EVALUATION OF VACCINES AND VACCINATTION AGAINST HERPES ZOSTER (ZOSTAVAX® AND SHINGRIX®)

ACCORDING TO THE EVALUATION CRITERIA FOR THE DEVELOPMENT OF NATIONAL GUIDELINES IN SWITZERLAND.

October, 2017, Update: September 2021

Shading:
NEW: Additional information for Shingrix® (in 2021) is shaded in **yellow.**
Information with respect of **immunocompromised patients** is shaded in **green**.

The **vaccination recommendations** against **herpes zoster** for **Zostavax®** were published in BAG/OFSP Bulletin Nr. 47 / 17 (20. November 2017) and integrated in the Swiss vaccination plan (Schweizerischer Impfplan / Plan de vaccination suisse 2018). The **vaccination recommendations** against **herpes zoster** for **Shingrix®** will be published in BAG/OFSP Bulletin by the end of 2021) and integrated in the Swiss vaccination plan 2022.

BACKGROUND INFORMATION

The live-attenuated vaccine Zostavax® to prevent herpes zoster ("shingles") and its complications was licenced by Swissmedic in February 2007 for persons aged 50 years or older. Zostavax® is available in Switzerland since 2008, and in 2017 a **complementary recommendation** was made for immunocompetent elderly persons aged **65 to 79 years of age** as well as a **risk group recommendation for future immunocompromised patients 50 to 79 years old**. However, Zostavax® is not reimbursed by the Swiss Compulsory health insurance, mainly due to unfavourable cost-effectiveness reasons.

Since then, an recombinant ('non-live') vaccine against herpes zoster (Shingrix®) has been approved by FDA and EMA and has been introduced into the vaccination plans of several countries worldwide. **Effectiveness and safety data** indicate a substantially **higher and longer-lasting effectiveness of Shingrix®** compared to Zostavax® without the limitations of live vaccines for their use in immunosuppressed patients.

The size of the group of persons treated with **immunosuppressive drugs** is likely to increase further with a considerably enlarged armamentarium to treat inflammatory diseases.

Furthermore, the trend that the population becomes older continues.

The the Federal Office of Public Health (FOPH) was informed that the pharmaceutical company producing Shingrix® (GSK) submitted an application for licensing by Swissmedic in 2020.

In this document, the Federal Commission for vaccinations (EKIF /CFV) and the FOPH evaluated a possible change of the current recommendations for the use of zoster vaccines and propose an **updated recommendation** (Link).

CONTENTS

Abbreviations:

CMI	Cell-mediated immunity
GMT	Geometric mean titer
H(S)CT	Haematopeitic (Stem) Cell Transplant
HZ	Herpes zoster
JAKi	Janus Kinase inhibitors
PHN	Post Eerpetic Neuralgia
R.A.	Rheumatoid arthritis
RCT	Randomized controlled trial
V.E.	Vaccine Efficacy or Effectiveness (according to context)
VZV	Varicella zoster virus

H.zoster vaccination recommendations (FOPH & EKIF/CFV 2021)

The FOPH and EKIF/CFV **recommend vaccination against herpes zoster** with **two doses** of **Shingrix®** in **two recommendation categories** for **specific target groups** and endorse **cost reimbursement** by the compulsory health insurance, as specified in the guidelines and recommendations of the Swiss Vaccination Plan. The two recommendations should come into effect in **November 2021**, concurrently with integration into the DHA Ordinance of 29 Sep. 1995 on Compulsory Health Insurance Benefits - HIBO (KLV/OPAS) and should be included in the list of reimbursable pharmaceutical specialities (Specialities List/SL). **Shingrix®** is an adjuvanted subunit-vaccine and is given **i.m. in two doses**, at an interval of 2 months.

A) (Category 2 according to Swiss vaccination plan: "Ergänzende Impfung"/"vaccination complémentaire") of vaccination with **Shingrix®** against herpes zoster (HZ) for **immunocompetent persons ≥65 years old,** regardless of the individual history of HZ and varicella. For persons who have previously received Zostavax®, a minimum interval between Zostavax® and the first dose of Shingrix® of at least **two months** is recommended. Serological tests before vaccination with Shingrix® are generally not recommended.

B) Recommendation for defined risk groups (Category 3 according to Swiss vaccination plan: "Impfung für Risikogruppen"/"vaccination pour groupes à risque") of vaccination with **Shingrix®** against herpes zoster (HZ) for immunocompromised persons**.**

B1. Shingrix® is recommended for all **patients aged ≥50 years** with a current or future (cellular) immunodeficiency associated with an increased risk for HZ, such as for patients during active cancer treatment*, HIV-positive patients, patients with end-stage renal disease or on dialysis, patients on biologicals, azathioprine, low-dose methotrexate or maintenance low-dose corticosteroid treatment or with other underlying conditions affecting (notably cellular) immunity. This includes, for example, patients with rheumatoid arthritis, severe asthma / COPD, inadequately controlled diabetes mellitus type 1 and other autoimmune diseases.

*) *Timing: The 1st dose should ideally be administered ≥ 2 weeks before starting chemotherapy. The 2nd dose with a minimal interval of **1 to 2** months after the 1st dose, or as soon as possible at a later time point during or after chemotherapy.*

B2. Shingrix® is recommended **for patients aged ≥18 years** with a current severe immunodeficiency or an immunosuppressive treatment in the foreseeable future. This includes e.g. patients with: haematological malignancies, hematopoietic stem cell and solid organ transplant recipients, persons who are treated with JAK inhibitors or intensive immunosuppression (e.g. combinations of immunosuppressants, high-dose corticosteroids) due to an immune-mediated disease such as e.g. rheumatoid arthritis or inflammatory bowel disease, and HIV-positive patients with <200 CD4 + T cells/µl or <15% of lymphocytes.

Timing: The vaccine should be administered ≥ 4 weeks before an assumed, anticipated or planned start of a severe immunosuppression ideally.

- In **pregnant** or **breastfeeding women** there should be a careful individual risk/benefit assessment.
- **VZV-Serology** is **not recommended** prior to vaccination with Shingrix nor Zostavax.
- The currently available live vaccine **Zostavax®** remains an option for immunocompetent subjects between 65 and 79 years old.
- **Zostavax®** is contra-indicated in subjects with a **compromised immune system**, and should **not** be used anymore in and those who will receive **immunosuppressive therapies** in the **near future**.

SUMMARY WITH RESPECT TO SHINGRIX®

1. Burden of disease: **Incidence** of herpes zoster (HZ) at age 18-40 years is about 4 per 1'000 person-years. It **increases** to 7 **at age 50**, to 11 at age 65, and to 14 at age 75 and older. HZ risk increases slightly for some chronic conditions, and more than doubles for immunocompromising conditions, and is highest with JAK-inhibitor therapy (RR=11). **Complications** develop in ≈30% of all HZ cases. They are more frequent with **increasing age** and in those with **cellular immune deficiency**. Post-herpetic neuralgia (**PHN**) can persist for weeks and months. At age 70 years, PHN affects ≈18% of HZ patients. **Ophthalmic** zoster affects 5-10% of HZ cases.

2. Vaccine characteristics: **Shingrix®**, a recombinant, AS01B-adjuvanted subunit-vaccine, given in 2 doses at 2-month interval. SM authorization in August 2021, probably from age 50+, for risk groups from age 18+. Long-term **immunological data** are available for 10 years: specific AB titers were 6-fold and Cell mediated immunity (CMI) parameters 3.5-fold higher compared to pre-vaccination. At the short term, Shingrix® generated higher IL-2 and other memory and effector-memory CD4+ peak responses compared to Zostavax®, but the latter generated higher effector CD4+ responses. **Efficacy** in study participants **aged 50+ years** against HZ was 97.2% (mean follow-up: 3.2 years). V.E. among participants **aged 70-79 years** was **90.0%** and in those **80+ years 89.1%** (follow-up: 3.7 years). A recent subset analysis with mean follow up of **7.1 years** in ZOE-50+/70+ study participants found V.E. of **90.9%**. Real-world post-licensure **effectiveness** for two doses after two years was found to be **71%** in >1 million beneficiaries US Medicare beneficiaries aged >65 years. After just one dose it was 57% (*Izurieta*). A systematic review among hematopoietic stem cell transplant (HSCT) recipients found a V.E. of 72% in the 18-49-year-olds, and 67% in the 50+-year-olds (follow-up: 21 months) (*Racine*). **Reactogenity** seems to be high, comparable to tetanus or the mRNA vaccines, but **no significant safety issues** were found. In the immuno-compromised aged <50 years, SAE's were reported in <1% of patients in both Shingrix® and placebo. No interactions with other vaccines have been identified.

3. Vaccine strategy: The main aim is to decrease burden of HZ, PHN & other complications. A complementary recommendation for all aged 65+ and a risk group recommendation is proposed. In order to adapt the latter as far as possible to the varying risks according to age and underlying disease, the risk groups are best divided into "risk" from 50+ years and "high risk" from 18+ years.

4. Cost-effectiveness: Vaccine price is predicted to be high compared to other vaccines. A 2021 GSK budget impact model for Shingrix® in Switzerland, showed the age group 65 years and older as the most cost-efficacious age limit for a recommendation.

5. Acceptability of recommendation: Among **466 GP's surved** in Switzerland, **67%** would recommend Shingrix at **age 60+** and **11% at age 70+**, and 4% would't recommend it (18% don't know). If Shingrix was not reimbursed still 63% would recommend it anyway (17% no, 21% don't know).

6. Feasibility of recommendation: Integration as a complementary recommendation seems most practical for age 65+, but would be possible also for younger age groups. Risk groups will have to be actively informed by treating physicians.

7. Ability to evaluate recommendation: Via Sentinella and Hospitalisations (BFS). Measuring impact for risk / high risk groups would require specific studies.

8. Open questions: Long-term V.E. beyond 10 years? Benefit of a 3rd dose or a booster dose in severely immunocompromised patients?

9. Equity of the recommendation: If not reimbursed, equity to access would not be given.

10. Legal questions: None identified.

11. Conformity of Recommendation: Similar recommendations (but partly different age groups) in Germany, Austria, Italy, Spain, the Netherlands, the U.K., Canada and the USA.

1. Burden of disease

1.1 Nature and characteristics of the infectious agent

Varicella-zoster virus (VZV) belongs to the subfamily of alpha-herpesviruses, which also includes Herpes simplex virus (HSV). VZV is responsible for two well-known clinical syndromes: chickenpox as the manifestation of primary infection and herpes zoster ("shingles") when VZV reactivates in latently infected subjects. VZV is highly contagious and acquired through airborne transmission.

1.2. Clinical manifestations and complications of infection, including pathogenic mechanisms.

Varicella (**chickenpox**) is the result of a primary infection with VZV. It is a highly contagious febrile illness, characterized by a generalized vesicular pruritic rash. Complications during childhood infections are rare, but frequency and severity of the disease increase when infection occurs at a higher age and especially during pregnancy. The disease is endemic worldwide. In temperate countries it primarily affects children all year round (with a slightly higher incidence in winter/spring). Following primary infection with VZV, the virus persists in a latent form in the ganglia of sensory neurons. More than 99.6% of adults over 40 are immune against varicella [1] and are thus carriers of latent VZV. Towards the equator and in tropical climates, an increasingly higher proportion of varicella cases occur at older ages i.e. in adults. Since 2004, in absence of a history of varicella primary infection (i.e. chickenpox), a vaccination against varicella is recommended for adolescents 11-15 years of age and up to 40 years of age as a catch-up vaccination. Vaccination is also recommended in women with a desire of pregnancy and negative VZV-specific IgG in serological test.

Herpes zoster (HZ) is caused by reactivation of latent VZV infection. VZV replicates and affects the spinal and cranial sensory ganglia, nerves and skin. HZ is characterized by a vesicular rash typically limited to a single dermatome and a unilateral radicular pain corresponding to the sensory ganglion in which the VZV has been reactivated. This ganglion is the subject of intense inflammation and haemorrhagic necrosis resulting in loss of neurons and fibrosis of the afferent nerve fibres. Since reactivation and inflammation originates in the ganglia, this explains why the pain usually precedes or accompanies the rash [2].

HZ related complications

Complications develop in about 30% of all HZ cases, and are more frequent in the elderly and in patients with cellular immune deficiencies (see point 1.4.). The most common complication is post-herpetic neuralgia (PHN). In PHN, neuropathic pain can persist for several weeks, months or even years after the resolution of the rash. The most commonly used definition for PHN is Neuropathic pain that continues for three months or more. PHN pain is typically described as burning, stabbing or gnawing. [3] Pain characteristics, severity, duration of pain episodes and overall pain persistence may vary considerably. PHN related pain impacts on quality-of-life and may have substantial psychological

consequences. At age 70 years, PHN affects about **18%** of HZ pateints (see also ***Fig. C***)
Table 1 shows a list of complications due to HZ.

Ophthalmic herpes zoster, a consequence of the reactivation of VZV in the trigeminal ganglion, is a particularly worrying complication that threatens the patient's eye sight and requires urgent antiviral treatment. Ophthalmic zoster makes up approximately 5-10% of HZ cases. [4]

***Table 1*.** List of complications of herpes zoster.

Involved body systems	Complications (frequency)
Dermatological	Bacterial superinfection (2-3%) Scars and granulomas Depigmentation Cutaneous dissemination Zoster sine herpetae Post-herpetic pruritus
Ophthalmic	Keratitis, scleritis, uveitis, choriortinitis, iridocyclitis Ptosis, mydriasis Secondary glaucoma Acute retinal necrosis (very rare in immunocompetent individuals)
Neurological	Post herpetic neuralgia (PHN) (depending on age and immune status) Motoneuron neuralgia (mainly associated with cervical HZ involving the accessory nerve) Motor neuropathy Delayed contralateral hemiplegia/encephalitis Myelopathy Encephalitis Cerebellitis Myelitis Cranial nerve palsies Sensory loss Allodynia / central pain sensitization Ramsay Hunt syndrome Granulomatous with secondary stroke Neuromuscular disease Diaphragmatic paralysis Hypoacusis in association with acoustic herpes zoster (0.2%) Meningitis and meningoencephalitis (0.5%) Acute urinary retention (due to sacral herpes zoster, rare) Vertigo
Visceral & vascular	Pneumonia Visceral dissemination (Disseminated zoster) Vasculopathy

Adapted from: Meylan P. et al. [5], Johnson et al. [3], Gilden D [6]

Immunity against VZV

The mechanisms controlling the latency of the virus are not fully elucidated, but it's generally accepted that cell-mediated immunity (CMI) is key in limiting viral replication and reactivation in the sensory ganglia. *In vitro* data suggest that robust CMI against VZV in early rash correlates with a lower severity of the disease and a decreased risk of subsequent PHN. [7] Reciprocally, immunocompromised patients are at risk for prolonged episodes of reactivation and disseminated disease, which can be fatal. [8]

Nonetheless, 90% of herpes zoster cases occur in immunocompetent indiviuals. The decline of immunity with age (immunosenescence), and in particular the decline of CMI increases the risk of zoster reactivation in the elderly. [2] [9]

In addition, VZV reactivation can be associated with comorbidities impacting immunity (such as diabetes [10] or malnutrition [11], physical trauma [12, 13] or psychological stressors [12] [14].

Most people only experience one episode of HZ in their lifetime. This is attributed to the boosting of VZV-specific CMI following an episode of VZV reactivation. [15–17] However, second and even third episodes are possible, especially in immunosuppressed individuals. Immunization against HZ is also associated with a strong boosting effect on T cell responses against VZV [18] which is the assumed correlation of vaccine efficacy in the prevention or mitigation of HZ.

1.3. Epidemiology of the disease, including incidence, time trends, seasonal and geographic variations, clustering of cases.

HZ is a sporadic disease, without seasonal prevalence. The frequency and severity increase with age and impaired immune status. [19] Each year, more than 1.7 million people in Europe suffer from HZ, with two thirds of patients being older than 50 years. A German study [20] shows that more than 306'000 persons over 50 years are affected by HZ annually. By extrapolation in Switzerland this would be about 30,000 new cases each year. Overall, incidence of HZ is comparable in different European countries and estimated at 7-8 / 1000 people over 50 years and 10 / 1000 people over 80 years. [18]. In the U.S., according to CDC 2021, shingles incidence overall has been increasing at least since 1998 for unclear reasons. This trend continues among younger and middle aged adults, while the rates among older people have been plateauing since 2008. [21]

1.4. Specific populations or patient groups affected and risk factors

Risk of HZ by immune status

Several studies assessed the relative risk or incidence/odds ratios of HZ for patients with a wide array of conditions and different immunosuppressive therapies. Among these are, in order of risk:

- **JAK inhibitor** therapy; RR around 11.0 and twice as high (HR 2.01 (95% CI 1.40 to 2.88) compared to therapy with **biologics** for **immune-mediated inflammatory diseases**; RR around 5.5 [22]
- **Lymphoma** (3.90, 3.21 to 4.74) [23]
- **HIV/AIDS** (RR = 3.22; 95% CI, 2.40-4.33) [24]
- **Myeloma** (2.16, 1.84 to 2.53) [23]
- Any **malignancy** (RR = 2.17; 95% CI, 1.86-2.53) [24]
- **Family history for HZ** (RR = 2.48; 95% CI, 1.70-3.60) [24]
- **Physical trauma** (RR = 2.01; 95% CI, 1.39-2.91) [24]
- **Chemotherapy:** around 1.9-2.0 [25] [26]
- **Older age** (RR = 1.65; 95% CI, 1.37-1.97) [24]
- **Rheumatoid arthritis (RA)** (adj OR 1.46, 99% CI 1.38 to 1.55) [23] [27] [28] [29]
- **Inflammatory bowel disease** (1.36, 1.26 to 1.46) [23]
- **Chronic obstructive pulmonary disease** (1.32, 1.27 to 1.37) [23]
- **Type 1 diabetes** (1.27, 1.07 to 1.50) [23]
- **Asthma** (1.21, 1.17 to 1.25) [23]
- **Depression** (1.15, 1.10 to 1.20) [23]
- **Chronic kidney disease** (1.14, 1.09 to 1.18) [23]
- For **Systemic Lupus Erythematosus**, the major trigger factor for HZ is **use of corticosteroid** and **immunosuppressors,** not active SLE disease. [30] [31].

