Evaluation of Zoster Vaccine According to the Evaluation Criteria for the Development of National Guidelines in Switzerland.

An analytic framework

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Contents

Introduction

A vaccine against herpes zoster (“shingles”) (Zostavax®) was licenced by Swissmedic in February 2007 for persons from age 50 years or older. Zostavax® is available in Switzerland since 2008. Since then, a possible recommendation for use by the Federal Office of Public Health (BAG) and the Federal Commission for vaccinations (EKIF / CFV) has been evaluated. In February 2010, it was decided not to introduce the vaccination in the Swiss Immunization Plan. Indeed, the benefit of the vaccine to public health as well as cost-effectiveness was perceived as limited. Therefore, until 2014 a recommendation for a zoster vaccine has not been introduced yet in the Swiss vaccination plan.

Since 2010, however, this vaccine has been included in the vaccination plans of several European, Asian and North American countries detailed in chapter 3.1. During the recent period furthermore, the aging, and potentially immunodepressed, population did not stop growing. The armamentarium to treat inflammatory diseases with immunosuppressant medications considerably enlarged, in parallel to the growing target population of young and older patients. Therefore, the objective of this paper is to review the recommendation criteria of such a vaccine in Switzerland in view of this novel social and medical context.

Information with respect on **“future immunocompromised patients”** are shaded in green.

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 and herpes zoster (”shingles”).

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 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). 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, 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) if anamnestically no history of varicella is present, or if IgG are negative (especially in women with a desire of pregnancy). After primary infection with VZV, viruses persist in a latent form in the sensory neurons of the spinal cord.

Herpes zoster (HZ) is caused by reactivation and replication of VZV and affects the sensory ganglia (spinal and cranial), 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 [2].This ganglion is the subject of intense inflammation and haemorrhagic necrosis resulting in loss of neurons and fibrosis of the afferent nerve fibres. This explains why the pain usually precedes or accompanies the rash [3].

HZ related complications

Complications develop in about 30% of all HZ cases. They 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). Neuropathic pain can persist for several weeks up to several months or even years after the resolution of the rash. In this case it is called PHN and is the most common complication of HZ. With resolution of the herpes zoster eruption, pain that continues for three months or more is defined in epidemiological surveys as PHN3 (the most commonly used definition). Another less used parameter is PHN1. I.e. pain that persists for one month or more after resolution of the herpes zoster. Pain severity, duration and duration of pain episodes may vary considerably, from discomfort to very severe. It is often described as burning, stabbing or gnawing.
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 situation because it may threaten the patient's sight and requires urgent treatment. Ophthalmic zoster affects approximately 10-20% of HZ cases. [7]

Immunity against VZV

The mechanisms controlling the latency of the virus are not fully elucidated. However, it is clear that the specific cellular immunity to VZV is necessary to prevent multiplication of reactivated virus in the sensory ganglia. *In vitro* data suggest that robust cellular immunity against VZV in early rash correlates with a lower severity of the disease

and a decreased risk of subsequent PHN [8] . Reciprocally, immunocompromised patients are at risk for prolonged episodes of reactivation and disseminated disease, which can be fatal. [9]

The decline of immunity with age (immunosenescence) in particular the decline of cellular immunity increases the risk of reactivation of the zoster virus in the elderly. [3] In fact, about 30-40% of persons over 55 years no longer have any detectable T cell response specific to VZV.

Nonetheless, 90% of Herpes zoster cases occur in immunocompetent patients. In addition, a reactivation of VZV may be associated with a transient decrease in immunity, comorbidities (such as diabetes [10] or malnutrition [11], physical trauma [12] [13] or certain psychological factors. [13] [14]

Most people typically have only one episode of HZ in their lifetime. However, second and even third episodes are possible. A second episode of HZ is very rare in immunocompetent patients, probably due to an immunological boost effect of the first episode of HZ, the frequency of recurrence is not known. [9] [15] [16] 2nd and even 3rd episodes of HZ are supposed to be more frequent in immunodeficient persons, but also in this subgroup, the frequency of multiple HZ episodes is not known precisely. Immunization against HZ is also associated with a boost effect in T cell responses specific to VZV. [17] This is likely to underlie the vaccine efficacy in the prevention or mitigation of the disease.

