participants of the ZOE-70 study during 7 days after each vaccination (Table 30). Local reactions (pain, swelling and redness) were more frequently present after RZV (81.5% in ZOE-50 and 74.1% in ZOE-70) compared to placebo (11.9% in ZOE-50 and 9.9% in ZOE-70). Most reactions were mild or moderate. In ZOE-50 and ZOE-70 respectively 9.5% and 8.5% of vaccine recipients reported grade 3 (severe) local reactions.<sup>31, 63</sup> Median duration of local reactions was up to 3 days.<sup>125</sup> Systemic reactions (myalgia, fatigue, fever<sup>b</sup>, shivering, headache, gastrointestinal symptoms) presented also more frequently after RZV (66.1% in ZOE-50 and 53.0% in ZOE-70) compared to placebo (29.5% in ZOE-50 and

<sup>a</sup> Reactogenicity subgroup: in ZOE-50: all participants who were 70 years or older and randomly selected participants in two other age groups (50-59 years and 60 to 69 years); in ZOE-70: a randomly selected subgroup of age stratified participants.

<sup>b</sup> Fever: (≥ 37.5 °C oral/axillary/tympanic).



25.1% in ZOE-70). In ZOE-50 and ZOE-70 respectively only 11.4% and 6.0% of reactions were graded severe.<sup>31, 63</sup> The median duration of symptoms was up to 2 days.<sup>125</sup> Since reactions were more frequent in ZOE-50 compared to ZOE-70, we might conclude (local or systemic) reactions increase with lowering age. This was confirmed in the ZOE-70 data where (any local or systemic) reaction was more frequent in the age group 70-79 years, compared to ≥80 years (and in ZOE-50 from unpublished GSK

assessment report for Shingrix). However, this was not the case for grade 3 (severe)<sup>a</sup> local or systemic reactions.

It should be noted that the second dose compliance in ZOE-50 and ZOE-70 was about 95%, so generally very high, and similar for RZV and placebo recipients, despite high frequency of reactogenicity after vaccine.<sup>31, 63</sup>

**Table 30 – Reactogenicity in immunocompetent individuals ≥50 years**

| Study                 | RZV       |                  | Placebo   |                  | RZV                        |                  | Placebo  |               |
|-----------------------|-----------|------------------|-----------|------------------|----------------------------|------------------|----------|---------------|
|                       | n/N       | % (95%CI)        | n/N       | % (95%CI)        | n/N                        | % (95%CI)        | n/N      | % (95%CI)     |
| Any local reaction    |           |                  |           |                  | Local reactions grade 3    |                  |          |               |
| ZOE-50 <sup>31</sup>  | 3571/4382 | 81.5 (80.3-82.6) | 522/4377  | 11.9 (11.0-12.9) | 417/4382                   | 9.5 (8.7-10.4)   | 16/4377  | 0.4 (0.2-0.6) |
| ZOE-70 <sup>63</sup>  | 374/505   | 74.1 (70.0-77.8) | 50/505    | 9.9 (7.4-12.8)   | 43/505                     | 8.5 (6.2-11.3)   | 1/505    | 0.2 (0.0-1.1) |
| Any systemic reaction |           |                  |           |                  | Systemic reactions grade 3 |                  |          |               |
| ZOE-50 <sup>31</sup>  | 2894/4375 | 66.1 (64.7-67.6) | 1293/4378 | 29.5 (28.2-30.9) | 498/4375                   | 11.4 (10.5-12.4) | 106/4378 | 2.4 (2.0-2.9) |
| ZOE-70 <sup>63</sup>  | 267/504   | 53.0 (48.5-57.4) | 127/505   | 25.1 (21.4-29.2) | 30/504                     | 6.0 (4.1-8.4)    | 10/505   | 2.0 (1.0-3.6) |

CI: confidence interval, n: number of events, N: number of participants in reactogenicity sub-cohort, RZV: recombinant zoster vaccine.

Information on incidence of SAE, fatal AE and pIMD from ZOE-50 and ZOE-70 can be found in Table 31.<sup>31, 63, 125</sup> A follow-up up to 4.4 years was documented by Lopez-Fouqued et al., mentioning the same number of patients pooled from ZOE-50 and ZOE-70 as was reported by Cunningham et al., so we can assume no patients were lost to follow-up.<sup>125, 156</sup> The incidence of SAEs was balanced between RZV and placebo, but higher in ZOE-70 (16.6% and 17.5%) compared to ZOE-50 (9.0% and 8.9%).<sup>31, 63, 125</sup>

Pooled data analysis confirmed these findings in different age groups (6.2% and 6.1% in 50-69 years and 12.7% and 13.3% in 70 years and older), in females (8.8% and 8.9%), in males (11.9% and 12.5%) and in different races. SAEs considered causally related to vaccination were reported by 15 individuals in each group (0.1%). Pneumonia and atrial fibrillation were the SAEs that were most frequently reported. The number of fatal AEs and occurrence of pIMD (new onset and possible exacerbations) was similar

<sup>a</sup> Grade 3 solicited AEs were defined as preventing normal activity (for headache, fatigue, gastrointestinal symptoms, myalgia, shivering and pain),

having a surface diameter >100 mm (for injection site redness and swelling) and having a body temperature higher than 39.0°C (for fever).<sup>63</sup>



between RZV and placebo recipients. Fatal AEs occurred in 4.3% of the RZV recipients and 4.6% of the pooled placebo recipients, whereas pIMDs occurred in 1.2% of the RZV and 1.4% of the placebo recipients during the entire study.<sup>125</sup>

Safety was also evaluated in different subgroups by post-hoc analysis on the pooled data from ZOE-50 and ZOE-70, including patients with at least one selected medical conditions at enrolment, with at least one pIMD at enrolment or within different frailty categories.<sup>122, 124, 126</sup> No differences were found in occurrence of SAEs and fatal AEs between the vaccine and placebo groups for each of the subgroups, and no difference in occurrence of pIMD for each of the pre-existing medical conditions or for different frailty categories.

**Table 31 – Serious adverse events, fatal adverse events and potential immune-mediated diseases in immunocompetent individuals ≥50 years**

| Study                                 | Serious adverse events |                     |             |                     | Fatal adverse events |                  |            |                  | pIMD       |                  |           |                  |
|---------------------------------------|------------------------|---------------------|-------------|---------------------|----------------------|------------------|------------|------------------|------------|------------------|-----------|------------------|
|                                       | RZV                    |                     | Placebo     |                     | RZV                  |                  | Placebo    |                  | RZV        |                  | Placebo   |                  |
|                                       | n/N                    | % (95%CI)           | n/N         | % (95%CI)           | n/N                  | % (95%CI)        | n/N        | % (95%CI)        | n/N        | % (95%CI)        | n/N       | % (95%CI)        |
| <b>ZOE-50<sup>31</sup></b>            | 689/7698               | 9.0<br>(8.3-9.6)    | 686/7713    | 8.9<br>(8.3-9.6)    | 167/7698             | 2.2<br>(1.9-2.5) | 174/7713   | 2.3<br>(1.9-2.6) | 78/7698    | 1.0<br>(0.8-1.3) | 97/7713   | 1.3<br>(1.0-1.5) |
| <b>ZOE-70<sup>63</sup></b>            | 1153/6950              | 16.6<br>(15.7-17.5) | 1214/6950   | 17.5<br>(16.6-18.4) | 426/6950             | 6.1<br>(5.6-6.7) | 459/6950   | 6.6<br>(6.0-7.2) | 92/6950    | 1.3<br>(1.1-1.6) | 97/6950   | 1.4<br>(1.1-1.7) |
| <b>ZOE-50/70 pooled<sup>125</sup></b> | 1482/14 645            | 10.1<br>(9.6-10.6)  | 1525/14 660 | 10.4<br>(9.9-10.9)  | 634/14 645           | 4.3<br>(4.0-4.7) | 680/14 660 | 4.6<br>(4.3-5.0) | 179/14 645 | 1.2<br>(1.1-1.4) | 202/14660 | 1.4<br>(1.2-1.6) |

CI: confidence interval, n: number of events, N: number of participants, pIMD: potential immune-mediated diseases, RZV: recombinant zoster vaccine.

#### 4.3.5 Immunogenicity

This section on immunogenicity was no part of the systematic review performed on efficacy and safety of RZV. The results of the immunogenicity in ZOE50 & ZOE 70 were published by Cunningham et al.<sup>27</sup> For the assessment of humoral immune responses a random subset of 3293 ZOE-50 and ZOE-70 participants from all 18 countries was selected.<sup>27</sup> Serum anti-gE antibody concentrations were measured using a GSK in-house enzyme-linked immunosorbent assay (ELISA). The humoral response threshold was defined as a ≥4-fold increase in the anti-gE antibody concentration as compared to the pre-vaccination concentration (for initially seropositive participants) or as compared to the anti-gE antibody cut-off

value for seropositivity (97 milli-International Units (mIU)/mL, for initially seronegative participants). One month after the second vaccination 97.8% of vaccine recipients met the criterion for humoral response, compared to 2.0% of placebo recipients. A humoral response above the response threshold decreased over time, such that 77.1% of RZV recipients remained above the humoral response threshold at 36 months post dose 2, with no difference across age groups.



For the assessment of gE-specific cell-mediated immunity (CMI) responses, 466 ZOE-50 participants from the Czech Republic, Japan, and the United States were randomly selected. gE-specific CMI responses were measured using a GSK in-house assay that assessed the frequency of CD4 T cells expressing 2 or more of the following activation markers (hereafter termed CD4<sup>2+</sup>): IFN- $\gamma$ , interleukin-2 (IL-2), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), and CD40 ligand (CD40L).<sup>27</sup>

The frequency of gE-specific CD4<sup>2+</sup> T cells was calculated as the difference between the frequency of CD4<sup>2+</sup> T cells stimulated in vitro with gE peptides and those stimulated with culture medium alone. The CMI-response threshold was defined as a  $\geq 2$ -fold increase in the frequency of CD4<sup>2+</sup> T cells, as compared to pre-vaccination frequencies (for participants with pre-vaccination CD4<sup>2+</sup> T-cell frequencies above the cut-off of 320 positive cells per 10<sup>6</sup> CD4 T cells counted) or a  $\geq 2$ -fold increase above the cut-off (for participants with pre-vaccination frequencies below the cut-off).<sup>27</sup> At 1 month post dose 2, the CMI response rate was 93.3% in RZV recipients. The proportion of RZV recipients above the CMI-response threshold decreased to 57.2% at 12 months post dose 2 and then remained stable through month 36. At 12, 24, and 36 months following vaccination, a slightly lower proportion of RZV recipients  $\geq 70$  years of age remained above the CMI-response threshold compared to RZV recipients  $< 70$  years. Overall, in RZV recipients  $\geq 50$  years of age, the median frequency of gE-specific CD4<sup>2+</sup> T cells increased 24.6-fold over baseline at 1 month post dose 2. Median CD4<sup>2+</sup> T-cell fold increases declined by 12 months post dose 2, but remained stable thereafter, and at 36 months post dose 2 were 7.9-fold over baseline and remained above 5.6-fold in all age groups.

In brief, the results showed that 77.1% of RZV recipients remained above the humoral response threshold at 36 months post dose 2. Whatsoever, gE-specific CMI is believed to be the main mechanistic driver of protection against HZ. Thirty-six months following dose 2, CD4<sup>2+</sup> T-cell responses were still above the CMI response threshold in half of the RZV vaccines. The observed kinetics of the humoral and cellular immune responses to RZV were comparable, and were characterized by peak levels at 1 month after dose 2 and a rapid decrease followed by a slow decline or a plateau from 1 year post-vaccination onward to maintain a long-term response level.

Regarding immunogenicity, more long-term data were available. A total of 129 subjects  $\geq 60$  years from a phase II, open-label, single group trial<sup>157</sup> were followed up to 6 years after vaccination. The gE-specific cell-mediated immune response 6 years after vaccination was still 3.8 times higher than the pre-vaccination values (7.3 times for anti-gE antibody concentration).<sup>158</sup> 70 of those individuals were followed up to 10 years post-vaccination.<sup>159</sup> The median gE-specific CD4<sup>2+</sup> response was 3.5 times higher (57 patients) than the pre-vaccination value and the anti-gE antibody concentration was 6.0 times higher (61 patients) than the pre-vaccination value. No comparison was made between individuals 60-69 years and  $\geq 70$  years. However, at year 9 the immunogenicity response was similar between these age groups.<sup>160</sup> The little impact of age on peak or persistence of immunity suggests that the vaccine can overcome effects of immunosenescence. Statistical models predicted that both humoral and cellular immune responses would remain above pre-vaccination levels at 20 years.<sup>159</sup> Despite these conclusions, 62 participants of the study received at least one additional RZV dose. This resulted in a strong anamnestic humoral and CMI response after one dose and no further increase after a second dose.<sup>159</sup>

However, inferring clinical efficacy beyond 7 years based on the results of immunogenicity studies should be done with caution. First, the immune response was measured on a limited number of individuals (129 at year 6 and 70 at year 9, out of the 166 subjects enrolled to receive RZV in the initial trial<sup>157, 158</sup>) and potential selection bias was not discussed by the authors. Second, the gE-specific cell-mediated immune response at 6 and 9 years was less than half the response observed at month 36. Third, the threshold required for protection against HZ is presently unknown.<sup>24</sup> In absence of an established immunological threshold of protection against HZ, a correlation between immune response level and clinical protection should not be inferred.<sup>158</sup>



#### 4.3.6 Discussion

The 2 pivotal RCTs ZOE-50 and ZOE-70 reported a very good vaccine efficacy against HZ and HZ-associated complications like PHN and burden of illness in older, immunocompetent individuals and all their studied subgroups. The vaccine efficacy was still 85.3% (95%CI: 71.3-93.3) in the 7<sup>th</sup> year after vaccination. It should be noted that the NNV was high for PHN (334.5 (95%CI: 251.5-499.4) for individuals  $\geq 50$  years and 261.2 (95%CI: 188.2-426.5) for individuals  $\geq 70$  years), over 3.8 years. Solicited reports of local and systemic reactions within 7 days after injection were more frequent after vaccination compared to placebo. A high incidence of local and systemic reactions has been previously linked to the addition of an adjuvant system, which enhances vaccine immune response and efficacy.<sup>157</sup> No excess of SAEs, fatal SAEs and pIMDs were reported in the vaccine recipients of ZOE-50 and ZOE-70 over a period of 4.4 years. Of note, the monitoring of participants in both trials is still on-going until 10 years post-vaccination (Zoster-049). Despite high rates of local and general symptoms after vaccination, second dose compliance was high and overall comparable between study groups (RZV and placebo). In the absence of head-to-head trials comparing RZV with ZVL, two network meta-analyses (NMA) reported a significantly higher vaccine efficacy against herpes zoster of RZV (intramuscular (IM)) compared to ZVL (subcutaneous (sc)). The first network meta-analysis by Tricco et al. had a Bayesian approach and reported a higher vaccine efficacy of RZV compared to ZVL (85%; 95%CI: 31-98).<sup>5</sup> The second network-analysis by McGirr et al., using a frequentist approach and stratification by age, showed a difference in vaccine efficacy of 41 percentage points (95%CI: 34-47) in the age group  $\geq 60$  years and 54 percentage points (95%CI: 43-65) in the age group  $\geq 70$  years.<sup>161</sup> Additionally a significantly higher vaccine efficacy against PHN was found after RZV compared to ZVL. The difference in vaccine efficacy was respectively 23 percentage points (95%CI: 9-37) in individuals  $\geq 60$  years

and 22 percentage points (95%CI: 7-37) in individuals  $\geq 70$  years.<sup>161</sup> Tricco et al. reported inconclusive results against PHN, due to lacking data.<sup>5</sup>

Regarding reactogenicity a significantly higher risk of local injection-site reactions was identified in both NMA after RZV compared to ZVL (RR 1.79; 95%CI: 1.05-2.34). McGirr et al. additionally included different formulations of ZVL and found similar results,<sup>a</sup> except for intradermal full-dose ZVL and an alternative dose of ZVL. A significant higher risk for systemic reactions was only identified in the NMA by McGirr et al. for RZV compared to most formulations of ZVL, except intradermal ZVL. No differences were reported between the different vaccines regarding serious adverse events, withdrawals related to adverse events and death.<sup>5, 161</sup>

#### 4.4 Clinical efficacy and safety in immunocompromised patients

Clinical efficacy and/or immunogenicity and safety of RZV in immunocompromised patients was studied in 5 RCTs. They were rated low risk of bias (Table 19 in Appendix 2.3). The five patient groups studied were patients who underwent a haematopoietic stem cell transplantation (ZOE-HSCT)<sup>129-131</sup> and patients with haematological malignancies (HM),<sup>132</sup> renal transplants,<sup>133</sup> solid malignancies<sup>134</sup> and HIV patients.<sup>162</sup> The trials were judged high quality (Table 37). The publication by Stadtmayer et al. was excluded from our report because of non-relevant subgroup analysis (underlying disease). Most data were from phase 3 studies, but we also included data from a phase 1/2 RCT in HIV patients.<sup>162</sup> Additional data were found in an overview of six trials in immunocompromised populations, including the above mentioned patients groups and data from the phase 1/2 trials in patients with HSCT.<sup>135</sup> An overview of the publications with information on study design and patient characteristics can be found in Table 32. Excluded publications can be found in Table 18 in Appendix 2.2.

<sup>a</sup> Refrigerated ZVL sc RR 2.93 (95%CI: 1.24-6.93); ZVL sc RR 2.24 (95%CI: 1.28-3.93); ZVL IM RR 4.23 (95%CI: 1.80-9.98).



Table 32 – Publications on RCTs in immunocompromised patients

| Reference                                                    | Study design                                                                                                                       | Patient characteristics                                                                                                                                                                                                                                      | Mean FU         | Number of patients    | Mean age (±SD)   | Gender and race (%)                        | Intervention                          | Outcome                                                                                                            |
|--------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|-----------------------|------------------|--------------------------------------------|---------------------------------------|--------------------------------------------------------------------------------------------------------------------|
| <b>ZOE-HSCT Zoster-002</b> <sup>129</sup>                    | Phase 3 RCT<br>1:1 randomized<br>Placebo controlled<br>Triple blinded<br>Multicentre<br>28 countries                               | <b>Inclusion criteria:</b><br>≥ 18 years<br>Autologous HSCT in previous 50-70d<br><b>Exclusion criteria:</b><br>Anti-VZV prophylaxis >6m<br>History of vaccination varicella or HZ (1y)<br>HIV infection                                                     | 21m<br>(median) | 1846 TVC<br>1721 mTVC | 54.9y            | Male 63.0<br>Female 37.0<br><br>White 78.4 | RZV IM versus placebo<br>(0 and 1-2m) | Efficacy against HZ<br>Secondary outcome:<br>Efficacy against HZ-related complications<br>Immunogenicity<br>Safety |
| <b>ZOE-HSCT Zoster-002</b> <sup>130</sup>                    | Funded by industry                                                                                                                 |                                                                                                                                                                                                                                                              |                 |                       |                  |                                            |                                       | QoL<br>ZBPI burden of illness<br>ZBPI burden of interference                                                       |
| <b>Zoster-028 Solid Tumour</b> <sup>134</sup>                | Phase 2/3 RCT<br>1:1 randomized<br>Placebo controlled<br>Triple blinded<br>Multicentre<br>6 countries<br><br>Funded by industry    | <b>Inclusion criteria:</b><br>≥ 18 years<br>≥ 1 solid tumour and receiving or scheduled to receive cytotoxic or immunosuppressive chemotherapy<br><b>Exclusion criteria:</b><br>History of vaccination varicella or HZ<br>History of HZ<br>Systemic GC > 14d | 12m             | 232 TVC               | 57.8y<br>(±11.2) | Female 60.0<br>Male 40.0<br>White 83.7     | RZV IM versus placebo<br>(0 and 1-2m) | Immunogenicity<br>Safety                                                                                           |
| <b>Zoster-039 Haematological Malignancies</b> <sup>132</sup> | Phase 3 RCT<br>1:1 randomized<br>Placebo controlled<br>Triple blinded<br>Multicentre<br>Multicentre (77)<br><br>Funded by industry | <b>Inclusion criteria:</b><br>≥18 years<br>Haematological malignancy<br>Life expectancy ≥12m<br>Receiving or just finished immuno-suppressive cancer treatment<br>Antiviral prophylaxis was permitted<br><b>Exclusion criteria:</b>                          | 12.1m           | 562 TVC               | 57.3y<br>(±15.2) | Male 59.4<br>Female 40.6<br><br>White 71.1 | RZV IM versus placebo<br>(0 and 1-2m) | Immunogenicity<br>Safety                                                                                           |



|                                 |                    |                                                                                                                                                                                      |     |         |       |             |              |                |
|---------------------------------|--------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|---------|-------|-------------|--------------|----------------|
|                                 |                    | CLL on oral chemotherapy only<br>HSCT (within 50d prior first dose<br>or scheduled during study)<br>History of vaccination varicella or<br>HZ<br>History of HZ (1y)<br>HIV infection |     |         |       |             |              |                |
| <b>Zoster-041</b>               | Phase 3 RCT        | <b>Inclusion criteria:</b>                                                                                                                                                           | 12m | 264 TVC | 52.4y | Female 29.9 | RZV IM       | Immunogenicity |
| <b>Renal</b>                    | 1:1 randomized     | ≥ 18 years                                                                                                                                                                           |     |         | ±12.6 | Male 70.1   | versus       | Safety         |
| <b>Transplant<sup>133</sup></b> | Placebo-controlled | 4-18m post Renal transplant                                                                                                                                                          |     |         |       | White 70.1  | placebo      |                |
|                                 | Triple blinded     | ABO compatible allograft                                                                                                                                                             |     |         |       |             | (0 and 1-2m) |                |
|                                 | Multicentre        | Daily immunosuppressive                                                                                                                                                              |     |         |       |             |              |                |
|                                 | 9 countries        | therapy                                                                                                                                                                              |     |         |       |             |              |                |
|                                 |                    | Stable renal function                                                                                                                                                                |     |         |       |             |              |                |
|                                 | Funded by industry | Free of rejection 3m before<br>vaccination                                                                                                                                           |     |         |       |             |              |                |
|                                 |                    | <b>Exclusion criteria:</b>                                                                                                                                                           |     |         |       |             |              |                |
|                                 |                    | PKD with high incidence of                                                                                                                                                           |     |         |       |             |              |                |
|                                 |                    | recurrence or previous allograft                                                                                                                                                     |     |         |       |             |              |                |
|                                 |                    | loss due to recurrence                                                                                                                                                               |     |         |       |             |              |                |
|                                 |                    | multiple organ transplant                                                                                                                                                            |     |         |       |             |              |                |
|                                 |                    | systemic AI or pIMD,                                                                                                                                                                 |     |         |       |             |              |                |
|                                 |                    | received HZ/varicella vaccination                                                                                                                                                    |     |         |       |             |              |                |
|                                 |                    | 12 m prior first dose                                                                                                                                                                |     |         |       |             |              |                |
|                                 |                    | clinical history of HZ or varicella                                                                                                                                                  |     |         |       |             |              |                |

AI: auto-immune, CLL: chronic lymphocytic leukemia, HIV: human immunodeficiency virus, HSCT: haematopoietic stem cell transplantation, HZ: herpes zoster, IM: intramuscular, pIMD: potential immune-mediated disease, PKD: polycystic kidney disease, RZV: recombinant zoster vaccine, TVC: total vaccinated cohort, ZBPI: Zoster Brief Pain Inventory.



#### 4.4.1 Haematopoietic Stem Cell Transplantation

A phase 3, observer-blind, randomized (1:1), placebo-controlled, multicentre study (Zoster-002 or ZOE-HSCT) investigated RZV vaccine efficacy, immunogenicity and safety in patients who underwent an autologous hematopoietic stem cell transplantation.<sup>129</sup>

The total vaccinated cohort consisted of 1846 participants and the modified vaccinated cohort consisted of 1721 participants. Participants were predominantly male (63%) and 75% were at least 50 years old.

During the 21-months follow-up, confirmed HZ episodes occurred in 49 RZV recipients (30.0 per 1000 person-years) and 135 placebo recipients (94.3 per 1000 person-years) of the modified vaccinated cohort, resulting in a vaccine efficacy against HZ of 68.2% (95%CI: 55.6-77.5). The NNV was 9.8 (95%CI: 7.6-13.6). Vaccine efficacy against PHN was estimated to be 89.3% (95%CI: 22.5-99.8;  $p=0.02$ ; 0.5 versus 4.9 cases per 1000 person-years), resulting in a NNV=115 (95%CI: 65-506) and against herpes zoster-related complications excluding PHN 77.8% (95%CI: 19.0-95.9,  $p=0.02$ ; 1.6 vs 7.1 cases per 1000 person-years). Estimation of vaccine efficacy against hospitalisation was 84.7% (95%CI: 32.1-96.6;  $p=0.01$ ; 1.1 vs 7.1 cases per 1000 person-years), resulting in a NNV=95. The ZOE-HSCT trial reported a lower vaccine efficacy compared to immunocompetent individuals, probably reflecting a weaker immune response due to underlying disease and/or medication. Due to low number of cases and resulting imprecision of estimates, it is difficult to draw firm conclusions comparing vaccine efficacy against PHN and other complications between patients from ZOE-HSCT and the ZOE-50/70.

Humoral vaccine response rate in RZV recipients was 67% after 1 month and 45% after 2 years. Anti-gE geometric mean concentration (GMC) remained above baseline 24 months after the second dose (Table 33). The CMI response in RZV recipients was 93% after 1 month and 71% after 2 years (Table 34). The CD4<sup>2+</sup> T-cell frequency remained higher than pre-vaccination after 2 years. Humoral and cellular immune responses did not increase post-vaccination in placebo recipients.

We found high quality of evidence that there is no statistical difference between patients vaccinated with RZV and placebo in the occurrence of serious adverse events, pIMD and death. Similar to results in ZOE-50/70, injection site reactions and systemic reactions (Table 22 in Appendix 2.4) were more frequent in RZV recipients compared to placebo recipients, but mostly mild and moderate, and of short duration (up to 3 days for local and 2 days for systemic reactions). In contrast to immunocompetent individuals, the participants from ZOE-HSCT showed more systemic reactions and the difference in frequency of systemic reactions between placebo and vaccine recipients was smaller. The occurrence of SAEs, fatal AEs and pIMDs was balanced between RZV and placebo group, but participants from ZOE-HSCT had more SAEs and fatal AEs compared to immunocompetent individuals, linked to their underlying disease and/or treatment (Table 22 in Appendix 2.4).<sup>129</sup>

#### 4.4.2 Haematological Malignancies

A phase 3, observer-blind, randomized (1:1), placebo-controlled study (Zoster-039) investigated safety and immunogenicity of RZV in adults with haematological malignancies who had completed or were due to undergo immunosuppressive cancer therapy. The study population included 562 participants in the total vaccinated cohort and 516 in the modified vaccinated cohort. Participants in both RZV and placebo group were predominantly male (59%) and mean age was 57.3 years.<sup>132</sup>

Two doses of vaccine induced strong humoral and cell-mediated immune responses that persisted above baseline 1 year after vaccination in this patient group. The humoral vaccine response was present in 119 (80.4%, 95%CI: 73.1–86.5) of 148 participants at month 2 and the adjusted anti-gE antibody GMC ratio (RZV over placebo) was 29.75 (95%CI: 21.09-41.96;  $p<0.0001$ ) in all patients, excluding those with non-Hodgkin B-cell lymphoma and chronic lymphocytic leukemia, Table 33. After 13 months follow-up, 22 (66.7%, 95%CI: 48.2–82.0) of 33 participants in the vaccine group had a cell-mediated immunity vaccine response, compared with two (6.5%, 95%CI: 0.8–21.4) of 31 participants in the placebo group, Table 34.