A meta-analysis focusing on immunocompromised subjects and the risk for HZ in the U.S. reported **widely varying incidences within** and between **immunocompromised** populations, ranging from 9 to 92 HZ cases/1000 patient-years. Incidence rates were highest in **hematopoietic cell transplants** and **hematologic malignancies**, followed by **solid organ transplants**, and **cancer**. [32]
PHN was found to be about 20-36% more frequent in immunocompromised patients in a cohort-study from Germany by *Hillebrand et al*. [33]

1.5. Current disease treatment and preventability by measures other than immunization

There is currently no completely effective antiviral treatment available to prevent sequelae of infection, once HZ or PHN are established. Antivirals (acyclovir, valacyclovir, famciclovir) should be introduced within 72 hours of the onset of the rash and have a limited effect on chronic pain, although a decrease in the total duration of PHN is possible. [34] Some studies [35] [36] suggest a decrease in duration of PHN by 2 - 2.5 months (duration of PHN 38 days with valaciclovir, 51 days with acyclovir, famciclovir with 63 days and 119 days with placebo). The analgesic treatment of persistent PHN often consists of drug combinations (analgesics, opioids, anticonvulsants, tricyclic antidepressants) with significant side effects and satisfactory pain control in only 50% of cases. [37]

1.6. Burden of disease; health impact of the disease in the population, including frequency of cases, deaths and loss of years of life.

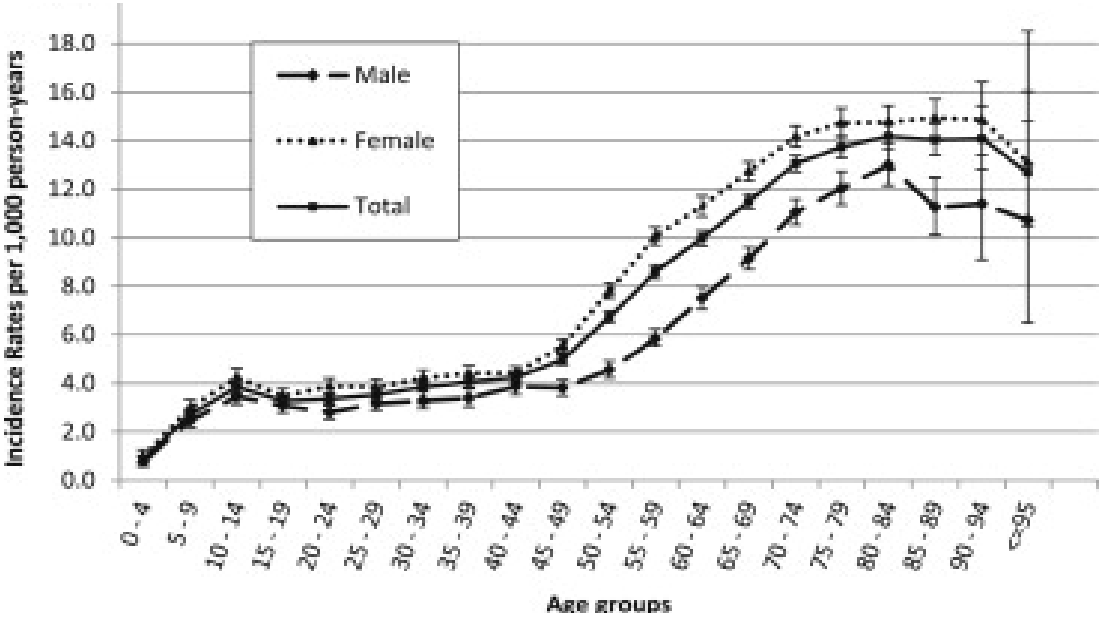
The burden of disease of HZ is influenced by its **incidence, severity and duration**, including those of **its complications** such as **PHN** or reduced vision due to **ophthalmic HZ**. [38] PHN in particular can cause significant pain over weeks, months and in some cases years.
A recent study from Germany [33] shows that above the age of 50 the incidence of HZ sharply increases to reach a plateau at the age of 70 and older (***Figure A***) [33]. In the general population, all manifestations and complications (***Table 2***) increased with age and with an acceleration between the 50 and 60 years old.
The incidence, duration and severity of PHN also increase with age especially in those over 50. Among HZ patients over 60 years of age, more than 40% develop PHN. [2] PHN becomes particularly debilitating for people in geriatric age, e.g. 80 years and older. Approximately 30% and 15% of elderly patients over 70 years report PHN three months and one year after HZ, respectively. Studies aimed at quantifying the pain intensity of PHN have shown, that chronic pain associated with PHN pain sometimes exceeds pain scores at childbirth, musculoskeletal pains and pain in connection with cancer. [39] In terms of quality of life, PHN can have a negative impact similar to congestive heart failure, diabetes and depression. [40] Finally, elderly people may experience loss of independence after an acute episode of HZ. [3]
Data from Switzerland and various European countries show that HZ and its complications result in hospitalisation and death, especially in elderly patients over 70 years. [41] Likewise it was shown in England, [42] Spain [43] and Italy, [44] that the rate of hospitalisation, morbidity and mortality related to HZ increases with age. The hospitalisation rate is particularly high in patients over 70 years, with an average hospital stay of 11-14 days.

Immunocompromised patients:
In the study by Hildebrand et al., the incidence of HZ in immunocompromised individuals (all ages) was comparable to the incidence in non-immunocompromised individuals aged 70 years or older, i.e. about 12-14 per 1000 person-years (***Figure B***). Immunocompromised individuals were defined as

patients with HIV positive, malignant neoplasm, immunodeficiency (ICD D80-84) or organ/tissue transplants in the previous 12 months.

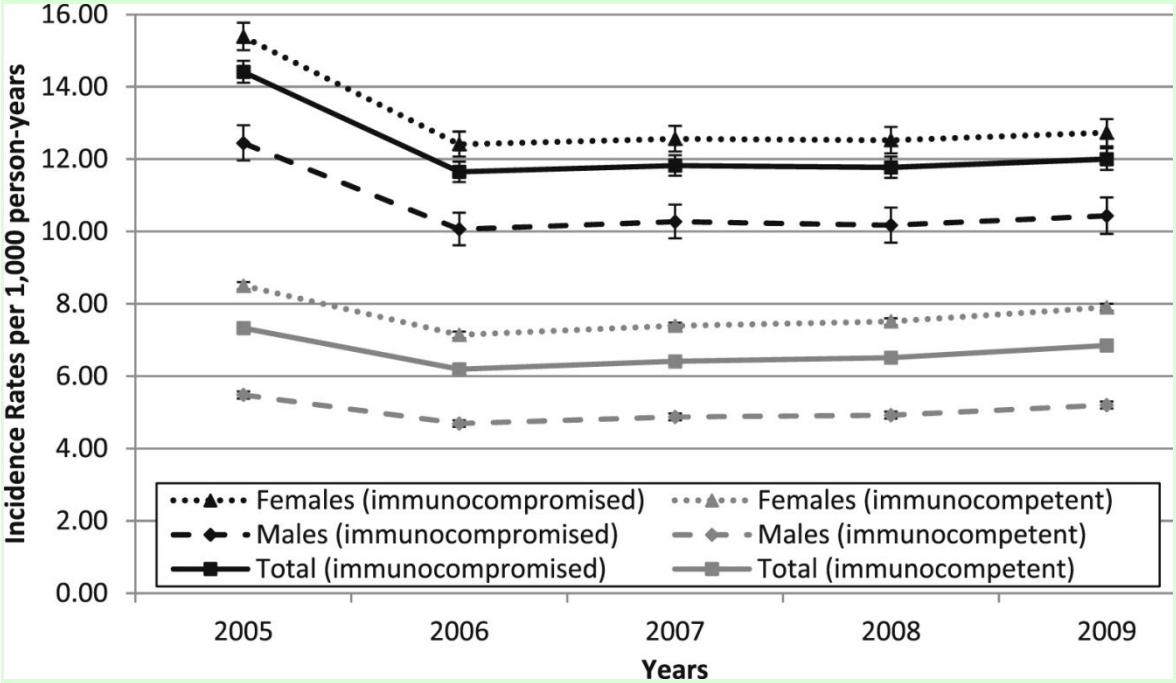
Post herpetic neuralgia (PHN):
With regard to the proportion of HZ infected patients who develop PHN, there is a strong linear increase in PHN with age, from about 3% around age 20, to 12% around age 50, reaching more than 20% among HZ-patients 70 years-old or older (***Figure C***).

Figure A: Incidence rates of HZ by 5-year age groups and sex in 2009



Source: Hillebrand et al. 2015 [33]

Figure B: Incidence rates of HZ stratified by sex and immune status from 2005 to 2009



Source: Hillebrand et al. 2015 [33]

The **mortality rate** due to HZ in general is lower than 1%. Most VZV-related fatalities result from disseminated infection, (meningo)-encephalitis and pneumonia. [34] The latter two are responsible

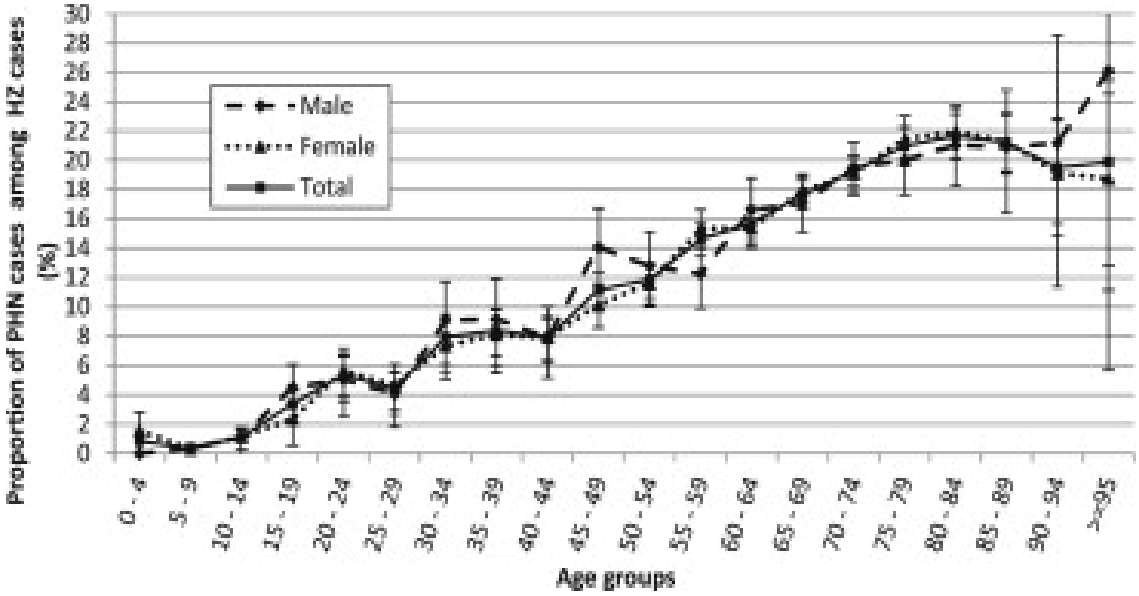
for about 80% of deaths due to HZ. A study from the United States showed death ranged between 0.19–0.51 per 1 million population and the rate of HZ as a contributing cause of death ranged between 0.21–0.58 per 1 million population. [45] Median age of the patients who died from HZ was 84 years (range, 50–99) and 60% had no contraindications for HZ vaccination. The same study estimated, that the HZ vaccination program in the U.S. could prevent 31% of all HZ deaths, though the true impact might be difficult to assess using national mortality data. [45]

Table 2. **Incidence rates (*95% C.I.)* of herpes zoster (HZ) cases per 1'000 person-years with and without complications (except PHN), by age group in 2009,** same data as in fig. A

Incidence rates (*95% C.I.)* of HZ with and without complications (except PHN), by age group, 2009								
Age group (years)	**Uncomplicated HZ**	**Zoster ophtalmicus**	**Zoster encephalitis**	**Zoster meningitis**	**other nervous system involvement**	**Disseminated HZ**	**HZ w. other complications**	**Multiple HZ complications**
<25	2.6 *(2.5-2.7)*	0.1 *(0.1-0.1)*	0.01 *(0.01-0.02)*	0 *(0-0.01)*	0.2 *(0.2-0.2)*	0.01 *(0.01-0.02)*	0.1 *(0.1-0.1)*	0.01 *(0-0.02)*
25-44	3.1 *(3.0-3.2)*	0.2 *(0.2-0.2)*	0.03 *(0.01-0.03)*	0.01 *(0-0.02)*	0.4 *(0.4-0.5)*	0.03 *(0.02-0.04)*	0.2 *(0.1-0.2)*	0.04 *(0.03-0.06)*
45-64	5.5 *(5.4-5.6)*	0.3 *(0.3-0.4)*	0.03 *(0.02-0.03)*	0 *(0-0.01)*	1.1 *(1.1-1.2)*	0.05 *(0.04-0.06)*	0.3 *(0.3-0.3)*	0.15 *(0.13-0.17)*
65-84	8.7 *(8.6-8.9)*	0.7 *(0.6-0.7)*	0.05 *(0.04-0.06)*	0.01 *(0-0.01)*	2.4 *(2.3-2.4)*	0.07 *(0.05-0.08)*	0.5 *(0.5-0.6)*	0.39 *(0.36-0.43)*
85+	9.4 *(9.0-9.9)*	0.7 *(0.7-0.9)*	0.09 *(0.05-0.14)*	0.01 *(0-0.03)*	2.6 *(2.4-2.9)*	0.1 *(0.06-0.16)*	0.6 *(0.5-0.7)*	0.41 *(0.32-0.51)*
Total	**5.3** *(5.2-5.4)*	**0.4** *(0.3-0.4)*	**0.03** *(0.03-0.04)*	**0.01** *(0-0.01)*	**1.1** *(1.1-1.2)*	**0.04** *(0.04-0.05)*	**0.3** *(0.3-0.3)*	**0.17** *(0.15-0.18)*

Source: Hillebrand et al. 2015 [33]

Figure C: Proportion of PHN cases among all HZ cases by 5 –year age group and sex in 2009



Source: Hillebrand et al. 2015 [33]

Susannah McKay et al. in 2020 published a systematic review to estimate **HZ risk in immuno-compromised adults** in the U.S. with hematopoietic cell transplants (HCT), cancer (hematologic and

solid tumor), HIV, and solid organ transplant (SOT; kidney and other). They found 34 eligible studies, of which the cumulative incidences for these conditions are summarized in ***Tables 3a and 3b*****.** [32] For different underlying conditions and age groups, odds ratios for HZ are shown in ***Figure D***, derived from patients from Germany by Batram et al. 2021. [46]

Table 3 a. HZ incidence among immunocompromised patients

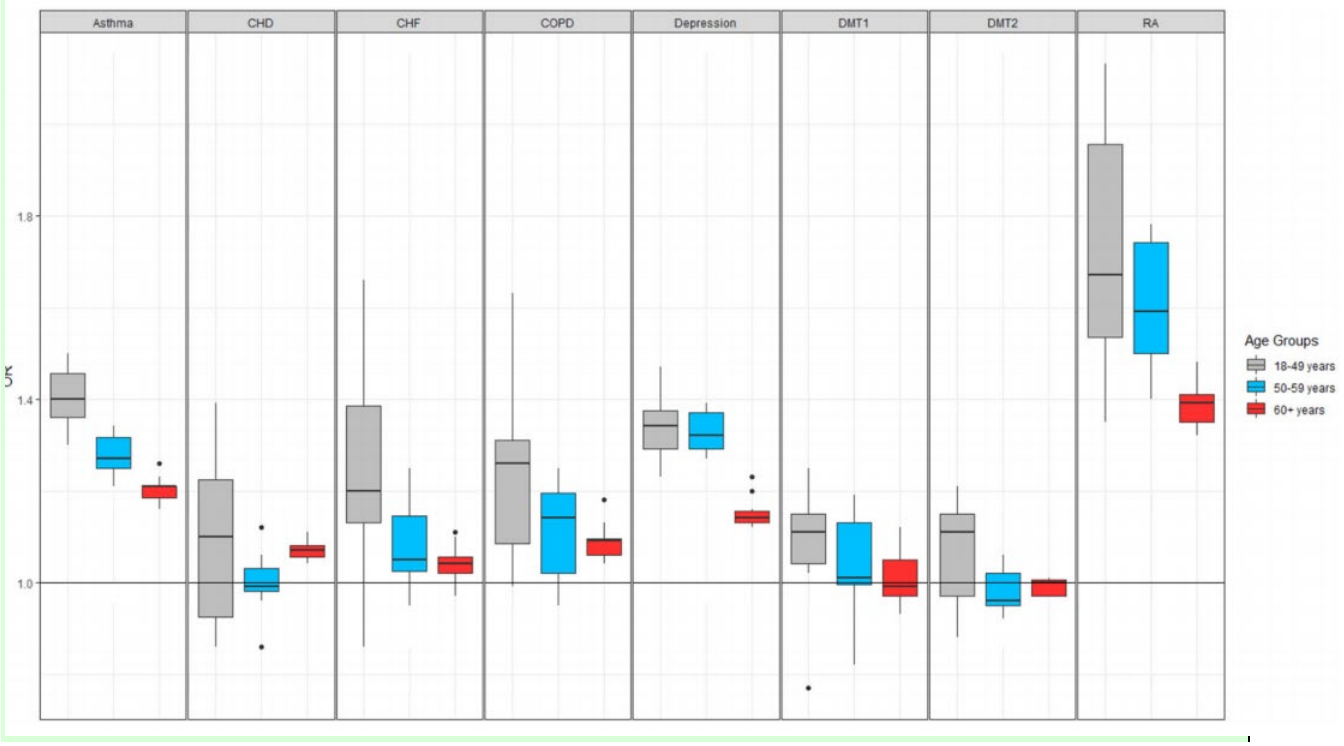
Patients	**Incidence per 1'000 patient years (median or OR (95% CI))**	**Selected studies: First authors / [ref.]:**
Imm.-**competent** (for comparison)	3 (age 50-59) 7 (age 60-69) 9 (age 70-79) 13 (age 80-89)	Prosser [32]
	3.9 (age 18–49) 5.4 (age 50-59) 8.2 (age 60+)	Batram [46]
With underlying conditions	5.3 (age 18–49) 7.1 (age 50-59) 9.7 (age 60+) **→ also see figure below**	**→ also see figure below**
Immunocompromised patients **total**	9-95 (according to study, age, condition)	CDC-Review by McKay [32]
HCT autologous + allogeneic transplants	42-96	Bastidas [47] Chen [48] Winston [49]
SOT transplant (kidney, heart, others)	17	Arness [50] Chen [48] Koo
HM (haematological malignancy)	31-41	Dagnew [51] Habel [52]
STM (solid tumor malignancy)	12-22	Habel [52] Tseng [26]
HIV+ / AIDS	10-17	Blank [53] Chen [48]
children+adolescents: **HIV+** **Juvenile SLE**	25.3% had HZ with average 1.6 episodes in 18 yrs follow-up 29.3% had HZ with average 1.0 episodes in 15 yrs follow-up	Da Silva [54]
TNFa-inhibitor therapy	OR 1.5 (1.1-2.1) OR 2.1 (1.2-3.6) age 50+ years OR 4.1 (2.3-7.2) additional use of steroids or immuno-suppressants	Santella [55]
JAK-inhibitors for Inflamm. Bowel Dis. and other Immune-mediated diseases	27-32	Olivera [56] Bechman [57]
Tofacitinib **Adalimumab** **Etanercept** **Infliximab**	5-39, 7 5 2	Curtis [22] Failla [58] Failla [58] Failla [58] Failla [58]
Rituximab therapy		
Cortisone use in haemodialysis	OR 20.2 (3.5-125.6)	Chao [59]

Table 3 b. PHN risk among immunocompromised patients

Patients	Risk of developing PHN (%; range)	Selected studies: First authors / / [ref.]:
Immunocompromised patients **total**	6% - 45% (according to study, age, condition)	CDC-Review by McKay [32]
HCT autologous + allogeneic transplants	6–41%, 10%	CDC-Review by McKay [32] Chen [48]
SOT transplant (kidney, heart, others)	7–45%, 7%	CDC-Review by McKay [32] Chen [48] Habel [52]
HM (haematological malignancy)	6–40%, 6%	CDC-Review by McKay [32] Habel [52]
STM (solid tumor malignancy)	9%	Habel [52]
HIV+ / AIDS	6%	Chen [48]

HCT = hematopoietic cell transplants, HM = hematologic malignancy, STM (solid tumor), and solid organ transplant (SOT; kidney, heart and other), HIV = human immunodeficiency virus + / AIDS

Figure D: Adjusted Odds Ratios of HZ risk by 3 age groups in patients with underlying conditions, Germany 2008-2018. Asthma, CHD Coronary heart disease, CHF chronic heart failure, COPD chronic obstructive pulmonary disease, Depression, DMT1 diabetes mellitus type 1, DMT2 diabetes mellitus type 2, RA rheumatoid arthritis. Batram et al. 2021 [46]



1.6.1 Epidemiological data from Switzerland

Swiss HZ sentinel data

In Switzerland the Swiss Sentinella surveillance system estimated yearly incidence of GP visits due to HZ for the four years from 1998 to 2001. The results showed a stable average of approximately 17‘000 cases per year in Switzerland (see also extrapolation of data from Germany in chapter 1.2.