Post-hoc analysis of vaccine efficacy against HZ was estimated at 87.2% (95%CI: 44.3-98.6). This result must be interpreted with caution since the study was not powered to measure efficacy (small number of cases and short follow-up). The incidence of HZ in RZV recipients was 8.5 per 1000 person-years and in placebo recipients 66.2 per 1000 person-years in the modified vaccination cohort. The safety profile was similar to the one observed in ZOE-HSCT (Table 22 in Appendix 2.4).

#### 4.4.3 Renal transplant

A phase 3, observer-blind, randomized (1:1), placebo-controlled, multicentre study (Zoster-041) evaluated immunogenicity and safety of RZV in 264 adult renal transplant patients (132 RZV and 132 placebo) who were 4 to 18 months posttransplant and receiving chronic immunosuppressive therapy. Except for one patient in the RZV group, all patients received both doses. The population was mainly male (70%) and mean age was 52.4 years.<sup>133</sup>

Humoral and cell-mediated immune responses were higher in vaccine recipients than placebo recipients at all time points post-vaccination and persisted above baseline 12 months after the second dose. Humoral vaccine response rate (VRR) in the RZV group was 80.2% (95%CI: 71.9-86.9) and the adjusted anti-gE antibody GMC ratio (RZV over Placebo) was 14.00 (95%CI: 10.90-17.99;  $p < 0.0001$ ) at month 2 (1 month after dose 1), Table 33. Cell-mediated immunity was assessed on a restricted number of patients, but the numbers are not presented in the paper. The proportion of subjects in the RZV group with a vaccine associated cell-mediated immune response following induction with gE was 71.4% (95%CI: 51.3-86.8) at 1 month post dose 2 and around 60% at 12-month post dose 2, Table 34.<sup>133</sup>

Safety profile was similar to ZOE-50/70 except for higher number of SAEs and more systemic reactions in placebo recipients, probably linked to underlying disease (Table 22 in Appendix 2.4). There seem to be generally less fatalities than in the immunocompetent individuals, but this can be explained by a shorter follow-up. Overall reported events are consistent with underlying disease or medication. Suspected HZ cases were reported in 3 participants receiving RZV (one after first dose) and 7 participants receiving

placebo (one after first dose). The study was not powered to estimate vaccine efficacy.<sup>133</sup>

#### 4.4.4 Solid tumour

A phase 2/3 observer-blind, placebo-controlled, randomized (1:1), multicentre study (Zoster-028) evaluated the immunogenicity and safety of RZV in 323 adults (117 RZV and 115 placebo) with solid tumours receiving or scheduled to receive cytotoxic or immunosuppressive chemotherapy. The vaccination phase was completed by 102 (87%) RZV and 107 (93%) placebo recipients.

RZV was found to be immunogenic in this patient group during 1 year of follow-up. Humoral immune response (anti-gE antibody concentration) was measured in all patients and was higher in RZV than placebo recipients at all different time points, Table 33. Cell-mediated immunity (CMI) was evaluated in 58 patients. At month 2, the CMI vaccine response rate was only 50.0% (95%CI: 28.2-71.8) in RZV recipients. The CMI vaccine response rate was around 20% at 13 months (Table 34). The safety profile was similar to the one observed in ZOE-HSCT (Table 22 in Appendix 2.4). Suspected HZ cases were reported 3 participants of the total vaccinated cohort: one participant of the RZV group (before second dose) and two participants of the placebo group (after second dose). The study was not powered to estimate vaccine efficacy.<sup>134</sup>



#### 4.4.5 HIV-infected patients

A phase 1/2, randomized, placebo-controlled study assessed immunogenicity and safety of the RZV vaccine in 123 HIV-infected individuals (108 receiving ART, 15 ART-naïve) who received 3 vaccine doses.<sup>162</sup> The proportion of subjects in the RZV group with a vaccine associated cell-mediated immune response following induction with gE increased across doses (40.0% 1 month after dose 1, 85.7% after dose 2, and 90.0% after dose 3) (Table 34). The cell-mediated immune responses

persisted over time, with 64.5% of the subjects in the RZV group still having CMI levels above the response threshold 1 year after the last dose. This study showed that RZV elicits strong gE-specific cellular and humoral immune responses in HIV infected individuals after 2 doses and that the third dose added little if any immunological advantage. The reactogenicity was similar to the one observed in immunocompetent individuals. No vaccine related SAEs, deaths or new onset of immune-mediated inflammatory diseases were reported.<sup>162</sup>

**Table 33 – Humoral immunity vaccine response rate against RZV<sup>a</sup>**

| Reference                           | Study                          | Humoral immunity VRR - 1m |                  | Humoral immunity VRR - 12m |                  | End of study        |                  |
|-------------------------------------|--------------------------------|---------------------------|------------------|----------------------------|------------------|---------------------|------------------|
|                                     |                                | n/N                       | % (95%CI)        | n/N                        | % (95%CI)        | n/N (total FU time) | % (95%CI)        |
| <b>Cunningham 2018<sup>27</sup></b> | ZOE-50/70                      | 1423/1455                 | 97.8 (96.9-98.5) | x/1384                     | ±85 (83-87)      | 986/1279 (36m)      | 77.1 (74.7-79.4) |
| <b>Bastidas 2019<sup>129</sup></b>  | ZOE-HSCT                       | 55/82                     | 67.1 (55.8-77.1) | 21/52                      | 40.4 (27.0-54.9) | 17/38 (24m)         | 44.7 (28.6-61.7) |
| <b>Dagnew 2019<sup>132</sup></b>    | Zoster-039                     | x/217                     | ±65 (58-71)      | 86/165                     | 52.1 (44.2-59.9) | 86/165 (12m)        | 52.1 (44.2-59.9) |
|                                     | Haematological malignancies    | 127/184*                  | 69.0 (61.8-75.6) |                            |                  |                     |                  |
|                                     |                                | 119/148**                 | 80.4 (73.1-86.5) |                            |                  |                     |                  |
| <b>Vink 2019<sup>133</sup></b>      | Zoster-041<br>Renal transplant | 97/121                    | 80.2 (71.9-86.9) | x/111                      | ±65 (55-74)      | x/111 (12m)         | ±65 (55-74)      |
| <b>Vink 2019<sup>134</sup></b>      | Zoster-028<br>Solid tumour     | 74/87                     | 85.1 (75.8-91.8) | 36/68                      | 52.9 (40.5-65.2) | 36/68 (12m)         | 52.9 (40.5-65.2) |
| <b>Berkowitz 2015<sup>162</sup></b> | Zoster-015<br>HIV              | 52/53                     | 98.1 (89.9-100)  | ND                         |                  | 44/48 (18m)         | 91.7 (80-97.7)   |

*HIV: human immunodeficiency virus; HSCT: hematopoietic stem cell transplantation; m: month; n number of participants with positive vaccine response rate, N: total number of participants, ND: no data; VRR: vaccine response rate; x: missing data point; \* all patients except non-Hodgkin B-cell lymphoma; \*\* all patients except non-Hodgkin B-cell lymphoma and chronic lymphocytic leukemia.*

<sup>a</sup> Humoral immunity vaccine response rate is defined as the percentage of participants with a postvaccination anti-glycoprotein E antibody concentration of at least 4-fold the cut-off (for participants with concentrations initially below the cut-off) or at least 4-fold the pre vaccination concentration (for participants with concentrations initially above the cut-off).

**Table 34 – Glycoprotein E specific cell-mediated immunity vaccination response rate against RZV**

| Reference                           | Study                                     | CMI VRR - 1m |                  | CMI VRR - 12m |                  | End of study |                  |
|-------------------------------------|-------------------------------------------|--------------|------------------|---------------|------------------|--------------|------------------|
|                                     |                                           | n/N          | % (95%CI)        | n/N           | % (95%CI)        | n/N          | % (95%CI)        |
| <b>Cunningham 2018<sup>27</sup></b> | ZOE-50/70                                 | 139/149      | 93.3 (88.0-96.7) | 87/152        | 57.2 (49.0-65.2) | x/133 (36m)  | ±55% (46-64)     |
| <b>Bastidas 2019<sup>129</sup></b>  | ZOE-HSCT                                  | 39/42        | 92.9 (80.5-98.5) | 19/27         | 70.4 (49.8-86.3) | 17/24 (24m)  | 70.8 (48.9-87.4) |
| <b>Dagnew 2019<sup>132</sup></b>    | Zoster-039<br>Haematological malignancies | 36/43        | 83.7 (69.3-93.2) | 22/33         | 66.7 (48.2-82.0) | 22/33(12m)   | 66.7 (48.2-82.0) |
| <b>Vink 2019<sup>133</sup></b>      | Zoster-041<br>Renal transplant            | 20/28        | 71.4 (51.3-81.8) | 17/30         | 56.7 (37.4-74.5) | 17/30 (12m)  | 56.7 (37.4-74.5) |
| <b>Vink 2019<sup>134</sup></b>      | Zoster-028<br>Solid tumour                | 11/22        | 50.0 (28.2-71.8) | 4/17          | 23.5 (6.8-49.9)  | 4/17 (12m)   | 23.5 (6.8-49.9)  |
| <b>Berkowitz 2015<sup>162</sup></b> | Zoster-015<br>HIV                         | 24/28        | 85.7 (67.3-96.0) | 20/31         | 64.5 (45.4-80.8) | 20/31 (12m)  | 64.5 (45.4-80.8) |

*HIV: human immunodeficiency virus, HSCT: hematopoietic stem cell transplantation, m: month, n: number of participants with positive vaccine response rate, N: total number of participants, ND: no data, VRR: vaccine response rate, x: missing data point.*

#### 4.4.6 Discussion

RZV was found effective to reduce substantially the risk of HZ (618 less per 10 000 person-years; high quality evidence) and of hospitalisation (77 less per 10 000 person-years; moderate quality evidence) in immunocompromised patients with HSCT and haematological malignancies (Table 34) and a high effect size (absolute risk reduction) was identified. The quality of evidence was downgraded because of serious imprecision due to low number of participants.

The ZOE-HSCT trial (in patients who underwent haematopoietic stem cell transplantation) reported a lower vaccine efficacy compared to immunocompetent individuals, probably reflecting a weaker immune response due to underlying disease and/or medication. However, the NNV was much smaller given the higher incidence of HZ in this population.

The smaller studies on patients with haematological malignancies, renal transplant and solid tumours treated with chemotherapy were not powered to measure vaccine efficacy on clinical outcomes.



Humoral immunity vaccine response rate against RZV 1 month after the second dose in the studied immunocompromised patients varied between 65% and 98%. The highest response rates were reported in HIV patients and were comparable to the response rates found in immunocompetent individuals (ZOE-50/70 study). The lowest rates were found in patients after HSCT and in patients with haematological malignancies. After 12 months the response rate decreased in all patient groups and varied between 40% and 92%, with lowest rates in patients after HSCT, and highest rates in HIV patients, even higher than immunocompetent individuals, where response rates were about 85% after 1 year and 77% after 3 years. Glycoprotein E specific cell-mediated immunity vaccine response rate 1 month after the second dose varied between 71% and 93%. Again, the highest response rate, comparable with response rate of immunocompetent individuals was found in HIV patients. The threshold of 60% was not reached in patients with solid tumours with CMI VRR of 50% after 1 month and 23.5% after 12 months. It remains uncertain why these results are worse than in other immunocompromised patients. After 12 months, the CMI VRR varied in the other immunocompromised patient groups between 57% and 70%. This response was comparable to immunocompetent individuals (ZOE-50/70) who reached a response rate of 57% after 12 months, which remained stable the two following years.

In patients with haematopoietic stem cell transplantation, with haematological malignancies and solid tumours, local reactions were more frequent in RZV compared to placebo recipients, similarly to immunocompetent individuals, but general reactions, SAEs and fatalities occurred more often also in placebo recipients, and the difference in frequency of systemic reactions between vaccine and placebo was less pronounced, which can probably be explained by their underlying diseases, known complications and concomitant therapies. Reactogenicity seems to increase with lowering age. Incidence of local injections-site pain and

systemic reactions (except gastro-intestinal) symptoms was higher in the patients between 18 and 49 years compared to the patients  $\geq 50$  years.<sup>135</sup> The safety profile of renal transplant patients is more similar to immunocompetent patients. Overall, there was no safety risk linked to vaccination in the immunocompromised patients studied, as reflected by similar percentages of SAEs, fatal AEs and pIMD in vaccine and placebo group. However, the studies were not powered to detect such outcomes. Despite high rates of local and general symptoms after vaccination, second dose compliance remained above 90%. In RCTs with immunocompromised patients the drop-out after first dose was between 5.3% and 10.2%, except for the RCT in renal transplant patients with a very high second dose compliance of 99.2% in RZV recipients and 100% in placebo recipients.<sup>124, 129, 133, 134</sup> Because the same immunosuppressive and immunomodulating treatments are used in other underlying diseases, such as autoimmune diseases and inflammatory disorders, current available data could be informative for the broad population of adults who is at increased risk of herpes zoster.<sup>135</sup> Of note, only VZV-specific T-cell-mediated immunity (CMI) is considered important in preventing the reactivation of latent VZV and preventing the propagation of the reactivated virus.<sup>24</sup> Antibodies to VZV does not play a significant role. Thus, the use of VZV antibody response as a proxy for zoster vaccine efficacy is inappropriate.<sup>24</sup> As regards CMI, the threshold required for protection is unknown.

#### 4.5 Real world vaccine effectiveness and safety

Study and patient characteristics of included observational studies can be found in Table 35. Data from observational studies report vaccine effectiveness that is largely in line with those from RCTs (Table 36). The observational studies were rated low or moderate risk of bias (Table 20 in Appendix 2.3).


**Table 35 – Study and patient characteristics from observational studies**

| Reference                              | Study Design number of patients and follow-up                                                                                                                                                         | Inclusion criteria                                                                                                                                                                                                                                                                                                       | Patient characteristics<br>Mean age<br>Gender and race                                                                                                   | Intervention                                           | Outcome                                                                |
|----------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------|------------------------------------------------------------------------|
| <b>Sun, Kim 2021<sup>140</sup></b>     | Retrospective observational cohort<br>OptumLabs Data Warehouse (OLDW) <sup>a</sup><br><br>Median FU: 7m (IQR 2.8-13m)<br><br>4 769 819 adults<br>7 300 036 PY<br>V2: 173 745 (3.6%)                   | <b>Inclusion criteria:</b><br>≥50y, ≥ 365d of continuous enrolment in OLDW<br>diagnosis of HZ before vaccination is accepted<br><br><b>Exclusion criteria:</b><br>Immunocompromised patients, HZ diagnosis between 2 doses and up to 30d after second dose, single dose RZV, second dose <30d or >210d after first dose  | 65.0y (IQR 56-73)<br>U: 64.0y (IQR 56-73)<br>V2 72.0y (IQR 69-77)<br><br>Female: 52.2%<br>U: 52%<br>V2: 58%<br><br>White: 65.4%<br>U: 65.1%<br>V2: 74.3% | Vaccinated with two doses (V2) versus Unvaccinated     | Effectiveness against HZ<br><br>First diagnosis of HZ during follow-up |
| <b>Sun, Jackson 2021<sup>139</sup></b> | Retrospective observational cohort<br>Electronic health records from Kaiser Permanente Hawaii (KPH) 1/2018-31/12/2019<br><br>Median FU: 730d<br><br>78 356 adults<br>128 010 PY<br>V2: 11 864 (15.1%) | <b>Inclusion criteria:</b><br>≥50y, ≥365d continuous enrolment<br><br><b>Exclusion criteria:</b><br>Immunocompromised patients, first dose RZV prior to index data, HZ diagnosis 1 year prior to index date, between 2 doses or up to 30d after second dose, single dose RZV, second dose <30d or >210d after first dose | 61y (IQR 54-69)<br>U: 59y (IQR 53-65)<br>V2: 74y (IQR 70-80)<br><br>Female: 51.5%<br><br>White: 30.0%<br>Asian: 37.1%                                    | Vaccinated with two doses (V2) versus Unvaccinated (U) | Effectiveness against HZ<br><br>First diagnosis of HZ during follow-up |
| <b>Izurieta 2021<sup>136</sup></b>     | Prospective observational cohort<br>USA, Medicare<br><br>Median FU 2.9 m (V1)                                                                                                                         | <b>Inclusion criteria:</b><br>≥65y, Medicare part D ≥ 12 months continuously, Medicare part A and B and not C at least 15 months, with and without                                                                                                                                                                       | U: 74.6±6.7y<br>V1: 73.8±5.9y<br>V2: 74.0±5.9y                                                                                                           | Vaccinated (V) with one dose (V1)                      | Effectiveness against HZ                                               |

<sup>a</sup> OLDW Healthcare claims administrative database: commercial insurance, Medicare advantage or Medicare part D.



|                                  |                                                                                                                                                                                                                                      |                                                                                                                                                                                                                     |                                                                                                                                                                 |                                                                                                         |                          |
|----------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------|--------------------------|
|                                  | 7.1m (V2)                                                                                                                                                                                                                            | influenza vaccine , including an autoimmune population <sup>a</sup>                                                                                                                                                 | Female: 58.9%                                                                                                                                                   | with two doses (V2)                                                                                     |                          |
|                                  | 15 589 546 adults                                                                                                                                                                                                                    | <b>Exclusion criteria:</b>                                                                                                                                                                                          | White: 88.0%                                                                                                                                                    | versus                                                                                                  |                          |
|                                  | V1: 1 498 275 (9.6%)                                                                                                                                                                                                                 | Not in nursing home, skilled nursing facility or hospice; no ZH diagnosis 1 year prior                                                                                                                              |                                                                                                                                                                 | Unvaccinated (U)                                                                                        |                          |
|                                  | V2: 1 006 446 (6.5%)                                                                                                                                                                                                                 |                                                                                                                                                                                                                     |                                                                                                                                                                 |                                                                                                         |                          |
| <b>Kochar 2021<sup>138</sup></b> | Retrospective observational cohort<br>USA, Explorys Health record database<br>10/2017-4/2020<br><br>Median FU: >9m<br><br><b>IBD</b><br>95 070 adults<br>V2: 1180 (1.2%)<br><b>Control</b><br>18 564 400 adults<br>V2: 14 180 (0.1%) | <b>Inclusion criteria:</b><br>≥50y, with and without Inflammatory bowel disease (IBD)<br><br><b>Exclusion criteria:</b><br>Control: no IBD or other autoimmune disease (RA, SLE, psoriasis, ankylosing spondylitis) | IBD<br>U : ≥65y: 49%<br>V2 ≥65y: 56%<br>Female: 50.5%<br>White: 72%<br><br>Control<br>U ≥65y: 49%<br>V ≥65y: 48%<br>Female: 53%<br>White U: 51%<br>White V2:81% | Vaccinated with two doses (V2)<br>versus<br>Unvaccinated (U)<br>and<br>IBD population<br>versus Control | Effectiveness against HZ |
| <b>Khan 2021<sup>144</sup></b>   | Retrospective cohort study<br>US National Veterans Affairs Healthcare system<br>3/1/2018-31/10/2020<br><br>Mean FU: 1.13y<br><br>33 000 adults<br>V2: 50-60y: 764 (10.9 %)<br>V2: ≥:60y: 2390 (20.5%)                                | <b>Inclusion criteria:</b><br>≥50y, diagnosis inflammatory bowel disease (IBD)<br><br><b>Exclusion criteria:</b><br>Control: no IBD or other autoimmune disease (RA, SLE, psoriasis, ankylosing spondylitis)        | 50-60y<br>U: 55.21y±3.15<br>V1: 55.88y±3.01<br>V2: 56.14y±2.9<br>Female: 17%<br>White: 71%<br><br>≥60y<br>U: 73.53±8.35<br>V1: 72.47±7.32                       | Vaccinated with one dose (V1)<br>with two doses (V2)<br>versus<br>Unvaccinated                          | Effectiveness against HZ |

<sup>a</sup> Beneficiaries were classified into an autoimmune population if they consulted for any of the selected autoimmune conditions (Graves' disease, Hashimoto's thyroiditis, Multiple sclerosis, myasthenia gravis Polymyalgia rheumatica, Primary biliary cirrhosis, Psoriasis, Psoriatic arthritis, Rheumatoid arthritis, Scleroderma, Sjögren's syndrome, Systemic lupus erythematosus, Ulcerative colitis (UC) and Vitiligo), included at least twice in the 1 year prior to the index date.



|                                |                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                         |                                                                            |                                                      |                               |
|--------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------|------------------------------------------------------|-------------------------------|
|                                |                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                         | V2: 72.95±7.04<br>Female: 4.5%<br>White: 89%                               |                                                      |                               |
| <b>Lu 2021<sup>142</sup></b>   | Retrospective observational cohort<br>USA; OptumLabs Data warehouse (OLDW)<br>1/1/2018-31/12/2019<br><br>Median FU: 2y<br><br>4 842 579 adults<br>7 491 570 PY<br>V2: 177 289 (3.7 %)                                                                                       | <b>Inclusion criteria:</b><br>≥50y, ≥ 365d of continuous enrolment in OLDW<br><br><b>Exclusion criteria:</b><br>Immunocompromised                                                                                                                                                                                                                       | U: 64y (IQR 56-73)<br>V2: 72y (IQR 69-77)<br><br>Majority female and white | Vaccinated with 2 doses (V2) versus Unvaccinated (U) | Effectiveness against HZO     |
| <b>Goud 2021<sup>143</sup></b> | Retrospective observational cohort<br>USA, Medicare<br>1/10/2017-31/3/2019<br><br>Median FU: 42d<br><br>RZV 849 397 adults<br>ZVL 1 871 099 adults<br>self-controlled case series (SCCS)<br>USA, Medicare<br>1/10/2017-31/3/2019<br>Median FU: 189d<br>RZV 2 113 758 adults | <b>Inclusion criteria</b><br>≥ 65 years, Medicare beneficiaries<br><br><b>Exclusion criteria:</b><br>Long term daily therapy, admitted to nursing home, skilled nursing facility or in hospice at any point during study period, Historical GBS diagnosis within 6 months prior to vaccination, RZV administration inconsistent with recommended dosing | RZV 74.8y<br>ZVL 74.3y<br>RZV Female 58%<br>ZVL Female 60%                 | RZV versus ZVL                                       | Guillain-Barré syndrome (GBS) |
|                                |                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                         | Not specified                                                              | RZV<br>Self-controlled                               |                               |

d: days, GBS: Guillain-Barré syndrome, HZ: herpes zoster, HZO: herpes zoster ophthalmicus, IBS: inflammatory bowel disease, IQR: interquartile range, m: months, KPH: Kaiser Permanente Hawaii, OLDW: OptumLabs Data Warehouse, PY: person-years, RA: rheumatoid arthritis, RZV: recombinant zoster vaccine, SLE: systemic lupus erythematosus, U: unvaccinated, USA: united states of America, V: vaccinated, V1: vaccinated with one dose, V2: vaccinated with 2 doses, y: years, ZVL: zoster vaccine live.



Six observational studies reported on vaccine effectiveness, either against HZ,<sup>136-140</sup> against HZO<sup>136, 140, 142</sup> and/or against PHN.<sup>136</sup> Moderate quality of evidence was found for these outcomes (herpes zoster, PHN and ophthalmic zoster) in the mentioned observational studies, where we upgraded the level of evidence because strong association between RZV and outcomes.

Two retrospective cohorts of immunocompetent individuals  $\geq 50$  years showed effectiveness results lower than those from the ZOE-50 over a shorter follow-up duration (Table 36), with an adjusted vaccine effectiveness against HZ of 85.5% (95%CI: 83.5-87.3) and 83.5% (95%CI: 74.9-89.2) after 7 and 24 months, respectively.<sup>139, 140</sup> Vaccine effectiveness was estimated to be similar in different subgroups like age and sex (Table 21 in Appendix 2.4).<sup>136, 139, 140</sup>

Lower vaccine effectiveness was also reported in a mixed cohort of immunocompetent and immunocompromised (around 4%) patients aged 65 years and older over a 7 months follow-up (VE: 70.1%; 95%CI: 68.6-71.5).<sup>136</sup> In that cohort, the reported vaccine effectiveness after 2 doses for immunocompromised individuals (VE: 64.1%; 95%CI: 57.2-69.8) was lower compared to immunocompetent individuals (VE: 70.5%; 95%CI: 69.0-72.0). Patients with auto-immune disease had vaccine effectiveness against HZ (VE: 68%; 95%CI: 57.2-69.8) similar to immunocompetent individuals from the same study.<sup>136</sup> Effectiveness was significantly higher after the second dose (VE: 70.1%; 95%CI: 68.6-71.5), compared to the first dose (VE: 56.9%; 95%CI: 56.5-60.7), showing the importance of a two dose schedule. Two-dose vaccine effectiveness against postherpetic neuralgia was 76.0% (95%CI: 68.4-81.8).