Epidemiology: 30'000 cases per year in CH). HZ cases were reported for all age groups including patients younger than 50 years. The highest incidence was reported in persons aged 50 years or older; an age group which accounted for roughly two thirds of all reported cases. In the age group 50–59 around 2700 cases per year were reported and a similar number among the 60–69-years olds; around 3000 cases per year among 70- to 79-year olds (maximum in absolute numbers) and among the age group 80 years and older around 2200 cases.
According to the 1998 to 2001 Sentinel data the extrapolated incidence of HZ in the age group <40 years was around 120/100'000 and increased with age to 410/100 000 among the 60- to 69-year olds and the yearly incidence was highest in persons aged 80 years and older with 760/100 000. In Europe and North America age specific incidence is comparable or slightly higher. [60] [61] [62] [63] [64] [65] [66]

Since 2016, HZ is again reported in the Sentinella surveillance system. The results, including hospitalisation data, by year and age group are shown in ***Table 4*****.** Again, HZ cases were reported in all age groups including subjects younger than 50 years. Yearly extrapolated incidences during the five **years (2016-2020)** were comparable to the surveillance period of 1998-2001. It is noteworthy that since 2016, HZ cases in subjects vaccinated against HZ reported via Sentinella were low (1-5 cases per year).

Table 4 **– HZ cases and incidence / 100'000 per age group, 1998-2001 and 2016-2020. reported via the Swiss Sentinella system, and hospital admissions (main and secondary diagnoses; from Statistique médicale des hôpitaux, Federal Statistical Office FSO)**

	Herpes zoster cases/100'000		HZ-hospitalisations/100'000
Age group / years	**1998-2001**	**2016-2020**	**2014-2019**
0-49 years	118-155	123	5
50-59 years	306	282	16
60-69 years	414	522	41
70-79 years	599	690	157
80-89 years	748	1012	
90+ years	817	1535	
All ages	**236**	**288**	**31**

Source: FOPH (Sentinella – Déclarations actuelles (admin.ch)**)**

HZ hospitalisation data provided by Federal Statistical Office (FSO)

Table 5 shows the number of hospitalisations for the six years 2014-2019, as well as the average number of yearly hospitalisations during the period 2014-2019.

Table 6 shows numbers and average duration of hospitalisations due to HZ, zoster ophthalmicus and their complications 2008-2013 in Switzerland, by age group and ICD-10 Diagnostic code (International Statistical Classification of Diseases and Related Health Problems). On average, **542 patients** had been hospitalised due to HZ and its complications (main diagnosis).

Table 5. **Hospitalisations due to HZ** for the years **2014-2019 in Switzerland**

Age class *population*	**2014-2019 (Total)**	**2014**	**2015**	**2016**	**2017**	**2018**	**2019**	**Average per year**	
								n	**per 100'000**
00-39 *3'991'724*	844	129	139	148	121	169	138	**141**	**3.53**
40-49 *1'198'325*	571	86	82	99	78	125	101	**95**	**7.93**
50-54 *662'817*	510	92	58	85	86	100	89	**85**	**12.82**
55-59 *630'020*	708	92	115	104	146	122	129	**118**	**18.73**
60-64 *517'347*	927	158	138	161	155	142	173	**155**	**29.67**
65-69 *430'612*	1'379	208	243	258	201	221	248	**230**	**53.36**
70-74 *400'091*	1'892	267	303	310	343	330	339	**315**	**78.75**
75+ *775'097*	9'196	1'296	1'333	1'498	1'522	1'766	1'781	**1'533**	**197.78**
TOTAL* ***8'606'033***	16'027	**2'328**	**2'411**	**2'663**	**2'652**	**2'975**	**2'998**	**2'671**	**31.04**

*) **ICD-10 Codes: B020, B021, B022, B023, B027, B028, B029;** Source: Federal Statistical Office (FSO), Neuchâtel, Switzerland; 2021 / Medizinische Statistik der Krankenhäuser

Table 6. **Yearly average** number of **Hospitalisations due to HZ (2008-2013) in Switzerland**

Description (Diagnostic code ICD-10) Total: 542	**age group**	**N per year (Average)**	**N per year (MIN)**	**N per year (MAX)**	**Av. Duration of Hosp. [days]**
Zoster without complications (B029) Total: 167	00-59	15.2	10	21	6.6
	60-64	10.5	6	14	6.5
	65-69	16.5	11	23	8.8
	70-74	19.8	14	29	8.6
	75+	105.0	98	110	11.4
Zoster (other) complications of the nervous system (B022) Total: 183	00-59	13.8	10	22	7.6
	60-64	12.3	5	22	9.1
	65-69	17.0	12	26	10.9
	70-74	23.5	16	28	10.6
	75+	115.8	102	137	13.4
Zoster ophthalmicus (B023) Total: 85	00-59	7.8	4	14	6.6
	60-64	6.5	3	10	7.1
	65-69	8.5	6	12	7.3
	70-74	11.3	8	15	9.0
	75+	50.5	39	65	12.3
Zoster with other complications (B028) Total: 53	00-59	4.8	3	8	7.7
	60-64	3.5	2	6	10.2
	65-69	5.3	2	9	12.7
	70-74	8.3	6	11	11.0
	75+	31.2	18	45	13.2
Zoster generalisatus (B027)	00-59	2.2	1	3	8.1

Total: 24	60-64	3.2	1	4	8.4
	65-69	4.2	2	9	12.4
	70-74	4.2	1	7	12.8
	75+	9.8	6	14	18.5
Zoster encephalitis (B020)	00-59	2.7	1	5	21.4
Total: 23	60-64	2.3	0	4	9.5
	65-69	2.5	0	5	9.9
	70-74	3.3	1	5	19.2
	75+	13.2	10	22	19.6
Zoster-meningitis (B021)	00-59	2.5	1	5	7.1
Total: 7	60-64	1.0	0	3	7.1
	65-69	0.8	0	2	7.4
	70-74	0.7	0	2	10.3
	75+	1.8	0	4	17.4

Source: Federal Statistical Office (FSO), Neuchâtel, Switzerland; 2015 / Shading > 10 / > 20

Deaths due to HZ

According to 2021 data of the Federal Statistical Office (FSO) there were a few deaths due to HZ based on the death certificate: during the 5-year period 2014-2018, a total of 51 patients died from HZ. This corresponds to an average of 17.2 HZ-related deaths in Switzerland per year. All of the deceased were aged 60 or older, with an increase of cases by age (***Table 7***). Around 80% of the deaths concerned women, likely due to their population share and HZ severity in the highest age.

Table 7. **Deaths due to HZ** for the years **2014-2018 in Switzerland**

Age group	**2014-2018 (Total)**	Women	Men	**Average per year**
60 - 64	1	1	0	0.2
70 - 74	2	1	1	0.4
75 - 79	6	2	2	1.2
80 - 84	13	6	3	2.6
85+	44	31	4	8.8
Total*	**86**	**41**	**10**	**17.2**

*) **ICD-10 Codes: B020, B021, B022, B023, B027, B028, B029**

Source: Federal Statistical Office (FSO), Neuchâtel, Switzerland; 2021

1.7. Social impact of the disease; including intensity of suffering, nature and frequency of sequelae in survivors, reduction of quality of life of affected individuals, and loss of QALY's, long-term disability, impact on families/caregivers, fear of disease, stress on communities.
→ *(Described in other chapters of this document)*

1.8. Economic impact of the disease, including direct and indirect costs for patients and families, health services utilisation, costs to the health system and productivity losses.

Suzcs et al. in 2011 outlined costs in Switzerland ranging from CHF 362 to CHF 386 "direct medical costs" from the third party payer (TPP) perspective or from CHF403 to CHF430 "indirect societal costs" from the societal (S) perspective for outpatient HZ cases. These included visits, diagnostic tests, medication and working day loss, depending on the severity of the illness. In parallel costs of mild PHN were estimated at CHF 127 (TPP) and CHF389 (S) respectively. For severe HZ cases the costs of outpatient treatment and hospitalisations were combined to add up for total costs per case

resulting in CHF 1'227 (TPP) and CHF1'874 (S). In the same way combined costs (outpatient and hospitalisation) for moderate and severe PHN study were estimated at CHF 600 (TPP) and CHF 1'040 (S) for moderate PHN. For severe PHN the costs added up to CHF 1'532 (TPP) and CHF 2'493 (S). [67]
In the Canton of Basel-Stadt, 2020 average inpatient costs (University hospital KSB) were 10'775 Euro per HZ case, versus 521 Euro for outpatients. (*personal communication University hospital KSB*).
Costs of medicaments' treatment of HZ (antivirals and analgesics) vary slightly on the drugs that will be used.

In other countries, there have been estimations on the costs and economic burden of HZ and its complications, including indirect costs. Gauthier et al. in 2009 analyzed the burden of HZ and PHN in the United Kingdom to assess management costs in immunocompetent individuals aged ≥50 years. 19.5% and 13.7%, respectively, of patients developed PHN at least 1 and 3 months after HZ diagnosis. Mean direct cost was £103 per HZ patient and £341 and £397 per PHN1 or PHN3 episode (1- and 3-month definition respectively). Both HZ and PHN costs increased with pain severity. [68]
In another study from Italy, of the immunocompetent patients aged ≥50 years , 9.4% and 7.2% developed PHN1 and PHN3 after HZ, respectively. Increasing age, female sex, and immunosuppression conferred increased risk for both HZ and PHN. Overall, about 1.3% of HZ and almost 2% of PHN cases required hospitalisation, with 16.9% of all HZ-related hospitalisations due specifically to PHN. In patients aged ≥50 years, mean stay was 7.8 ± 5.4 days for HZ and 10.2 ± 8.6 days for PHN, and direct costs associated with inpatient care were more than 20 times outpatient costs per HZ case (mean: € 2592 vs. € 123) and over 5 times more per episode of PHN (€ 2806 vs. € 446). Total annual costs were € 41.2 million, of which €28.2 million were direct costs and € 13.0 million indirect costs. [69]
In Sweden, in 2011, HZ incidence was estimated at 315 and 577 cases per 100,000 for patients at all ages and ≥50 years, respectively. Almost 30'000 patients at all ages were diagnosed with HZ in Sweden, and the societal cost to treat these patients, including the cost to treat those patients who later developed PHN, added up to nearly 31.6 Million € which corresponds to € 870 per patient. The main contributors to the total cost for the treatment of HZ patients were primary care (43 %); sick leave (28 %); hospitalization (10 %) and specialist care (7 %). Medication was a relatively small contributor with 4 %, i.e.1.0 Million € to the overall costs for patients at all ages. The corresponding total cost including only patients 50 years and older was 19.2 Million € or €939 per patient. [70]
Finally, in a cohort study of a US claims database 2008-2013, costs of HZ complications were evaluated: approximately 10% of immunocompetent older patients with HZ develop complications, which considerably increase the economic burden of HZ. 22'948 HZ patients (60% women, median age 62 years) who experienced HZ complications were compared to matched patients with uncomplicated HZ. Overall, the mean annual incremental unadjusted costs for the patients with HZ-related complications were US$ 4716, ranging from US $ 2173 for ophthalmic to US$ 18'323 for neurologic complications. Most of the incremental costs associated with HZ complications were accrued during the first quarter after HZ onset. For each complication type, the incremental costs increased with age. [71]

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2. Vaccine characteristics

2.1. Nature and characteristics of the vaccine

Zostavax®: The attenuated live zoster vaccine Zostavax contains the Oka/Merck strain of varicella virus. This is the same strain used in the vaccines against chickenpox (Varilix® and Varivax®), but Zostavax contains about 14 times more virus (over 19'400 plaque forming units PFU) vs. 2000 and 1350 PFU in the varicella vaccines. Zostavax is administered as a single subcutaneous dose (0,65 ml) and containins in addition to the live virus water, saccharose, gelatine, stabilizers and traces of neomycin. (Documed).

Shingrix®: The recombinant, adjuvanted subunit-vaccine is given i.m. in two doses, at an **interval of 2 months.** (According to EMA, in some special cases of immunosuppression **1-2- months** might be considered). One dose (0.5 mL) contains **50 µg of VZV glycoprotein E (gE) antigen**, produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology. The **adjuvans** AS01B containing 50 µg of plant extract Quillaja saponaria Molina, fraction 21 (QS-21) and 50 µg of the Toll-like receptor ligand 3-O-desacyl-4'-monophosphoryl lipid A (MPL) from *Salmonella minnesota*. (EMA – 2021; [72]). The adjuvant AS01B is the same used in the Malaria vaccine RTS,S/AS01 (Mosquirix™), approved by EMA in 2015 for implementation in Sub-Saharan Africa. AS01B is described in detail in a 2019 publication by Lacaille-Dubois. [73]

2.2. Vaccine registration, manufacturer and availability of the vaccines in Switzerland

Zostavax® was approved by Swissmedic in February 2007 for use in adults 50 years of age or older. **C**ompany: Sanofi Pasteur-MSD (SPMSD). The vaccine is currently available in Switzerland.

Shingrix®: Approval by Swissmedic is expected in Q3 of 2021 (not before the end of August). **C**ompany: GlaxoSmithKline - GSK.

Availability of Shingrix® from January 2022 on for elderly adults as well as younger risk groups is ensured (personal communication GSK, May 2021). Also already in 2021, a somewhat limited number of doses might be available in Switzerland after approval.

2.3. Administration schedule and number of doses

Zostavax®: Only one vaccine dose is recommended by the manufacturer and the duration of protection is considered for at least 3 years, starting from age 50 years upwards (Documed). The vaccine can be administered at the same time as other live-attenuated vaccines, but an interval of 1 month between two live-attenuated vaccines is recommended if not administered at the same time. No specific interval is needed between Zostavax® and other non-live-attenuated vaccines. Some studies investigated immune responses to a booster dose of Zostavax® in elderly adults who had previously been vaccinated for up to 10 years. [74]

Shingrix®: Two doses, with a minimum interval of 2 months are required. The company recommends a maximum interval of 6 months, although there is no data which indicates that vaccine effectiveness **(V.E.)** would be lower, if the interval was longer between the two doses.

For subjects who are or might become immunosuppressed due to disease or therapy, and who would benefit from a shorter vaccination schedule, the second dose can be given already after 1 month. In allogeneic HCT recipients $CD4^+$ T-cell count did not influence vaccine response. [75]

So far, apart from few immunogenicity data, the need for booster doses following the primary vaccination schedule has not been established. Shingrix® can be given to persons previously vaccinated with live attenuated HZ vaccine. (EMA – 2021; [72] [76]

2.4. Immunogenicity, and persistence of immunity

Zostavax®:

Immunogenicity: Antibody geometric mean titers (GMT) were examined at day 28 post-vaccination. for a refrigerated (n = 182) and a frozen (n = 185) vaccine formulation. GMTs of 727.4 and 834.4 gpELISA units/ml, respectively were induced, and the geometric mean rise (days 1 to 28) was 2.6- and 2.9-fold, respectively. [77] A follow-up study with subjects from the Shingles Prevention Study has been initiated. In this study volunteers ≥ 70 years of age of the SPS were administered a booster dose 10 years after the initial vaccination and paired with volunteers of the same age getting a first vaccination. Interim results show, that immune responses are similar in both groups. (*Préaud E, Baron-Papillon F*, SPMSD Zostavax® duration of protection)

However vaccination schedules of booster in subjects ≥ 70 at one month or 3 months did not increase VZV antibody response compared to a single vaccine dose and antibody persistence after 12 months was similar regardless of boosters. [78]

For the **immunogenicity in subjects <50 years of age**, there is a paucity of published study results available. A small study published in 2007 by *Macaladad et al*. tested Zostavax® in 18 healthy subjects (age 27 to 69 years, median 35.5). Results show HZ vaccine to be immunogenic and well tolerated, regardless of initial VZV antibody serostatus. All four of the initially seronegative subjects (age 32 to 36 years; median 33.5) seroconverted and 6 of the 13 (46.2%), and initially seropositive subjects had a ≥4-fold rise in VZV-specific antibody titer at 6 weeks post-vaccination. [79] In a 2006 study, *Diaz et al*. tested 647 healthy subjects aged 13 to 69 (median age: 22 years) with two-dose regimen of an experimental "high-titered varicella vaccine" (~50,000 PFU). Immunogenicity was similar compared to a matched group of seronegative subjects who received standard varicella vaccine. [80]

Shingrix®:

Shingrix® induces antibody and T cell responses to the vaccine antigen, i.e. the structural envelop protein glycoprotein E (gE). T cell reactivity following natural infection and Zostavax® vaccination dominantly targets nonstructural (NS) proteins. Voic et al. mapped the gE-specific responses following Shingrix® vaccination to 89 different gE epitopes, 34 of which accounted for 80% of the response. [81] VZV-specific immune responses induced by Shingrix®, including the generation of polyfunctional T cells, are driven by the synergistic actions of the components of the vaccine adjuvant system. [82]

In **immunogenicity studies on the ZOE-50 study participants**, most Shingrix® recipients developed robust immune responses persisting for at least 3 years following vaccination. A humoral response was found in 97.8% (versus 2.0% of placebo recipients). Geometric mean anti-gE antibody concentrations increased 39.1-fold and 8.3-fold over baseline in HZ/su recipients at 1 and 36 months post-dose 2, respectively. A gE-specific CD4+ T-cell response was shown in 93.3% of Shingrix®, and

0% of placebo recipients. Median CD4+ T-cell frequencies increased 24.6-fold (1 month) and 7.9-fold (36 months) over baseline in Shingrix® recipients and remained ≥5.6-fold above baseline in all age groups at 36 months. The proportion of CD4 T cells expressing all 4 activation markers increased over time in all age groups. [83]

Weinberg et al did a **direct comparison of immunogenicity of Zostavax® and Shingrix®** in an RCT, stratified by two age-groups (50–59 and 70–85 years). Immune responses peaked on day 30 after Zostavax® and on day 90 (i.e., 30 days after the second dose) after the 2 doses of Shingrix®. Age and vaccination status did not affect peak responses, but higher baseline CMI correlated with higher peak responses. Shingrix® generated significantly higher VZV-specific IL-2+ and gE-specific IL-2+, IFN-γ+, and IL-2+/IFN-γ+ peak responses and 1-year baseline-adjusted responses compared to Zostavax®. Total VZV-specific IFN-γ+ and IL-2+/IFN-γ+ T cell responses did not differ between the two vaccines. Shingrix generated higher memory and effector-memory CD4+ peak responses and Zostavax generated higher effector CD4+ responses. The higher IL-2 and other memory responses generated by Shingrix may contribute to its superior efficacy. [84]

In an open-label RCT with patients aged 50+ with a **previous history of HZ**, a "vaccine response rate" was defined as a 4-fold increase in anti-gE over baseline at month 3. This primary immunogenicity objective was met in 90.2% (95% CI: 81.7–95.7) of the vaccine recipients. Geometric mean anti-gE antibody concentrations at month 3 were similar across age groups. Shingrix® was considered immunogenic in adults aged 50+ y with a physician-documented history of HZ while no safety concerns were identified.[85]

With regards to persons that had **previously received the live vaccine Zostavax®,** a relatively recent study compared 215 such persons (age ≥65 years) with a matched group of 215 persons who never received Zostavax®. Through 12 months after dose 2, anti-gE antibody concentrations, gE-specific CD4 T-cell frequencies, and activation marker profiles were similar between groups. [86] A trial with involvement of GSK with 430 participants by Grupping et al. found that Shingrix® induced a strong immune response irrespective of prior vaccination with live zoster vaccine. Humoral immune responses to Shingrix® were noninferior in persons vaccinated <5 years ago with Zostavax®, compared with those who never received Zostavax® (adjusted GMC ratio, 1.04 [95% CI, .92–1.17]). Cellular immunogenicity, reactogenicity, and safety appeared to be comparable between groups. [87]

Regarding **long-term immunological data,** Hastie et al. assessed persistence of **humoral and CMI** responses **10 years after** the initial two doses of Shingrix®. They found **6- (humoral) and 3.5-fold (CMI) higher values** compared to pre-vaccination. Using **modelling,** the authors extrapolate these findings **to 20 years post-immunization**. To assess the possible role of booster vaccines, they also evaluated immunogenicity and safety of 2 additional doses, showing good booster effects after the first dose with no further increase after a second booster. [76]

With regards to **immunocompromised patients**, Hirzel et al. enrolled 49 **lung transplant** recipients (≥50 years) who received at least one dose of Shingrix®. Anti-glycoprotein E (gE) antibody levels (n = 43) increased significantly compared to baseline (median optical density [OD] 1.96; interquartile range [IQR]: 1.17-2.89) after the first (median OD 3.41, IQR 2.54-3.81, p < .0001) and second vaccine dose (median OD 3.63, IQR 3.39-3.86, p < .0001). gE-specific polyfunctional CD4+ T cell frequencies (n = 38) also increased from baseline (median 85 per 106 CD4+ T cells; IQR: 46-180) to the first (median 128 per 106 CD4+ T cells; IQR: 82-353; p = .023) and after the second dose (median 361 per 106 CD4+ T cells; IQR: 146-848; p < .0001). The study concluded that Shingrix® was safe and elicited significant humoral and cell-mediated immunity in lung transplant recipients. [88]

Among **renal transplant** recipients ≥18 years of age, a randomized, observer-blind, multicenter trial compared 2 doses of Shingrix® versus placebo 1-2 months apart, between 4 and 18 months posttransplant. Anti-gE-specific humoral and cell-mediated immune responses increased from 1354 mIU/mL to 19'1634 mIU/mL in vaccine recipients, versus no change in placebo recipients. They were high across postvaccination time points and persisted above prevaccination baseline at 12-13 months (8545 mIU/mL). Overall, renal function was comparable. Shingrix® was considered as immunogenic in chronically immunosuppressed RT recipients. [89]

Camargo et al. found in a single-center retrospective study of 135 consecutive adult allogeneic and autologous **HCT recipients** after 2 doses a somewhat reduced immunogenicity, and thus potentially also effectiveness among hematopoietic cell transplantation (HCT) recipients. Shingrix® was poorly immunogenic in subjects with allogeneic HCT. Vaccine response was defined as seroconversion or 4-fold increase of anti-gE-IgG. Only 27% of allogeneic HCT recipients seroconverted, compared to 73% of autologous HCT recipients. Vaccine response was independent of age, CD4 T cell counts, and B-cell recovery. They also state that further studies are required to determine, whether delaying vaccination 1 to 2 years after transplant, administering a booster dose or nonstandard formulation (high dose) can overcome low responsiveness to aVZV. [75]

Zent et al. in a small study (n=32) report a high rate of IgG and T-cell responses to 2 doses of Shingrix® in patients with **CLL** or **lymphoplasmacytic lymphoma** on **BTK inhibitor therapy**. Of the 24 (75%) subjects with a humoral immune response, 21 (87.5%) also achieved a T-cell response. [104]

2.5. Vaccine efficacy in trials and effectiveness in the population (short and long-term), incl. reduction of disease and death risks in different population groups

Zostavax®:

Zostavax®-efficacy in the prevention of HZ and PHN was demonstrated by two large Phase III clinical studies:

The **"Shingles Prevention Study" (SPS)** [38] is a randomized, controlled, multicenter, large scale study involving 38'546 patients over 60 years (median age 69 years; 7% over 80 years). With follow-up rate of 95% at 3 years, this study shows that the vaccine against HZ can reduce the burden of disease in this population. Indeed, Zostavax® significantly reduced the incidence of HZ by 51.3%, the total burden of disease in 61.1% of cases and show an overall PHN vaccine efficacy of 66.5%. In a post hoc study of SPS, [90] the incidence of persistent and severe forms of PHN is reduced by 73% in the vaccinated population. About 80% of these severe cases occur in patients over 70 years. In addition, although the effectiveness of the vaccine on the incidence of HZ is less important in patients over 70 years, the effect of the vaccine on the severity of the disease is higher in this sub-population. [90]

The **"Zostavax® efficacy and safety trial" (ZEST)** [91] is a multicenter randomized controlled trial involving 22'439 subjects aged 50 to 59 in North America and Europe. This study shows a significant decrease from 69.8% in the incidence of HZ in this population. The vaccine was generally well tolerated.

After the SPS, part of the subjects (n = 14'270) were included in two studies to measure the duration of vaccine efficacy (Table 4): the **"Short-term persistence substudy" (STPS)** [92] and the **"Long-term persistence substudy" (LTPS)** [93] These studies enabled the observation of the volunteers and data collection for up to 7 years and 12 years after vaccination, respectively. The STPS study shows the persistence of vaccine efficacy up to 5 years on all the parameters studied (burden of disease,

incidence of HZ and PHN incidence), although the protection becomes gradually weaker with time and increasing patient age and persistence of vaccine efficacy varies with age (Table 4).
The benefit from disease prevention in the younger age group shifts towards a PHN prevention, respectively attenuation in the older age group. In the LTPS there is still a reduction of incidence of HZ, incidence of PHN and BOI but at a lower level than seen in the SPS.

Zostavax®-effectiveness of vaccination against HZ was also demonstrated by **Tseng et al.** in general medical practices, in patients aged over 60 years of age. [94] This retrospective cohort study showed a 55% reduction in incidence of HZ, regardless of age at vaccination, sex, race or the presence of comorbidities.

Another study by **Tseng et al.** [25] shows a decreased risk (adj. HR: 0.58; 95% CI 0.46–0.73) of ophthalmic zoster and hospitalisation due to HZ among previously vaccinated ≥60 year old patients treated with chemotherapy. This retrospective study suggested that HZ vaccine continues to protect against HZ if recipients later undergo chemotherapy, at least during a short time follow up.

Table 8 shows data on efficacy against HZ and its duration of Zostavax® protection by 5-years age groups.

***Table 8*. Persistence of vaccine efficacy by age group according to SPS, STPS and LTPS studies**

	Mean age at enrolment in SPS	VE HZ (95% CI)	VE PHN (95% CI)	VE BOI (95% CI)
SPS 0.0-4.0 yrs.	**≥60**	51% (44-58)	67% (66-79)	61% (51-69)
	60-69	64% (56-71)	66% (20-87)	67% (52-76)
	≥70	38% (25-48)	67% (43-81)	55% (40-67)
STPS 4.0-7.0 yrs.	**≥60**	40% (18-56)	60% (<0-87)	50% (14-71)
	60-69	44% (16-63)	81% (<0-98)	63% (19-82)
	≥70	33% (<0-58)	31% (<0-84)	24% (<0-63)
LTPS 7.0-10.0 yrs.	**≥60**	21% (11-30)	35% (9-56)	37% (27-46)
	60-69	20% (7-32)	17% (<0-51)	33% (17-45)
	≥70	22% (6-37)	50% (16-73)	43% (27-54)

Sources: Shingles Prevention Study (SPS) [38] ; Short-term persistence substudy (STPS) [92] ; Long-term persistence substudy (LTPS) [93]

Shingrix®:

The immunological data for different age groups, for immunocompromised individuals and for different time points after vaccination, seem to reflect the observations in clinical trials and epidemiological studies with regards to **efficacy and effectiveness**.

In 2015, the ZOE-50 (Zoster efficacy study in subjects older than 50) study group and GSK published the results of a phase 3 placebo-controlled RCT with 15'411 adult participants **aged 50 or olde**r in a 1:1 assignment. During a mean **follow-up of 3.2 years**, 6 participants developed HZ in the vaccine group and 210 in the placebo group (incidence rate, 0.3 vs. 9.1 per 1000 person-years) in the vaccinated cohort. **Overall vaccine efficacy (V.E.) against HZ was 97.2%** (95% CI, 93.7 to 99.0; P<0.001). V.E. was between 96.6% and 97.9% for **all age** groups. [95]

In 2016, the ZOE-70 Study Group and GSK published the phase 3 placebo-controlled RCT results, with 13'900 elderly adults **aged 70 or older** from 18 countries in a 1:1 assignment. Mean age was 76 years and mean follow-up 3.7 years. HZ occurred in 23 Shingrix versus 223 placebo recipients (0.9 vs. 9.2

per 1000 person-years). **V.E. against HZ** was **89.8%** (95% CI 84.2-93.7; P<0.001) and was similar in participants **70 to 79 years** of age **(90.0%**) and participants **80 years or older (89.1%**). [96]

In **pooled analyses** of data from participants 70 years of age or older in **ZOE-50 and ZOE-70** (16'596 participants), **V.E. against HZ** was **91.3%** (95% CI, 86.8 to 94.5; P<0.001), and **V.E. against PHN** was **88.8%** (95% CI, 68.7 to 97.1; P<0.001). [96]

One of the authors then analyzed the pooled ZOE-50/ZOE-70 V.E. data against HZ-related complications other than PHN (i.e. hospitalization, HZ-associated vasculitis, stroke, and disseminated, ophthalmic, neurologic, and visceral diseases). Only 1 of the 32 Shingrix® recipients (3.1%) and 16 of 477 placebo recipients (3.4%) with a confirmed HZ had non-PHN complications. **Efficacy against HZ-related (non PHN-)complications was 93.7%** (95% confidence interval, 59.5–99.9%) in adults **≥50 years** and **91.6%** (43.3–99.8%) in adults **≥70 years**. Five HZ-related hospitalizations, all in placebo recipients, and no HZ-related deaths were reported. [97]

In a 2018 meta-analysis sponsored by GSK, **Shingrix®** demonstrated significantly higher V.E. against HZ (**0.92** (95% CI: 0.88, 0.94) compared to **Zostavax®** (**0.51** (95%CI: 0.44, 0.57)) in **adults ≥60 years** of age. For **adults ≥70 years** old the difference in V.E. was even higher: **0.91** (95%CI: 0.87, 0.94) for **Shingrix®** versus **0.37** (95%CI: 0.25, 0.48)) for **Zostavax®.** Shingrix® also demonstrated higher V.E. against PHN: in adults ≥60 years old **0.89** (95%CI: 0.70, 0.96) for Shingrix® versus **0.66** (95%CI: 0.48, 0.78)) and for Zostavax. For adults ≥70 years old the corresponding figures were **0.89** (95%CI: 0.69, 0.96) for Shingrix®, and **0.67** (95%CI: 0.44, 0.80)) for Zostavax®. [98]

Long-term efficacy: A recent, unpublished interim analysis by GSK by Boutry C. & Hastie A. et al. (2020) of a subset of ZOE-50/70 praticipants found V.E. of **90.9%** after a mean follow up o**f 7.1 years.**

V.E. in younger adults: The same interim analysis also followed up a placebo-controlled cohort of 0-49 year olds, and after **2.0 years** of follow-up found an effectiveness of **84.0%.**

With regards to **effectiveness** data (real-world, outside of trials), after the first two years post-licensure, Izurieta et al. conducted a large observational cohort study among **US Medicare beneficiaries aged >65 years**. The cohort included **1,01 million** beneficiaries who received two doses of Shingrix®, and 1,50 million that had received only one dose at time of analysis. A non-vaccinated control group consisted of >10 million people. They found a V.E. of **56.9%** (95% CI, 55.0-58.8) **after one dose,** and of **70.1%** (95% CI, 68.6-71.5) **after the two doses**. In persons aged 65-79 years, the V.E. (2 doses) was **70.6%** ((95% CI 68.9%-72.1%).
The 2-dose V.E. was comparable for persons aged ≥80 (**68.5%** (95% CI 65.1%-71.6%)), for individuals with autoimmune diseases **(68.0%** (95% CI. 62.3%-72.8%)), and also for 2nd doses received at ≥180 days **(71.7%** (95% CI. 66.1%-76.3%)). Thus, 2nd doses administered later than the recommended 6 months did not reduce V.E. In individuals of **all ages ≥65 with immunosuppressive** conditions, the vaccine was also effective (**64.1%** (95% CI. 57.2%, 69.8%)). This was only slightly lower than for immunocompetent vaccinees (70.5%). Overall 2-dose V.E. against **PHN** was **76.0%** (95% CI, 68.4-81.8). [99]

These observed **"real-world" effectiveness** estimates of **around 70% of *Izurieta H et al.*** were somewhat lower than those of the clinical trials (89-97%). The authors suggest that one of the **reasons for the observed difference in V.E.** might be differences in **outcome measurements**: The case identification in the observational cohort relied on diagnosis codes and prescriptions observed in Medicare claims and thus measured medically attended HZ-related disease cases from insurance data, while in the clinical trials all clinically suspected cases of HZ were PCR-confirmed or adjudicated by an expert panel. Using a less specific clinical definition in the ZOE-50 and ZOE-70 studies, efficacy

would have been approximately 76% (156 suspected cases among 13,881 vaccinated and 653 suspected cases among 14'035 placebo recipients). Another factor that may be driving a difference in VE estimates was that **the real-life study population was older, possibly more frail**, and included immunocompromised individuals who demonstrate lower V.E. However, the HZ incidence rate in the unvaccinated subjects (10.3/1000 person-years) was comparable to those observed in the placebo groups of ZOE-50 (9.1/1000 person-years) and ZOE-70 (9.2/1000 person-years). [99]

Finally, a 2018 modelling of the epidemiological effects of vaccination by the **Robert-Koch-Institute** RKI for the German population suggested that vaccination with Shingrix® starting from **60 years** of age had the greatest effect on preventing **all cases of HZ,** while vaccination from **70 years** of age had the greatest effect on preventing **PHN cases** in a vaccinated cohort. [100]

Shingrix® efficacy or V.E. in immunocompromised subjects or other risk groups:

In a 2020 systematic review of vaccine trial efficacy of Shingrix® among immunocompromised persons, Racine et al. found efficacy in hematopoietic stem cell transplant (HSCT) patients was **72%** (95%CI, 39–88%) in 18- to 49-year-olds, and **67%** (95%CI, 53–78%) in ≥50-year-olds (median follow-up: 21 months). Vaccine efficacy in ≥18-year-old patients with hematologic malignancies was estimated at **87.2%** (95%CI, 44.3–98.6%) during the observation period that was up to 13 months post-vaccination. [101]

In a very similar subgroup analysis from ZOE-50/70, Oostvogels L. et al. examined efficacy and safety with regards to more general pre-existing medical conditions overall. At enrollment, around 83% of participants had at least one **pre-existing medical condition.** Efficacy against HZ ranged from 84.5% (95% CI: 46.4-97.1) in those with respiratory disorders to 97.0% (95% CI: 82.3-99.9) for those with coronary heart disease. Efficacy remained >90% irrespective of the number of medical conditions. [102] A second similar subgroup-analysis (Curran et al.) used a **"frailty"** index for 26'960 ZOE-50/70 participants with a mean age of 69 years; 45.6% were pre-frail and 11.3% frail. Frailty increased with age from 5.7% aged 50-59 years to 22.7% aged ≥80 years. Shingrix® efficacy against HZ was >90% for all frailty subgroups (non-frail: 95.8% (95% confidence interval = 91.6-98.2), pre-frail: 90.4% (84.4-94.4), frail: 90.2% (75.4-97.0)). Immunological parameters remained high for at least 3 years in all frailty subgroups. [103]

Dagnew et al. performed a post hoc subgroup analysis of Shingrix®'s efficacy against HZ and safety in ZOE-50 and ZOE-70 phase 3 RCT participants who reported **pre-existing potential immune-mediated diseases (pIMDs)** at enrollment and were not on immunosuppressive therapies. 1'943 participants of either study had at least one pre-existing pIMD at enrollment, most frequently psoriasis, spondylo-arthropathy and Rheumatoid arthritis (R.A.) efficacy against HZ was **90.5%** (95% CI: 73.5, 97.5%) overall with the lowest being 84.4% (95% CI: 30.8, 98.3%) in the 70-79-year-old age group. [104]

An RCT in persons aged 50 or older (Bastidas A. et al.) looked at efficacy and safety in **autologous hematopoietic stem cell transplantation (HSCT)** recipients. 1'846 participants with a mean age of 55 years received either Shingrix® or placebo 50 to 70 days after transplantation and the second dose 1 to 2 months thereafter and were followed up for 21 months. They found HZ episodes in 49 vaccine and 135 placebo recipients (incidence, 30 and 94 per 1000 person-years, respectively), an incidence rate ratio (IRR) of 0.32 (95% CI, 0.22-0.44; P < .001), equivalent to a **68.2%** vaccine efficacy during the first two years follow-up. [47] Additionally, Shingrix® recipients showed higher Quality of Life scores than placebo recipients 1 week following rash onset among participants with confirmed HZ, and in those who developed breakthrough disease despite receipt of Shingrix®, disease severity and

duration was significantly lower. **After** the **two years f**ollow-up vaccine efficacy seemed to wane, with a HR of 0.79 (95%CI, 0.23–2.72) in an exploratory post-hoc analysis, equivalent to a **21%** vaccine efficacy. [105]

These and other study results for vaccine efficacy among **severely immunocompromised** patients are summarized in ***Table 9*****.**

Table 9. Studies investigating HZ incidence among vaccinated and unvaccinated immunocompromised patients and Shingrix V.E.