Two studies reported vaccine efficacy among patients with inflammatory bowel disease (IBD). A study by Khan et al. showed high vaccine efficacy in adults 50-60y with IBD (100%), but VE was only 60.6% (95%CI: 20.5-80.5) in adults  $\geq 60$ y. However, the results were very unprecise because of a small cohort of patients and low number of events.<sup>137</sup> A retrospective cohort study by Kochhar et al. was performed using Explorys, an electronic health record database and included patients with IBD  $\geq 50$  years and a general population of patients  $\geq 50$  years without IBD, HIV, malignancy, auto-immune disease or a history of chemotherapy and some specific other mediations (calcineurin inhibitors, corticosteroids, cyclophosphamide, azathioprine for non IBD related indications and mycophenolate). In this study 95 880 participants with IBD were included of which 1340 received RZV (1.4%). After two vaccinations with RZV, patients had a significantly lower probability of developing HZ compared to no vaccinations (OR 0.36; 95%CI: 0.23-0.56). RZV recipients with IBD were still 3 times more likely (OR 3.06; 95%CI: 1.87-5.02) compared to vaccinated general population to develop HZ during the study period. Unvaccinated IBD patients were 6 times more likely (OR 6.21; 95%CI: 6.02-6.41) to develop HZ compared to unvaccinated general population.<sup>138</sup>

Lower vaccine effectiveness in observational studies could have two origins: measurement error in the form of outcome misclassification (e.g. less accuracy in claim data vs. PCR-confirmed diagnosis) and population composition differences between studies (e.g. general population may be more frail than participants in RCT).<sup>136</sup>


**Table 36 – Observational studies: vaccine effectiveness against HZ**

| Study                             | Patients               | FU         | Incidence rate of HZ per 1000 PY (n/PY) |                           | Unadjusted<br>VE (95%CI) | Adjusted<br>VE (95%CI) |
|-----------------------------------|------------------------|------------|-----------------------------------------|---------------------------|--------------------------|------------------------|
|                                   |                        |            | RZV- 2 doses                            | Unvaccinated              |                          |                        |
| <b>OLDW USA<sup>140</sup></b>     | ≥50 years, not IC      | 7 m        | 2.6 (298/115 125)                       | 8.9 (64 169/7 184 911)    | 68.3 (64.4-71.7)         | 85.5 (83.5-87.3)       |
| <b>KPH USA<sup>139</sup></b>      | ≥50 years, not IC      | 730 d (2y) | 3.3 (27/8291)                           | 10.6 (1 273/119 719)      | 73.8 (60.7-82.5)         | 83.5 (74.9-89.2)       |
| <b>Medicare USA<sup>136</sup></b> | ≥65 years              | 7.1 m      | 3.1 (1880/609 000)                      | 10.3 (258 293/25 026 026) | 70.1 (68.6-71.5)         |                        |
|                                   | Not immuno-compromised |            | 3.0 (1737/584 000)                      | 10.0 (239 789/23 947 000) | 70.5 (69.0-72.0)         |                        |
|                                   | Immuno-compromised     |            | 5.9 (143/24 000)                        | 17.2 (18 504/1 079 000)   | 64.1 (57.2-69.8)         |                        |
|                                   | Auto-immune disease    |            | 4.4 (167/38 000)                        | 14.9 (20 640/1 387 000)   | 68.0 (62.3-72.8)         |                        |
| <b>VAHS USA<sup>137</sup></b>     | IBD 50-60y             | 1.13y      | 0 (0/716)                               | 3.9 (69/17 561)           | 100                      |                        |
|                                   | IBD ≥60y               |            | 1.8 (8/4445)                            | 4.6 (268/58 663)          | 60.6 (20.5-80.5)         |                        |

FU: follow-up, KPH: Kaiser Permanente Hawaii, n: number of cases, OLDW: OptumLabs Data Warehouse, PY: person-years, VAHS Veterans Affairs Healthcare system; OLDW adjusted for age, sex, race, region, prior zoster vaccine live, antiviral use, healthcare utilization and Charlson comorbidity index and KPH adjusted for sex, race, ethnicity, vaccination with ZVL in the one year before the index date, age, healthcare utilisation, Deyo comorbidity index and systematic antiviral use.

Real-world data on prevention against herpes zoster ophthalmicus (HZO) in three observational studies showed estimated vaccine effectiveness of 93.3% (95%CI: 48.7-99.1),<sup>139</sup> 89.1% (95%CI: 82.9-93.0)<sup>142</sup> and 66.8% (95%CI: 60.7-72.0).<sup>136</sup> The first two studies were on not-immunocompromised patients, whereas the third was performed in a mixed population of immunocompetent and immunocompromised patients, which might partly explain a lower efficacy. Vaccine effectiveness against PHN was 76.0% (95%CI: 68.4–81.8) in a USA cohort study among individuals >65 years.

Two observational studies reported on the risk of Guillain-Barré syndrome (GBS) following RZV vaccine in community-dwelling (not admitted to a nursing home, skilled nursing facility or in hospice during the study) Medicare beneficiaries of 65 years or older.<sup>143</sup> Participants undergoing long-

term dialysis or with a GBS diagnosis within 6 months before vaccination were excluded. Participants were predominantly female (about 60%) and their mean age was about 74.5 years. The first study consisted of a cohort analysis comparing 849 397 beneficiaries who received RZV and 1 817 009 beneficiaries who received ZVL. The relative risk (RR) for GBS in the RZV group compared to the ZVL group was 2.34 (95%CI: 1.01-5.41; p=0.047). The second study consisted of a self-controlled case series analysis of eligible RZV vaccinees with an incident GBS outcome during 6 months follow-up. An increased risk for GBS syndrome was observed in the risk window (42 days after vaccination) compared to the control window (RR: 2.84; 95%CI: 1.53-5.27; p=0.001), resulting in an attributable risk of 3 per million RZV doses (95%CI: 0.62-5.64).<sup>143</sup>



Three reports on post-licensure safety surveillance in the United States were recently published.<sup>149-151</sup> No unexpected patterns were detected in reports of adverse events or serious adverse events. Findings from early monitoring of RZV were consistent with the safety profile observed in prelicensure clinical trials. Reporting rates for Shingrix were 136 per 100 000 doses distributed (all adverse event reports) and 4.0 per 100 000 (serious adverse event reports) at the timing when about 3.2 million doses were administered. No adverse events reported for Shingrix were disproportionate to adverse event reporting patterns observed for other vaccines in the Vaccine adverse event reporting system (VAERS) database.<sup>149</sup> At the timing when about 9.3 million doses were administered, 15 638 spontaneous AE reports involving RZV were received of which 4.7% were serious including 9 deaths. Reports were linked to reactogenicity in 49.8 per 100 000 doses, to pIMD in 1.1 per 100 000 doses, to HZO in 0.3 per 100 000 doses and to PHN in 0.2 per 100 000 doses. For Guillain-Barré syndrome, the observed versus expected (O/E) analyses of reports, assessed as Brighton Collaboration level 1 to 4 of diagnostic certainty and considering a risk period of 42 days following vaccination, were found to be below the expected number considering several scenarios of underreporting and background incidence rates.<sup>151</sup> The report by Pirrotta et al. only concentrated at vesicular and bullous cutaneous eruptions occurring following vaccinations.<sup>150</sup> According to the EMA risk management plan for Shingrix, additional data (preclinical, clinical study data, scientific literature, spontaneous report data in the GSK safety database and external databases such as Eudravigilance and VAERS) does not indicate there is an increased occurrence of GBS following vaccination with Shingrix. Because of the substantial limitations of the currently available data and confounding variables, the Company has concluded that the strength of evidence of the overall data currently available to the Company are insufficient to determine a causal relationship of GBS with Shingrix.

#### 4.6 Meta-analysis of results

An overview of the meta-analysed results can be found in Table 37. Following GRADE methodology, the quality of evidence was downgraded by one level in case of serious imprecision, and by 2 levels in case of very serious imprecision. The quality of evidence of observational studies was upgraded by one level when a large effect was reported. There is high quality evidence that Shingrix is highly effective in preventing HZ in immunocompetent individuals  $\geq 50$  years over a period of approximately 4 years. There are good indications that this protection is still high nearly 8 years after vaccination. Post-marketing in-population studies ( $n=3$ ) reported a lower vaccine efficacy (vaccine efficacy: 70%; 95%CI: 69-72; moderate quality evidence). There is also good quality evidence that the risk of PHN, which is considered the main complication of HZ, is drastically reduced by the vaccine. However, the absolute rate reduction is much smaller than for HZ (8 per 10 000 person-years vs. 86 per 10 000 person-years for HZ), resulting in a NNV over the first 4 years after vaccination higher than 330 in individuals  $\geq 50$  years and 260 in individuals  $\geq 70$  years (Table 27). A big size cohort study confirmed similar level of protection in individuals  $>65$  years. There is currently no data on protection against PHN over a period longer than 4 years. There is no solid data from clinical studies on protection of other complications, including hospitalisation. There is moderate quality evidence from post-marketing in-population studies that Shingrix can reduce significantly the risk of ophthalmic zoster (vaccine efficacy: 67%; 95%CI: 62-71). Here again, the absolute risk reduction is small (5 fewer cases per 10 000 person-years). Such information does not exist for hospitalisation.

There is good quality data that the vaccine is effective in reducing the risk of HZ also in immunocompromised individuals  $\geq 18$  years with haematopoietic stem cell transplantation or haematological malignancies. Although the relative reduction is smaller than in immunocompetent persons (vaccine effectiveness: 70%; 95%CI: 53-81), the number of cases prevented for a given number of vaccinations is much higher because of the higher baseline risk (618 cases per 10 000 person-years vs. 86 per 10 000 person-years in immunocompetent individuals  $\geq 50$  years). There is also some evidence that the vaccine would reduce significantly hospitalisation rate in these patients (moderate quality evidence). Vaccine efficacy in the presence of other



immunosuppressive conditions is not well known as only immunogenicity studies are available, and the threshold of cell-mediated immunity ensuring protection is unknown. However, 2 post-marketing in-population studies in immunocompromised individuals (various conditions) reported a vaccine efficacy similar to the one observed in clinical studies on the 2 above-mentioned immunosuppressive conditions. All the studies carried out in immunocompromised individuals were of short duration (maximum 2 years)

and protection on a longer period is unknown. There are indications that the vaccine would yield the same level of protection in patients with auto-immune diseases.

Based on post-marketing studies and surveillance, the vaccine safety appears high. An association with Guillain-Barré syndrome was reported in 2 studies but the attributable risk was very low.

**Table 37 – Meta-analysis of effectiveness results**

| Certainty assessment                             |              |               |              |             |         |                               | Summary of findings               |          |                         |                                     |                          |
|--------------------------------------------------|--------------|---------------|--------------|-------------|---------|-------------------------------|-----------------------------------|----------|-------------------------|-------------------------------------|--------------------------|
| Total number of person-years (studies) Follow-up | Risk of bias | Inconsistency | Indirectness | Imprecision | Remarks | Overall certainty of evidence | Number of events per person-years |          | Relative effect (95%CI) | Anticipated absolute effects        |                          |
|                                                  |              |               |              |             |         |                               | With placebo or no vaccination    | With RZV |                         | Rate with placebo or no vaccination | Rate difference with RZV |

#### HZ in immunocompetent adults ≥ 50 years

|                                   |             |             |             |             |      |              |            |           |                                  |                     |                                                                        |
|-----------------------------------|-------------|-------------|-------------|-------------|------|--------------|------------|-----------|----------------------------------|---------------------|------------------------------------------------------------------------|
| 95 041<br>(2 RCTs)<br>FU 3.2-3.7y | not serious | not serious | not serious | not serious | None | ⊕⊕⊕⊕<br>High | 433/47 339 | 29/47 702 | <b>RR 0.06</b><br>(0.02 to 0.21) | 91<br>per 10 000 PY | <b>86 fewer</b><br><b>per 10 000 PY</b><br>(from 90 fewer to 72 fewer) |
|-----------------------------------|-------------|-------------|-------------|-------------|------|--------------|------------|-----------|----------------------------------|---------------------|------------------------------------------------------------------------|

#### HZ in immunocompromised adults with haematopoietic stem cell transplantation or haematological malignancies ≥ 18 years

|                                  |             |             |             |             |      |              |          |         |                                  |                      |                                                                           |
|----------------------------------|-------------|-------------|-------------|-------------|------|--------------|----------|---------|----------------------------------|----------------------|---------------------------------------------------------------------------|
| 3581<br>(2 RCTs)<br>FU 12.1m-21m | not serious | not serious | not serious | not serious | None | ⊕⊕⊕⊕<br>High | 149/1689 | 51/1892 | <b>RR 0.30</b><br>(0.19 to 0.47) | 882<br>per 10 000 PY | <b>618 fewer</b><br><b>per 10 000 PY</b><br>(from 715 fewer to 468 fewer) |
|----------------------------------|-------------|-------------|-------------|-------------|------|--------------|----------|---------|----------------------------------|----------------------|---------------------------------------------------------------------------|



| Certainty assessment                             |              |               |              |             |         |                               | Summary of findings               |          |                         |                                     |                          |
|--------------------------------------------------|--------------|---------------|--------------|-------------|---------|-------------------------------|-----------------------------------|----------|-------------------------|-------------------------------------|--------------------------|
| Total number of person-years (studies) Follow-up | Risk of bias | Inconsistency | Indirectness | Imprecision | Remarks | Overall certainty of evidence | Number of events per person-years |          | Relative effect (95%CI) | Anticipated absolute effects        |                          |
|                                                  |              |               |              |             |         |                               | With placebo or no vaccination    | With RZV |                         | Rate with placebo or no vaccination | Rate difference with RZV |

### HZ in real world immunocompetent adults ≥ 50 years (unadjusted data)

|                                                     |             |             |             |             |              |                  |                       |              |                                  |                     |                                                                        |
|-----------------------------------------------------|-------------|-------------|-------------|-------------|--------------|------------------|-----------------------|--------------|----------------------------------|---------------------|------------------------------------------------------------------------|
| 31 959 046<br>(3 observational studies)<br>FU 7m-2y | not serious | not serious | not serious | not serious | Large effect | ⊕⊕⊕○<br>Moderate | 305 231/31 251<br>630 | 2062/707 416 | <b>RR 0.30</b><br>(0.28 to 0.31) | 98<br>per 10 000 PY | <b>68 fewer</b><br><b>per 10 000 PY</b><br>(from 70 fewer to 67 fewer) |
|-----------------------------------------------------|-------------|-------------|-------------|-------------|--------------|------------------|-----------------------|--------------|----------------------------------|---------------------|------------------------------------------------------------------------|

### HZ in real world immunocompromised adults ≥ 50 years

|                                                         |             |             |             |             |              |                  |                  |            |                                  |                      |                                                                          |
|---------------------------------------------------------|-------------|-------------|-------------|-------------|--------------|------------------|------------------|------------|----------------------------------|----------------------|--------------------------------------------------------------------------|
| 1 184 385<br>(2 observational studies)<br>FU 7.1m-1.13y | not serious | not serious | not serious | not serious | Large effect | ⊕⊕⊕○<br>Moderate | 18 841/1 155 224 | 151/29 161 | <b>RR 0.35</b><br>(0.30 to 0.41) | 163<br>per 10 000 PY | <b>106 fewer</b><br><b>per 10 000 PY</b><br>(from 114 fewer to 96 fewer) |
|---------------------------------------------------------|-------------|-------------|-------------|-------------|--------------|------------------|------------------|------------|----------------------------------|----------------------|--------------------------------------------------------------------------|

### PHN in immunocompetent adults ≥ 50 years

|                                       |             |             |             |             |      |              |           |          |                                  |                 |                                                                     |
|---------------------------------------|-------------|-------------|-------------|-------------|------|--------------|-----------|----------|----------------------------------|-----------------|---------------------------------------------------------------------|
| 106 717<br>(2 RCTs)<br>FU 3.8y (mean) | not serious | not serious | not serious | not serious | None | ⊕⊕⊕⊕<br>High | 46/53 545 | 4/53 172 | <b>RR 0.09</b><br>(0.03 to 0.24) | 9 per 10 000 PY | <b>8 fewer</b><br><b>per 10 000 PY</b><br>(from 8 fewer to 7 fewer) |
|---------------------------------------|-------------|-------------|-------------|-------------|------|--------------|-----------|----------|----------------------------------|-----------------|---------------------------------------------------------------------|



| Certainty assessment                             |              |               |              |             |         |                               | Summary of findings               |          |                         |                                     |                          |
|--------------------------------------------------|--------------|---------------|--------------|-------------|---------|-------------------------------|-----------------------------------|----------|-------------------------|-------------------------------------|--------------------------|
| Total number of person-years (studies) Follow-up | Risk of bias | Inconsistency | Indirectness | Imprecision | Remarks | Overall certainty of evidence | Number of events per person-years |          | Relative effect (95%CI) | Anticipated absolute effects        |                          |
|                                                  |              |               |              |             |         |                               | With placebo or no vaccination    | With RZV |                         | Rate with placebo or no vaccination | Rate difference with RZV |

### PHN in real world mixed population, mostly immunocompetent > 65 years

|                                                           |             |             |             |             |              |                  |                   |            |                                  |                  |                                                                     |
|-----------------------------------------------------------|-------------|-------------|-------------|-------------|--------------|------------------|-------------------|------------|----------------------------------|------------------|---------------------------------------------------------------------|
| 20 097 000<br>(1 observational study)<br>FU 7.1m (median) | not serious | not serious | not serious | not serious | Large effect | ⊕⊕⊕○<br>Moderate | 19 586/19 857 000 | 55/240 000 | <b>RR 0.24</b><br>(0.18 to 0.32) | 10 per 10 000 PY | <b>8 fewer</b><br><b>per 10 000 PY</b><br>(from 8 fewer to 7 fewer) |
|-----------------------------------------------------------|-------------|-------------|-------------|-------------|--------------|------------------|-------------------|------------|----------------------------------|------------------|---------------------------------------------------------------------|

### Ophthalmic zoster in immunocompetent adults ≥50 years

|                                        |             |             |             |              |      |             |          |          |                                  |                 |                                                                |
|----------------------------------------|-------------|-------------|-------------|--------------|------|-------------|----------|----------|----------------------------------|-----------------|----------------------------------------------------------------|
| 106 755<br>(2 RCTs)<br>FU 3.8 y (mean) | not serious | not serious | not serious | very serious | none | ⊕⊕○○<br>Low | 7/53 582 | 1/53 173 | <b>RR 0.04</b><br>(0.00 to 0.31) | 1 per 10 000 PY | <b>1 fewer</b><br><b>per 10 000 PY</b><br>(from 1 fewer to --) |
|----------------------------------------|-------------|-------------|-------------|--------------|------|-------------|----------|----------|----------------------------------|-----------------|----------------------------------------------------------------|

### Ophthalmic zoster in real world mixed population, mostly immunocompetent ≥50 years (unadjusted data)

|                                                       |             |             |             |             |              |                  |                   |             |                                  |                 |                                                                     |
|-------------------------------------------------------|-------------|-------------|-------------|-------------|--------------|------------------|-------------------|-------------|----------------------------------|-----------------|---------------------------------------------------------------------|
| 33 473 713<br>(3 observational studies)<br>FU 7.1m-2y | not serious | not serious | not serious | not serious | Large effect | ⊕⊕⊕○<br>Moderate | 25 047/32 729 792 | 188/743 921 | <b>RR 0.33</b><br>(0.29 to 0.38) | 8 per 10 000 PY | <b>5 fewer</b><br><b>per 10 000 PY</b><br>(from 5 fewer to 5 fewer) |
|-------------------------------------------------------|-------------|-------------|-------------|-------------|--------------|------------------|-------------------|-------------|----------------------------------|-----------------|---------------------------------------------------------------------|



| Certainty assessment                             |              |               |              |             |         |                               | Summary of findings               |          |                         |                                     |                          |
|--------------------------------------------------|--------------|---------------|--------------|-------------|---------|-------------------------------|-----------------------------------|----------|-------------------------|-------------------------------------|--------------------------|
| Total number of person-years (studies) Follow-up | Risk of bias | Inconsistency | Indirectness | Imprecision | Remarks | Overall certainty of evidence | Number of events per person-years |          | Relative effect (95%CI) | Anticipated absolute effects        |                          |
|                                                  |              |               |              |             |         |                               | With placebo or no vaccination    | With RZV |                         | Rate with placebo or no vaccination | Rate difference with RZV |

### Hospitalisation in immunocompetent adults ≥ 50 years

|                                          |             |             |             |              |      |             |          |          |                                  |                 |                                                                    |
|------------------------------------------|-------------|-------------|-------------|--------------|------|-------------|----------|----------|----------------------------------|-----------------|--------------------------------------------------------------------|
| 106 755<br>(2 RCTs)<br>FU 3.8y<br>(mean) | not serious | not serious | not serious | very serious | none | ⊕⊕○○<br>Low | 5/53 582 | 4/53 173 | <b>RR 0.09</b><br>(0.01 to 1.66) | 1 per 10 000 PY | <b>1 fewer</b><br><b>per 10 000 PY</b><br>(from 1 fewer to 1 more) |
|------------------------------------------|-------------|-------------|-------------|--------------|------|-------------|----------|----------|----------------------------------|-----------------|--------------------------------------------------------------------|

### Hospitalisation in immunocompromised adults with haematopoietic stem cell transplantation ≥ 18 years (follow-up: mean 21 months)

|                                     |             |             |             |         |      |                  |         |        |                                  |                  |                                                                        |
|-------------------------------------|-------------|-------------|-------------|---------|------|------------------|---------|--------|----------------------------------|------------------|------------------------------------------------------------------------|
| 4185<br>(1 RCT)<br>FU 21m<br>(mean) | not serious | not serious | not serious | serious | none | ⊕⊕⊕○<br>Moderate | 20/2068 | 4/2117 | <b>RR 0.20</b><br>(0.07 to 0.57) | 97 per 10 000 PY | <b>77 fewer</b><br><b>per 10 000 PY</b><br>(from 90 fewer to 42 fewer) |
|-------------------------------------|-------------|-------------|-------------|---------|------|------------------|---------|--------|----------------------------------|------------------|------------------------------------------------------------------------|

CI confidence interval; m months, RR: rate ratio, y years; PY: person-years.



#### 4.7 Co-administration with other vaccines

In four RCTs the co-administration of RZV with other vaccines was assessed for immunogenicity and safety, including the reduced-antigen-content diphtheria-tetanus- acellular pertussis vaccine (Tdap),<sup>148</sup> Influenza,<sup>147</sup> 13-valent pneumococcal conjugate vaccine (PCV13)<sup>146</sup> and 23-valent pneumococcal polysaccharide vaccine (PPSV23)<sup>145</sup> in adults aged 50 years or older. The RCTs were open-label, multicentre studies. Participants were randomized 1:1 either to the co-administration group (RZV first dose and other vaccine were administered at the same time) or to the control group (sequential administration of the different vaccines, RZV vaccine was administered 2 and 4 months after the other study vaccine). Humoral immune response in the co-administration group was not inferior to sequential administration in RZV and 4/5 Tdap antigens. Non-inferiority of co-administration was also demonstrated for co-administration of RZV with Influenza, PCV13 and PPSV23. Effect on CMI was not reported. The safety profile was in all studies acceptable. An ongoing study will evaluate co-administration of RZV with a vaccine against COVID-19 (mRNA-1273).<sup>163</sup>

#### 4.8 Summary of burden of disease and vaccination impact in Belgium

Main findings on burden of disease and vaccination impact in Belgium are presented in Table 38. Based on incidence results (section 3) and results on vaccine efficacy (section 4), it can be inferred that the vaccination of individuals  $\geq 50$  years would result in around 64 (95%CI: 63-66) cases of zona avoided per 10 000 person-years vaccinated, between 8 and 10 cases of PHN and less than 2 hospitalisations. This means that for 10 000 persons vaccinated today there will be in the coming years 64 cases of HZ avoided per year, e.g. 320 cases of HZ avoided over a period of 5 years. The

corresponding numbers for individuals  $\geq 60$  years will be 77 cases of zona avoided per 10 000 person-years vaccinated, between 10 and 12 cases of PHN, and between 2 and 3 hospitalisations.

Of note, these results might be slightly overestimated. First, the vaccine efficacy used to compute the number of cases avoided per 10 000 person-years vaccinated was the one reported in RCTs in immunocompetent individuals. Post-marketing in-population studies in immunocompetent individuals reported a lower vaccine efficacy than in RCTs (section 4.5). This was also the case for studies (both RCTs and in-population studies) evaluating vaccine efficacy in immunocompromised individuals (section 4.4). Second, we used the vaccine efficacy against PHN as reported in RCTs to evaluate the impact of vaccination on hospitalisation rates, whereas the validity of that extrapolation is unknown. Lastly, the validity of our impact estimates hold for the duration of follow-up in RCTs (around 7 years for HZ; around 4 years for PHN), as long-term vaccine efficacy is still unknown. On the other hand, the results might be underestimated as a proportion of immunocompromised individuals might consult primarily a medical specialist, and thus be undetected by the Sciensano network of SGPs, whereas their risk of HZ is higher than in immunocompetent persons (Table 51 for numbers of immunocompromised persons per age group). In such case, the incidence rate of HZ may be underestimated, as well as the number of cases avoided per 10 000 person-years vaccinated. It is estimated that 5% of individuals  $\geq 50$  years are immunocompromised. If we hypothesize that the risk of HZ is 5 times greater in immunocompromised than in immunocompetent ones, that would result in an incidence rate of 85.7 per 10 000 person-years, and 78 (95%CI: 75.5-79.8) cases avoided per 10 000 person-years vaccinated, if we apply the vaccine efficacy reported in RCTs in immunocompetent persons. Because of this possible overestimation and underestimation, our approximation of vaccination impact in Belgium is likely valid.



Table 38 – Burden of disease and vaccination impact in Belgium

|                                    | Age range | Incidence rate<br>per 10 000 person-years<br>(95%CI) | Source            | Cases per year | Cases avoided<br>per 10 000 person-years vaccinated<br>(95%CI) |
|------------------------------------|-----------|------------------------------------------------------|-------------------|----------------|----------------------------------------------------------------|
| <b>HZ</b>                          | All       | 39.7 (28.3-54.1)                                     | Sciensano 2006-12 | 47 682°        | -                                                              |
|                                    | ≥50 years | 70.1 (54.7-88.6)                                     | id.               | 32 669°        | 64.5 (62.6-66.2)**                                             |
|                                    | ≥60 years | 84.9 (67.8-104)                                      | id.               | 25 500°        | 76.9 (74.6-78.8)**                                             |
| <b>PHN</b>                         | ≥50 years | 10.5*                                                | -                 | 4831           | 9.6 (8.0-10.3)***                                              |
|                                    | ≥60 years | 12.7*                                                | -                 | 3829           | 11.6 (9.6-12.4)***                                             |
| <b>Hospitalisation<sup>#</sup></b> | All       | 1.0 (0.8-1.1)                                        | MCD 2019          | 1 092          | -                                                              |
|                                    | ≥50 years | 1.9 (1.8-2.1)                                        | id.               | 873            | 1.7 (1.4-1.9)***                                               |
|                                    | ≥60 years | 2.7 (2.5-2.8)                                        | id.               | 780            | 2.5 (2.0-2.6)***                                               |
| <b>Death</b>                       | All       | 0.011 (0.010-0.013)                                  | Statbel 1998-2016 | 12             | -                                                              |

° In 2022; number of cases were calculated by applying the incidence rates 2006-2012 to the Belgian population on 01/01/2022 as reported by the Belgian statistical office (whole population=11 584 008; ≥50yr=4 601 079; ≥60yr=3 015 078) by age strata (0-49, 50-59, 60-69, 70-79, 80-89, 90+) for direct standardisation. <sup>#</sup> Inpatients hospitalisations with HZ as principal diagnosis. \* Assuming 15% of HZ cases develop PHN, based on literature; this approximation might overestimate slightly the incidence in individuals ≥50 years and under-estimate it in individuals ≥60 years. \*\* Assuming a vaccine efficacy of 90.9% (95%CI: 88.2–93.2) over 7.1 years as reported in Boutry et al.<sup>120</sup> \*\*\* Assuming a vaccine efficacy of 91.2% (95%CI: 75.9-97.7) over 3.7 years as reported in Cunningham et al.<sup>63</sup>; the same vaccine efficacy was applied to calculate cases of hospitalization avoided. CI: confidence interval; HZ: Herpes Zoster; MCD: Minimum Clinical Data; PHN: post-herpetic neuralgia.