Patients / condition	**Incidence per 1'000 patient years (median or OR (95% CI))**	**incidence rate ratio (IRR)**	**vaccine efficacy**	**Selected studies / [ref.]:**
HCT autologous + allogeneic transplant			72 (age 18-49) 67 (age 50+) 100 (age 60-69) 84 (age 70-79)	Systematic review by Racine [101]
HM (haematological malignancy)			87.2% (age 18+)	
HSCT n=1'846, mean age 55 yrs.	30 Shingrix® vs. 94 placebo	0.32 (95% CI, 0.22-0.44; P < .001)	68% for 2 years follow-up	Bastidas [47]
Psoriasis, RA, spondylo-arthropathy, other IMDs	Shingrix® vs. placebo 1 vs. 11 (age 50-59) 0 vs. 14 (age 60-69) 1 vs. 8 (age 70-79) 2 vs. 15 (age 80+)		93 (age 50-59) 100 (age 60-69) 84 (age 70-79) 86 (age 80+)	Dagnew [104]
JAK-inhibitors for immune-mediated diseases				

2.6. Potential impact of the vaccine recommendation on the transmission of pathogens (e.g. reduction in carriage rate, replacement or resistance to anti-infective agents).

Even if broadly applied, HZ vaccination is expected to have almost no impact on transmission in a population, since the main route of VZV transmission occurs early in life, most often in childhood. Consequently, a HZ vaccination recommendation will not impact herd immunity; also see point 3.3. "Alternative strategies" and point 2.7.2 Contraindications, precautions.

2.7. Safety: rates and severity of adverse events, contraindications, precautions

2.7.1 Safety: rates and severity of adverse events

Zostavax®:

The vaccine against HZ is generally well tolerated. The study population (n = 38'546) in the Shingle Prevention Study [38] was also subject to a safety study. [106]

The most common side effects are local reactions at the injection site: very frequently (more than 1/10 cases) pressure pain, erythema, swelling, and frequently (between 1/10 and 1/100 cases) haematoma, pruritus and local hyperthermia. No disseminated vesicular rash related to vaccinations

had been documented. Within 42 days of vaccination, the study noted significantly more confirmed cases of HZ in the placebo arm (24 cases in the placebo group and 7 in the vaccine group). Headaches are the most common systemic adverse effects. Other adverse effects are described but their frequency cannot be estimated and their association with the vaccine remains doubtful (lymphadenopathy, hypersensitivity reactions, nausea, arthralgia and myalgia).

Shingrix®:

Shingrix®, which contains an adjuvant called AS01B, seems to be **safe and well tolerated**, but shows **higher reactogenicity** and injection site pain than most other vaccines.

Chlibek et al. in 2013 performed a **phase 2**, observer-blind, randomized trial in 410 adults ≥50 years old, who were randomized 4:4:2:1 to receive either the antigen gE combined with a high (=standard)- or low (=half-)dose (AS01E) adjuvant, unadjuvanted gE, or placebo. Following each dose, solicited events were recorded for 7 days and unsolicited Ae's for 30 days. Serious AE's were collected for 1 year. No vaccine-related severe AE's were reported. Solicited AE's were generally mild to moderate and transient. For the high (=standard) dose adjuvant group, 87% reported any symptom, of which 9% were classified as grade 3 (Placebo: 21% and 5%, respectively). Pain was the most common local symptom (83%), followed by redness (29%) and swelling (15%); (Placebo: 8%-0%-0%). Fatigue (48%) was the most common general symptom, followed by myalgia (41%), headache (37%) and fever (17%); (Placebo: 18%-5%-10%-3%, respectively). [107]

In the **ZOE-70 trial,** solicited reports of **injection-site and systemic reactions** within 7 days after injection were more frequent among Shingrix® recipients than among placebo recipients (**79.0%** vs. 29.5%). Serious adverse events, potential immune-mediated diseases, and deaths occurred with similar frequencies in the two study groups. [96] In a 2018 meta-analysis also sponsored by GSK, Shingrix® was associated with significantly more injection-site and systemic reactions compared to Zostavax® and compared to placebo. There were **no statistically significant** differences found between Shingrix® and any formulation of Zostavax® or placebo for **SAE's**. [98] In a third safety analysis by GSK, López-Fauqued et al. analysed unsolicited AEs among 14'645 Shingrix® and 14'660 placebo recipients pooled from the ZOE-50/ZOE-70 studies. Frequencies of unsolicited AEs were 50.5% versus 32.0%; the difference was driven by transient injection site and solicited systemic reactions that were generally seen in the first week post-vaccination. The occurrence of Severe AEs (Shingrix®: 10.1%; Placebo: 10.4%), fatal AEs (Shingrix®: 4.3%; Placebo: 4.6%), and pIMDs (Shingrix®: 1.2%; Placebo: 1.4%) was similar between groups. **Overall, except for the expected local and systemic symptoms ('reactogenicity'), the safety results were comparable between the Shingrix® and placebo groups** irrespective of participant age, gender, or race. [108] In an open-label RCT with patients aged 50+ with a previous history of HZ, 77.9% and 71.6% of participants reported local and general solicited AEs, respectively. The most frequent solicited AEs were pain at injection site, fatigue, headache, myalgia and shivering. No safety concerns were identified.[85] In a single-arm study in the U.S., 401 adults aged ≥50 and older (mean age 64.6), Quality of Life scores, reactogenicity, safety, productivity loss, and healthcare resource utilization were evaluated. 97.5% of participants received the 2nd dose. Post-dose 2, the most common solicited local symptoms were injection site pain (75.1%), erythema (22.4%), and swelling (13.9%), and the most common systemic AE's were fatigue (46.3%), headache (37.5%), and myalgia (32.9%). Grade 3 solicited (local and systemic) AE's were reported by 61 (15.6%) participants. No clinically important reduction in mean QoL (SF-36 PF) score was observed from baseline to post-dose 2 (mean change -0.4), and no quality-adjusted-life-year loss was recorded. [109]

Among **renal transplant** recipients ≥18 years of age, a randomized, observer-blind, multicenter trial found that overall, renal function was comparable for Shingrix® versus placebo, and **no safety** issues could be detected. [89]

In 2020, the **Paul-Ehrlich Institute** PEI published **a case report** of a 74-year-old female patient with a history of ulcerative proctosigmoiditis on mesalamine who presented with a blistering skin disease after each Shingrix vaccination. [110] Whether there is a general risk for blistering skin disease is currently being investigated in an observational study by the PEI.

2.7.2 Contraindications, precautions

Zostavax®:

As all live attenuated vaccines, Zostavax® is in principle contra-indicated in:

1) Patients with moderate to severe primary or acquired immunodeficiency (including patients with leukaemia, lymphoma or other haematological malignancies, patients with AIDS or immuno-suppressive therapy)
2) Individuals with a history of anaphylaxis to gelatine or neomycin and/or a serious allergic reaction (including an anaphylactic reaction) to a previous dose of VZV-vaccine
3) Pregnant women; the vaccine against HZ is contra-indicated during pregnancy. Therefore, pregnancy has to be excluded (pregnancy test) in women of childbearing age before the HZ live-attenuated vaccine is administered. However, an interval of 4 weeks is suggested between vaccination and the beginning of a pregnancy. [111]
4) Patients with active (symptomatic) untreated tuberculosis[1]

Shingrix®:

For Shingrix® the only contraindication according to EMA is **hypersensitivity** to the active substances or to any of the excipients, e.g. Polysorbate 80 (E 433) with a potential of pseudo-allergies or cross-reactivity in polyethylenglycol allergic subjects. Vaccination with Shingrix® should be postponed during an active HZ episode.

There are no human safety data available for the use of Shingrix® in **pregnant women.** Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or post-natal development. As a precautionary measure, it is preferable to avoid the use of Shingrix® during pregnancy. The effect on breast-fed infants of administration of Shingrix to their mothers has not been studied. It is unknown whether Shingrix® is excreted in human milk. Fertility: Animal studies do not indicate direct or indirect effects on males or females. [72]

Neither Zostavax® nor Shingrix® should be used for the prevention of **primary VZV** infections (chickenpox).

2.8. Safety in specific populations: adverse events, contraindications and precautions

Immunocompromised patients

[1] NHS. U.K. 28/7/2015 http://www.nhs.uk/Conditions/vaccinations/Pages/who-can-have-the-shingles-vaccine.aspx

The review of the vaccination records ('Impfausweis' / "carnet de vaccination") is an important task for physicians in the medical evaluation of immunocompetent patients who may need immunosuppressive therapy or who suffer from a disease causing immunodeficiency.

Zostavax®:

Zostavax® is a live-attenuated vaccine. Cheetham et al. showed in a large cohort of immunosuppressed individuals (>14'000; between 2006 and 2009) that patients currently on immunosuppression (less than 4 weeks before or at the time of vaccination) had an increased risk of HZ in the 42 days after vaccination compared to patients with "remote use", i.e. who had taken immunosuppressant medications in the past[2] (adj. O.R. 2.99; 95% CI 1.58-5.70). The results suggested that patients taking low-dose corticosteroids have an increased risk for HZ, and they affirm the suggested 4 weeks interval before immunosuppression as well as the contra-indication for patients with a current moderate to severe immunodeficiency. The authors note that the development of HZ was primarily due to reactivation of VZV than dissemination of the vaccine-derived varicella virus. For dissemination of the vaccine-virus, the Oka strain would need to infect the patient, migrate to a dermatome, and reemerge as a HZ rash within 42 days. [112] A cohort study by Tseng et al. 2014 using Cox proportional hazards regression including 4710 subjects ≥ 60 years vaccinated with Zostavax® prior to initiation of chemotherapy with myelosuppressive agents showed a similar HZ incidence hazard ratios compared to an immunocompetent cohort. The results suggest that immunity is maintained in the presence of chemotherapy. The 42% protection found in this study translates into a large reduction in disease burden given the high incidence of HZ in this high-risk population. The incidence of HZ for cohort members vaccinated ≤30 days, 31–59 days, 60–180 days, 181–365 days, and >365 days before initiation of chemotherapy was 26.71 (95% CI, 10.01–71.21), 19.01 (95% CI, 6.11–59.02), 9.01 (95% CI, 4.05–20.05), 12.34 (95% CI, 7.31–20.84), and 12.89 (95% CI, 10.09–16.47) per 1000 person-years, respectively. Vaccine effectiveness in this study was assessed after initiation of chemotherapy, on average 2.4 years after vaccination. HZ incidence rates in unvaccinated patients receiving chemotherapy were 22.1 per 1000 person-years (95% CI, 20.3–23.9), much higher than the rates in comparable immunocompetent patients (13.0 [95% CI, 12.6–13.3]). The findings provide an additional rationale for offering zoster vaccine to future immunocompromised adults before the vaccine becomes contraindicated. [25]. Another retrospective cohort study among ≥ 60 year-old subjects suffering from various immune mediated diseases (i.e. rheumatoid arthritis, psoriasis, psoriatic arthritis, ankylosing spondylitis, or inflammatory bowel disease), some of them exposed to biologics at the time of vaccination or within 42 days of vaccination, did not reveal an increase of short term incidence of HZ but rather a lower incidence of HZ in a median, 2 year follow-up [113]. Therefore, these results suggest that in some cases (e.g. biologics treatment) vaccination with a live-attenuated HZ vaccine may be less problematic than believed (see also point 8 "open questions").

The chapter „Proposed recommendation" at the end of the document contains a **list** published by the **US Centers for Disease Control and Prevention (CDC)** detailing the specific conditions when zoster vaccination can be considered in immunodeficient patients. [111] As previously mentioned in chapter 2.5., immunogenicity, safety and tolerability of Zostavax® in subjects <50 years of age, was investigated only in the study published in 2007 by Macaladad et al. among 18 healthy subjects (age 27 to 69 years, median 35.5). No serious vaccine-related AE's or laboratory-confirmed varicella-like rashes (>50 lesions) were reported. [79] The 2006 study by Diaz et al. testing 647 healthy adults 13 to

[2] "Remote immunosuppressant drug use" occurred in the year before the vaccination but stopped more than 30 days before the vaccination date.

69 years old (median: 22 years) with an experimental high-titered (~50,000 PFU) varicella vaccine found that the vaccine was generally well tolerated. No clinical serious adverse experience were reported in the respective study arm. Injection-site adverse experiences were experienced by 70.0%, but generally were mild. [80]

Shingrix®:

In a 2020 systematic review of Shingrix® among **18- to 49-year old immunocompromised** persons, Racine et al. found a proportion of patients reporting serious AE's ranged between 8.1 and 30.8% in Shingrix and between 4.1 and 36.5% in placebo groups. However, **SAE's** deemed **related to vaccination** were reported in **less than 1%** of patients in both Shingrix® and placebo groups. The proportion of patients that experienced clinically significant underlying disease-related events ranged between 0.0 and 20.0% in Shingrix and 0.0 and 26.7% in placebo groups [101]

Dagnew et al. performed a post hoc subgroup analysis of Shingrix®'s efficacy against HZ and safety profile [specifically, the occurrence of serious adverse events (SAEs)] in ZOE-50 and ZOE-70 phase 3 RCT participants who had at least one pre-existing potential immune-mediated disease (pIMDs) at enrollment but were not on immunosuppressive therapies. 983 Shingrix® and 960 placebo recipients were analysed. The most frequent pre-existing conditions were psoriasis, spondyloarthropathy and RA. SAEs and fatal SAEs were similar between Shingrix® and placebo recipients. [104] An RCT by Bastidas A. et al. looked at efficacy and safety in autologous hematopoietic **stem cell transplantation** (HSCT) recipients. 1'846 participants with a mean age of 55 years received either Shingrix® or placebo 50 to 70 days after transplantation and the second dose 1 to 2 months thereafter and were followed up for 21 months. Five secondary objectives were descriptive. Injection site reactions were recorded in 86% of vaccine and 10% of placebo recipients, of which pain was the most common, occurring in 84% of vaccine recipients (grade 3: 11%). Unsolicited and **serious adverse events**, potentially immune-mediated diseases, and underlying disease relapses were **similar between group**s at all time points. [47]

In the study by Hirzel et al with 49 **lung transplant** recipients, tenderness (83.0%; 95%CI: 69.2-92.4%) and redness (31.9%; 95%CI: 19.1-47.1%) at injection site were common, and in the range observed in non-immuncompromised subjects. One rejection episode within 3 weeks of vaccination was observed. [88]

Concern has been raised that Shingrix® may trigger **disease flares** in patients with **immune-mediated inflammatory diseases (IMID).** Stevens et al. assessed safety of Shingrix® in 403 for patients with a variety of IMID (59.3% with Rheumatoid Arthritis (RA), the remaining 40.7% included patients with connective tissue diseases (e.g.SLE) or systemic vasculitis). Of those, 78.4% were being treated with any immunosuppressant medication, most commonly methotrexate, prednisone and TNFa-inhibitors. A flare was defined as occurring within 12 weeks of vaccine receipt by either 1) documentation of RA flare in office notes, telephone encounter, or patient portal communication or 2) new or increased dose of corticosteroids. The authors found a **6.7%** (n = 27) **incidence of flare,** more frequently after dose 1. Mild adverse events occurred in 12.7% (n = 51) of patients. Three cases of HZ were reported as occurring 2, 10, and 11 months after the vaccination [114]

Olivera et al. in a systematic review assessed safety of **JAK-inhibitors** in patients with immune-mediated diseases: incidence rate of AEs was 42.65 per 100 person-years and of **serious AEs was 9.88 per 100 person-years**. Incidence rates of serious infections, HZ infection, malignancy, and major cardiovascular events were 2.81 per 100 person-years, 2.67 per 100 person-years, 0.89 per 100

person-years, and 0.48 per 100 person-years, respectively. Mortality was not increased in patients treated with JAK inhibitors. [56]

2.9. Potential interactions with other vaccines.

Zostavax®:
Coadministration of Zostavax® with the **23-valent pneumococcal polysaccharide vaccine PPV23** may lead to lower antibody titers. However, a retrospective study found no impact on V.E. [44] [45] [115]
PPV23 is currently not recommended in Switzerland.
Administration of **DTPa** at the same time has not been investigated.
Simultaneous administration with **influenza vaccine** at different injection sites is possible.

Shingrix®:
RCTs found n**o immunological interference** of Shingrix® and other vaccines, specifically co-administration with PPV23 [116], Tdap [117], or inactivated seasonal influenza vaccines. [118]
According to CDC, concomitant administration of Shingrix® with Fluarix Quadrivalent® (influenza vaccine) (QIV) has been studied, without evidence that the immune response or safety to either vaccine is altered. Currently, no data is available for co-administration with other vaccines. As Shingrix is a non-live subunit vaccine, it is generally considered to be safe to be administered concomitantly with other vaccines.

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3. Vaccination strategy

3.1. Existing recommendations and guidelines; 2021 (e.g. ACIP, WHO, CCMP, AAP, recommendations of other countries, consensus conferences, monograph of the product).

A **WHO** position paper on Varicella and HZ (dating from June 2014, i.e. published before Shingrix® was available) did not offer specific recommendations concerning the routine use of HZ vaccines at this time, but recommended that countries with a HZ vaccination programme, the optimal age and dosing schedule of HZ vaccination should take into consideration the age-dependent burden of disease, vaccine effectiveness, duration of protection, and cost-effectiveness [119]
Recommendations of **other countries** (vaccines: Zostavax + Shingrix) are summarized in the **overview table** in chapter 11. → Jump to chap. 11 (Conformity)

3.2. Goal of national or international prevention (reduction of burden of disease, disease control, elimination, or eradication of the disease).

The principal aim of a vaccine recommendation against HZ in Switzerland is the reduction of the burden of disease in the population(s) that are the most at risk of HZ and its major complications such as PHN and ophthalmic HZ. These include, disease episodes, prolonged periods of pain, hospitalisations, absences from work, sequalae (e.g. from rare cases of blindness due to ophthalmic zoster), as well as rare cases of deaths. Other goals include a reduction of antiviral and pain medication, and finally a reduction of direct and indirect costs for health care, economy and society.

3.3. Strategies to achieve the goal (e.g. selective vaccination or generalized, catch up), including alternative immunisation strategies and programs for meeting goal.

A broader strategy to achieve the goals formulated in 3.2. would be the **prevention of primary varicella infection in childhood**. A varicella vaccination recommendation, is currently under evaluation by the EKIF / CFV. The effects of a reduced number of VZV-infected persons resulting in less latent zoster infections and hence less HZ, **will take several decades** to become relevant. [120] Therefore, the strategy in Switzerland will be to selectively vaccinate according to the risk for HZ. The risk groups include a specific **age group** (**complementary** recommendation category for all persons from a certain age, e.g. 50+ or 65+), and additionally for younger persons with a compromised **immune status** (**risk group** recommendation category).

To reduce the risk of HZ in elderly persons a **complementary vaccine recommendation** against HZ seems adequate, because the vaccine can only offer individual protection against a clearly defined risk and has practically only a negligible effect on VZV circulation in the population. A complementary HZ vaccine recommendation is expected to reduce the number of severe cases of HZ and its complications, even if their overall yearly incidence is moderate and some therapies exist.

Complementary / Age group recommendation:

The current HZ vaccine recommendation for Zostavax includes subjects aged 65-79 years old and those older than 50 that will become immunosuppressed in the near future. This complementary recommendation was largely backed by results from a modelling study performed in 2015 by the vaccine producer, using latest available input parameters, specified in advance with the EKIF working group (CEA Zostavax® report by Sanofi Pasteur MSD, 28 May, 2015).

Shingrix

GSK by the end of June 2021 presented a budget impact model for Shingrix in Switzerland, recommended for the age group 65 years and older. This age group was under the currently available data, the most cost-efficacious age limit for a general or complementary recommendation. Details of this model are not yet available for publication.

Risk group recommendation

As HZ incidence is increased in patients with conditions or situations in which they are immunodeficient (due to inherited syndrome, disease and/or therapy), the aim and strategy should be to protect these patients as early as possible with the most efficient, and safe vaccine available from Hz and its complications.

Zostavax:

Due to the higher efficiency of the Shingrix vaccine, there is no place for the Zostavax in this category of patients except in the group of 50+ with a contraindication to Shingrix and in the absence of severe immunosuppression or before it, if timing allows it.

As soon as the non-live vaccine Shingrix is authorized and available in Switzerland, **Zostavax** should **not** be recommended anymore for immunocompromised or future immunocompromised patients, due to reduced effectiveness and potential safety issues (adverse events related to the use of a live vaccine in immunocompromised persons).

Shingrix:

Physicians should identify current or future immunodeficient patients aged 18 years and older, with an increased risk for HZ or its complications, and actively recommend HZ (Shingrix®) vaccination ideally before immunosuppression (2 doses 1 to 2 months apart) or at least with the first dose ≥ 2

weeks prior to immunosuppression. This will in principle target patients under certain immune-modulating and/or immunosuppressive therapies, such as treatments for haematological malignancies, immunodeficiencies affecting T cells including subjects following HSCT or SOT, cytotoxic chemotherapy, JAK-inhibitors ect. → exact wording see page 3, Proposed recommendations of FOPH and EKIF/CFV.
In order to attain an effectiveness as high as possible, in these patients the **optimal timing** for application of the 2 recommended doses should be established on an **individual patient level** by the treating specialists.

3.4. Alternative immunisation strategies and programs for meeting goal (i.e. selective vs. universal immunisation programs, catch-up programs).

For the currently available HZ vaccines, the proposed strategy consists of two selective recommendations: 1. for a specific age group **(complementary recommendation)** and 2. additionally for a specified group of future (and in case of Shingrix also 'currently') immunosuppressed patients with an increased risk for HZ and HZ-complications **(risk group recommendation)**.

The reasons for a complementary vaccine recommendation for elderly persons are explained in chapter 3.3.

Whether **booster** doses against HZ are necessary, effective and safe is currently being investigated, and future results might eventually lead to adaptions in the currently proposed strategy.

An alternative to reach the goal of protecting the most vulnerable population groups from HZ related complications would be to introduce a **routine childhood vaccine recommendation against varicella virus** ("Basisimpfung"/ "vaccination de base") for toddlers in Switzerland. With a basic reproductive number R0 of around 3-7, VZV is highly transmissible but effectiveness of varicella vaccination in healthy children and adults below 40 years is well over 80% [121]. Theoretically, if vaccine coverage would be high enough in the long-term, VZV-transmission would decrease. This might not only reduce varicella- and HZ-incidence in Varicella vaccinated subjects, but also in those not vaccinated or in vaccine non-responders due to herd immunity. The concern that a decrease in VZV-circulation would reduce "naturally occurring VZV boosting" and thus might actually increase HZ-incidence in some population groups or overall has not been confirmed in the **USA** where a **routine childhood** vaccine recommendation against **VZV** was introduced **in 1995**. More than 20 years later, there is **no signal that the rate of HZ in the elderly US populations was negatively affected** by the introduction of VZV vaccine, when compared to other countries. [122] By 2021, many countries European have begun to routinely immunize children against VZV, including the neighbouring countries Austria, Germany and Italy.

3.5. Program delivery strategy/system: nurses versus physicians, private versus public, different locations (i.e. schools, private clinics, public health clinics).

HZ-vaccine will be administered by GP's or specialists.
GP's and specialists should inform their adult patients from a certain age about the complementary vaccination recommendation (age group) and also their younger immunocompromised patients of the risk group recommendation against HZ according to the Swiss vaccination plan.
Vaccination should be recommended to and discussed with the patient, and administered by the GP or the specialist according to immunosuppression status.

For **Zostavax:** (in principle at least 4 weeks prior to treatment with immunosuppressors and according to the CDC recommendations listed in **„Proposed recommendation“**). This will in principle only target individuals 50 years and above who are facing an immunosuppressive therapy at short term and have not been vaccinated previously and cannot receive Shingrix.

For the non-live **Shingrix** vaccine, there are no limitations regarding intervals to immunosuppressive treatments. However, in certain immunocompromised patients, the optimal timing of 1st and 2nd dose must be thoroughly assessed at individual level to ensure best immunogenicity.

3.6. Objectives of each strategy in terms of reduction of incidence, complications, sequelae and mortality.

The objective of the strategy would be the reduction of burden of disease as much as possible. According to V.E. data the goal for Zostavax would be at least 50% decrease of HZ cases and 60% PHN and for Shingrix >70% for both conditions for the **complementary age group recommendation**. In immunosuppressed, the reduction of BOD is expected to be lower for both vaccines, yet, the absolute number of prevented cases will be higher, given the high incidence of HZ in this risk group **(risk group recommendation)**.

3.7. Specific operational objectives/targets in terms of coverage for different target groups.

For the complementary recommendation for elderly persons there is no operational target in terms of coverage.

For the risk group recommendation, the objective would be to vaccinate as many patients as possible for who the vaccine is recommended.

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4. Cost-effectiveness of strategies

Cost of each strategy from the perspective of society, including direct costs and indirect for families and the health system, the costs for the implementation and unwinding.

Zostavax:

Pharmacoeconomic evaluation of the vaccine for the prevention of HZ and PHN in Switzerland was published in 2011 [67] and well summarized by Baron-Papillon et al. (Sanofi Pasteur MSD) in 2013. The primary objective was to assess the cost-benefit ratio of a universal vaccination strategy against VZV, and a vaccination strategy to vaccinate elderly persons of 70-79 years was estimated to be cost-effective in Switzerland.

Szucs et al. [67] used for this purpose the previously mentioned model originally developed for England and then adapted to the Swiss population. This model simulates the natural history of HZ and PHN and the effects of vaccination. It distinguishes between different health states: full health, HZ, PHN and deaths. Pain is sub-classified according to its severity (mild, moderate and severe). Finally, it takes into account the aging of the population. By vaccinating 20% of the Swiss population aged 70 to 79, the model by Szucs et al. predicts the prevention of 3'412 HZ cases, 1,460 cases of

PHN3 and 885 additional QALY in the Swiss population. The number needed to vaccinate was estimated at 31 and 73 to prevent one case of HZ or PHN, respectively. In summary, this study suggests that the cost-benefit of a Zostavax vaccination strategy would just be cost effective in people 70 years of age or over in Switzerland. However, this study has some limitations. Indeed, some Swiss data are missing and required the extrapolation of European data. In addition, the model used incorporates the assumption that a single dose of the vaccine against HZ confers lifelong protection. However, several studies show that immunity induced by the vaccine decreases over time and suggest that a booster may be necessary. In a review article from the same author about cost-effectiveness only one out of eleven analyses from various countries did not show any cost-effectiveness after vaccination. [123]

Shingrix:
Since 2018, several cost-effectiveness (C.E.) modelling studies have been published for the United States, Canada, Japan and Germany.

United States: At US$ 280 for two doses, Shingrix was the most expensive adult vaccine in 2019 in the USA. A lifetime-horizon modelling study by Prosser L. et al., funded by the US Centers for Disease Control and Prevention evaluated the C.E. of vaccination with Shingrix for immuno-competent U.S. adults aged ≥50 years compared with Zostavax and with no vaccination. Additionally they modelled C.E. of Shingrix for persons who have previously received Zostavax. The main outcome measures was the incremental cost-effectiveness ratio (ICER) from a direct (health care sector) and an indirect (societal) costs perspective. For vaccination with Shingrix compared with no vaccination, ICERs ranged by age from US$ 10'000 to US$ 47'000 per quality-adjusted life-year (QALY), using a societal perspective and assuming 100% completion of the 2-dose Shingrix regimen. For persons aged ≥60 years or older, ICERs were less than US$ 60'000 per QALY. Vaccination with Zostavax was dominated by vaccination with Shingrix for all age groups ≥60 years. Vaccination with Shingrix after previous receipt of Zostavax yielded an ICER of US$ < 60'000 per QALY for persons aged ≥60 years. The results of the sensitivity analysis were robust over a wide range of plausible values and scenarios, including only 50% completion of the 2nd dose, but assuming a fixed price, most sensitive to changes in V.E., duration of protection, HZ incidence and probability of PHN. In conclusion, vaccination with Shingrix yielded ICERs lower than those for many recommended adult vaccines, including Zostavax. [124]
Another US-Study used a Markov model with lifelong follow-up to compare ICER, costs and quality-adjusted life-years (QALYs) for Shingrix vs no vaccination with variations of vaccination age from ≥50 to ≥59 years, including the effects of a Shingrix booster 0 to 10 years after Zostavax administered at 60, 70, and 80 years of age. One input parameter was "adherence rate to the 2nd Dose of Shingrix", assumed to be 56% or 100%. At 50 years of age, Shingrix had an ICER of US$ 151'430/QALY, which declined below US$ 100'000/QALY at 53.2 years and below US$ 50'000/QALY at 57.1 years. Higher adherence to the 2nd dose made Shingrix cost-effective at younger ages. Varying the following inputs produced ICER's below US$ 100'000 per QALY: probability of PHN lasting ≥12 months, QALY loss due to HZ, efficacy waning rate, and cost of Shingrix. In the probabilistic sensitivity analysis, Shingrix at 50 years of age had only a 23% chance of being cost-effective. In people previously vaccinated with Zostavax at 60 years of age, a booster was cost-effective at thresholds of US$ 50'000/QALY and US$ 100'000/QALY after 6 and 4 years, respectively. If adherence was 100%, immediate revaccination was be reasonable. Only changes in the efficacy-waning rate of Shingrix produced ICERs of less than US$ 100'000/QALY. In the probabilistic sensitivity analysis, the Shingrix-booster after 5-year had a 75% chance of being cost-effective. This modelling study found that the recommendation by ACIP was only cost-effective if adherence to the 2-dose regimen approached 100%. **Using a more realistic**

estimate, cost-effective was found to begin at vaccination at 55 years of age and to offer Zostavax recipients a booster after 5 years. [125]
Three C.E.-studies were conducted with GSK-implication and published since 2018: The "ZOster ecoNomic Analysis" ZONA-model, a deterministic Markov model used a hypothetical cohort of 1 mio. US adults previously vaccinated with Zostavax. Curran et al. estimated that vaccination with Shingrix 5 years after previous Zostavax vaccination would reduce disease burden compared with no additional vaccination, resulting in a gain of 1'633 QALYs at a total societal cost of US$ 96 million (incremental cost-effectiveness ratio: US$ 58'793 per QALY saved). Shingrix was predicted to be cost-effective relative to no additional vaccination, assuming a threshold of US$ 100'000/QALY in US adults previously vaccinated with Zostavax, aged ≥60+ years. [126] A similar study using the same hypothetical cohort of 1 mio., but for not previously vaccinated US adults aged 50 years or older, assuming a 2nd dose compliance of 69%. The model estimated that, compared to "no Vaccine" against HZ, Shingrix would prevent 103'603 HZ cases, 11'197 PHN cases, and 14'455 other complications, at an incremental cost of US$ 11'863 per QUALY saved from a societal perspective. [127] A third study, also sponsored by GSK, compared the incremental clinical and economic impact of Shingrix with real-world data of different insurance plans in a budget impact model at 5-year to 15-year time horizons. The incremental HZ cases avoided over 5 and 15 years were estimated to be 1'800 and 15'000 for a commercial health insurance plan, 3'800 and 21'000 for a Medicare plan, and 8'600 and 71'000 for a specific Integrated Delivery Network. The incremental per-member-per-month budget impact over the same time horizons was estimated to be US$ 0.42 and US$ 0.31, respectively, for a commercial plan, US$ 0.35 and US$ 0.10 for a Medicare plan, and US$ 0.39 and US$ 0.25 for a specific ID Network. [128]

Canada: A modelling study from Québec by Drolet et al. analyzed the incremental cost per QALY gained for Shingrix, relative to no vaccination or Zostavax, running simulations varying all model parameters, including vaccine costs, efficacy and waning. **For persons exactly 65 years old, to prevent 1 case of HZ, the median number needed to vaccinate (NNV) was 8** (90% uncertainty interval [UI] 6-18) versus 21 (90% UI 13-31) for Zostavax. **To prevent 1 case of PHN, NNV was 31** (90% UI 23-73) for Shingrix, and 64 (90% UI 33-93) for Zostavax. For Shingrix, the median cost-effectiveness ratios varied between cost-saving and CAN$ 25'881 per QALY gained for adults aged ≥50 years. For Zostavax, the cost-effectiveness ratios varied between cost-saving and CAN$ 130'587 per QALY gained and were less than CAN$ 45'000 per QALY gained only for the age groiup 65 to 75 years old. Given its higher efficacy, it was estimated that the cost for 2 doses of Shingrix could be CAN$ 150-200 more than the cost of 1 dose of Zostavax and still be considered cost-effective. [129] A Public Health cost-utility analysis with a Markov-model suggested that Shingrix would be cost effective in the Canadian population (37 Million) compared with no vaccination with an ICER of CAN$ 28'360 per QALY in persons aged ≥ 60 years, avoiding 554'504 HZ and 166'196 PHN cases. [130]

Japan: An independent C.E.-modelling study from different universities in Japan calculated that the vaccination cost ¥ 8000 (≈US$ 73) for 1-dose Zostavax and ¥ 30'000 (≈US$ 273) for 2-dose Shingrix, ICERs for Zostavax ranged from ¥ 2,63 million (≈ US$ 23'942) in age group 80-84 years to ¥ 3,4 million (≈ US$ 31'221 in age group 65-84 years per QALY gained versus ¥ 5,26 million (≈US$ 47'838) in age group 80-84 years to ¥ 6,28 million (≈US$ 57'078) per QALY gained in age group 65-84 years) for Shingrix. Cost-effectiveness acceptability curves derived from probabilistic sensitivity analyses showed that if the cost-effective threshold for 65-84 year olds was ¥ 3,0 million (≈US$ 27'730) per QALY, the acceptability was met in 90.7% for Zostavax and in 8.8% for Shingrix. When the threshold was set at ¥ 5,0 million (≈US$ 45'455) per QALY, the acceptability was 56.2% for Zostavax and 43.8%

for Shingrix, and if at ¥ 10 million (≈ US$ 90'909) per QALY it was met in 11.9% for Zostavax and 88.1% for Shingrix. Vaccinating persons in age groups 65-84 years, 70-84 years, 75-84 years, and 80-84 years with Zostavax or Shingrix was found to be cost-effective from a Japanese payer's perspective. The results **suggested that only the age group 65-84 years should be considered for introducing a HZ immunisation programme.** [131] In a Markov-model analysis sponsored by GSK, vaccine coverage was assumed to be 40% with a 2nd dose compliance of 95%. Vaccination with Shingrix was projected to prevent 48,943 HZ cases and 12,136 PHN cases per million people aged ≥ 65 years compared with no vaccination. The incremental costs and QALYs gained were ¥ 9.99 billion and 2314 QALYs from a payer's perspective and ¥ 9.34 billion and 2314 QALYs from a societal perspective. The resulting ICERs were around ¥ 4.3 million (≈ US$ 39'000) and ¥ 4.0 million (≈ US$ 36'000) per QALY gained from a payer's and the societal perspective, respectively. The ICER remained below a willingness-to-pay threshold of ¥ 5 million (≈ US$ 45'000) for most sensitivity analyses carried out. In conclusion, Shingrix would be cost-effective for the Japanese population aged ≥ 65 years. [132]

Germany: A 2019 modelling study by Van Oorschot et al., sponsored by GSK, found that assuming each year, around 300'000 HZ cases are observed in the German population, which result in costs over € 182 million to society, that **starting vaccination with Shingrix in individuals aged ≥60 years would demonstrate the best value from a combined economic and public health standpoint.** The study assumed a vaccination coverage of 40% and a 2nd-dose compliance of 70% in a population of 1 million. Vaccinating the population aged ≥ 60 years would result in 45'000 HZ cases avoided, 1'713 QALYs gained at a total cost of approximately € 63 million compared to 38'000 cases avoided, 1'545 QALYs gained at a total cost of approximately € 68 million in the population aged ≥70. This would result in an ICER of approximately € 37'000 and € 44'000 per QALY, for the age cohort ≥ 60 and ≥70 years, respectively. Scenario analyses showed that vaccinating at age ≥60 or ≥65 years would show greater public health impact and would result in the lowest observed ICER compared to vaccinating at ≥70 years. [133] Finally, a health economic modelling by the Robert Koch Institute RKI found that the most cost-effective vaccination age for Shingrix in Germany is 65 years. Furthermore, it was found that for the two vaccination ages of 60 and 65 years, the NNV to prevent 1 case of HZ was the same. However, in view of the public health goals and the fact that the prevention of HZ is the decisive prerequisite for reducing the age-related burden of disease due to complications and late complications, such as PHN, it was decided that the vaccination age of 60 years was the most favourable vaccination age. [100]

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5. Acceptability of the recommendations

5.1. Public perception of disease risk, severity, fear and demand for disease control

A survey from the EKIF in 2008 showed that HZ in the outpatient setting is not perceived as a major health issue neither by the population nor by GPs. [66] However, the perception may have changed over the past 13 years due to a more effective vaccine becoming available (i.e. Shingrix), the growing population of senior citizen and the quest for an optimal quality of life in this population. Media

reports of an increased HZ incidence due to the Covid-19 pandemic may have heightened public awareness of HZ further. [134] A similar effect could be expected from the information that a new vaccine against HZ is available and recommended in Switzerland. One of the main factors influencing vaccine uptake will be whether it is reimbursed by health insurance.