## 5 PATIENT PREFERENCES REGARDING VACCINATION AGAINST HZ

We did not formally assess patient preferences (acceptability of vaccination, willingness to pay) in Belgium. Such an assessment would have required a survey with a sample size big enough to allow good statistical power and representativeness, and was beyond the scope of the present study. Moreover, there is little ethical issues given the positive risk-benefit balance of the vaccine. We summarize here the results of studies carried out in the USA and the Netherlands.

In the US a discrete choice experiment, including 1454 individuals of 50 years and older, showed that the most influential factors to get vaccinated for herpes zoster were out-of-pocket costs and vaccine effectiveness. In this study vaccination was preferred over no vaccination. Vaccine effectiveness was considered 5 times more important than reducing the number of days with flu-like symptoms and the severity of injection-site reactions, and ten times more important than decreasing the number of doses from two to one. Location of vaccination was identified as the least important factor.<sup>164</sup> High patient co-payment was also found to be a barrier to vaccinations against herpes zoster (GSK study identifier HO-14-14319) in a retrospective analysis of administrative Medicare Part D claims data (2012-2014).<sup>165</sup>

In the Netherlands, a discrete choice experiment showed that expected vaccination rates for herpes zoster were 58.1% in individuals of 50 years and older and 67.5% in individuals of 65 years and older.<sup>166</sup> In this study herpes zoster vaccination was compared to other vaccinations used in older individuals: pneumococcal vaccination, pertussis vaccination and influenza vaccination. Although pneumococcal vaccination was preferred over influenza vaccination and influenza vaccination over herpes zoster vaccination, the overall acceptance is quite reasonable and driven by high mortality risk of the infectious disease (no so much the case for herpes zoster), high susceptibility of getting the infectious disease and high vaccine effectiveness. Cost of the vaccine was not included as a characteristic in this study

Previous studies on general or specific (other than HZ) vaccine preferences also identified vaccine effectiveness and out-of-pocket costs as key-factors in decisions about vaccination. A South-African study showed a vaccine effectiveness was the most important attribute for the patients (followed by population coverage and burden of disease). The most favourable vaccine profile had a vaccine effectiveness of 90%.<sup>167</sup> In a Chinese study about Hepatitis B, patients preferred a vaccination with higher protection rates, longer duration of protection and low risk for side effects. Although patients preferred vaccination with lower out-of-pocket costs, they were willing to pay more for increased vaccine effectiveness (e.g. two times more for duration 20 years instead of 10 years).<sup>168</sup>



## 6 ECONOMIC ASPECTS OF HERPES ZOSTER VACCINATION

The objectives of this section are twofold. The first is to assess the cost-effectiveness of Shingrix in Belgium to provide the Commission de Remboursement des Medicaments / Commissie Tegemoetkoming Geneesmiddelen (CRM/CTG) with independent information to decide upon its potential reimbursement by the National Institute for Health and Disability (NIHDI, Institut National d'Assurance Maladie-Invalidite / Rijksinstituut voor Ziekte- en Invaliditeitsverzekering INAMI/RIZIV). The second is to estimate the potential impact on the INAMI/RIZIV budget of recommending vaccination of adults with Shingrix and granting its reimbursement.

**Table 39 – General characteristics of the HZ vaccines**

|                               | Zostavax                                                                            | Shingrix                                                                       |
|-------------------------------|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| <b>Vaccine type</b>           | Live attenuated varicella-zoster virus vaccine (ZVL)                                | New adjuvant recombinant subunit vaccine (RZV)                                 |
| <b>Manufacturer</b>           | Merck Sharpe & Dohme                                                                | GSK                                                                            |
| <b>EMA approval</b>           | May 2006                                                                            | March 2018                                                                     |
| <b>Status in Belgium</b>      | Licensed in Belgium, not reimbursed                                                 | Licensed in Belgium, reimbursement request soon to be submitted to INAMI/RIZIV |
| <b>Vaccination schedule</b>   | 1-dose                                                                              | 2-dose (2 months apart)                                                        |
| <b>Vaccine price per dose</b> | € 137.40                                                                            | € 170.26                                                                       |
| <b>Cost-effectiveness</b>     | Vaccine not judged to be cost-effective in KCE report 151 (2010) <sup>28, 169</sup> | -                                                                              |

Source for vaccine price: Centre belge d'information pharmacothérapeutique / Belgisch centrum voor farmacotherapeutische informatie (CBIP/BCFI), accessed April 2022.

The general characteristics of the two vaccines that protect adults against herpes zoster (HZ) and postherpetic neuralgia (PHN), Zostavax (zoster vaccine live, ZVL) and Shingrix (recombinant zoster vaccine, RZV) are presented in Table 39.

### 6.1 Economic evaluation of HZ vaccination in Belgium

This section is based on the assessment of the cost-utility analysis of HZ vaccination performed by Pieters et al.<sup>21</sup> and published early 2022. This is, so far, the only economic evaluation of Shingrix performed in Belgium by a research group independent from the industry (Hasselt University and University of Antwerp).

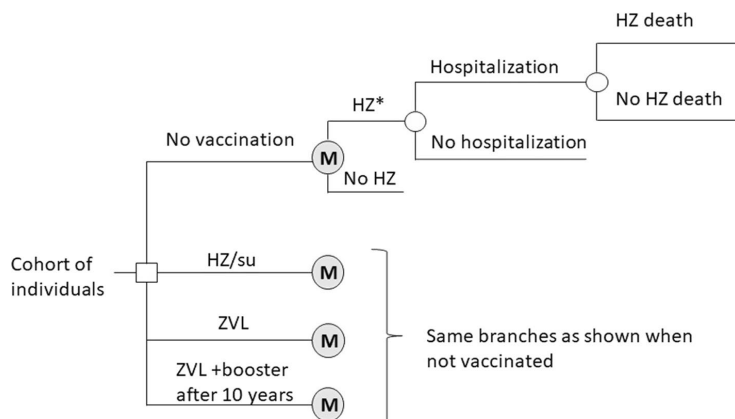
#### 6.1.1 Technical characteristics

Pieters et al.<sup>21</sup> performed a cost-utility analysis of HZ vaccination using a Markov model (Figure 12). The model is static, assuming a constant force of infection over time (i.e., the rate at which susceptible individuals become infected), as HZ vaccination is not expected to influence the transmission dynamics of the varicella-zoster virus (VZV).

The model includes two health states "does not develop herpes zoster (No HZ)" or "develops herpes zoster (HZ)". Individuals developing HZ can subsequently be hospitalised (health state "hospitalisation") and/or die. HZ can also lead to complications and the number of PHN cases were calculated as a proportion of the number of HZ cases.



**Figure 12 – Markov decision tree**



Four strategies were compared:

- No vaccination (the strategy that reflects current practice <sup>a</sup>);
- Vaccination with Shingrix (2 doses, 2 months apart);
- Vaccination with Zostavax (one dose);
- Vaccination with Zostavax and a booster after 10 years (2 doses, 10 years apart). The rationale advocated by Pieters et al.<sup>21</sup> for considering this strategy is that Zostavax is not expected to provide protection after 10 years, hence a booster could be administered 10 years after the initial dose.

The vaccination strategy with 1 dose of Zostavax was recommended in 2017 by the Belgian Superior Health Council for  $\geq 65$ -year adults, on an individual basis (no organised public vaccination programme and no reimbursement). This strategy was further implemented in Belgium, though at a low uptake. Hence in our views, vaccination with Zostavax (1dose) is a relevant comparator to Shingrix. By contrast the strategy of vaccination with Zostavax and a booster dose after 10 years, as simulated in Pieters et al.,<sup>21</sup> was never recommended by the Superior Health Council and was never implemented in Belgium. This strategy is thus not a relevant comparator to Shingrix and will not be considered further.

Five vaccination strategies were simulated: vaccination at the age of 50, 60, 70, 80, and 85 years. Only immunocompetent persons were modelled as ZVL is not indicated in the immunocompromised. Individuals are followed over their remaining lifetime (i.e., from the age at vaccination until they die or reach 103 years). Each cycle lasts one year.

The economic evaluation adopted the perspective of the health care payer, including only direct medical costs (ambulatory and hospitalisation treatment costs, the vaccine costs and the vaccine administration costs) borne by the health care system and the patients. Outcomes were expressed as quality-adjusted life-years (QALY), therefore capturing both years of life lost due to premature death and loss of quality of life due to morbidity.

As per the Belgian guidelines on economic evaluations,<sup>170</sup> future costs were discounted at a rate of 3% and benefits (e.g. QALYs) at a rate of 1.5%.

<sup>a</sup> Though precise figures are not available, current practice regarding HZ vaccination in Belgium is rather a very low uptake of this vaccine. This situation is usually depicted as the "no vaccination" strategy in models, even though this does not perfectly reflect reality.



## 6.1.2 Input parameters

### 6.1.2.1 Epidemiological parameters

HZ incidence was reported in terms of “medically attended HZ” which was the addition of the number of ambulatory treated HZ patients and the number of patients hospitalised for HZ who did not have a GP consultation first.

The age-specific HZ hospitalisation rates were obtained from the Minimal Clinical Data (MCD), a registry in which every hospital in Belgium must report information (including age, length of stay, diagnosis...) on hospitalized patients. For the period 2000-2007, the number of HZ-related hospitalisations was identified as those hospitalisations with an ICD-9-CM code ‘053’ in primary diagnosis. HZ hospitalization rates were calculated by dividing the yearly number of HZ hospitalizations from the MCD by the Belgian population from the same year.

The age-specific number of persons with HZ who consulted a general practitioner (GP) at least once was obtained from the sentinel network of 150 GPs from Sciensano (the Belgian Institute for Health) for the years 2006-2008. GP consultation rates were then calculated by dividing the age-specific yearly number of GP consultations by the age-specific sentinel catchment population.

The proportion of HZ hospitalised patients that did not visit a GP was estimated from the National Christian Sickness Fund (NCSF) survey, a survey performed in 2009-2010 among hospitalized (n=153) and ambulatory (n=130) HZ patients in Belgium.<sup>20, 169</sup> It showed that 10.44% of the hospitalized HZ patients (95% credibility interval (95% CrI) 6.18–15.77) did not visit a general practitioner for HZ but were either (i) admitted directly through the emergency department, (ii) referred to the hospital through a specialist doctor, or (iii) hospitalized for another reason and got HZ in the hospital. The age-specific HZ incidence was then computed by adding

10.44% of the estimated average HZ hospitalization rate to the estimated average rate at which people consult a GP at least once for HZ.

Both the HZ hospitalisation and consultation rates were further adjusted to represent immunocompetent individuals only. This was done by multiplying the rates by the age-specific conditional probabilities of an individual being immunocompetent given that the person was hospitalised for HZ or ambulatory treated for HZ. These conditional probabilities were derived from the NCSF survey described above.<sup>20, 169</sup> Depending on age, the probabilities of being immunocompetent ranged 37.1–59.1% for hospitalised patients and 46.5–71.4% for ambulatory patients (Table 46).

In the absence of Belgian data, the age-specific proportion of HZ cases that develop postherpetic neuralgia (PHN) was obtained from a UK study,<sup>49</sup> together with the distribution of HZ and PHN patients according to 4 pain severity stages: ‘No pain’, ‘Mild pain’, ‘Moderate pain’ and ‘Severe pain’. PHN patients were assumed to suffer from moderate to severe pain.

No other HZ complications (other than PHN) were included in the model.

The HZ mortality rate was obtained from all death certificates from 1998 to 2007 managed by the Flemish Agency for Care and Health that contained ICD10 codes B01 and B02 as cause of death.

### 6.1.2.2 Cost parameters

Direct medical costs were considered in the model (health care payer’s perspective).

The costs related to the treatment of an HZ and a PHN episode (for ambulatory and hospitalised patients) were obtained from the 2009 National Christian Sickness Fund survey.<sup>20, 169</sup> These costs were stratified per pain state and adjusted to the 2018 price year, see Table 40.

**Table 40 – Direct medical treatment costs (2018 price year)**

|                      | Mean treatment costs for an ambulatory patient (95% CrI) |                           | Mean treatment costs for a hospitalised patient (95% CrI) |                        | Source                                                                        |
|----------------------|----------------------------------------------------------|---------------------------|-----------------------------------------------------------|------------------------|-------------------------------------------------------------------------------|
|                      | HZ without PHN                                           | HZ with PHN               | HZ without PHN                                            | HZ with PHN            |                                                                               |
| <b>No pain</b>       | € 26.78 #                                                | -                         | € 5334 (3859–7025) §                                      | -                      | Bilcke et al. (2010) <sup>28, 169</sup><br>Bilcke et al. (2012) <sup>20</sup> |
| <b>Mild pain</b>     | € 85.81 (52.18–126.26)                                   | -                         | € 5330 (3826–7118)                                        | -                      |                                                                               |
| <b>Moderate pain</b> | € 204.91 (142.32–278.39)                                 | € 457.49 (278.16–671.43)  | € 5560 (4771–6397)                                        | € 6241 (5183–7377)     |                                                                               |
| <b>Severe pain</b>   | € 208.22 (115.72–326.27)                                 | € 710.02 (334.16–1160.70) | € 6152 (4397–8245)                                        | € 10 411 (7473–13 854) |                                                                               |

95% CrI: 95% credibility interval, HZ: herpes zoster, PHN: postherpetic neuralgia. # In the absence of data, it was assumed that the cost incurred is the cost for one GP consultation, and no uncertainty distribution is assigned to the parameter. § In the absence of data, it was assumed that patients hospitalised reporting no pain incur the same average cost as those reporting mild pain.

The cost of one dose of ZVL was € 137.40, as reported by the Belgian Centre for Pharmacotherapeutic Information. This is the private sector price of Zostavax as this vaccine is not reimbursed in Belgium. For RZV, the private sector price in the US market was used, i.e., € 140.26 per dose. Note that meantime the private sector price of Shingrix has been set up in Belgium at € 170.26 per dose.

The cost of vaccine administration was valued at € 26.78 per dose, which is the cost of a consultation to an accredited GP.

### 6.1.2.3 Quality of life parameters

Quality of life was reported in terms of utility loss according to the severity of the pain of the patient. For the base-case, the utilities per pain severity states were derived from van Hoeck et al.<sup>171</sup> and were 0.7787 (95% CrI 0.7509–0.8567) for mild pain, 0.6075 (95% CrI 0.5826–0.6788) for moderate pain and 0.2731 (95% CrI 0.2288–0.4030) for severe pain. Pieters et al.<sup>21</sup> did not use the Belgian population norms as the baseline reference population. Instead, the above pain states for HZ patients were compared

with the utility weight of a patient with HZ reporting no pain (0.8559, 95% CrI 0.7750–0.9212), which was also taken from van Hoeck et al.<sup>171</sup> The decrements for mild, moderate, and severe pain were thus obtained by subtracting the utility of the pain states from the baseline ‘no pain’ utility value.

Utility losses for a HZ case stratified according to the presence or absence of PHN were calculated through a weighted average of the utility loss for mild, moderate and severe pain according to the percentage of HZ with or without PHN cases in each pain state. The proportions of HZ with or without PHN patients according to pain severity are reported in the table below (Table 41), together with the weighted average of the utility loss for a HZ case stratified per age and according to the presence/absence of PHN.

The weighted average utility losses were finally multiplied by the duration of illness for HZ with or without PHN to obtain the QALY losses. The estimated mean durations were derived from the National Christian Sickness Fund survey<sup>20, 169</sup> and were 28.66 (<70 years) and 44.38 (≥70 years) days for HZ, and 254.06 (<70 years) and 319.46 (≥70 years) days for PHN.



Table 41 – Age-specific utility loss per HZ case (according to the presence or absence of PHN)

| Table 41 Age-specific utility losses for HZ case (according to the presence or absence of PHN) |                         |              |                                                       |           |             |           |                                                                                  |
|------------------------------------------------------------------------------------------------|-------------------------|--------------|-------------------------------------------------------|-----------|-------------|-----------|----------------------------------------------------------------------------------|
|                                                                                                | Utility, mean (95% CrI) | Utility loss | Proportion (%) of patients according to pain severity |           |             |           |                                                                                  |
|                                                                                                |                         |              | HZ without PHN                                        |           | HZ with PHN |           | Source                                                                           |
|                                                                                                |                         |              | 50-69 years                                           | 70+ years | 50-69 years | 70+ years |                                                                                  |
| Base-case                                                                                      |                         |              |                                                       |           |             |           |                                                                                  |
| No pain                                                                                        | 0.8559 (0.7750–0.9212)  | 0            | 65%                                                   | 45%       | 0%          | 0%        | Utilities: van Hoeck et al. <sup>171</sup>                                       |
| Mild pain                                                                                      | 0.7787 (0.7509–0.8567)  | 0.0772       | 24%                                                   | 41%       | 0%          | 0%        | Proportion of patients according to pain severity: Gauthier et al. <sup>49</sup> |
| Moderate pain                                                                                  | 0.6075 (0.5826–0.6788)  | 0.2484       | 4%                                                    | 5%        | 89%         | 89%       |                                                                                  |
| Severe pain                                                                                    | 0.2731 (0.2288–0.4030)  | 0.5828       | 8%                                                    | 9%        | 11%         | 11%       |                                                                                  |
| Weighted average utility loss                                                                  |                         |              | 0.075                                                 | 0.097     | 0.285       | 0.285     |                                                                                  |
| Scenario analysis “Increased burden of disease” #                                              |                         |              |                                                       |           |             |           |                                                                                  |
| No pain                                                                                        | 0.8559 (0.7750–0.9212)  | 0            | 27%                                                   | 26%       | 0%          | 0%        | Utilities: van Hoeck et al. <sup>171</sup>                                       |
| Mild pain                                                                                      | 0.7787 (0.7509–0.8567)  | 0.0772       | 41%                                                   | 32%       | 0%          | 0%        | Proportion of patients according to pain severity: Oxman et al. <sup>25</sup>    |
| Moderate pain                                                                                  | 0.6075 (0.5826–0.6788)  | 0.2484       | 18%                                                   | 23%       | 51%         | 33%       |                                                                                  |
| Severe pain                                                                                    | 0.2731 (0.2288–0.4030)  | 0.5828       | 14%                                                   | 14%       | 49%         | 67%       |                                                                                  |
| Weighted average utility loss                                                                  |                         |              | 0.158                                                 | 0.163     | 0.412       | 0.472     |                                                                                  |

Note: Percentages may not total 100 due to rounding. # A scenario analysis explored the impact of using the estimates of Oxman et al.<sup>25</sup> instead of Gauthier et al.<sup>49</sup> for the proportion of PHN (per HZ case) and the distribution of patients according to disease severity (see below). 95% CrI: 95% credibility interval, HZ: herpes zoster, PHN: postherpetic neuralgia.



### 6.1.2.5 Vaccine uptake, efficacy, duration of protection

For both HZ vaccines, the coverage was assumed to be the same as the coverage for adult influenza and pneumococcal vaccination in Belgium in 2018, i.e., 46.2%.<sup>172</sup> Compliance for the second dose of the RZV vaccine was assumed to be 100%, i.e. all vaccine recipients comply with both doses of RZV. The same assumption was done for the ZVL booster dose, administered 10 years after the initial dose, implying that all individuals who received the initial ZVL vaccine dose and are still alive at the time of the booster will comply.

ZVL vaccine efficacy was obtained from a RCT conducted in immunocompetent 60+ adults,<sup>25</sup> and from two follow-up studies.<sup>173, 174</sup> Efficacy data were available up to 11 years post-vaccination. Based on (the first 10 years of) those data, the best fit was provided with a one-minus-exponential function. This function was adjusted to account for the variation of the initial protection of ZVL depending on age. For the booster dose administered 10 years after the initial dose, following a study by Levin et al.,<sup>175</sup> ZVL booster was assumed to provide the same vaccine efficacy as the initial vaccination. In this study vaccine protection was measured with immunological surrogate endpoints rather than with clinical endpoints. The waning rate for the ZVL booster (10 years later) was assumed to be the same as for the initial ZVL dose.

The efficacy of RZV against HZ was obtained from 2 RCTs: the ZOE-50 trial<sup>31</sup> conducted in adults aged 50+ years, and the ZOE-70 trial<sup>156</sup> conducted in adults aged 70+ years (see section 4.3). Several fits were performed on the raw data (vaccine efficacy against medically attended HZ cases) but, due to the short duration of the trials at the time of the analysis (average follow-up time of 3.2 years in ZOE-50 and 3.7 years in ZOE-70) none of the functions simulated emerged as a best fit. The functions resulting in the longest (logarithmic) and shortest (one-minus-exponential) durations of protection were therefore selected. From the simulations, the duration of protection of the RZV vaccine was more than 50 years with the logarithmic waning function; and around 8-10 years with the 1-minus-exponential waning function which was similar to the duration of protection modelled for the ZVL vaccine.

### 6.1.3 Base-case results

#### 6.1.3.1 Effectiveness

In all age groups, vaccination with 2 doses of RZV was more clinically effective (in terms of QALYs gained) than vaccination with a single dose of ZVL, whatever the assumed duration of protection conferred by RZV.

However, the age at which RZV vaccination resulted in the highest clinical benefit differed according to assumed duration of protection. Assuming the longest duration of protection, the highest numbers of QALYs gained was obtained when vaccination occurred in younger age-groups, i.e. 258.52 QALYs gained when vaccinating at 50 years and 197.61 QALYs gained when vaccinating at 60 years. Assuming a shorter duration of protection, the highest clinical benefit was obtained when vaccination occurred at a later age, with 63.91 QALYs gained for a vaccination at 70 years and 70.09 QALYs gained for a vaccination at the age of 80 years (Table 42).

The same pattern is observed, whatever the clinical outcome considered, i.e., the HZ cases avoided, the PHN cases avoided, the hospitalisations avoided, and the HZ deaths avoided.

- **RZV is more clinically effective than ZVL.**
- **Assuming the longest duration of protection of RZV (logarithmic waning function), vaccination at a younger age (50 years) results in the highest avoided burden. Assuming the shortest duration of protection for RZV (1-minus-exponential waning function), the highest avoided burden is obtained when vaccinating at an older age (≥70 years).**


**Table 42 – Burden of HZ (in terms of QALYs lost) and QALYs gained per vaccination strategy (base-case)**

| Age categories     | Burden of HZ in Belgium in terms of QALY's lost, mean (95 CrI) | Age at vaccination | QALY's gained per vaccination strategy, mean (95% CrI) |                                 |                                  |
|--------------------|----------------------------------------------------------------|--------------------|--------------------------------------------------------|---------------------------------|----------------------------------|
|                    |                                                                |                    | ZVL vaccination                                        | RZV vaccination (low estimate*) | RZV vaccination (high estimate*) |
| <b>50-59 years</b> | 77 (44–118)                                                    | <b>50 years</b>    | 22.53 (14.11–33.34)                                    | 38.02 (23.72–56.34)             | 258.52 (189.23–337.91)           |
| <b>60-69 years</b> | 186 (116–270)                                                  | <b>60 years</b>    | 49.07 (33.62–67.65)                                    | 44.36 (27.91–64.43)             | 197.61 (143.35–259.69)           |
| <b>70-79 years</b> | 282 (197–385)                                                  | <b>70 years</b>    | 31.95 (21.98–44.18)                                    | 63.91 (43.93–88.25)             | 171.41 (114.4–236.39)            |
| <b>80-84 years</b> | 80–89 y: 278 (132–427)                                         | <b>80 years</b>    | 7.8 (3.68–12.22)                                       | 70.09 (33.15–107.55)            | 102.97 (49.49–157.09)            |
| <b>≥85 years</b>   | ≥90 y: 57 (28–92)                                              | <b>85 years</b>    | 2.35 (1.05–3.87)                                       | 50.76 (23.18–80.51)             | 59.36 (27.93–92.74)              |
| <b>Total</b>       | 880 (631–1162)                                                 |                    |                                                        |                                 |                                  |

\* Low estimate of the RZV vaccine efficacy (1-minus-exponential function) giving the shortest duration of protection; High estimate of the RZV vaccine efficacy (logarithmic function) giving the highest duration of vaccine protection. 95% CrI: 95% credibility interval, QALY: quality-adjusted life-year, RZV: Shingrix, y: year, ZVL: Zostavax.

### 6.1.3.2 Cost-effectiveness

Assuming the longest vaccine duration of protection (logarithmic waning function) and the base-case price of € 140.26 per dose, RZV vaccination dominated (i.e., it was more clinically effective and less costly) ZVL, making “no vaccination” the relevant comparator to RZV vaccination. Compared with no vaccination, the incremental cost-effectiveness ratios (ICER) for RZV vaccination were high at € 87 412 per QALY gained in the 50-year-olds, and even higher in older ages (Table 43).

Assuming the shortest vaccine duration of protection (1-minus-exponential waning function), RZV vaccination remained the dominant strategy, with ICERs (against no vaccination) well above € 146 000 per QALY gained in the 70-, 80- and 85-year-olds.