5.2. Demand for/acceptability of a recommendation for the control or prevention of the disease. Acceptance of a recommendation for vaccination of target groups, i.e. the general public, health professionals (nurses, doctors, public health staff) and political authorities.

HZ often is not perceived as a major health issue by the general population. Therefore good information on the vaccine and the potentially serious complications of the disease (ophthalmic zoster, PHN) would be necessary to motivate vaccination in the elderly population.

The survey in 2008 did not specify the perception of the disease in well informed individuals, patients with immunosuppressive treatments or immunodeficiency and their treating physicians. For these groups, a very high acceptance of a recommendation for Shingrix can be assumed.

In England, where vaccination with Zostavax® is recommended for 70 year old persons, the PHE-report (Public Health England) "HZ (shingles) immunisation programme 2014/15" indicates a **59%** vaccine **coverage** for those aged =70 years in 2014 [135]. In Germany, according to GSK in the 1 year **before** Shingrix was recommended by STIKO, a total of 23'000 doses where prescribed by physicians. In the first year after recommendation (with reimbursement), this figure increased to 822'000 doses (representing roughly ≈5% of the population).

In Switzerland, an online survey was conducted among Swiss GPs in May and June 2021. The survey was advertised through the Swiss Society for General and Internal Medicine and Infovac. The following ***Tables 13a-c*** show the answers for three of the questions. Overall, **n= 646 general practitioners** replied. Acceptance and willingness among GP's to recommend Shingrix from age 60 years on was very high (**67%)**. An additional **11%** would recommend it for patients 70 or older. **18%** were unsure, and only **4%** of GPs replied that they would not recommend Shingrix. Notably, **63%** of the GPs would recommend Shingrix even if the costs would not be reimbursed by health insurance. **18%** were unsure, and **21%** of GPs replied that they would not recommend it in this case.

***Table 13a*:** If Shingrix is recommended, I would recommend it for patients aged ≥60 or ≥70 years

	German-speaking CH		French-speaking CH		Italian-speaking CH		Total	
Yes for 60+	330	70.8%	55	48.3%	44	68.8%	429	**66.6%**
Yes for 70+	49	10.5%	10	8.8%	12	18.8%	71	**11.0%**
No	20	4.3%	6	5.3%	2	3.1%	28	**4.4%**
Don't know	67	14.4%	43	37.7%	6	9.4%	116	**18.0%**
Total	466	100.0%	114	100.0%	64	100.0%	644	100.0%

Table 13b: If Shingrix is recommended but not reimbursed, I would recommend it anyway

	German-speaking CH		French-speaking CH		Italian-speaking CH		Total	
Yes	308	66.2%	49	42.6%	47	73.4%	404	**62.7%**
No	76	16.3%	22	19.1%	8	12.5%	106	**16.5%**
Don't know	81	17.4%	44	38.3%	9	14.1%	134	**20.8%**
Total	465	100.0%	115	100.0%	64	100.0%	644	100.0%

Table 13c: Varicella: I think the possibility to prevent some cases of severe varicella complications, as well as H. zoster later in life, justifies a routine vaccination recommendation against varicella in childhood

	German-speaking CH		French-speaking CH		Italian-speaking CH		Total	
Yes	288	62.9%	53	45.7%	49	76.6%	390	**61.1%**
No	99	21.6%	27	23.3%	10	15.6%	136	**21.3%**
Don't know	71	15.5%	36	31.0%	5	7.8%	112	**17.6%**
Total	458	100.0%	116	100.0%	64	100.0%	638	100.0%

5.3. Relative priority compared to other existing or potential recommendations.

Moderate for elderly persons.

Moderate to high in immunocompromised patients at high risk for HZ and HZ-related complications. Both groups have to be targeted before and duringa potential routine vaccination recommendation against Varicella, which might reduce VZV circulation und thus reduce natural boosting. [136]

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6. Feasibility of recommendation

6.1. Availability of vaccine and long-term supply.

Zostavax is available since October 2015, and currently there are no pending issues for availability and supply. As stated in **2.2.**, Shingrix will be available with enough doses to cover demand for both, the elderly population as well as for younger persons belonging to a risk group from 2022 on. (personal communication GSK, May 2021). Also already in 2021, a somewhat limited number of doses might be available in Switzerland after approval.

6.2. Existence of an operational plan.

There is no operational plan available yet. As the vaccination of the target populations would take place in combination with either vaccination visits (for instance at 65+ for flu or dT) or follow up visits (future immunocompromised patients) at the GPs or medical specialist the implementation of the

recommendation should be of acceptable difficulty. In case of a recommendation at age 50+, presumably more "extra" vaccination visits would be needed.

6.3. Integration of a new vaccine into existing immunisation programs and schedules.

The recommendation will be added to the existing vaccination plan. Currently, at age 50 years no vaccine, but at age 65 years three vaccinations are recommended, a dT booster dose the vaccination against seasonal influenza and since 2017 the live vaccine Zostavax against HZ: any medical (GP) consultation of patients aged ≥65 years represents a favourable occasion to inform about the **complementary** HZ vaccination.

For immunocompromised patients however, the treating physicians are advised to actively recommend HZ vaccination. For Zostavax, this has to be before treatment initiation, for Shingrix preferably to have an optimal immunogenicity.

6.4. Impacts of the strategy (including catch up) on existing immunisation services and other health care sectors (doctors, long-term care facilities, hospitals, vocational schools...)

The information about the vaccine and its administration can be integrated in an otherwise planned medical visit for the majority of cases. Check-ups on immunization records are part of the consultation of immunosuppressed patients. There is also the possibility that Shingrix® might be offered in pharmacies for healthy people.

6.5. Accessibility of the target population and expected levels of target group coverage.

The access to the target groups is expected to be easy, nevertheless the level of coverage stays undefined. However, a repeated information to the GPs for the recommendations is likely critical. The risk group of the immunosuppressed subjects will more likely be vaccinated by their specialists (i.e. rheumatologists, haematologists, etc…). The practice approach should be in line with other recommendations for patients with immune-mediated inflammatory diseases (IMIDs).

6.6. Availability of appropriate documentation and consent forms for population and health care providers.

As for all recommended vaccinations, the appropriate documentation will be prepared.

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7. Ability to evaluate the recommendations

7.1. Availability of information systems to measure coverage (including vaccination registries) and vaccine utilisation, as well as the quality of immunization services.

Vaccine producers provide the FOPH with their monthly or yearly vaccine sales figures at regular intervals upon request.

For certain vaccinations, mandated by FOPH, vaccine coverage is measured for different age groups in children and adolescents by the University of Zurich (Epidemiology, Biostatistics and Prevention

Institute) using triennial data from the Swiss cantons. For other vaccinations specific studies, mostly surveys, are mandated by FOPH to measure vaccine coverage in certain risk groups and populations. Currently there is no system in place measuring HZ vaccination coverage or utilisation in Switzerland. A system could be put in place on the same model as for flu, with a survey in the appropriate age group for the complementary recommendation. It would probably not be possible for the risk group recommendation.

7.2. Availability of information systems to monitor reduction of disease incidence, complications, sequelae and mortality.

The current reporting of HZ and PHN in the **Swiss Sentinella surveillance system** since January 2016 will continue in order to monitor disease trends following introduction of Shingrix, and possibly also the routine VZV vaccination of children. **For hospitalised HZ cases**, long-term data exist and can be provided by **FSO (Swiss Federal Statistical Office)** for different age groups, ICD-10 codes (including HZ complications) and duration of hospitalisation.

However, these two sources will not provide data on immunocompromised patients. Implementation of the recommendations within this risk group may be evaluated via defined specialists following such patients (rheumatologists, oncologists, immunologists…) in retrospective surveys to be organized by this specialists or within known cohort studies (for instance Swiss lupus patient cohort, Swiss rheumatoid arthritis cohorts).

7.3. Availability of information systems for monitoring and assessing adverse effects associated with vaccine administration.

Suspected "serious" as well as "non-serious but unlabelled" adverse events following immunisation (AEFI) must be reported by medical doctors to Swissmedic according to Swiss legal requirements. Additionally, anyone can report suspected AEFI's and reporting of "non-serious and labelled" AEFI is strongly recommended by Swissmedic.

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8. Open questions

8.1. Significant uncertainty regarding the effects of the vaccine and the impacts of recommendation.

Data for **Zostavax** long-term protection suggest that it is limited depending on age of administration and time since vaccination. [137] Although the results of the 2012 study by Zhang J et al. [54] suggest that already immunocompromised subjects might benefit from vaccination without severe adverse events. Long-term duration of protection after vaccination with Zostavax® is unknown in future immuno-compromised patients. Neither has long-term efficacy of Zostavax® been evaluated yet in persons below the age of 50, a limitation which needs to be taken into account in off-label use. With the exception of 2 rather small studies [138] [139] the same also applies to safety and long-term efficacy.

For **Shingrix,** there are robust data on V.E. and safety, although the reasons for a difference found between efficacy trial results and real-world effectiveness data, as mentioned in point 2.5. are not

fully understood. For certain immunocompromised patients, the optimal timing of first and second doses of Shingrix has to be determined. Finally, it is hardly possible to exactly know a) demand for Shingrix from patients and physicians, and b) to foresee the compliance in the Swiss target groups for the 2nd dose of Shingrix.

8.2. Currently ongoing and planned research projects in the fields of vaccine development, immunogenicity, efficacy and safety.

2017, Zostavax:

The University of Colorado, Denver, was investigating the Safety, Tolerability and Immunogenicity of a Booster Dose of Zostavax® Administered ≥10 Years After a First Dose Compared With a First Dose of Zostavax® http://clinicaltrials.gov/show/NCT01245751" \o "Current version of study NCT01245751 on ClinicalTrials.gov A double-blind RCT to assess the safety and tolerability of V212 (an inactivated vaccine) when administered to adults with solid tumour malignancy (STM) or hematologic malignancy (HM) and to determine whether V212 reduces the incidence of HZ in adults with STM or HM, as compared to placebo by Merck Sharp & Dohme Corp. was investigating in the US (http://clinicaltrials.gov/show/NCT01254630) In a study published in 2015, Cheetham et al. found a slightly elevated HZ incidence in patients taking immunosuppressant medication within 42 days after HZ vaccination. The authors note that this was primarily due to reactivation of VZV rather than dissemination of the vaccine-derived Oka strain virus. The role of Zostavax as a potential trigger for natural VZV-reactivation remained unclear. [62]

Another **vaccine attenuated by heat** demonstrated its immunogenicity and safety among immunocompromised patients (either with haematological or solid organ malignancy or HIV) in a randomized, controlled multicentre-study [58]

Shingrix:

Safety and Immunogenicity of a Recombinant Subunit **HZ** Vaccine in Patients With Rheumatic Diseases Undergoing Immunosuppressive or Biologic/Targeted DMARD Therapies: a Double-blind Randomized Placebo-controlled Trial, Start in November 2021: https://clinicaltrials.gov/ct2/show/NCT04748939

9. Equity of the recommendation

9.1. Equity of a new recommendation including accessibility and cost management for the most vulnerable target groups.

An equitable access to the HZ vaccination could be assumed for all persons for which the vaccination will be recommended, under the provision of reimbursement by the Swiss “compulsory basic health insurance scheme” according to KVG/LAMal.

If there is no **reimbursement** for this preventive measure, this will introduce considerable inequity in that only those parts of the population who can afford two doses of Shingrix will be able to protect themselves from HZ and its complications. People who cannot afford it, will be left with the risk of VZV-reactivation and thus eventually must be treated with pain-medication, antivirals and other therapies necessary in cases of HZ and HZ-complications.

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10. Legal considerations

10.1. Legal Considerations concerning use of the vaccine (i.e. departure from manufacturers' recommendations).

Information on Zostavax® and on Shingrix® is available on the website of Swissmedic: https://www.swissmedicinfo.ch/

Vaccination recommendations of FOPH (BAG/OFSP) and the Federal Commission for vaccinations (EKIF/CFV) may differ from the indications in the officially approved prescribing information and thus lead to off-label use of the vaccine concerned. For physicians, the principle of "freedom of practice in treatment" is harder to apply in the areas of prevention and publicly-funded immunisation programs. Any off-label use should be performed according to the **BAG Bulletin article published in March 2015** on **off-label use** of vaccines "Bundesamt für Gesundheit (BAG). Impfempfehlungen des BAG, welche einen Off-label use beinhalten: Erklärungen und Bedeutung für die behandelnden Ärztinnen und Ärzte" [140]. In principle, physicians who follow these recommendations cannot be prosecuted legally if after taking into account each patient's individual situation, they act under the medical due diligence and in compliance with the recognized rules of medical science. The duty to report suspected severe and/or unexpected AE's should be observed, and in case of problems the usual liability rules apply.

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11. Conformity of Recommendation

11.1. Conformity of the intended or planned recommendations with those in other countries.

Though recommendations vary slightly in different countries (age group) conformity for the proposed recommendation for elderly and immunocompromised persons is given. The following ***Table 13*** gives an overview of current HZ vaccination recommendation in selected countries:

Table 13 **Current HZ vaccination recommendation in selected countries; as of 20. June 2021**

COUNTRY (June 2021)	**Shingrix reco?**	**Shingrix Authorized**	**Shingrix Routine (age)**	**Shingrix immuno-compromised?**	**Shingrix for Zostavax recipients?**	**Zostavax?**	**HZ vaccine Reimbursed?**	**LINKS to schedules**
Germany	yes	50+ / 18+ imm.c.	60+	18+ / 50+	yes, Shingrix after 5 yrs	no, not anymore	yes - Shingrix	STIKO Siedler 2019
France	--	yes	--	--	--	yes: 65+	yes - Zostavax	hcsp zostavax
Italy	yes Start: April 2021	50+ / 18+ imm.c.	65+	50+ at high risk	?	(yes: 65+) ?	Shingrix	quotidianosanita
Austria	(yes)	yes	50+	<50 high risk	?	yes: 51+	no	ECDC - Ö
Spain	(yes)	yes	65+	18+ HSCT, SOT, JAKi, HIV, chemo-therapy	?	--	?	ECDC - ES
Netherl.	(yes)	yes	60+	18+ individlly.	?	--	?	ECDC - NL
Sweden	evaluatn. ongoing	yes	--	No, evaluatn. ongoing	--	(Zostavax 2013-14)	(Zostavax 2013-14)	clinicaltrials
U.K.	yes	yes	60+	50+	?	yes: 70-79	yes - Zostavax	NHS U.K.
Canada	yes	50+	50+ (ONT, QBC)	18+	yes, restart w. Shingrix	Shingrix if available	yes - Shingrix	Canada gov
U.S.A.	yes	50+	50+	50+ low-dose i.s.	yes, restart w. Shingrix	no, not anymore	yes - Shingrix	CDC
Japan	--	yes	--	--	--	--	--	Shiragami 2019
Australia	--	yes	--	--	--	yes: 60+ / 50+ house-holds of imm.c.	yes - Zostavax for 70+	health.gov.au

Sources: ECDC and WHO vaccine-preventable diseases: monitoring system. 2020 global summary

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→ jump to chap. 3.1. (Strategy in international context)

Annex 1

HZ risk in immunocompromised populations (tables from 3 recent papers)

Table 2 Incidence rates of HZ (per 1000 persons - year) by age groups and IC condition in the Valencia Region in 2009–2014