- **Whatever the assumption about RZV duration of protection, ZVL vaccination was dominated by RZV vaccination.**
- **Using the base-case parameters, the ICERs of RZV vaccination were high, starting at € 87 500 per QALY gained versus no vaccination at 50-year-old when the longest duration of vaccine protection was assumed.**

**Table 43 – Cost-effectiveness of RZV vaccination in adults: base-case results and sensitivity analyses**

| Age at vaccination                                                                 | Base-case ICER (€/QALY) #                    | Max RZV price (€) per dose at the following WTP thresholds *: |                 | ICER (€ / QALY) in the scenario analysis “increased burden of disease” § # | Base-case number needed to vaccinate (NNV, 95% CrI) to prevent a HZ case | NNV in the scenario analysis “increased HZ incidence” ‡ |
|------------------------------------------------------------------------------------|----------------------------------------------|---------------------------------------------------------------|-----------------|----------------------------------------------------------------------------|--------------------------------------------------------------------------|---------------------------------------------------------|
|                                                                                    |                                              | € 30 000 / QALY                                               | € 40 000 / QALY |                                                                            |                                                                          |                                                         |
| Base-case 1: longest duration of protection (logarithmic waning function)          |                                              |                                                               |                 |                                                                            |                                                                          |                                                         |
| 50 years                                                                           | 87 412                                       | 37.49                                                         | 55.40           | 59 069                                                                     | 12 (10-14)                                                               | 6                                                       |
| 60 years                                                                           | 107 951                                      | 26.40                                                         | 40.99           | 72 740                                                                     | 16 (14-20)                                                               | 8                                                       |
| 70 years                                                                           | 98 226                                       | 30.60                                                         | 46.74           | 59 507                                                                     | 20 (15-27)                                                               | 10                                                      |
| 80 years                                                                           | 97 522                                       | 31.80                                                         | 48.03           | 64 251                                                                     | 23 (14-46)                                                               | 12                                                      |
| 85 years                                                                           | 125 938                                      | 19.14                                                         | 31.78           | 79 777                                                                     | 29 (17-58)                                                               | Not reported                                            |
| Base-case 2: shortest duration of protection (1-minus-exponential waning function) |                                              |                                                               |                 |                                                                            |                                                                          |                                                         |
| 50 years                                                                           | ICER RZV versus no vaccination not available | - **                                                          | - **            | ICER RZV versus no vaccination not available                               | 48 (38-63)                                                               | Not reported                                            |
| 60 years                                                                           |                                              | - **                                                          | - **            |                                                                            | 46 (37-58)                                                               | Not reported                                            |
| 70 years                                                                           | 272 907                                      | - **                                                          | 0.92            | 150 864                                                                    | 47 (37-63)                                                               | Not reported                                            |
| 80 years                                                                           | 146 082                                      | 13.24                                                         | 24.23           | 97 928                                                                     | 34 (21-68)                                                               | Not reported                                            |
| 85 years                                                                           | 148 311                                      | 12.61                                                         | 23.31           | 93 474                                                                     | 33 (20-66)                                                               | Not reported                                            |

Note: 95% credibility intervals around the mean ICERs are not reported in the original publication. Costs are reported in Euro for the year 2018. # Compared with no vaccination unless otherwise stated. \* Maximum RZV price per dose for the ICER to be below € 30 000 or € 40 000 per QALY gained. \*\* Even when the RZV price is € 0 (i.e., only administration costs are considered) vaccination is not cost-effective. § In this scenario, the proportion of PHN per HZ case and the distribution of pain severity for HZ and PHN are taken from Oxman et al.<sup>25</sup> instead of Gauthier et al.<sup>49</sup> in the base-case. ‡ In this scenario, the number of medically attended HZ cases is doubled. 95% CrI: 95% credibility interval, HZ: herpes zoster, NNV: number needed to vaccinate, PHN: postherpetic neuralgia, RZV: Shingrix, WTP: willingness to pay.



### 6.1.4 Sensitivity analyses

A probabilistic sensitivity analysis (PSA) was conducted to characterise the uncertainty around the following parameters: the probabilities of being immunocompetent (among hospitalised / ambulatory treated HZ); the HZ GP visit rate; the proportion of HZ hospitalised patients that did not visit a GP; the HZ mortality rate; the durations of HZ and a PHN; the utility and QALY weight per pain severity state and the direct treatment cost parameters. Distributions were used to represent these input parameters. The model was run over 5000 Monte Carlo simulations, each time using a different set of input values randomly sampled from the parameters' uncertainty distributions. From the PSA, the 2.5<sup>th</sup> and 97.5<sup>th</sup> percentiles were retrieved to construct the 95% credibility interval (95% CrI) of the results.

The sensitivity of the results to the vaccine price per dose was explored in a univariate scenario analysis. In another scenario, the model was run using the estimates of Oxman et al.<sup>25</sup> instead of Gauthier et al.<sup>49</sup> for the percentage of HZ cases developing PHN and the proportion of patients according to disease severity, both parameters having an impact on the QALYs estimates and the treatment costs. A final scenario explored the impact of doubling the medically attended HZ cases (e.g., the HZ hospitalisation rate, the proportion of HZ hospitalised patients that did not visit a GP, the number of ambulatory treated HZ patients...).

#### 6.1.4.1 Scenario analysis on the vaccine price

Pieters et al.<sup>21</sup> varied the price per dose of the RZV vaccine and estimated the maximum price at which RZV vaccination becomes cost-effective for different willingness-to-pay thresholds ranging between € 30 000 to € 50 000 per QALY gained.

Assuming a long duration of vaccine protection (logarithmic waning function), RZV price per dose should drop to € 55.40 and € 37.49 (instead of € 140.26 in the base-case) for RZV vaccination at 50-year to become

cost-effective at the € 40 000 and € 30 000 per QALY thresholds, respectively (Table 43). Higher reductions to this price are required to reach cost-effective in older age groups. Assuming a short duration of protection (1-minus-exponential waning function), there is no price reduction allowing RZV vaccination to become cost-effective in the 50- and 60-year-old groups. In the older age classes, RZV vaccination can become cost-effective with huge price drops per dose, e.g., down to € 0.92 to reach cost-effectiveness in the 70-year-olds at a € 40 000 per QALY threshold.

#### 6.1.4.2 Scenario analysis on the probability of PHN and the proportion of individuals per pain category (Scenario analysis "increased burden of disease")

Using the proportion of PHN per HZ case (Table 47) and the distribution of pain severity for HZ with or without PHN (Table 41) by Oxman et al.<sup>25</sup> resulted in a 50% increase in the current burden of disease with the total number QALYs lost at 1306 (95% CrI 920–1743) in this scenario (Table 44) instead of 880 (95% CrI 631–1162) in the base-case (Table 42). The treatment costs also increased but in a much smaller proportion with a total of € 7 859 286 (95% CrI € 6 487 938–€ 9 352 845) in this scenario compared with € 6 900 000 (95% CrI € 6 890 000–€ 8 310 000) in the base case analysis.

This led to more favourable results for RZV vaccination with ICERs reduced to about € 59 000 per QALY gained in the 50 and 70-year-olds (instead of € 87 000 and € 98 000 in the base-case, respectively) compared with no vaccination and assuming the longest duration of protection, see Table 43.

Whatever the duration of the RZV vaccine protection assumed, the number of QALYs gained in this scenario is higher than in the base-case analysis, making RZV vaccination more attractive from a cost-effectiveness point of view. This is reflected in the lower ICERs reported for this scenario.

**Table 44 – Burden of HZ and QALYs gained per vaccination strategy (Scenario analysis “Increased burden of disease”)**

| Age categories     | Burden of HZ in Belgium in terms of QALY's lost, mean (95% CrI) | Age at vaccination | QALY's gained per vaccination strategy, mean (95% CrI) |                                 |                                  |
|--------------------|-----------------------------------------------------------------|--------------------|--------------------------------------------------------|---------------------------------|----------------------------------|
|                    |                                                                 |                    | ZVL vaccination                                        | RZV vaccination (low estimate*) | RZV vaccination (high estimate*) |
| <b>50-59 years</b> | Not reported                                                    | <b>50 years</b>    | 29.24 (18.95-41.97)                                    | 49.1 (31.77-70.56)              | 379 (273.13- 500.24)             |
| <b>60-69 years</b> | Not reported                                                    | <b>60 years</b>    | 62.35 (44.55-82.54)                                    | 49.24 (32.57-68.48)             | 291.31 (207.59-388.34)           |
| <b>70-79 years</b> | Not reported                                                    | <b>70 years</b>    | 57.49 (38.76-80.19)                                    | 114.6 (77.08-159.59)            | 279.45 (184.88-387.44)           |
| <b>80-84 years</b> | Not reported                                                    | <b>80 years</b>    | 11.3 (5.12-17.92)                                      | 104.51 (47.24-164)              | 155.53 (71-242.32)               |
| <b>85+ years</b>   | Not reported                                                    | <b>85 years</b>    | 3.68 (1.59-6.14)                                       | 79.89 (35.62-127.53)            | 92.68 (41.73-147)                |
| <b>Total</b>       | 1306 (920–1743)                                                 |                    |                                                        |                                 |                                  |

\* Low estimate for the RZV vaccine efficacy (1-minus-exponential function) giving the shortest duration of protection; High estimate for the RZV vaccine efficacy (logarithmic function) giving the highest duration of vaccine protection. 95% CrI: 95% credibility interval, QALY: quality-adjusted life-year, RZV: Shingrix, y: year, ZVL: Zostavax.

#### 6.1.4.3 Scenario analysis on the number of medically attended HZ cases (Scenario analysis “increased HZ incidence”)

Doubling the number of medically attended HZ cases resulted in a proportional decrease in the number needed to vaccinate (NNV) with RZV to avoid one HZ case, i.e., from 12, 16, 20 and 23 in the base-case to 6, 8, 10, 12 in this scenario for vaccination at 50, 60, 70 and 80 years, respectively (under the assumption of a logarithmic waning of RZV efficacy), Table 43.

Though the impact of considering a higher HZ incidence on the cost-effectiveness of RZV vaccination was not explicitly reported in Pieters et al.<sup>21</sup> it can be expected that this would result in more favourable ICERs as the potential to reduce the burden of HZ and associated treatment costs is higher.

## 6.2 Uncertainties in the economic evaluation of HZ vaccination in Belgium

### 6.2.1 Epidemiological parameters

#### 6.2.1.1 HZ incidence

HZ incidence in Pieters et al.<sup>21</sup> was reported in terms of medically attended HZ, and was computed as the addition of:

- the number of ambulatory GP consultations obtained from the 2006-2008 Belgian GP sentinel network at Sciensano, and
- the fraction (10.44%, 95% CrI 6.18–15.77) of hospitalised HZ that did not consult a GP first, with HZ hospitalisations obtained from the 2000-2007 MCD registry.

The estimated incidence of HZ is a crucial parameter that was reported to be influential on the results of the economic evaluation. As shown in Table 45, the age-specific incidence of GP consultations for HZ modelled in Pieters et al.<sup>21</sup> is comparable with other Belgian estimates that were derived (and modelled from) from the national GP surveillance system at Sciensano or from the Flemish GP network INTEGO.



By contrast the age-specific incidences modelled in the other European economic evaluations was higher than the incidences modelled in Pieters et al.<sup>21</sup> However, variations in the number of observed medically attended HZ cases across European countries most likely reflect different methodological approaches rather than a truly different epidemiological pattern. Various types of data are collected, such as claim data from national databases versus surveillance systems (sentinel network) covering a fraction of the population.

Section 3.2 further reported that incidences based on GP surveillance are systematically lower than incidences derived from claim data. There are also evolutions in the analytical methods over time, e.g., adapted methods were applied since 2012 by the Netherlands institute for health services research (NIVEL) implying a considerably higher HZ incidence from that date onwards.<sup>6</sup>

**Table 45 – Incidence of medically attended herpes zoster in the total population**

|                                                                                                               | Incidence of medically attended herpes zoster in the total population (per 1000 persons per year) |                                                |                            |                                             |                           | Source                                             |
|---------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|------------------------------------------------|----------------------------|---------------------------------------------|---------------------------|----------------------------------------------------|
|                                                                                                               | 50-59 years                                                                                       | 60-69 years                                    | 70-79 years                | 80-89 years                                 | ≥90 years                 |                                                    |
| <b>KCE data analysis</b><br>(see section 3.2.1 of the current report)                                         | 4.5<br>(4.4-4.6)                                                                                  | 6.3<br>(6.2-6.5)                               | 9.0<br>(8.9-9.2)           | 11.9<br>(11.7-12.2)                         | 13.0<br>(11.4-14.7)       | GP sentinel network, Sciensano, 2006-2012          |
|                                                                                                               | 4.69                                                                                              | 6.97                                           | 6.61                       | 8.21                                        | 4.31                      | Flanders GP network, Intego, 2017                  |
|                                                                                                               | 3.75                                                                                              | 5.88                                           | 6.49                       | 6.64                                        | 7.54                      | Idem supra, 2018                                   |
|                                                                                                               | 4.24                                                                                              | 5.81                                           | 7.38                       | 7.60                                        | 8.60                      | Idem supra, 2019                                   |
|                                                                                                               |                                                                                                   |                                                |                            |                                             |                           |                                                    |
| <b>Incidence modelled in economic evaluations of HZ vaccination performed in Belgium</b>                      |                                                                                                   |                                                |                            |                                             |                           |                                                    |
| <b>Pieters et al. (2022)<sup>21</sup></b>                                                                     | 4.0 (2.7-5.5)                                                                                     | 5.6 (3.9-7.5)                                  | 7.8 (5.4-10.4)             | 80-84: 9.9 (6.9-13.4)<br>85+: 10 (6.4-14.5) | 10 (6.4-14.5)             | GP sentinel network, Sciensano, 2006-2008 *        |
| <b>Bilcke et al. (2010 and 2012)<sup>20, 28</sup></b>                                                         | -                                                                                                 | 60-64: 5.48<br>65-69: 6.42                     | 70-74: 7.44<br>75-79: 8.84 | 80-84: 10.75<br>85-89: 12.87                | 12.87                     | GP sentinel network, Sciensano, 2006-2008 *        |
| <b>Annemans et al. (2010)<sup>40</sup></b>                                                                    | 50-54: 4.0<br>55-59: 3.5                                                                          | 60-64: 5.6<br>65-69: 5.8                       | 70-74: 7.1<br>75-79: 10.2  | 80-84: 11.6<br>85-89: 13.9                  | 90-94: 11.2<br>≥95+: 18.2 | GP sentinel network, Sciensano, 2006               |
| <b>Incidence modelled in other economic evaluations of HZ vaccination performed in neighbouring countries</b> |                                                                                                   |                                                |                            |                                             |                           |                                                    |
| <b>Van Oorschot et al. (2019)<sup>176</sup> Germany</b>                                                       | -                                                                                                 | 60-64: 10 (6.3-10.3)<br>65-69: 11.4 (7.2-11.8) | 13.4<br>(8.5-13.8)         | 13.9<br>(9.4-14.8)                          |                           | German claim data, 2005-2009 <sup>51</sup>         |
| <b>Ultsch et al. (2017)<sup>177 177</sup> Germany</b>                                                         | 4.64-9.31†                                                                                        | 7.22-12.30†                                    | 9.87-13.02†                | 11.35-12.91†                                | 11.98-13.57†              | German claim data <sup>44, 45</sup> (year unknown) |
| <b>De Boer et al. (2018)<sup>56</sup> Netherlands</b>                                                         | 5.91<br>(5.75-6.1)                                                                                | 8.57<br>(8.35-8.8)                             | 11.90<br>(11.57-12.22)     | 14.81<br>(14.35-15.27)                      |                           | Dutch GP sentinel network, NIVEL, 2012-15          |

\* In the model, data from the Belgian GP sentinel network were increased by 10.5% of the estimated number of hospitalised HZ patients to account for the proportion of hospitalised HZ patients that did not visit a GP for their HZ episode. † Data varies per gender. GP: general practitioner, NIVEL: Netherlands institute for health services research.



In a next step, the incidence of HZ cases in Pieters et al.<sup>21</sup> was adjusted downwards to represent the immunocompetent population, thereby excluding the immunosuppressed patients who could potentially benefit most from HZ vaccination.

The incidence of medically attended HZ in the total population (Table 45) was multiplied by the probability of an individual being immunocompetent when ambulatory treated for HZ (Table 46). The same adjustment was performed for the incidence of hospitalized HZ, and the probabilities of being immunocompetent given hospitalized for HZ are also reported in Table 46.

The validity of these probabilities can be questioned as they were obtained from a quite small sample of patients comprising 130 ambulatory treated and 153 hospitalized HZ patients surveyed in the 2009-2010 NCSF survey.<sup>20, 28</sup> Assessment of the immunocompromised status of the HZ patients enrolled in this survey was manually done by a clinician, based on the complete exclusion criteria list<sup>a</sup> of the SPS trial,<sup>25</sup> 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. Following those criteria, of the 130 ambulatory HZ patients, 50 were identified as being immunosuppressed (38%), and of the 136 hospitalised HZ patients (information is not available for 17 patients) 76 were identified as being immunosuppressed (56%). According to the authors of the NCSF study,<sup>20, 28</sup> the survey amongst hospitalized HZ patients is not likely to be biased. By contrast for the survey for HZ ambulatory patients a call was made on the internet and magazines, which may have caused a bias in the respondents of the ambulatory NCSF survey towards more severe cases (as they may be keener on participating), and consequently towards a higher percentage of immunocompromised persons.

<sup>a</sup> Immunocompromised persons were excluded from the SPS Zostavax trial. Immunosuppression was defined as A) Immunosuppression resulting from disease (e.g., malignancy; HIV infection), corticosteroids (except intermittent topical or inhaled corticosteroid [ $<800$  mcg/day beclomethasone dipropionate

**Table 46 – Probabilities of being immunocompetent reported in Pieters et al.**

| Probability of being immunocompetent | Given treated ambulatory for HZ (mean, 95% CrI) | Given hospitalised for HZ (mean, 95% CrI) |
|--------------------------------------|-------------------------------------------------|-------------------------------------------|
| <b>≤59 years</b>                     | 0.465 (0.3299–0.6255)                           | 0.3708 (0.2048–0.5481)                    |
| <b>60-69 years</b>                   | 0.7139 (0.5730–0.8386)                          | 0.5915 (0.4034–0.7609)                    |
| <b>70-79 years</b>                   | 0.6652 (0.5044–0.8069)                          | 0.4000 (0.2672–0.5335)                    |
| <b>80+ years</b>                     | 0.6203 (0.2831–0.8998)                          | 0.4356 (0.2673–0.6051)                    |

Source: National Christian Sickness Fund study.<sup>20, 28</sup>

This adjustment to the immunocompetent population resulted in a substantial decrease (approximately, from a 29% reduction in the 60-year-old group to 54% in the 50-59-year group) in the HZ incidence modelled, and in a reduced number of individuals who may benefit from vaccination, hence limiting the potential effectiveness and cost-effectiveness of HZ vaccination.

Assuming that 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. Further, section 4.4 of the current report states that RZV vaccination is clinically effective and safe in the immunocompromised population. It is thus likely that the results in Pieters et al. would be more favourable if the whole population (and not only the immunocompetent population) was considered for vaccination.

In a recent Dutch study, DeBoer et al.<sup>56</sup> assessed the cost-effectiveness of RZV vaccination by modelling the HZ incidence obtained from the total

or equivalent]], or other immunosuppressive/cytotoxic therapy (cancer chemotherapy or organ transplantation); and B) Active neoplastic disease (except local skin cancer or other malignancies [e.g., prostate cancer] that are stable in the absence of immunosuppressive/cytotoxic therapy).



population in their base-case analysis. The impact of modelling the HZ incidence derived for the immunocompetent fraction of the population was explored in a sensitivity analysis. DeBoer et al.<sup>56</sup> estimated that the incidence of HZ-related GP visits, hospitalizations and deaths was 0.78, 0.88 and 0.87 times lower among the immunocompetent population compared with the total population, and they multiplied the Dutch incidence rates by these figures. In their base-case, considering the incidence of HZ for the whole Dutch population, the maximum vaccine cost per series (2 doses of RZV) to be cost-effective at a threshold of € 20 000 per QALY gained was estimated at € 109.09 for the 70-year-olds. When the estimates of HZ incidence were limited to the immunocompetent population (as in Pieters et al.<sup>21</sup>), vaccination with RZV was less cost-effective and the vaccine cost per series had to decrease to € 80.54 for RZV vaccination to be cost-effective at the same threshold. The impact on the cost-effectiveness results of using the epidemiological estimates for the immunocompromised population was not explored.

#### 6.2.1.2 *Percentages of herpes zoster cases with postherpetic neuralgia*

The age-specific proportions of HZ cases that develop PHN were identified as being an influential parameter on the results of Pieters et al.,<sup>21</sup> as an increase in these proportions (or in the distribution of pain severity in PHN) resulted in more favourable results for RZV vaccination.

There are no Belgian estimates of the rates of PHN in the overall HZ population (see section 3.3.1 of the current report). In the absence of such Belgian data, Pieters et al.<sup>21</sup> used the results of a study<sup>49</sup> analysing the GP Research Database in the UK. Other economic evaluations of HZ vaccination in Belgium similarly used data from other European countries (Table 47). There were substantial variations in the PHN rates modelled in the economic evaluations. Such variability in the proportions of HZ cases suffering from PHN is also reflected in the results of the review of 20 European studies which was performed in the current report (see section 3.3.2). For example, in the age group 50-59 years, the range for the reported rate of PHN is wide from 2% to 19.3%.

**Table 47 – Age-specific proportion of herpes zoster cases that develop postherpetic neuralgia modelled in Belgian economic evaluations**

| PHN definition                                                       |                   |                                                  | Proportion of HZ cases that develop PHN |                              |                              |                            | Source                                                                                 |
|----------------------------------------------------------------------|-------------------|--------------------------------------------------|-----------------------------------------|------------------------------|------------------------------|----------------------------|----------------------------------------------------------------------------------------|
|                                                                      |                   |                                                  | 50-59 years                             | 60-69 years                  | 70-79 years                  | ≥80 years                  |                                                                                        |
| <b>Pieters et al. (2022)<sup>21</sup></b>                            | Base-case         | Moderate or severe pain persisting for ≥3 months | 50-54: 8%<br>55-59: 10%                 | 60-64: 11%<br>65-69: 13%     | 70-74: 15%<br>75-79: 18%     | 80-84: 21%<br>85+: 19%     | Gauthier et al. (2009) <sup>49</sup><br>UK GP Research Database                        |
|                                                                      | Scenario analysis |                                                  | 6.9%                                    |                              | 18.5%                        |                            | Oxman et al. (2005) <sup>25</sup><br>Zostavax trial, USA                               |
| <b>KCE literature review (see section 3.3 of the current review)</b> |                   | ≥3 months                                        | 2.2 to 19.3%                            | 3.3 to 28.7%                 | 7.8 to 37.3%                 | 7.8 to 40.5%               | Review of 20 European studies <sup>8</sup>                                             |
| <b>Bilcke et al. (2010 and 2012)<sup>20, 28</sup></b>                | Base-case         | Clinical relevant pain after 3 months §          | -                                       | 60-64: 8%<br>65-69: 10%      | 70-74: 13%<br>75-79: 17%     | 80-84: 23%<br>85-89: 31%   | Van Hoek et al. (2009) <sup>171</sup><br>UK                                            |
| <b>Annemans et al. (2010)<sup>40</sup></b>                           | Base-case         | Moderate or severe pain persisting for ≥3 months | 50-54: 7.6%<br>55-59: 9.8%              | 60-64: 11.0%<br>65-69: 13.1% | 70-74: 15.2%<br>75-79: 18.0% | 80-84: 20.6%<br>85+: 18.5% | Gauthier et al. (2009) <sup>49</sup><br>UK GP Research Database                        |
|                                                                      | Scenario analysis |                                                  | 50-54: 3.9%<br>55-59: 6.5%              | 60-64: 6.5%<br>65-69: 10.7%  | 70-74: 10.7%<br>75-79: 18.0% | 18.0%                      | Opstelten et al. (2002) <sup>67</sup><br>Utrecht GP Research Database, The Netherlands |

§ Van Hoek et al.<sup>171</sup> defined “clinical relevant pain” 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 is used). HZ: herpes zoster, PHN: postherpetic neuralgia.

### 6.2.1.3 Mortality and hospitalisation rates

Pieters et al.<sup>21</sup> extracted the estimates for the age-specific HZ hospitalisation rates from the Belgian MCD database (in 2000-2007), by retrieving the number of hospitalisations (inpatients) with a primary diagnosis of HZ. The estimates available for Belgium were all consistent (Table 48), and no important variation across the years is observed. Pieters et al.<sup>21</sup> did not account for uncertainty in the hospitalisation rate for HZ as, since the MCD database registers all hospital admissions in Belgium, there is no sample size uncertainty that should be taken into account (sample size uncertainty

is the uncertainty caused by observing a sample instead of the complete population).

Just as for the incidence of medically attended HZ, the incidence of hospitalised HZ in Pieters et al.<sup>21</sup> was adjusted downwards to represent the immunocompetent population. The HZ hospitalisation incidence derived for the total Belgian population was multiplied with the probability of an individual being immunocompetent when hospitalised for HZ (Table 46). This resulted in a substantial decrease (from 41% reduction in the 60-year-old group to 63% in the 50-59-year group) in the incidence modelled. Immunocompromised patients are more likely to be hospitalised due to HZ



or its complications, and as such they contribute largely to the clinical and economic burden of HZ (see section 3.8.2 of the current report). It remains to be explored however whether and for how long HZ hospitalisations in the immunocompromised could be avoided with RZV vaccination. So far there is no evidence on this.

HZ mortality is usually rare and typically arises in older patients. As such this parameter has a limited impact on the burden of HZ (in terms of life-years lost) and it plays a less important role on the cost-effectiveness results.

**Table 48 – Herpes zoster mortality and hospitalisation incidences in the total Belgian population**

|                                                                                            | Hospitalisation incidence (per 100 000 person-year)                                                                                |                        |                        |                      | Mortality incidence (per million person-year) |                             |         |                         |               | Source                                                                                     |
|--------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------|------------------------|------------------------|----------------------|-----------------------------------------------|-----------------------------|---------|-------------------------|---------------|--------------------------------------------------------------------------------------------|
|                                                                                            | 50-59 y                                                                                                                            | 60-69 y                | 70-79 y                | ≥80 y                | 50-59 y                                       | 60-69 y                     | 70-79 y | 80-89 y                 | ≥90 y         |                                                                                            |
| <b>Pieters et al. (2022)<sup>21</sup></b>                                                  | 9.4                                                                                                                                | 19                     | 33                     | 80-84: 68<br>85+: 89 | 0                                             | 60-74: 0.18<br>(0.059-0.35) |         | 75-89: 5.4<br>(4.7-6.2) | 40<br>(34-45) | National database, MCD 2000-2007 <sup>§</sup><br>Flemish death certificates 1998-2007      |
| <b>KCE data analysis<br/>(see section 3.5.1.2<br/>and 3.6.1 of the<br/>current report)</b> | 5.84-12.43                                                                                                                         | 12.67-<br>30.17        | 23.04-<br>59.81        | 62.59-173.04         | 0.00                                          | 0.33                        | 1.75    | 10.86                   | 72.59         | National database, MCD 2019 <sup>#</sup><br>Belgian (Statbel) death certificates 1998-2016 |
| <b>Bilcke et al. (2010<br/>and 2012)<sup>20, 28</sup></b>                                  | -                                                                                                                                  | 60-64: 17<br>65-69: 24 | 70-74: 31<br>75-79: 44 | 80-84: 63<br>85+: 85 | 0                                             | 0.3<br>(0-0.6)              |         | 1.5<br>(0-6.3)          | 3<br>(0-32.5) | National database, MCD 2000-07 <sup>§</sup><br>Flemish death certificates 1998-2007        |
| <b>Annemans et al.<br/>(2010)<sup>40</sup></b>                                             | Rates are expressed as % of HZ case and per severity stage; and are therefore not comparable with the data reported in this table. |                        |                        |                      | 0                                             | 0                           |         | 0                       | 0             | Hospitalisation: not reported<br>Mortality: assumption and expert opinion                  |

<sup>§</sup> ICD-9-CM codes 053 as primary diagnosis. <sup>#</sup> ICD-10 codes B02 as principal diagnosis (lower value) and as principal and not principal diagnosis (higher value), see section 3.5.1.2 for the computational details. MCD: minimal clinical data, y: year.