IC condition	Incidence rate of HZ per 1000 PY (95% CI)							
	18–29	30–39	40–49	50–59	60–69	70–79	≥ 80	Overall
Population	2.32 (2.27–2.37)	2.46 (2.42–2.51)	2.93 (2.88–2.98)	5.88 (5.80–5.96)	8.63 (8.53–8.74)	9.82 (9.69–9.95)	10 (9.83–10.16)	5.02 (4.99–5.04)
IC-free cohort	2.26 (2.21–2.31)	2.36 (2.32–2.41)	2.75 (2.70–2.80)	5.52 (5.44–5.61)	8.12 (8.01–8.23)	9.29 (9.15–9.43)	9.54 (9.36–9.71)	4.64 (4.61–4.67)
IC-cohort	3.61 (3.33–3.91)	4.28 (4.02–4.54)	5.52 (5.26–5.79)	9.55 (9.22–9.90)	12.42 (12.05–12.80)	12.93 (12.54–13.33)	12.69 (12.21–13.29)	9.15 (9.02–9.29)
HSCT	42.37 (21.89–74.02)	38.94 (24.11–59.53)	50.13 (35.81–68.26)	69.24 (54.08–87.33)	61.82 (47.5–79.1)	51.99 (24.93–95.61)	0	56.07 (48.86–64.04)
SOT	6 (3.61–9.37)	6.23 (4.58–8.29)	7.31 (5.83–9.05)	14.89 (12.87–17.14)	17.02 (14.93–19.32)	14.21 (12.06–16.62)	17.26 (13.83–21.29)	12.65 (11.8–13.54)
HN	4.96 (4.1–5.94)	4.53 (3.77–5.41)	5.86 (4.97–6.87)	13.95 (12.5–15.52)	18.03 (16.46–19.7)	20.06 (18.37–21.85)	18.44 (16.46–20.6)	11.99 (11.48–12.52)
SON	3.87 (2.59–5.56)	4.94 (4.1–5.9)	5.84 (5.25–6.49)	10.24 (9.66–10.85)	12.27 (11.76–12.80)	12.12 (11.64–12.62)	12 (11.43–12.59)	10.97 (10.73–11.22)
NEOPLASIAS	4.64 (3.92–5.45)	4.71 (4.14–5.33)	5.86 (5.36–6.40)	10.70 (10.16–11.26)	12.86 (12.40–13.40)	12.91 (12.43–13.39)	12.53 (11.98–13.11)	11.01 (10.79–11.23)
HIV	11.9 (8.08–16.89)	12.34 (10.28–14.7)	13.44 (11.96–15.06)	12.8 (10.65–15.27)	13.99 (9.9–19.2)	11.38 (5.68–20.36)	3.87 (0.1–21.56)	12.94 (11.95–13.99)
AUTOIMMUNE	3.35 (3.05–3.67)	3.9 (3.62–4.2)	4.7 (4.4–5.01)	8.97 (8.54–9.42)	12.41 (11.87–12.98)	13.98 (13.32–14.66)	13.34 (12.45–14.27)	7.88 (7.71–8.05)
RA	4.19 (2.74–6.14)	5.34 (4.1–6.83)	6.03 (5.04–7.16)	10.22 (9.11–11.42)	13.88 (12.65–15.2)	14.3 (13–15.7)	13.71 (12.05–15.53)	11.05 (10.52–11.59)
SLE	9.76 (5.33–16.37)	8.62 (5.93–12.1)	8.37 (6.01–11.36)	17.2 (13.27–21.92)	20.37 (15.07–26.94)	21.8 (14.81–30.94)	19.63 (10.73–32.93)	13.36 (11.75–15.14)
IBD	4.83 (3.66–6.25)	4.6 (3.78–5.56)	5.16 (4.31–6.12)	9.65 (8.3–11.16)	13.4 (11.59–15.4)	12.97 (11.01–15.18)	16.21 (13.21–19.67)	8.29 (7.77–8.84)
PSORIASIS	2.97 (2.63–3.34)	3.37 (3.03–3.74)	3.74 (3.37–4.14)	7.55 (6.98–8.16)	10.39 (9.65–11.16)	12.4 (11.41–13.44)	11.11 (9.72–12.64)	6.13 (5.92–6.34)
MS	5.48 (2.51–10.4)	4.39 (2.75–6.64)	4.13 (2.67–6.09)	7.22 (4.87–10.31)	12.34 (8.33–17.62)	10.96 (5.47–19.62)	12.15 (2.51–35.51)	6.33 (5.29–7.51)
AT	1.35 (0.37–3.47)	2.07 (1.1–3.55)	4.21 (2.88–5.94)	10 (7.9–12.5)	11.06 (8.42–14.27)	13.56 (9.64–18.54)	17.97 (10.82–28.06)	7.19 (6.31–8.15)

CI Confidence interval, *IC* immunocompromised, *HSCT* haematopoietic stem cell transplant, *SOT* solid organ transplantation, *HN* haematological neoplasia, *SON* solid organ neoplasia, *NEOPLASIAS* neoplasias overall, *HIV* human immunodeficiency virus, *AUTOIMMUNE RA* rheumatoid arthritis, *SLE* systemic lupus erythematosus, *IBD* Inflammatory bowel disease, *MS* multiple sclerosis, *AT* autoimmune thyroiditis, *AUTOIMMUNE* immunodeficiency disorders and autoimmune diseases overall (See supplementary Table 1)

Muñoz-Quiles, 2020; Spain [141]

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Table 2 Incidence rates of HZ per IC status and IC conditions, overall and by age group, HES-CPRD, 2000–2012

	Incidence rate of HZ per 1000 PY (95% CI)						
IC status/condition	**18–49 years**	**50–59 years**	**60–64 years**	**65–69 years**	**70–79 years**	**≥80 years**	**Overall**
IC-free cohort (N=621 588)	2.12 (2.03 to 2.22)	4.90 (4.72 to 5.08)	6.92 (6.64 to 7.20)	8.62 (8.30 to 8.95)	11.04 (10.75 to 11.34)	11.02 (10.64 to 11.41)	6.21 (6.12 to 6.30)
IC cohort (N=621 588)	3.55 (3.42 to 3.68)	6.85 (6.62 to 7.08)	8.80 (8.46 to 9.14)	9.93 (9.56 to 10.30)	11.32 (11.03 to 11.63)	12.61 (12.22 to 13.02)	7.77 (7.67 to 7.88)
Haematopoietic stem cell transplant (HSCT) (n=1312)	34.14 (26.62 to 43.14)	50.46 (37.45 to 66.53)	60.32 (41.26 to 85.16)	46.98 (25.01 to 80.34)	34.37 (13.82 to 70.81)	10.35 (0.26 to 57.67)	41.70 (35.72 to 48.40)
Solid organ transplantation (SOT) (n=4759)	11.01 (8.91 to 13.46)	11.93 (9.08 to 15.39)	12.35 (8.39 to 17.53)	12.25 (8.00 to 17.94)	13.12 (9.29 to 18.01)	16.85 (10.90 to 24.87)	12.13 (10.74 to 13.66)
Haematological malignancies (HM) (n=26 959)	8.46 (7.29 to 9.77)	15.41 (13.61 to 17.37)	18.41 (16.09 to 20.97)	16.62 (14.41 to 19.07)	17.47 (15.81 to 19.26)	17.53 (15.47 to 19.79)	15.19 (14.45 to 15.97)
Solid organ malignancies (SOM) (n=210 259)	4.32 (3.96 to 4.70)	6.79 (6.36 to 7.25)	8.59 (8.01 to 9.20)	9.33 (8.75 to 9.94)	10.79 (10.34 to 11.25)	11.63 (11.08 to 12.20)	8.81 (8.61 to 9.02)
HIV (n=2522)	11.24 (8.81 to 14.13)	15.00 (8.74 to 24.02)	7.19 (0.87 to 25.99)	12.93 (1.57 to 46.71)	27.16 (3.29 to 98.10)	0.00 (0.00 to 207.06)	11.78 (9.54 to 14.38)
End-stage renal disease (ESRD) (n=38 134)	8.33 (6.84 to 10.06)	10.57 (8.66 to 12.77)	11.65 (9.37 to 14.32)	13.78 (11.58 to 16.28)	12.84 (11.58 to 14.21)	13.49 (12.25 to 14.83)	12.25 (11.58 to 12.95)
Polymyalgia rheumatica (PR) (n=26 868)	5.21 (2.92 to 8.59)	7.83 (6.08 to 9.92)	11.38 (9.40 to 13.66)	11.20 (9.57 to 13.03)	12.87 (11.85 to 13.96)	14.94 (13.85 to 16.10)	12.79 (12.18 to 13.42)
Systemic lupus erythematosus (SLE) (n=5041)	7.91 (6.34 to 9.76)	10.45 (8.16 to 13.18)	12.81 (9.11 to 17.52)	11.06 (7.22 to 16.21)	18.11 (13.72 to 23.46)	17.20 (10.90 to 25.81)	10.95 (9.75 to 12.26)
Rheumatoid arthritis (RA) (n=35 326)	4.74 (4.05 to 5.51)	8.79 (7.86 to 9.81)	11.00 (9.69 to 12.44)	12.61 (11.18 to 14.17)	14.02 (12.83 to 15.29)	14.47 (12.97 to 16.10)	10.58 (10.11 to 11.07)
Inflammatory bowel disease (IBD) (n=31 884)	3.99 (3.56 to 4.46)	6.82 (6.01 to 7.71)	7.98 (6.72 to 9.40)	12.22 (10.46 to 14.20)	11.50 (10.04 to 13.12)	13.86 (11.63 to 16.39)	7.02 (6.63 to 7.42)
Multiple sclerosis (MS) (n=9210)	3.71 (2.96 to 4.61)	5.99 (4.85 to 7.31)	6.94 (5.06 to 9.29)	10.18 (7.43 to 13.63)	7.00 (4.69 to 10.06)	10.17 (5.26 to 17.77)	5.69 (5.07 to 6.36)
Autoimmune thyroiditis (AT) (n=7140)	2.50 (1.82 to 3.35)	6.82 (5.19 to 8.80)	6.49 (4.11 to 9.73)	9.71 (6.22 to 14.45)	10.30 (7.04 to 14.54)	12.52 (7.54 to 19.55)	5.42 (4.70 to 6.22)
Psoriasis (PSOR) (n=117 760)	2.64 (2.47 to 2.82)	5.45 (5.06 to 5.87)	7.43 (6.76 to 8.14)	8.73 (7.93 to 9.60)	10.50 (9.75 to 11.30)	12.24 (11.04 to 13.54)	5.33 (5.15 to 5.51)
Other immunodeficiency conditions (OIC) (n=41 484)	6.16 (5.46 to 6.94)	11.45 (10.23 to 12.78)	13.46 (11.74 to 15.37)	15.00 (13.14 to 17.05)	15.22 (13.81 to 16.72)	16.06 (14.42 to 17.84)	11.83 (11.29 to 12.38)
Corticosteroids exposure (CORTDS) (n=183 646)	3.27 (3.02 to 3.54)	6.99 (6.50 to 7.51)	9.02 (8.30 to 9.78)	9.68 (8.92 to 10.49)	11.47 (10.80 to 12.18)	13.29 (12.22 to 14.43)	7.46 (7.23 to 7.69)
Other immunosuppressive therapies (OIT) (n=12 594)	5.24 (3.76 to 7.11)	7.44 (5.12 to 10.45)	8.46 (5.02 to 13.38)	17.48 (11.88 to 24.81)	14.60 (10.17 to 20.31)	8.09 (3.49 to 15.95)	8.49 (7.25 to 9.89)

CPRD, Clinical Practice Research Datalink; HES, Hospital Episode Statistics; HZ, herpes zoster; IC, immunocompromised; N, total number of individuals; n, Number of individuals with that type of IC; PY, person-years.

Yanni, 2017; England [142]

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Table 1. HZ incidence rates per 1000 patient-years (with 95% CI)[†] in the overall study cohort, the total IC cohort and in each IC and chronic conditions by age and sex

		Age strata (years)				Sex	
Condition category	Overall	18–49	50–59	60–64	≥65	Female	Male
Overall study cohort	4.92 (4.86–4.98)	4.02 (3.96–4.08)	7.21 (7.04–7.39)	9.71 (9.31–10.11)	12.63 (11.99–13.30)	5.33 (5.24–5.43)	4.61 (4.53–4.68)
Total IC cohort	8.87 (8.29–9.48)	6.50 (5.86–7.20)	10.50 (9.32–11.79)	14.59 (12.12–17.42)	16.94 (13.37–20.90)	9.83 (8.99–10.71)	7.80 (7.02–8.65)
IC conditions							
Autoimmune thyroiditis (AT)	8.34 (6.64–10.34)	5.91 (4.20–8.07)	10.81 (7.06–15.84)	17.12 (8.21–31.48)	20.76 (8.34–42.76)	9.01 (7.09–11.30)	4.92 (2.12–9.69)
Congenital immune deficiency (CID)	6.28 (5.06–7.70)	5.82 (4.53–7.36)	6.87 (3.84–11.33)	17.80 (7.16–36.67)	5.44 (0.14–30.28)	8.56 (6.42–11.20)	4.61 (3.28–6.30)
Hematological malignancies (HM)	28.18 (22.75–34.52)	20.21 (14.23–27.86)	31.94 (21.85–45.09)	53.87 (30.15–88.85)	50.44 (23.06–95.75)	31.60 (22.77–42.71)	25.88 (19.27–34.02)
Hematopoietic stem cell transplant (HSCT)	151.68 (111.45–201.71)	115.34 (71.40–176.31)	215.79 (129.92–336.99)	180.28 (58.54–420.72)	–	201.09 (127.47–301.73)	122.77 (78.66–182.68)
Inflammatory bowel disease (IBD)	7.35 (5.15–10.17)	6.76 (4.49–9.76)	8.33 (2.70–19.43)	10.76 (0.27–59.95)	19.52 (0.49–108.75)	8.00 (4.26–13.68)	7.03 (4.45–10.54)
Psoriasis (PSOR)	5.55 (4.26–7.09)	3.49 (2.28–5.11)	8.28 (5.31–12.33)	12.64 (5.78–24.00)	10.64 (2.19–31.08)	7.30 (5.03–10.26)	4.38 (2.96–6.26)
Rheumatoid arthritis (RA)	9.18 (6.95–11.89)	6.17 (3.82–9.44)	10.27 (6.44–15.55)	13.30 (4.88–28.95)	39.75 (17.16–78.33)	10.51 (7.72–13.98)	5.75 (2.76–10.58)
Systemic lupus erythematosus (SLE)	15.91 (8.91–26.25)	16.71 (8.34–29.89)	13.71 (2.83–40.08)	–	–	16.50 (8.78–28.21)	12.94 (1.57–46.74)
Solid organ malignancies (SOM)	9.41 (8.51–10.38)	6.73 (5.59–8.03)	9.81 (8.28–11.53)	13.42 (10.55–16.82)	14.94 (11.29–19.40)	9.50 (8.26–10.86)	9.31 (8.03–10.74)
Vasculitis (autoimmune) (VAS)	6.06 (3.23–10.36)	4.76 (1.91–9.81)	4.42 (0.54–15.98)	21.58 (4.45–63.08)	12.77 (0.32–71.14)	7.87 (3.60–14.95)	3.99 (1.09–10.22)
Other autoimmune/collagen-connective tissue disease (OAI)	9.93 (6.84–13.95)	8.54 (5.06–13.49)	12.73 (6.35–22.77)	9.18 (1.11–33.18)	16.96 (2.05–61.26)	11.18 (7.31–16.39)	7.01 (2.82–14.45)
Chronic conditions							
Asthma (AST)	5.40 (4.57–6.34)	4.92 (4.04–5.95)	6.76 (4.53–9.71)	8.36 (3.61–16.47)	7.42 (2.02–19.01)	5.64 (4.43–7.07)	5.19 (4.08–6.50)
Chronic hepatitis, cirrhosis (CHC)	5.91 (5.34–6.52)	4.86 (4.26–5.52)	8.02 (6.62–9.63)	11.18 (7.78–15.54)	8.07 (4.17–14.10)	6.89 (5.82–8.09)	5.45 (4.80–6.17)
Chronic obstructive pulmonary disease (COPD)	7.25 (6.06–8.60)	5.97 (4.63–7.59)	9.71 (7.03–13.08)	6.92 (3.32–12.73)	11.66 (5.82–20.87)	7.55 (5.62–9.92)	7.07 (5.61–8.80)
Depression (DEP)	5.98 5.48–6.51	5.26 (4.74–5.82)	7.80 (6.36–9.47)	15.63 (10.12–23.08)	15.97 (9.30–25.56)	7.05 (6.16–8.03)	5.37 (4.78–6.01)
Heart failure (HF)	6.57 (5.90–7.29)	5.15 (4.42–5.95)	8.63 (7.10–10.38)	8.99 (6.26–12.50)	12.72 (8.45–18.38)	7.18 (6.10–8.41)	6.16 (5.34–7.07)
Ischemic heart disease (IHD)	8.64 (7.49–9.92)	5.81 (4.38–7.57)	9.16 (7.25–11.41)	10.45 (7.19–14.67)	15.17 (10.44–21.30)	9.92 (7.69–12.60)	8.13 (6.82–9.61)
Osteoarthritis (OA)	8.08 (7.60–8.57)	5.00 (4.44–5.62)	8.85 (8.06–9.71)	12.20 (10.50–14.10)	15.83 (13.38–18.60)	9.52 (8.82–10.26)	6.39 (5.77–7.05)
Osteoporosis (OST_PO)	12.90 (10.83–15.26)	9.11 (5.57–14.08)	11.26 (8.22–15.07)	14.72 (9.86–21.14)	17.98 (12.96–24.30)	12.46 (10.30–14.93)	16.57 (9.98–25.88)
Stroke (ST)	9.26 (6.37–13.00)	9.24 (4.23–17.55)	8.38 (4.18–15.00)	8.13 (2.64–18.97)	12.23 (5.28–24.10)	3.81 (1.04–9.75)	11.53 (7.72–16.56)
Renal failure (RF)	6.68 (3.82–10.84)	3.58 (0.98–9.17)	14.73 (7.61–25.72)	–	–	8.86 (3.56–18.25)	5.60 (2.56–10.64)
Type 2 diabetes mellitus (DM2)	6.79 (6.05–7.59)	4.85 (3.93–5.92)	6.97 (5.79–8.32)	10.14 (7.60–13.27)	12.93 (9.00–17.98)	8.70 (7.11–10.56)	6.12 (5.31–7.01)
Viral hepatitis (VH)	7.89 (6.63–9.33)	6.28 (4.83–8.03)	9.16 (6.71–12.22)	10.47 (5.86–17.27)	14.30 (7.39–24.98)	7.47 (5.56–9.82)	8.17 (6.53–10.09)

[†]95% CIs calculated using the exact Poisson test. Only condition categories with at least 100 subjects and at least 10 HZ cases overall are reported (see also Fig. 1). For each condition, IR and associated CI are not reported within strata with less than 10 cases or less than 100 subjects (annotated as "–"). A person can have more than one IC or chronic condition and can be included in several condition categories. CI, confidence interval; HZ, herpes zoster, IC, immunocompromised.

Imafuki, 2020; Japan [143]

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