#### 6.2.1.4 Herpes zoster complications others than postherpetic neuralgia

HZ complications others than PHN include disseminated HZ, and neurological, visceral, or vascular diseases, including stroke. There are no Belgian estimates of the rates of such complications. Pieters et al.<sup>21</sup> did not separately model HZ complications others than PHN.

#### 6.2.2 Shingrix efficacy parameters

Vaccine efficacy parameters (2-doses) in Pieters et al.<sup>21</sup> were modelled based on the 4-year post-vaccination data from the ZOE-50<sup>31</sup> and ZOE-70 trials.<sup>156</sup> Two waning functions were selected that represented:

- a best-case simulating the longest duration of vaccine protection, i.e. more than 50 years of protection at a relatively constant efficacy around 90% in the 50–69-years, and about 40 years of protection with a rapidly declining immunity in the 70-years and older; and
- a worst-case simulating the shortest duration of vaccine protection, i.e. slightly more than 10 years of protection with a rapid decline in efficacy in the 50–69-year olds, and no more than 7-8 years of protection in those aged 70-years and over.

Considering the yearly point estimates for vaccine efficacy reported in the ZOE-50 and ZOE-70 trials, Pieters et al.<sup>21</sup> estimated that the rate of waning would be different according to age, see Table 49, Figure 13 and Figure 14.

The persisting efficacy of 2 doses of RZV up to 8 years post-vaccination is now available from the ZOE-LTFU follow-up study of the pooled ZOE-50/70 population.<sup>120</sup> Yearly efficacy slowly decreased from 97.7% in the first-year post-vaccination to 84.1% (95%CI: 64.4-94.0) in year 8, see section 4.3. The authors further report a trend toward a plateau with a vaccine efficacy at 84.9% (95%CI: 70.4-93.1) in year 6 and at 85.3% (95%CI: 71.3-93.3) in year 7 post-vaccination.

**Table 49 – Efficacy of Shingrix (2 doses) modelled in Peters et al.**

| Fitted function                                                   |                                                  | Source                                                                                    |
|-------------------------------------------------------------------|--------------------------------------------------|-------------------------------------------------------------------------------------------|
| <b>Logarithmic (Long duration of vaccine protection)</b>          |                                                  | Lal et al. (2015) <sup>31</sup><br>Cunningham et al. (2016) <sup>156</sup><br>Assumptions |
| <b>50-69 years</b>                                                | $0.9768 - 0.0179 * \log(\text{years})$           |                                                                                           |
| <b>≥ 70 years</b>                                                 | $0.9702 - 0.1058 * \log(\text{years})$           |                                                                                           |
| <b>1-minus-exponential (Short duration of vaccine protection)</b> |                                                  |                                                                                           |
| <b>50-69 years</b>                                                | $1 - e^{(\log(0.0162) + 0.3068 * \text{years})}$ |                                                                                           |
| <b>≥ 70 years</b>                                                 | $1 - e^{(\log(0.0456) + 0.3434 * \text{years})}$ |                                                                                           |

We fitted several functions on the 8 years ZOE-LTFU vaccine efficacy data (Figure 15). The best fit is given by the power function, simulating a low waning and providing a vaccine efficacy around 74% after 50 years. Two other functions with a good fit are the one-minus-exponential and exponential functions, both simulating a slightly faster waning and providing a vaccine efficacy of about 35% after 50 years.

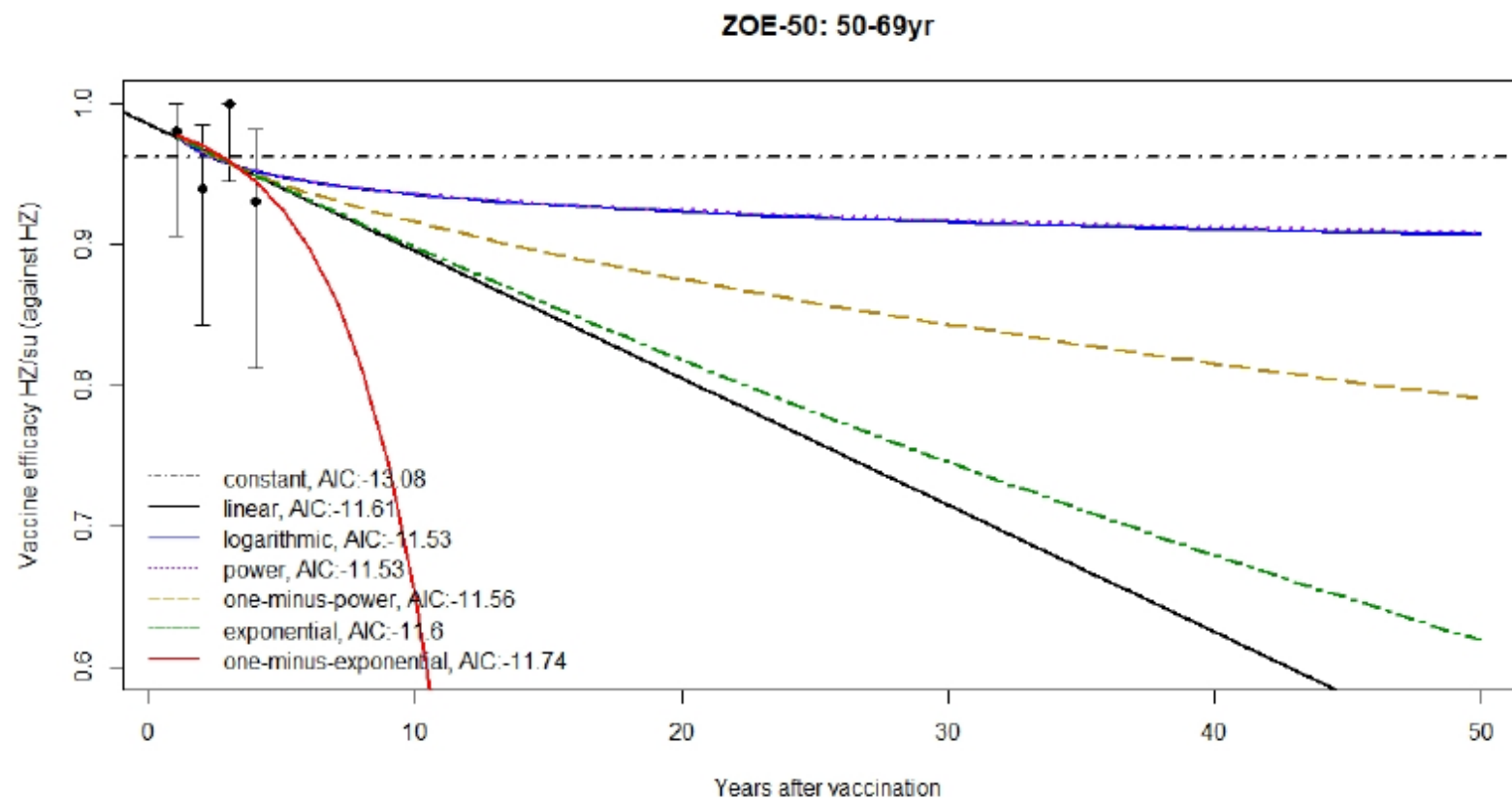
Those simulations clearly illustrate that the scenario of short duration of protection hypothesised in Pieters et al.<sup>21</sup> and in which a sharp waning is simulated offering 7 to 10 years of protection, is too pessimistic and can be discarded.

The simulations also illustrate that the scenario of long duration of protection hypothesised in Pieters et al., and assuming nearly no waning with a vaccine efficacy of about 90% after 50 years, is plausible though the vaccine efficacy is lower, and the waning of immunity is faster than estimated in Pieters et al.<sup>21</sup>

Unfortunately, the long-term data of the ZOE-LTFU study are not available per age category. It is thus not possible to assess whether the waning of vaccine efficacy is different for the younger (50- to 69-year-olds) and the older (the ≥70-year-olds) adults.

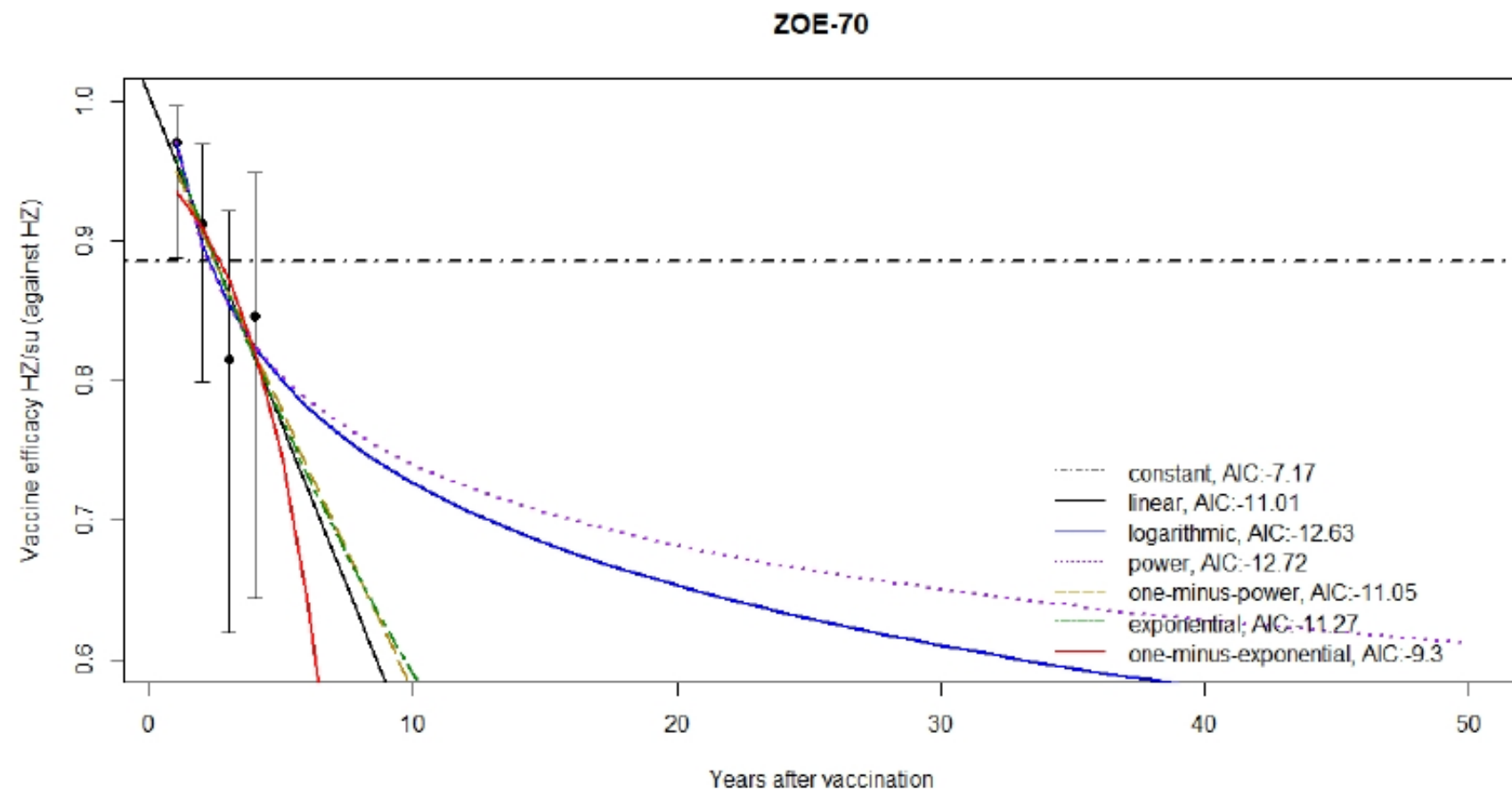


Figure 13 – Vaccine efficacy of RZV against HZ simulated in Pieters et al. for adults aged 50-69 years

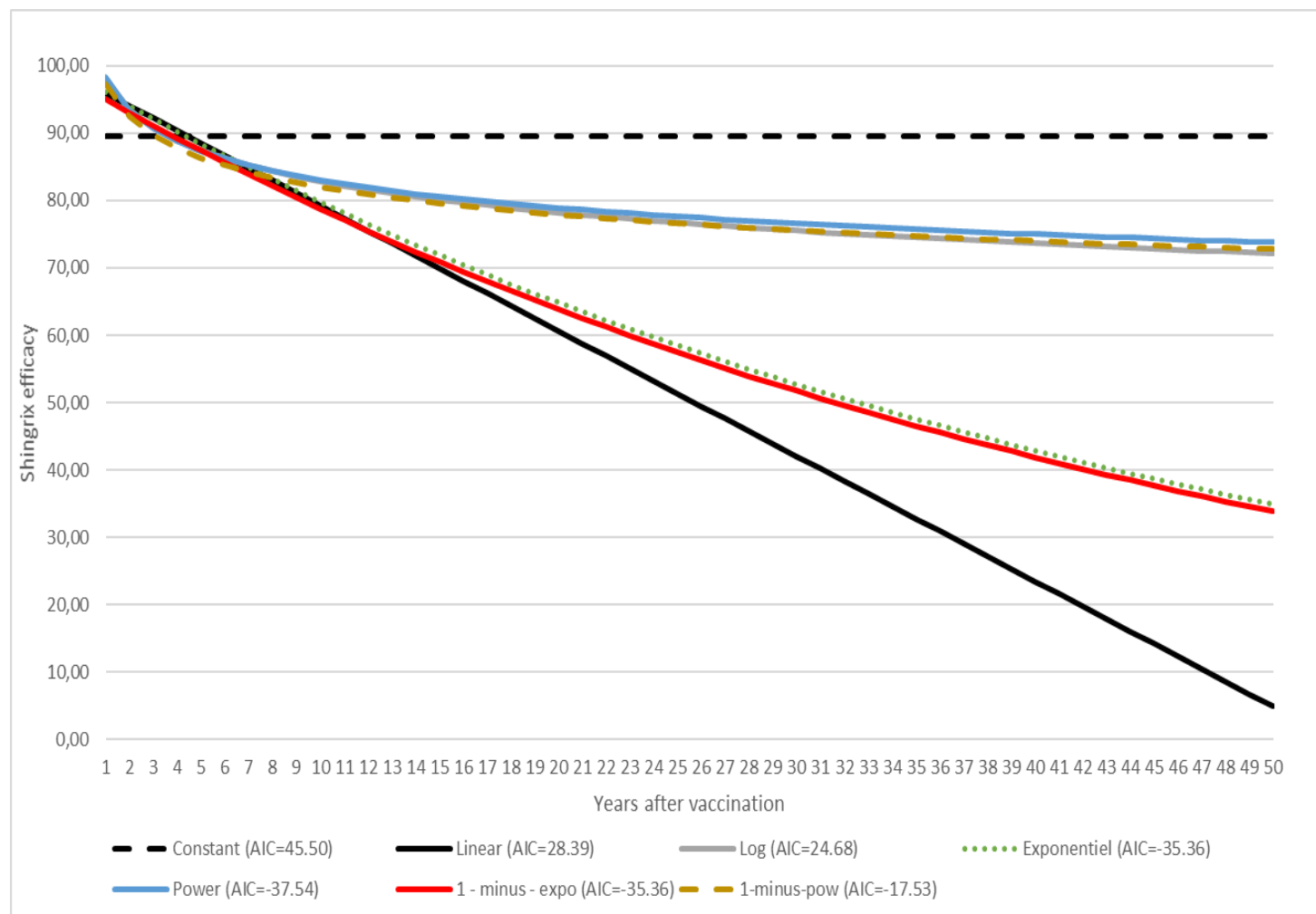


The best-case, resulting in the longest duration of protection is represented by the blue line (logarithmic function).  
The worst case, resulting in the shortest duration of protection is represented by the red line (1-exponential function).

Figure 14 – Vaccine efficacy of RZV against HZ simulated in Pieters et al. for adults aged 70 years and over



The best-case, resulting in the longest duration of protection is represented by the blue line (logarithmic function). The worst case, resulting in the shortest duration of protection is represented by the red line (1-exponential function). Note: the Power function was not considered as judged unrealistic.

**Figure 15 – Fitted functions to the ZOE-LTFU vaccine efficacy of Shingrix in adults  $\geq 50$  years**



### 6.3 Budget impact of HZ vaccination in Belgium

Next to cost-effectiveness, budget impact is often considered to be important to decision-makers.

The focus for this budget impact exercise is set on the strategies recently recommended by the Superior Health Council: vaccination of the immunocompetent adults aged  $\geq 60$  years and of the immunocompromised  $\geq 18$  years<sup>a</sup>.

#### 6.3.1 Budget impact in Pieters et al.

From the simulations in Pieters et al.,<sup>21</sup> vaccination with 2 doses of Shingrix (€ 140.26 per dose) would increase the total healthcare expenditure on HZ considerably while the savings obtained due to the reduction of the burden of illness would be limited. For example, vaccinating at 60 years would cost € 22.60 million upfront, while between € 0.43 to € 1.26 million could be avoided in HZ treatment costs (Table 50).

**Table 50 – Budget impact of vaccinating the immunocompetent population with Shingrix reported in Pieter et al. (costs in million €)**

| Age at vaccination                                                                                                   | 50 years           | 60 years           | 70 years           | 80 years           | 85 years           |
|----------------------------------------------------------------------------------------------------------------------|--------------------|--------------------|--------------------|--------------------|--------------------|
| <b>Vaccination costs (2 doses of Shingrix + administration costs in the immunocompetent population) <sup>§</sup></b> | € 24.13            | € 22.60            | € 17.84            | € 10.72            | € 7.87             |
| <b>HZ treatment costs saved (discounted at 3%):</b>                                                                  |                    |                    |                    |                    |                    |
| - <b>Shortest duration vaccine protection</b>                                                                        | € 0.36 (0.27–0.46) | € 0.43 (0.33–0.54) | € 0.40 (0.30–0.51) | € 0.48 (0.32–0.66) | € 0.34 (0.23–0.46) |
| - <b>Longest duration of vaccine protection</b>                                                                      | € 1.53 (1.27–1.83) | € 1.26 (1.03–1.52) | € 1.01 (0.78–1.25) | € 0.68 (0.45–0.92) | € 0.39 (0.26–0.53) |

Data reported: mean (95% credibility interval) from 5000 Monte Carlo simulations. <sup>§</sup> Vaccination costs: 46.2% of the immunocompetent population is vaccinated with 2 doses of Shingrix (at a cost of € 140.26 per dose) and the cost of vaccine administration is € 26.78 per dose. HZ: herpes zoster.

<sup>a</sup> The Superior Health Council recommends vaccination of immunocompromised  $\geq 16$  years. In our simulations however, the age of 18 years will be considered as the EMA market authorisation of Shingrix is for adults only.



### 6.3.2 Budget impact simulations for various prices of Shingrix

#### 6.3.2.1 Methods

In Pieters et al.,<sup>21</sup> vaccination costs were computed assuming a price of € 140.26 per dose. Recently however, the publicly available list price of Shingrix has been set up by the Belgian authorities at € 170.26 per dose. This is the retail price of the vaccine on the Belgian market without any price rebate (such rebates can be obtained by the Belgian/regional authorities through negotiations, bulk procurement programmes or other agreements). The simulations performed in this section use this latter price to better depict the budgets required if HZ vaccination is to be implemented. Price reductions are also simulated, as Pieters et al.<sup>21</sup> demonstrated that large price decreases are critical to reach cost-effectiveness. For example, Pieters et al.<sup>21</sup> identified that Shingrix price should drop to € 26.40 per dose such that vaccination at 60 years (assuming the longest duration of vaccine protection) would be cost-effective at the € 30 000 per QALY threshold (Table 43). Considering that the ICERs in Pieters et al. might have been overestimated as well as underestimated (see 6.4), a rounded cost of € 30 per dose was used for the budget impact. Other price reductions are simulated, ranging from a 10% to a 90% decrease (in 10% increments) of the official vaccine price.

The costs are computed from the perspective of the health care payers, being the institutional funders of vaccination (the national health insurer INAMI/RIZIV and/or the regional governments of the Flemish, Walloon and Brussels regions) and the patients. The distribution of the vaccine costs between the health authorities and the patients is not considered, as it is unknown whether Shingrix will be funded at all (if not funded the vaccine would be totally at the patient's charge); and if it is funded, which proportion of the total cost will be covered by the health authorities. As an illustration, the public price of the influenza vaccine (which is recommended and funded for healthy adults aged 65 years and over) is € 16.71 per dose in Belgium, of which a regular patient pays € 4.08, the rest being covered by the INAMI/RIZIV.

The budget impact simulations will quantify the upfront costs required to implement Shingrix vaccination. Return on investment and net costs will not be derived as they would require computing the avoided treatment costs. With their Markov model however, Pieters et al.<sup>21</sup> clearly highlighted that, in the immunocompetent population, the avoided HZ treatment costs would be much lower than the required vaccination costs (Table 50).

Three target groups will be considered: the whole Belgian population, the immunocompromised population and the immunocompetent population. Age-specific cohort sizes were obtained from the Belgian statistical office (STATBEL), for the population on 01/01/2022. The target population of adults aged ≥50 years comprises 4.6 million individuals (Table 51). The number of immunosuppressed adults was provided by the SPF Public Health, based on the following selection criteria: people with congenital immune disorders, chronic renal failure, inflammatory and/or autoimmune conditions treated with immunosuppressants, solid cancers and haematological malignancies treated within the past three years, or who received hematopoietic stem cell or solid organ transplantation (including in the pre-transplantation phase) and HIV-positive people whose CD4 cell count is less than 200 per mm<sup>3</sup> of blood. According to this definition, immunocompromised patients (≥18 years) represented 320 268 adults in Belgium.

We started by simulating the budgetary impact of the strategies recommended by the Superior Health Council, i.e. vaccination of all immunocompetents aged 60 years and over and vaccination of all immunocompromised aged 18 years and over. The budgets of more generic strategies considering the whole population were further explored, such as vaccination of those aged ≥50, ≥60, ≥70 and ≥80 years. Each time two budgets were computed: first the one-off budget in year 1 covering the vaccination of all the age-cohorts above a specified age (e.g. ≥60 years), and second the subsequent annual budgets (starting in year 2) covering the vaccination of each new cohort of individuals reaching a specified age (e.g. individuals turning 60 years).



**Table 51 – Size of the Belgian population (total and immunocompromised) per age group on 01/01/2022**

| Age (years)  | Total population § | Immunocompromised population # | Immunocompetent population |
|--------------|--------------------|--------------------------------|----------------------------|
| <18          | 2 314 231          | -                              | -                          |
| ≥18          | 9 269 777          | 320 268                        | 8 949 509                  |
| ≥50          | 4 601 079          | 237 258                        | 4 363 821                  |
| ≥60          | 3 015 078          | 165 878                        | 2 849 200                  |
| ≥70          | 1 624 279          | 86 562                         | 1 537 717                  |
| ≥80          | 643 721            | 29 912                         | 613 809                    |
| 0-49         | 6 982 929          |                                |                            |
| 50-54        | 783 107            | 1 586 001                      |                            |
| 55-59        | 802 894            |                                |                            |
| 60-64        | 745 762            | 1 390 799                      |                            |
| 65-69        | 645 037            |                                |                            |
| 70-74        | 559 225            | 980 558                        |                            |
| 75-79        | 421 333            |                                |                            |
| 80-84        | 304 814            | 304 814                        |                            |
| 85-89        | 213 118            |                                |                            |
| 90-94        | 99 421             | 338 907                        |                            |
| 95-99        | 23 807             |                                |                            |
| ≥100         | 2561               |                                |                            |
| <b>Total</b> | <b>11 584 008</b>  |                                |                            |

§ From the Belgian statistical office, structure of the Belgian population on 01/01/2022. # Data provided by the SPF Public Health.

The way the vaccine is paid (i.e., (totally or partially) reimbursed by the health authorities, or not funded) has no impact on the cost-effectiveness results as the perspectives of all health care payers are combined. However, vaccine uptake is expected to be higher in case of funding. As in Pieters et al.<sup>21</sup> vaccine uptake in the immunocompetent population was assumed to be 46.2%, similar to the 2018 uptake of influenza vaccination which is partially funded by the INAMI/RIZIV for the target groups recommended by the Superior Health Council, such as individuals aged 65 years and over.<sup>172</sup> Vaccine recipients were assumed to comply with both doses of the vaccine. For the immunocompromised patients we assumed that all efforts would be done to vaccinate this specific population and a 90% uptake was modelled.

In a separate scenario, we assumed that HZ vaccination would be recommended by the Superior Health Council, but would not be funded by the health authorities. Shingrix would then be administered in the private market only, with a lower vaccine uptake (assumed to be 20%) and be totally at the patient's charge (except for the INAMI/RIZIV share of the GP consultations required to inject the vaccine).

We assumed that the first dose of Shingrix would be co-administered with the influenza vaccine, and therefore imputed only half of the cost of a GP consultation for the administration of the first dose of Shingrix (€ 23.06 / 2 = € 11.5). The full cost of a GP consultation (€ 23.06) is incurred for the administration of the second dose of the vaccine, 2 months later. Of this cost, the INAMI/RIZIV reimburses € 17.06 (ordinary patient), and the patient co-payment is € 6.

### 6.3.2.2 Results

The total vaccination costs of the strategies recommended by the Superior Health Council and of strategies considering the whole population are presented in Table 52. The details of the total vaccination costs between vaccine acquisition and vaccine administration costs for the strategies listed in Table 52 (and other strategies) and for various decreases in vaccine prices are presented in Table 53 for the immunocompetent population, Table 54 for the immunocompromised population and Table 55 for the total (immunocompetent and immunocompromised) population.



### Vaccination strategies recommended by the Superior Health Council

The average upfront (year 1) budget for vaccinating 46.2% of the immunocompetent population aged 60 years and over would be € 493.77 million considering the list price of Shingrix (€ 170.26 per dose), the vaccine acquisition costs representing € 448.24 million and the administration costs € 45.53 million (€ 33.68 million for the INAMI/RIZIV and € 11.85 million for the patients). From year 2 on, the average budgets for each subsequent year would be € 24.37 million, with € 22.13 million for the vaccine costs and € 2.25 million for the administration costs (€ 1.66 million for the INAMI/RIZIV and € 0.58 million for the patients), see Table 52 and Table 53.

If the price of the vaccine is negotiated at € 30 per dose, the average one-off budget for vaccinating 46.2% of the immunocompetent population aged ≥60 years would be € 124.51 million, the vaccine acquisition costs representing € 78.98 million and the administration costs € 45.53 million (€ 33.68 million for the INAMI/RIZIV and € 11.85 million for the patients). From year 2 on, the average budgets for each subsequent year would be € 6.15 million, with € 3.90 million for the vaccine costs and € 2.25 million for the administration costs (€ 1.66 million for the INAMI/RIZIV and € 0.58 million for the patients), see Table 52 and Table 53.

In contrast to Zostavax, Shingrix is registered for the immunocompromised population. Considering the examined efficacy and safety (see section 4.4) of this recombinant vaccine in particularly vulnerable groups of patients with an impaired immune system, it can be assumed that Shingrix is safe and effective for immunocompromised people who also have an increased risk of HZ disease and complications. As the size of this population is limited while it is more vulnerable to (complications of) HZ and likely incurs a substantial part of the total HZ burden (see section 3.8.2), targeting the immunocompromised for Shingrix vaccination could considerably reduce the vaccination costs and increase the potential for net return on investment.

However, if Shingrix is targeted to immunocompromised adults ≥18 years while it remains at its official price of € 170.26, the one-off budget to start this vaccination would still be important and be roughly the same as the budget for vaccinating the immunocompetent population aged ≥60 years at the negotiated price of € 30 per dose. The budget would indeed be € 108.12 million in the first year to vaccinate 90% of the immunocompromised population ≥18 years at € 170.26 per dose; while it would only be slightly higher, at € 124.51 million, to vaccinate 46.2% of the immunocompetent population ≥60 years at € 30 per dose. The annual budgets for the subsequent years would amount € 0.78 million and € 6.15 for each population, respectively (Table 52).

At € 30 per dose, the average one-off budget for vaccinating 90% of the immunocompromised adults aged ≥18 years would be € 27.26 million, the vaccine acquisition costs representing € 17.29 million and the administration costs € 9.97 million (€ 7.38 million for the INAMI/RIZIV and € 2.59 million for the patients). From year 2 on, the average budgets for each subsequent year would be € 0.20 million, with € 0.12 million for the vaccine costs and € 0.07 million for the administration costs<sup>a</sup> (€ 0.05 million for the INAMI/RIZIV and € 0.02 million for the patients), see Table 52 and Table 54.

In total, implementing the two vaccination strategies recommended by the Superior Health Council would amount € 601.89 million in the first year and € 22.90 million each subsequent year at the official price of the vaccine. At € 30 per dose, the budget would be € 151.77 million the first year and € 6.34 for each following year, Table 52.

### Vaccination strategies of the total population

For pragmatic and organisational reasons, vaccination of the whole population above a specified age could be envisaged. Vaccination of the 50-year-olds was identified as being the most clinically effective strategy in Pieters et al.,<sup>21</sup> when assuming the longest duration of vaccine protection. This strategy would however be the extremely costly, with a first-year budget of € 797.37 million at the official vaccine price (€ 201.07 at € 30 per dose)

<sup>a</sup> Totals may not match due to rounding.



and € 27.14 million each subsequent year (€ 6.84 million yearly at € 30 per dose), Table 52. The distribution of those budget between vaccine acquisition and vaccine administration costs can be found in Table 55.

Targeting older age groups decreases the costs, but the budgets required are still high. For example, vaccination of the total population aged 70 years and over would cost € 281.49 million the first year, at the official vaccine price (€ 70.98 at € 30 per dose), and € 19.38 million each subsequent year (€ 4.88 million yearly at € 30 per dose), Table 51 and Table 55.

#### **Shingrix recommended but not funded at all – vaccination in the private sector**

If the vaccine is not funded at all, vaccination will occur in the private sector in the GP office and at a much lower uptake rate as the vaccine acquisition costs (at the list price of € 170.26 per dose) will be totally at the patients' charge. However, the vaccine administration costs will be shared between

the INAMI/RIZIV and the patient. It can further be expected that vaccination will mainly occur in the elderly, aged 70-years and over.

Each individual willing to be vaccinated would have to pay € 340.52 to obtain both doses of the vaccines (nevertheless with a small contribution from some health insurance companies), plus the costs of a GP consultation to administer the vaccines (at least for the second dose as the first dose of the vaccine could be administered during a consultation initiated for another reason). This represents a substantial cost. Shingrix vaccination in the private sector would further not be neutral for the INAMI/RIZIV as GP consultations are reimbursed. If 20% of the adults aged 70 years and over were vaccinated, this would cost the INAMI/RIZIV € 8.3 million in GP consultations.

If Shingrix vaccination effectively occurs in the private sector, in the GP office, attention should be paid to provide clear and pragmatic guidance to the GP's as to who should benefit most from this vaccine.

**Table 52 – Budget impact of the strategies recommended by the Superior Health Council and of other selected strategies**

| Vaccination age                             | Population        | Number of individuals | Vaccine uptake | Official vaccine price: € 170.26 per dose |                                 | Negotiated vaccine price: € 30 per dose |                                 |
|---------------------------------------------|-------------------|-----------------------|----------------|-------------------------------------------|---------------------------------|-----------------------------------------|---------------------------------|
|                                             |                   |                       |                | One-off budget in the first year          | Budget for each subsequent year | One-off budget in the first year        | Budget for each subsequent year |
| Strategies of the Superior Health Council   |                   |                       |                |                                           |                                 |                                         |                                 |
| 1 ≥60 years                                 | Immunocompetent   | 2 849 200             | 46,20%         | 493 768 696                               | 24 374 132                      | 124 511 693                             | 6 146 328                       |
| 2 ≥18 years                                 | Immunocompromised | 320 268               | 90%            | 108 122 157                               | 778 348                         | 27 264 735                              | 196 273                         |
| 3 1+2                                       | -                 | 3 169 468             | -              | 601 890 853                               | 22 904 869                      | 151 776 428                             | 6 342 601                       |
| Strategies considering the whole population |                   |                       |                |                                           |                                 |                                         |                                 |
| ≥50 years                                   | All               | 4 601 079             | 46,20%         | 797 370 764                               | 27 142 617                      | 201 069 821                             | 6 844 446                       |
| ≥60 years                                   | All               | 3 015 078             | 46,20%         | 522 515 490                               | 25 848 233                      | 131 760 657                             | 6 518 046                       |
| ≥70 years                                   | All               | 1 624 279             | 46,20%         | 281 488 883                               | 19 382 830                      | 70 981 934                              | 4 887 691                       |
| ≥80 years                                   | All               | 643 721               | 46,20%         | 111 557 377                               | 10 564 903                      | 28 130 981                              | 2 664 110                       |

*The budget impact represents the total vaccination costs, comprising the vaccine acquisition costs and the vaccine administration costs.*



**Table 53 – Budget impact of Shingrix in the immunocompetent population, for various vaccine prices and per type of budget (total, vaccine acquisition and vaccine administration costs)**

| In million €                                                                          |          |         | Reduction (%) in vaccine price and associated vaccine price per dose (€) |          |          |          |         |         |         |         |         |
|---------------------------------------------------------------------------------------|----------|---------|--------------------------------------------------------------------------|----------|----------|----------|---------|---------|---------|---------|---------|
|                                                                                       |          |         | 10%                                                                      | 20%      | 30%      | 40%      | 50%     | 60%     | 70%     | 80%     | 90%     |
| Vaccination target age                                                                | € 170.26 | € 30.00 | € 153.23                                                                 | € 136.21 | € 119.18 | € 102.16 | € 85.13 | € 68.10 | € 51.08 | € 34.05 | € 17.03 |
| Year 1 (One-off budget to vaccinate multiple-age cohorts)                             |          |         |                                                                          |          |          |          |         |         |         |         |         |
| Total vaccination costs (= Vaccine costs + total administration costs)                |          |         |                                                                          |          |          |          |         |         |         |         |         |
| ≥ 50 years                                                                            | 732.05   | 166.50  | 663.40                                                                   | 594.75   | 526.09   | 457.44   | 388.79  | 320.14  | 251.49  | 182.84  | 114.18  |
| ≥ 60 years                                                                            | 493.77   | 124.51  | 448.95                                                                   | 404.12   | 359.30   | 314.47   | 269.65  | 224.83  | 180.00  | 135.18  | 90.36   |
| ≥ 70 years                                                                            | 287.45   | 88.16   | 263.25                                                                   | 239.06   | 214.87   | 190.68   | 166.49  | 142.30  | 118.11  | 93.91   | 69.72   |
| ≥ 80 years                                                                            | 142.10   | 62.55   | 132.44                                                                   | 122.78   | 113.13   | 103.47   | 93.81   | 84.16   | 74.50   | 64.84   | 55.19   |
| Vaccine acquisition costs (2 doses)                                                   |          |         |                                                                          |          |          |          |         |         |         |         |         |
| ≥ 50 years                                                                            | 686.52   | 120.97  | 617.87                                                                   | 549.21   | 480.56   | 411.91   | 343.26  | 274.61  | 205.96  | 137.30  | 68.65   |
| ≥ 60 years                                                                            | 448.24   | 78.98   | 403.41                                                                   | 358.59   | 313.77   | 268.94   | 224.12  | 179.29  | 134.47  | 89.65   | 44.82   |
| ≥ 70 years                                                                            | 241.91   | 42.63   | 217.72                                                                   | 193.53   | 169.34   | 145.15   | 120.96  | 96.77   | 72.57   | 48.38   | 24.19   |
| ≥ 80 years                                                                            | 96.56    | 17.01   | 86.91                                                                    | 77.25    | 67.60    | 57.94    | 48.28   | 38.63   | 28.97   | 19.31   | 9.66    |
| Administration costs                                                                  | Total    | NIHDI   | Patient                                                                  |          |          |          |         |         |         |         |         |
| ≥ 50 years                                                                            | 69.74    | 51.59   | 18.14                                                                    |          |          |          |         |         |         |         |         |
| ≥ 60 years                                                                            | 45.53    | 33.68   | 11.85                                                                    |          |          |          |         |         |         |         |         |
| ≥ 70 years                                                                            | 24.57    | 18.18   | 6.39                                                                     |          |          |          |         |         |         |         |         |
| ≥ 80 years                                                                            | 9.81     | 7.26    | 2.55                                                                     |          |          |          |         |         |         |         |         |
| Subsequent years (annual budgets to vaccinate single cohorts reaching a specific age) |          |         |                                                                          |          |          |          |         |         |         |         |         |
| Total vaccination costs (= Vaccine costs + total administration costs)                |          |         |                                                                          |          |          |          |         |         |         |         |         |
| 50 years                                                                              | 25.92    | 6.54    | 23.57                                                                    | 21.21    | 18.86    | 16.51    | 14.16   | 11.80   | 9.45    | 7.10    | 4.74    |
| 60 years                                                                              | 24.37    | 6.15    | 22.16                                                                    | 19.95    | 17.74    | 15.52    | 13.31   | 11.10   | 8.89    | 6.67    | 4.46    |
| 70 years                                                                              | 18.26    | 4.61    | 16.61                                                                    | 14.95    | 13.29    | 11.63    | 9.97    | 8.32    | 6.66    | 5.00    | 3.34    |
| 80 years                                                                              | 10.07    | 2.54    | 9.16                                                                     | 8.24     | 7.33     | 6.42     | 5.50    | 4.59    | 3.67    | 2.76    | 1.84    |
| Vaccine acquisition costs (2 doses)                                                   |          |         |                                                                          |          |          |          |         |         |         |         |         |
| 50 years                                                                              | 23.53    | 4.15    | 21.18                                                                    | 18.82    | 16.47    | 14.12    | 11.77   | 9.41    | 7.06    | 4.71    | 2.35    |
| 60 years                                                                              | 22.13    | 3.90    | 19.91                                                                    | 17.70    | 15.49    | 13.28    | 11.06   | 8.85    | 6.64    | 4.43    | 2.21    |
| 70 years                                                                              | 16.58    | 2.92    | 14.92                                                                    | 13.26    | 11.61    | 9.95     | 8.29    | 6.63    | 4.97    | 3.32    | 1.66    |



|                             |              |              |                |      |      |      |      |      |      |      |      |
|-----------------------------|--------------|--------------|----------------|------|------|------|------|------|------|------|------|
| <b>80 years</b>             | 9.15         | 1.61         | 8.23           | 7.32 | 6.40 | 5.49 | 4.57 | 3.66 | 2.74 | 1.83 | 0.91 |
| <b>Administration costs</b> | <b>Total</b> | <b>NIHDI</b> | <b>Patient</b> |      |      |      |      |      |      |      |      |
| <b>50 years</b>             | 2.39         | 1.77         | 0.62           |      |      |      |      |      |      |      |      |
| <b>60 years</b>             | 2.25         | 1.66         | 0.58           |      |      |      |      |      |      |      |      |
| <b>70 years</b>             | 1.68         | 1.25         | 0.44           |      |      |      |      |      |      |      |      |
| <b>80 years</b>             | 0.93         | 0.69         | 0.24           |      |      |      |      |      |      |      |      |

*Note: budget impact for a 46.2% vaccine uptake as in Pieters et al. and similar to the 2018 uptake of influenza vaccination which is partially funded by the INAMI/RIZIV. Totals may no match due to rounding. NIHDI: National Institute for Health and Disability.*



**Table 54 – Budget impact of Shingrix in the immunocompromised population, for various vaccine prices and per type of budget (total, vaccine acquisition and vaccine administration costs)**

| In million €                                                                          |          |         | Reduction (%) in vaccine price and associated vaccine price per dose (€) |                 |                 |                 |                |                |                |                |                |
|---------------------------------------------------------------------------------------|----------|---------|--------------------------------------------------------------------------|-----------------|-----------------|-----------------|----------------|----------------|----------------|----------------|----------------|
| Vaccination target age                                                                | € 170.26 | € 30.00 | 10%<br>€ 153.23                                                          | 20%<br>€ 136.21 | 30%<br>€ 119.18 | 40%<br>€ 102.16 | 50%<br>€ 85.13 | 60%<br>€ 68.10 | 70%<br>€ 51.08 | 80%<br>€ 34.05 | 90%<br>€ 17.03 |
| Year 1 (One-off budget to vaccinate multiple-age cohorts)                             |          |         |                                                                          |                 |                 |                 |                |                |                |                |                |
| Total vaccination costs (= Vaccine costs + total administration costs)                |          |         |                                                                          |                 |                 |                 |                |                |                |                |                |
| ≥ 18 years                                                                            | 108.12   | 27.26   | 98.31                                                                    | 88.49           | 78.68           | 68.86           | 59.05          | 49.23          | 39.42          | 29.60          | 19.79          |
| ≥ 50 years                                                                            | 80.10    | 20.20   | 72.83                                                                    | 65.56           | 58.28           | 51.01           | 43.74          | 36.47          | 29.20          | 21.93          | 14.66          |
| Vaccine acquisition costs (2 doses)                                                   |          |         |                                                                          |                 |                 |                 |                |                |                |                |                |
| ≥ 18 years                                                                            | 98.15    | 17.29   | 88.34                                                                    | 78.52           | 68.71           | 58.89           | 49.08          | 39.26          | 29.45          | 19.63          | 9.82           |
| ≥ 50 years                                                                            | 72.71    | 12.81   | 65.44                                                                    | 58.17           | 50.90           | 43.63           | 36.36          | 29.08          | 21.81          | 14.54          | 7.27           |
| Administration costs                                                                  | Total    | NIHDI   | Patient                                                                  |                 |                 |                 |                |                |                |                |                |
| ≥ 18 years                                                                            | 9.97     | 7.38    | 2.59                                                                     |                 |                 |                 |                |                |                |                |                |
| ≥ 50 years                                                                            | 7.39     | 5.46    | 1.92                                                                     |                 |                 |                 |                |                |                |                |                |
| Subsequent years (annual budgets to vaccinate single cohorts reaching a specific age) |          |         |                                                                          |                 |                 |                 |                |                |                |                |                |
| Total vaccination costs (= Vaccine costs + total administration costs)                |          |         |                                                                          |                 |                 |                 |                |                |                |                |                |
| 18 years                                                                              | 0.78     | 0.20    | 0.71                                                                     | 0.64            | 0.57            | 0.50            | 0.43           | 0.35           | 0.28           | 0.21           | 0.14           |
| 50 years                                                                              | 2.38     | 0.60    | 2.16                                                                     | 1.95            | 1.73            | 1.52            | 1.30           | 1.08           | 0.87           | 0.65           | 0.44           |
| Vaccine acquisition costs (2 doses)                                                   |          |         |                                                                          |                 |                 |                 |                |                |                |                |                |
| 18 years                                                                              | 0.71     | 0.12    | 0.64                                                                     | 0.57            | 0.49            | 0.42            | 0.35           | 0.28           | 0.21           | 0.14           | 0.07           |
| 50 years                                                                              | 2.16     | 0.38    | 1.94                                                                     | 1.73            | 1.51            | 1.30            | 1.08           | 0.86           | 0.65           | 0.43           | 0.22           |
| Administration costs                                                                  | Total    | NIHDI   | Patient                                                                  |                 |                 |                 |                |                |                |                |                |
| 18 years                                                                              | 0.07     | 0.05    | 0.02                                                                     |                 |                 |                 |                |                |                |                |                |
| 50 years                                                                              | 0.22     | 0.16    | 0.06                                                                     |                 |                 |                 |                |                |                |                |                |

Note: budget impact for a 90% vaccine uptake. Totals may no match due to rounding. NIHDI: National Institute for Health and Disability.



**Table 55 – Budget impact of Shingrix in the total Belgian population, for various vaccine prices and per type of budget (total, vaccine acquisition and vaccine administration costs)**

| In million €                                                                          |          |         | Reduction (%) in vaccine price and associated vaccine price per dose (€) |          |          |          |         |         |         |         |         |
|---------------------------------------------------------------------------------------|----------|---------|--------------------------------------------------------------------------|----------|----------|----------|---------|---------|---------|---------|---------|
|                                                                                       |          |         | 10%                                                                      | 20%      | 30%      | 40%      | 50%     | 60%     | 70%     | 80%     | 90%     |
| Vaccination target age                                                                | € 170.26 | € 30.00 | € 153.23                                                                 | € 136.21 | € 119.18 | € 102.16 | € 85.13 | € 68.10 | € 51.08 | € 34.05 | € 17.03 |
| Year 1 (One-off budget to vaccinate multiple-age cohorts)                             |          |         |                                                                          |          |          |          |         |         |         |         |         |
| Total vaccination costs (= Vaccine costs + total administration costs)                |          |         |                                                                          |          |          |          |         |         |         |         |         |
| ≥ 50 years                                                                            | 797.37   | 201.07  | 724.99                                                                   | 652.60   | 580.22   | 507.83   | 435.45  | 363.07  | 290.68  | 218.30  | 145.91  |
| ≥ 60 years                                                                            | 522.52   | 131.76  | 475.08                                                                   | 427.65   | 380.22   | 332.78   | 285.35  | 237.92  | 190.48  | 143.05  | 95.62   |
| ≥ 70 years                                                                            | 281.49   | 70.98   | 255.94                                                                   | 230.38   | 204.83   | 179.28   | 153.72  | 128.17  | 102.62  | 77.06   | 51.51   |
| ≥ 80 years                                                                            | 111.56   | 28.13   | 101.43                                                                   | 91.30    | 81.18    | 71.05    | 60.92   | 50.80   | 40.67   | 30.54   | 20.41   |
| Vaccine acquisition costs (2 doses)                                                   |          |         |                                                                          |          |          |          |         |         |         |         |         |
| ≥ 50 years                                                                            | 723.84   | 127.54  | 651.46                                                                   | 579.07   | 506.69   | 434.31   | 361.92  | 289.54  | 217.15  | 144.77  | 72.38   |
| ≥ 60 years                                                                            | 474.33   | 83.58   | 426.90                                                                   | 379.47   | 332.03   | 284.60   | 237.17  | 189.73  | 142.30  | 94.87   | 47.43   |
| ≥ 70 years                                                                            | 255.53   | 45.03   | 229.98                                                                   | 204.43   | 178.87   | 153.32   | 127.77  | 102.21  | 76.66   | 51.11   | 25.55   |
| ≥ 80 years                                                                            | 101.27   | 17.84   | 91.14                                                                    | 81.02    | 70.89    | 60.76    | 50.64   | 40.51   | 30.38   | 20.25   | 10.13   |
| Administration costs                                                                  | Total    | NIHDI   | Patient                                                                  |          |          |          |         |         |         |         |         |
| ≥ 50 years                                                                            | 73.53    | 54.40   | 19.13                                                                    |          |          |          |         |         |         |         |         |
| ≥ 60 years                                                                            | 48.18    | 35.65   | 12.54                                                                    |          |          |          |         |         |         |         |         |
| ≥ 70 years                                                                            | 25.96    | 19.20   | 6.75                                                                     |          |          |          |         |         |         |         |         |
| ≥ 80 years                                                                            | 10.29    | 7.61    | 2.68                                                                     |          |          |          |         |         |         |         |         |
| Subsequent years (annual budgets to vaccinate single cohorts reaching a specific age) |          |         |                                                                          |          |          |          |         |         |         |         |         |
| Total vaccination costs (= Vaccine costs + total administration costs)                |          |         |                                                                          |          |          |          |         |         |         |         |         |
| 50 years                                                                              | 27.14    | 24.68   | 22.21                                                                    | 19.75    | 17.29    | 14.82    | 12.36   | 9.89    | 7.43    | 4.97    | 27.14   |
| 60 years                                                                              | 25.85    | 23.50   | 21.16                                                                    | 18.81    | 16.46    | 14.12    | 11.77   | 9.42    | 7.08    | 4.73    | 25.85   |
| 70 years                                                                              | 19.38    | 17.62   | 15.86                                                                    | 14.10    | 12.34    | 10.59    | 8.83    | 7.07    | 5.31    | 3.55    | 19.38   |
| 80 years                                                                              | 10.56    | 9.61    | 8.65                                                                     | 7.69     | 6.73     | 5.77     | 4.81    | 3.85    | 2.89    | 1.93    | 10.56   |
| Vaccine acquisition costs (2 doses)                                                   |          |         |                                                                          |          |          |          |         |         |         |         |         |
| 50 years                                                                              | 24.64    | 22.18   | 19.71                                                                    | 17.25    | 14.78    | 12.32    | 9.86    | 7.39    | 4.93    | 2.46    | 24.64   |
| 60 years                                                                              | 23.46    | 21.12   | 18.77                                                                    | 16.43    | 14.08    | 11.73    | 9.39    | 7.04    | 4.69    | 2.35    | 23.46   |
| 70 years                                                                              | 17.60    | 15.84   | 14.08                                                                    | 12.32    | 10.56    | 8.80     | 7.04    | 5.28    | 3.52    | 1.76    | 17.60   |



|                             |              |              |                |      |      |      |      |      |      |      |      |
|-----------------------------|--------------|--------------|----------------|------|------|------|------|------|------|------|------|
| <b>80 years</b>             | 9.59         | 8.63         | 7.67           | 6.71 | 5.75 | 4.80 | 3.84 | 2.88 | 1.92 | 0.96 | 9.59 |
| <b>Administration costs</b> | <b>Total</b> | <b>NIHDI</b> | <b>Patient</b> |      |      |      |      |      |      |      |      |
| <b>50 years</b>             | 2.50         | 1.85         | 0.65           |      |      |      |      |      |      |      |      |
| <b>60 years</b>             | 2.38         | 1.76         | 0.62           |      |      |      |      |      |      |      |      |
| <b>70 years</b>             | 1.79         | 1.32         | 0.47           |      |      |      |      |      |      |      |      |
| <b>80 years</b>             | 0.97         | 0.72         | 0.25           |      |      |      |      |      |      |      |      |

*Note: budget impact for a 46.2% vaccine uptake as in Pieters et al. and similar to the 2018 uptake of influenza vaccination which is partially funded by the INAMI/RIZIV. NIHDI: National Institute for Health and Disability.*



## 6.4 Discussion

The **effectiveness and cost-effectiveness of Shingrix** vaccination in adults modelled in Pieters et al.<sup>21</sup> was highly dependent on the potential long-term duration of protection of this vaccine.

In this study, when the longest duration of protection for Shingrix was modelled, providing 40 to 50 years of protection without significant waning, starting vaccination at an early age (50-year) was the most clinically effective and cost-effective option. By contrast, when the shortest duration of protection for Shingrix was modelled, providing no more than 7 to 10 years of protection, starting vaccination at a later age (80- or 85-year) was the most clinically effective and cost-effective option. In both cases however, the ICERs were high, at € 87 412 per QALY gained in 50-year-olds assuming the longest duration of protection; and € 146 082 per QALY gained in 80-year-olds assuming the shortest duration of protection.

According to our assessment, the most favourable ICERs in Pieters et al. may be overestimated, as well as underestimated. On the one hand, our simulations on the 8-years ZOE-LTFU data showed that the hypothesis of a long duration of vaccine protection is plausible though too optimistic. The lowest ICER is thus likely underestimated. On the other hand, Pieters et al. assumed that only HZ episodes in immunocompetent people can be avoided by vaccination, hence overestimating the ICERs, as consideration of the whole population (including the immunocompromised) is likely to improve the results.

These ICERs provided by Pieters et al. lie well above those of childhood vaccine interventions that have been funded or reimbursed in Belgium in the past. They also lie well above the ICER for influenza vaccination of adults that is funded for the target groups recommended by the Superior Health Council, e.g. for healthy adults aged 65 years and over. In KCE report

204,<sup>178</sup> the option of increasing the coverage of influenza vaccination in the ≥65 years (while decreasing it in the young healthy adults below 50 years, which are not a current target group), was estimated to be cost-effective with ICERs below € 19 125 per QALY gained or even generating savings. The public price of the influenza vaccines is € 16.71<sup>a</sup> per dose in Belgium, of which a regular patient only pays € 4.08, the rest being covered by the INAMI/RIZIV.

The ICERs for Shingrix are also above those of other adult vaccination strategies that have not been reimbursed in Belgium, such as pneumococcal vaccination that is recommended for healthy adults aged 65–85 years and that was estimated to cost on average € 83 000, € 57 000 and € 52 000 per QALY gained in 50-64, 65-74 and 75-84 year-old (Pneumovax 23, public price of € 33.66 per dose<sup>a</sup>).<sup>179</sup> Other interventions that have not been funded had ICERs higher than those for Shingrix, such as hepatitis A vaccination in adults that was estimated to cost € 200 000 per QALY gained (public price per dose of € 43.31 for Avaxim 160 and € 30.04 for Havrix and Vaqta 50<sup>a</sup>),<sup>180, 181</sup> or pneumococcal vaccination of adults with Prevenar 13 whose ICERs were estimated at about € 201 000, € 171 000 and € 338 000 per QALY gained in 50-64, 65-74 and 75-84 year-olds, respectively (public price of € 74.55 per dose<sup>a</sup>).<sup>179</sup>

There is however no willingness-to-pay threshold defined in Belgium for deciding on the introduction of health interventions.<sup>170</sup>

The sensitivity analyses in Pieters et al.<sup>21</sup> showed that an increase in the burden of HZ (through a higher probability of PHN and a change in the proportion of patients per disease pain severity) would improve the results for Shingrix, e.g. the ICER decreased from € 87 412 in the base-case down to € 59 069 in the “Increased burden of disease” scenario analysis<sup>b</sup> for the vaccination of adults at 50 years and assuming the longest duration of

<sup>a</sup> The source for the vaccine price is the Centre belge d'information pharmacothérapeutique / Belgisch centrum voor farmacotherapeutische informatie (CBIP/BCFI), accessed in June 2022. Note that similar prices were modelled in the referenced cost-effectiveness analysis.

<sup>b</sup> In this scenario, the proportion of PHN (per HZ case) and the distribution of pain severity for HZ and PHN are taken from Oxman et al.<sup>25</sup> instead of Gauthier et al.<sup>49</sup> in the base-case.



protection. These changes were however not sufficient for Shingrix vaccination to be considered cost-effective.

Shingrix price reductions would considerably improve the cost-effectiveness of Shingrix-containing adult vaccination strategies. But in the most favourable situation, i.e. assuming a long duration of vaccine protection, the price for 1 dose of Shingrix should drop to € 37.49 per dose (instead of € 140.26 in the model base-case, and while the public price is € 170.26) such that vaccination at 50 years would cost € 30 000 per QALY gained.

As in Pieters et al.,<sup>21</sup> two recent European non-sponsored studies reported similar, rather pessimistic, results about the cost-effectiveness of Shingrix. The 2018 Dutch study by De Boer et al.<sup>56</sup> found that vaccination with Shingrix would not be cost-effective at the current vaccine price, considering the threshold of € 20 000 per QALY gained which is the general Dutch cost-effectiveness threshold for healthcare interventions such as vaccination. They found that the maximum vaccine cost per series (2 doses) of Shingrix to remain cost-effective at this threshold was € 64 for 50-year-olds, € 104 for 60-year-olds, € 109 for 70-year-olds, and € 106 for 80-year-olds. Hence, at the optimum vaccination age of 70 years, the vaccine should cost at most € 109 per series to remain cost-effective. The economic evaluation was performed from the societal perspective and the targeted population was restricted to immunocompetent adults. In the 2021 Swedish study by Wolff et al.,<sup>182</sup> the cost-effectiveness of Shingrix was explored in a sensitivity analysis while the base-case relied on Zostavax. Although Shingrix was available in the Swedish private market since 2020, this vaccine was not considered relevant for a national vaccination programme at the time of this study due to the small number of doses available. With an assumed cost of \$ 144 per dose and under a societal perspective, vaccination of the overall Swedish population aged 65 years was not found to be cost-effective, with an ICER valued at € 170 000 per QALY gained.

By contrast to those unfavorable results, many other recent economic evaluations (both sponsored and non-sponsored) performed in setting similar to the Belgian context reported positive results.

The GSK-sponsored studies consistently reported that vaccinating the overall population (i.e. the immunocompetent and the immunocompromised) aged ≥50-years with Shingrix is a cost-effective option. These studies were all based on the same ZONA model, a static multi-cohort Markov model built in MS Excel and that followed hypothetical cohorts of 1 million people over their lifetime. In Germany, the ICERs were € 35 000, € 37 000 and € 44 000 per QALY gained, for the age cohorts ≥ 50, ≥ 60 and ≥ 70 years, respectively, from a societal perspective and with a cost of € 110 per dose.<sup>176</sup> In Canada, the ICER for Shingrix was CAN\$ 28 400 in persons aged ≥ 60 years, from the health care payer perspective and with a vaccine cost of CAN\$ 122 per dose. Both studies modelled vaccine efficacy based on the 4-year vaccine persistence data from the ZOE-50 and ZOE-70 trials.<sup>183</sup> In 2021, the German study was updated with the latest 8-year vaccine efficacy and waning estimates from the ZOE-LTFU trial. This resulted in improved ICERs valued at € 32 000, € 33 000, and € 40 000 per QALY gained for the age cohorts ≥ 50, ≥ 60 and ≥ 70 years, respectively. The ICERs for vaccinating single-age cohorts were also reported and were approximately € 30 000, € 26 000, and € 35 000 per QALY gained when starting vaccination at 50-, 60-, and 70-years, respectively.<sup>184</sup> Finally, a 2021 GSK-sponsored abstract was the first to report about the cost-effectiveness of Shingrix in the immunocompromised population in the USA. Shingrix was estimated to be cost-effective (at the US willingness to pay threshold \$ 100 000 per QALY) in this specific population with ICERs valued at \$ 95 972 per QALY gained for Hodgkin lymphoma and \$ 67 682 for breast cancer patients, from a societal perspective. Methodological details are awaited with the full text publication of this study.<sup>1</sup>

Other non-sponsored studies similarly reported favorable results about the cost-effectiveness of Shingrix. For the USA, a 2019 study by Carpenter et al. reported that vaccinating the immunocompetent adults with Shingrix at age 50 years would cost \$ 91 000 per QALY while dropping to \$ 19 300 and \$ 1400 per QALY when vaccinating at age 60 and 70, respectively. Vaccination was judged to be cost-effective as all ICERs were below the US willingness-to-pay threshold of \$ 100 000 per QALY. The study was performed from the societal perspective and Shingrix price was \$ 102.19 per dose.<sup>185</sup> In Prosser et al.<sup>186</sup> even lower ICERs were reported, that is \$47 000,



\$ 26 000, \$ 11 600, \$ 10 000, and \$ 27 000 when vaccinating the US immunocompetent adults at 50, 60, 70, 80, and 90 years, respectively, with a price of \$ 140 per dose of Shingrix and for the societal perspective. As expected in this largely retired population, ICERs for the health care payer perspective were only slightly higher at \$ 61 000, \$ 37 000, \$ 20 000, \$ 16 500, and \$ 32 000 per QALY for the same ages at vaccination. In Le et al.,<sup>187</sup> the ICERs were \$ 30 000, \$ 20 000 and \$ 21 726 per QALY gained when vaccinating the immunocompetents at 60, 70 and 80 years, respectively. The perspective adopted in this study was the societal perspective, and a cost of \$ 140 per dose of Shingrix was modelled. In Canada, the study by Drolet et al.<sup>188</sup> found that whatever the age at vaccination (50, 60, 70 or 80 years) the median cost-effectiveness ratios (from the health care payer perspective) varied between cost-saving and \$ 26 000 per QALY gained for a vaccine cost ranging from \$ 100 to \$200 per dose. Vaccination between 60 to 80 years generated the most efficient results (between cost-saving and \$ 10 900 per QALY gained). This study informed the 2018 updated Canadian recommendations on herpes zoster vaccination.<sup>189</sup> Finally, in Germany, the economic evaluation that backed up the German recommendations on the use of Shingrix reported that among the various ages at vaccination simulated (between 50 and 80 years in 5 year steps), the lowest ICER (€ 24 000 per QALY gained) was achieved with vaccination of the overall population at age 65 years. The study was performed from the societal perspective and a low vaccine cost was modelled (€ 84 per dose).<sup>177, 190</sup>

The cost-effectiveness of RZV vaccination in specific populations such as the immunocompromised still needs to be explored, as only one GSK-sponsored conference abstract on this topic was published so far.<sup>1</sup>

Following the recent recommendations of the Superior Health Council, the **budget-impact analysis** showed that vaccination of the immunocompetent population aged ≥60 years, at a 46.2% uptake and at the official vaccine price (€ 170.26 per dose) would cost € 493.77 million the first year and € 24.37 million annually afterwards to vaccinate each new cohort of immunocompetent individual turning 60 years. However, Pieters et al. identified that the price of the vaccine should decrease to € 26.40 such that vaccination of the immunocompetents aged 60 years would be cost-effective

at the € 30 000 per QALY threshold. At a cost of € 30 per dose, the budget required for this strategy would be € 124.51 million the first year, and € 6.15 million annually afterwards.

Targeting vaccination to people most at risk of experiencing severe HZ and PHN, such as the immunocompromised, could improve the cost-effectiveness and the budget impact of Shingrix. However, at the official vaccine price (€ 170.26 per dose) and assuming that all efforts are made to reach this specific population with a 90% uptake, the budget remains high at € 108.12 million the first year and € 0.78 million each subsequent year. At a negotiated price of € 30 per dose, the budget would decrease to € 27.26 million the first year and € 0.20 million each following year.

If vaccination with Shingrix was not funded at all, vaccination would occur in the private sector in the GP offices and the vaccine acquisition costs (2 doses at the list price of € 170.26 per dose) would be totally at the patients' charge. Shingrix vaccination in the private sector would further not be neutral for the INAMI/RIZIV as GP consultations are reimbursed.



## 7 INTERNATIONAL RECOMMENDATIONS REGARDING HERPES ZOSTER VACCINATION

A limited, but growing number of countries in the Europe and worldwide have recommended Herpes Zoster vaccination and implemented it into their national immunisation programme. An overview of recommendations and funding of herpes zoster vaccines in Europe can be found in Table 56. After the marketing authorisation of ZVL by the European Medicines Agency (EMA) in 2006, Austria, Czech Republic, France, Greece, Italy and Switzerland recommended ZVL for routine vaccination and the costs were (and are) covered at national level in France, Greece and Italy. After marketing authorisation of RZV by EMA in 2018, Estonia, Spain and Germany recommended RZV and Austria stopped recommending ZVL but switched to RZV. In Czech Republic and Italy no preference between RZV and ZVL was mentioned in their recommendations. The Netherlands recommended RZV in 2019, but the health council recommended its funding conditionally with reservations about the program's cost-effectiveness. The eligible age for vaccination of immunocompetent adults varies between 50 (Austria, Czech Republic) and 65 years (Estonia, France, Italy, Switzerland, Spain), with some countries deciding on 60 years (and older) (Germany, Greece, The Netherlands and UK).<sup>190-192</sup> Shingrix received 9 national clinical recommendations in Europe up to February 2022 (Germany, UK, The Netherlands, Spain, Czech Republic, Austria, Italy, Switzerland and Estonia).<sup>193-195</sup> In Sweden and Ireland Shingles vaccine can be given (may be considered) to people over the age of 50 years on individual basis, but is not included in the national immunisation recommendations.<sup>196, 197</sup> Very recently (August 2022), the Superior Health Council of Belgium also recommended RZV in immunocompetent adults  $\geq 60$  years and in

immunocompromised patients  $\geq 16$  years (including patients receiving treatment with Janus kinase (JAK) inhibitors).<sup>a</sup>

Germany, Austria and Ireland specified in their recommendation that the Shingrix vaccine can also be administered after a herpes zoster episode but recommend an interval, varying from when the acute disease is over and symptoms have subsided until 1 year after the herpes zoster episode, before vaccination.<sup>197-199</sup>

Arguments for choosing the specific age cut-off include epidemiological and cost-effectiveness data. For example in Germany, although the lowest cost per QALY was achieved with vaccination at 65 years, the Standing Committee on Vaccination (STIKO) decided 60 years to be the most favourable age because the difference in cost per QALY between vaccination at age 60 and age 65 years is small and because vaccination at age 60 has the greatest effect in preventing herpes zoster cases, and preventing herpes zoster is a key prerequisite to prevent complications and sequelae. Moreover, the number needed to vaccinate is the same for vaccination at 60 and 65 years.<sup>190</sup> The vaccine is also recommended in individuals  $\geq 50$ y with underlying health conditions such as congenital or acquired immunodeficiency, immunosuppression, HIV, rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, chronic obstructive pulmonary disease, bronchial asthma, chronic renal failure and diabetes mellitus. The vaccination costs in Germany are covered by the statutory health insurances, if the vaccination is recommended by the STIKO. About 85% of German citizens are covered by statutory health insurances. Vaccines are sold by pharmacies at the market price.

The Dutch health council decided on vaccination at the age of 60 years because this would achieve the highest efficiency and the most health gain. They calculated in a base-case analysis, the most health gain would be derived from vaccination between 60 and 70 years. Maximal price for vaccination to reach the threshold of € 20 000 per QALY was practically the

<sup>a</sup> The advice of the Superior Health Council of Belgium can be found at (accessed 09/09/2022): [20220906-css-9684-herpes-zoster-vweb.pdf](https://www.vlaanderen.be/document/20220906-css-9684-herpes-zoster-vweb.pdf) ([belgium.be](https://belgium.be))



same (104 euro in case of vaccination at 60 years, 109 euro in case of vaccination at 70 years). The Dutch health council estimated it important that RZV vaccination would not cost more than the € 20 000 per QALY threshold and highlighted that this was not the case at the current vaccine list prices. The council stated that vaccine prices should decrease to reach this goal.<sup>191</sup> Meanwhile, there is no cover from national health insurance.

In the UK, the advices of the Joint committee on vaccination and immunization (JCVI) on 6 February 2019 concluded that vaccination with RZV of immunocompetent individuals was likely to be the most cost-effective strategy from 56 to 71 years (a range from 50 to 90 years was explored). The highest net monetary benefit was reached at 65 years. However, the committee recommended zoster vaccination should be offered routinely at the age of 60 years because a greater number of cases would be prevented. The Committee recommended that those aged between 60 and 70 years should also be offered Shingrix. Regarding immunization of immunocompromised population, the committee concluded RZV would be cost-effective at any age from 50 to 90 years and they recommended that Shingrix should be offered to immunocompromised individuals aged 50 and over.<sup>200</sup> The JCVI further added that all the recommendations provided would be subject to procurement of Shingrix® at a cost-effective price. Although plans exist to expand the age eligibility for RZV vaccination in the UK, it seems to be still limited to adults between 70 and 79 years in whom ZVL vaccination is contra-indicated.<sup>201</sup> Availability of RZV has been an issue in multiple European countries causing delay in actually following recommendations.<sup>192</sup>

In Belgium, the Superior Health Council of Belgium followed a line of argument similar to Germany, UK, and the Netherlands, opting for an

eligibility age (60 years) deemed to have the best clinical return on investment in immunocompetent individuals. The Council also recommended the policy-makers to account for upcoming cost-effectiveness analysis (i.e. the current report).

Recommendations for RZV vaccination of adults with increased risk for herpes zoster mostly because of immunodeficient disease or immunosuppressive therapy have been made by Austria, Czech Republic, Spain, Switzerland and The Netherlands from the age of 18 years and from the age of 50 years by Germany, Ireland, Italy and UK.<sup>191-193</sup>

Worldwide we note recommendations for RZV vaccination of immunocompetent adults from 50 years in US and Canada and of immunocompromised adults from 19 years in the US and 50 years in Canada.<sup>163, 192, 202, 203</sup> ZVL vaccine was no longer offered in the US after November 2020 and RZV vaccine is covered by private insurance or pay out of pocket.<sup>192</sup> Medicare Part D plans cover the shingles vaccine, but there may be a cost to you depending on the plan.<sup>204</sup> Australia recommends herpes zoster vaccination (RZV or ZVL) from 50 years for immunocompetent and from 18 years for immunocompromised adults.<sup>205</sup> For immunocompetent adults, RZV is preferred over ZVL. ZVL is offered free of charge through the NIP (National immunisation program) between the age of 70 and 79 years. RZV is preferred above ZVL, but is not funded by the NIP.<sup>192</sup> For immunocompromised adults ZVL can only be used in case of mild immunocompromised status, otherwise RZV should be used.<sup>205</sup>



Table 56 – Shingrix recommendations in Europe

| Country                               | Recommending body/bodies                        | Vaccine | Recommended from  | Age    | Specified high risk group                                                                                                                                                                                                                             | Funded                                                    |
|---------------------------------------|-------------------------------------------------|---------|-------------------|--------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------|
| <b>Austria</b> <sup>198</sup>         | National Vaccination Committee                  | ZVL     | 2017-2019         | ≥60y   |                                                                                                                                                                                                                                                       | No                                                        |
|                                       |                                                 | RZV     | 2019              | 18-49y | Seriously underlying disease, severe immunosuppression, based on individual case basis                                                                                                                                                                |                                                           |
|                                       |                                                 |         |                   | ≥50y   |                                                                                                                                                                                                                                                       |                                                           |
| <b>Czech Republic</b> <sup>206</sup>  | Czech Vaccination society                       | RZV/ZVL | 2019              | 18-49y | Immunocompromised                                                                                                                                                                                                                                     | No                                                        |
|                                       |                                                 |         |                   | ≥50y   |                                                                                                                                                                                                                                                       |                                                           |
| <b>Estonia</b> <sup>195</sup>         | Health board/ Terviseamet                       | RZV/ZVL | yes               | ≥65y   |                                                                                                                                                                                                                                                       | No                                                        |
| <b>Germany</b> <sup>199</sup>         | Standing Committee on Vaccination (STIKO)       | ZVL     | Never recommended |        |                                                                                                                                                                                                                                                       | No                                                        |
|                                       |                                                 | RZV     | 2018              | ≥50y   | Congenital or acquired immunodeficiency, immunosuppression, HIV, rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, chronic obstructive pulmonary disease, bronchial asthma, chronic renal failure and diabetes mellitus | Yes                                                       |
|                                       |                                                 |         |                   | ≥60y   |                                                                                                                                                                                                                                                       |                                                           |
| <b>Ireland</b> <sup>197</sup>         | National Immunisation Advisory Committee (NIAC) | RZV     | 2018*             | ≥50y   | Haematological malignancies and solid tumours                                                                                                                                                                                                         | No                                                        |
|                                       |                                                 | RZV/ZVL | 2018              | ≥50y   | Prior to immunosuppressive therapy or solid organ transplant (RZV preferred over ZVL)                                                                                                                                                                 |                                                           |
|                                       |                                                 |         |                   | ≥50y   |                                                                                                                                                                                                                                                       |                                                           |
| <b>Italy</b> <sup>207§</sup>          | Italian Ministry of Health                      | RZV/ZVL | 2017**            | ≥50y   | Diabetes Mellitus, cardiovascular disease, chronic obstructive pulmonary disease, prior to immunosuppressive therapy                                                                                                                                  | Yes                                                       |
|                                       |                                                 |         |                   | 65y    |                                                                                                                                                                                                                                                       |                                                           |
| <b>The Netherlands</b> <sup>191</sup> | Health Council of the Netherlands               | ZVL     | Never recommended |        |                                                                                                                                                                                                                                                       | No                                                        |
|                                       |                                                 | RZV     | 2019              | ≥18y   | Immunocompromised patients, based on individual case basis or guidelines on off-label use in certain patient groups                                                                                                                                   | Conditional (vaccine pricing to reach cost-effectiveness) |
|                                       |                                                 |         |                   | ≥60y   |                                                                                                                                                                                                                                                       |                                                           |



|                                   |                                                             |         |                                |         |                                                                                                                                 |                 |
|-----------------------------------|-------------------------------------------------------------|---------|--------------------------------|---------|---------------------------------------------------------------------------------------------------------------------------------|-----------------|
| <b>Spain</b> <sup>208</sup>       | International Council of the Spanish National Health System | ZVL     | Pilot in Castilla-Leon in 2015 | 60-64y  | Chronic obstructive pulmonary disease                                                                                           | ?               |
|                                   |                                                             | RZV     | 2021                           | ≥18y    | Haematopoietic stem cell transplant, solid organ transplant, anti-JAK treatment, HIV, haematological malignancies, solid tumour | Planned in 2022 |
| <b>UK</b> <sup>200</sup>          | Joint Committee on Vaccination and Immunisation (JCVI)      | ZVL     | 2013-2014                      | 70-79y  |                                                                                                                                 | Yes             |
|                                   |                                                             | RZV     | 2019**                         | ≥50y    | Immunocompromised individuals                                                                                                   |                 |
| <b>France</b> <sup>209</sup>      | Haut Conseil de la Santé Public                             | ZVL     | 2015                           | 65-74y  |                                                                                                                                 | Yes             |
| <b>Greece</b> <sup>210</sup>      | Ministry of Health                                          | ZVL     | 2011                           | ≥60y    |                                                                                                                                 | Yes             |
| <b>Sweden</b> <sup>196</sup>      | Folkhälsomyndigheten                                        | ZVL/RZV | permissive                     | ≥50y    | Depending on individual risk factors for developing shingles and its complication                                               | No              |
| <b>Switzerland</b> <sup>193</sup> | Federal Commission for Vaccination                          | RZV     | 2022                           | ≥18y    | Severe immunodeficiency                                                                                                         | Yes             |
|                                   |                                                             |         |                                | ≥50y    | Immunodeficiency                                                                                                                |                 |
|                                   |                                                             |         |                                | ≥65y    |                                                                                                                                 |                 |
|                                   |                                                             | ZVL     | 2017-2022                      | ≥50y    | If immunosuppression                                                                                                            | No              |
|                                   |                                                             |         | 2017                           | 65-79y# |                                                                                                                                 |                 |

\* available from 2020, \*\* available from 2021, § update expected, # for people who prefer ZVL over RZV.



## 8 CONCLUSION

There is high quality evidence that Shingrix is very effective in preventing HZ in immunocompetent individuals  $\geq 50$  years over a period of approximately 4 years. Vaccine efficacy appears similar in all age ranges. There are good indications that this protection is still high nearly 8 years after vaccination. Data collection is on-going to assess if vaccine efficacy is maintained on a longer period. There is also good quality evidence that the risk of PHN, which is considered the main complication of HZ, is drastically reduced by the vaccine. However, the absolute risk reduction is much smaller than for HZ (10 per 10 000 person-years in individuals  $\geq 50$  years), resulting in a NNV higher than 330 over the first 4 years after vaccination. Moreover, there is currently no data on protection over a longer period. There is no solid data from clinical studies on protection of other complications, including hospitalisation. Good vaccine efficacy against HZ and PHN was confirmed in post-marketing in-population studies, although lower than in the pivotal trials. There is moderate quality evidence from post-marketing in-population studies that Shingrix can reduce significantly the risk of ophthalmic zoster. Here again, the absolute risk reduction is small (5 fewer cases per 10 000 person-years). Such information does not exist for hospitalisation.

There is good quality data that the vaccine is effective in reducing the risk of HZ also in immunocompromised adults  $\geq 18$  years with haematopoietic stem cell transplantation or haematological malignancies. Although the relative reduction is smaller than in immunocompetent persons, the number of cases prevented for a given number of vaccinations is much higher because of the higher baseline risk (618 cases avoided per 10 000 person-years). Vaccine efficacy in the presence of other immunosuppressive conditions is not well known as only immunogenicity studies are available, and the threshold of cell-mediated immunity ensuring protection is unknown. However, 2 post-marketing in-population studies in immunocompromised individuals (various conditions) reported a similar vaccine efficacy (around 65%). There are

indications of a similar vaccine efficacy also for patients with auto-immune diseases. All studies carried out in immunocompromised individuals were of short duration (maximum 2 years) and protection on a longer period is unknown.

Vaccine efficacy derived from RCTs applied to Belgium would result in around 64 (95%CI: 63-66) cases of zona avoided per 10 000 person-years vaccinated  $\geq 50$  years, between 8 and 10 cases of PHN and less than 2 hospitalisations. The corresponding numbers for individuals  $\geq 60$  years would be 77 cases of zona avoided per 10 000 person-years vaccinated, between 10 and 12 cases of PHN, and between 2 and 3 hospitalisations.

Based on post-marketing studies and surveillance, the vaccine safety appears high. An association with Guillain-Barré syndrome was reported in 2 studies but the attributable risk was very low.

KCE shared a preliminary version of the present clinical review with the Superior Health Council of Belgium in early 2022. The latter very recently recommended RZV in immunocompetent adults  $\geq 60$  years,<sup>a</sup> following the example of a number of other European countries. The cut-off of 60 years was deemed to yield the best clinical return in an immunocompetent population. The Council also recommended vaccination in immunocompromised patients  $\geq 16$  years. Of note the vaccine is off-label between 16 and 18 years.

As regards the economic evaluation of Shingrix vaccination, a Belgian study was published in 2021. It estimated that, compared to Zostavax, Shingrix was more clinically effective (in terms of QALYs gained and avoided clinical outcomes) in all age groups. Further, administering Shingrix at a younger age (50 years) was more cost-effective assuming a long duration of protection of the vaccine (providing on average 40-50 years of protection), while vaccination at a later age (80 years) was more cost-effective assuming a short duration of protection of the vaccine (providing around 7 to 10 years of protection).

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<sup>a</sup> Including patients receiving treatment with Janus kinase (JAK) inhibitors.



However, with incremental cost-effectiveness ratios (ICER) above € 87 000 per QALY gained, RZV vaccination was not found to be cost-effective at any of the explored vaccination ages (at 50, 60, 70, 80 or 85 years) or at any of the assumed duration of protection (long or short) when the US private sector price of RZV was used (€ 140.26 per dose). Meantime the Belgian list price of RZV was set up at € 170.26 per dose. Hence strong decreases in the price of RZV vaccine were advocated for a better balance between the health gains and the costs. For example, assuming a long duration of vaccine protection, the price for 1 dose of Shingrix should drop to € 37.49 per dose such that vaccination at 50 years would cost € 30 000 per QALY gained. As a comparison, the ICER for influenza vaccination in ≥65-year-olds, a strategy recommended and funded in Belgium, was previously estimated at € 19 125 per QALY at most.

The assumed duration of protection of Shingrix had a strong impact on the cost-effectiveness results. This duration of protection was estimated based on the 4-year data from the two pivotal ZOE trials. Our extrapolations based on the 8-year data of the ZOE-LTFU trial showed that the assumption of a short duration of vaccine protection can clearly be discarded. They also showed that the assumption of a long duration of vaccine protection is plausible though too optimistic. The lowest ICER in Pieters et al. is thus likely underestimated. The incidence of HZ cases also had a strong impact on the cost-effectiveness results. This incidence was derived from the medically attended cases and was limited to the immunocompetent population, providing a lower estimate of the number of individuals who can benefit from vaccination. Consideration of the whole population (including the immunocompromised) would likely improve the ICERs.

The results of recent economic evaluations performed in settings similar to Belgium (Europe and North America) were explored. The bulk of those evaluations (both sponsored and non-sponsored) reported more favourable results about the cost-effectiveness of RZV vaccination in the overall or immunocompetent population, with ICERs not exceeding € 47 000 per QALY (see section 6.4 for a full description of those results). Only two studies reported less favourable results. A Dutch economic evaluation estimated that RZV prices should decrease to be cost-effective at the € 20 000 per QALY gained, while, in a Swedish study, RZV was not found to be cost-effective as it costed € 170 000 per QALY. The cost-effectiveness of RZV vaccination in specific populations such as the immunocompromised still needs to be explored, as only one GSK-sponsored conference abstract on this topic was published so far.<sup>1</sup>

The budget required to fund RZV vaccination would be substantial, with annual budgets of € 27.14 or € 10.56 million to vaccinate 46.2% (coverage observed for other vaccines in Belgium) of the adults at 50- or 80-year-old, respectively, at the list price of the vaccine (€ 170.26 per dose). Vaccinating 90% of the severely immunocompromised adults aged ≥18 years was estimated to cost € 26.26 million.



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