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 (depending on age and immune status: up to 50 % of HZ patients) 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. [4], Johnson et al. [5], Gilden D [6]

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. [18] Each year, more than 1.7 million people in Europe suffer from HZ. Two thirds of patients are older than 50 years. A German study [19] shows that more than 306'000 persons over 50 years are affected by HZ annually, equivalent in Switzerland, by extrapolation, to about 30,000 new cases each year. A review article published recently [18] establishes that the incidence of zoster is comparable in different European countries (7-8 / 1000 people over 50 years and 10 / 1000 people over 80 years). Over the last fifteen years, the incidence of zoster shows signs of increase in the United States (CDC www.cdc.gov/shingles/surveillance.html) [20] and some other countries, before the era of vaccination.

1.4. Specific populations or patient groups affected and risk factors

Risk of HZ by immune status

Factors associated with increased risk of zoster in a recent case-control study by Forbes HJ et al. included rheumatoid arthritis (adj OR 1.46, 99% CI 1.38 to 1.55), inflammatory bowel disease (1.36, 1.26 to 1.46), chronic obstructive pulmonary disease (1.32, 1.27 to 1.37), asthma (1.21, 1.17 to 1.25), chronic kidney disease (1.14, 1.09 to 1.18), and depression (1.15, 1.10 to 1.20). Type 1 diabetes (1.27, 1.07 to 1.50), but not type 2, showed some association with zoster. The relative effects of many assessed risk factors were larger in younger patients. Patients with severely immunosuppressive conditions were at greatest risk of zoster-for example, patients with lymphoma (3.90, 3.21 to 4.74) and myeloma (2.16, 1.84 to 2.53), who are not eligible for zoster vaccination. [21]
The risk for HZ is also elevated in RA and SLE patients [22] [23] [24] [25] Tseng et al. found HZ incidence rates in unvaccinated patients receiving chemotherapy were 22.05 per 1000 person-years (95% CI, 20.33–23.92), an thus much higher than the rates in comparable immunocompetent patients (13.0 255 [95% CI, 12.6–13.3]). [26]
Habel et al [Ref. to be added] reported very similar rates in patients receiving chemotherapy (23.0 [95% CI, 18.9–27.1]). [27]

Risk of PHN by immune status

Immunocompromised patients are particularly at risk of not only developing HZ but also PHN. [28] [29] [30] In a cohort-study from Germany by *Hillebrand et al*. PHN was about 20-36% more frequent in immunocompromised patients. [31]

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

There is currently no completely effective antiviral treatment 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. [32] Indeed, some studies [33] [34] suggest a decrease in duration of PHN from about 2 to 2.5 months (duration of PHN 38 days with valaciclovir, 51 days with acyclovir, famciclovir with 63 days and 119 days with placebo). In addition, the analgesic treatment of persistent PHN often consists of drug combinations (analgesics, opioids, anticonvulsants, tricyclic antidepressants). These treatments are themselves responsible for significant side effects and allow satisfactory relief from PHN in only 50% of cases. [35]

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 herpes zoster is influenced by its incidence, severity and duration, including those of its complications such as PHN. [16] PHN in particular can cause debilitating pain over weeks, months and in some cases years.

The incidence, duration and severity of PHN increase with age and PHN becomes particularly debilitating for people in geriatric age. Approximately 30% and 15% of elderly patients over 70 years report PHN three months and one year after HZ, respectively.

Although PHN can develop at any age, people over 50 are more at risk of developing this complication. Among HZ patients over 60 years of age, more than 40% develop PHN. [3] PHN can be particularly debilitating. Some studies on the severity of pain have shown, that chronic pain associated with PHN pain sometimes exceeds pain scores at childbirth, musculoskeletal pains and pain in connection with cancer. [36] In terms of quality of life, PHN can have a negative impact similar to congestive heart failure, diabetes and depression. [37] Finally, some older people may experience loss of independence after an acute episode of HZ. [5]

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. [38] Likewise it was shown in England, [39] Spain [40] and Italy, [41] 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.

A recent study from Germany (*Hillebrand et al.* 2015) shows that from the age of 50 the incidence of HZ sharply increases to reach a plateau at the age of 70 and older (***Figure A***) [31]. In the general population, all manifestations and complications (***Table 2***) increased with age and with an acceleration between the 50 and 60 years old.

Immunocompromised patients:

The incidence of HZ in immunocompromised individuals (all ages) was as high as in non-immunocompromised individuals of 70 years and more, i.e. about 12-14 per 1000 person-years (***Figures A&B***). Immunocompromised individuals were defined as patients with a diagnosis of HIV, malignant neoplasm, immunodeficiency (ICD D80-84) or organ/tissue transplants in the previous 12 months.

Post herpetic neuralgia (PHN):

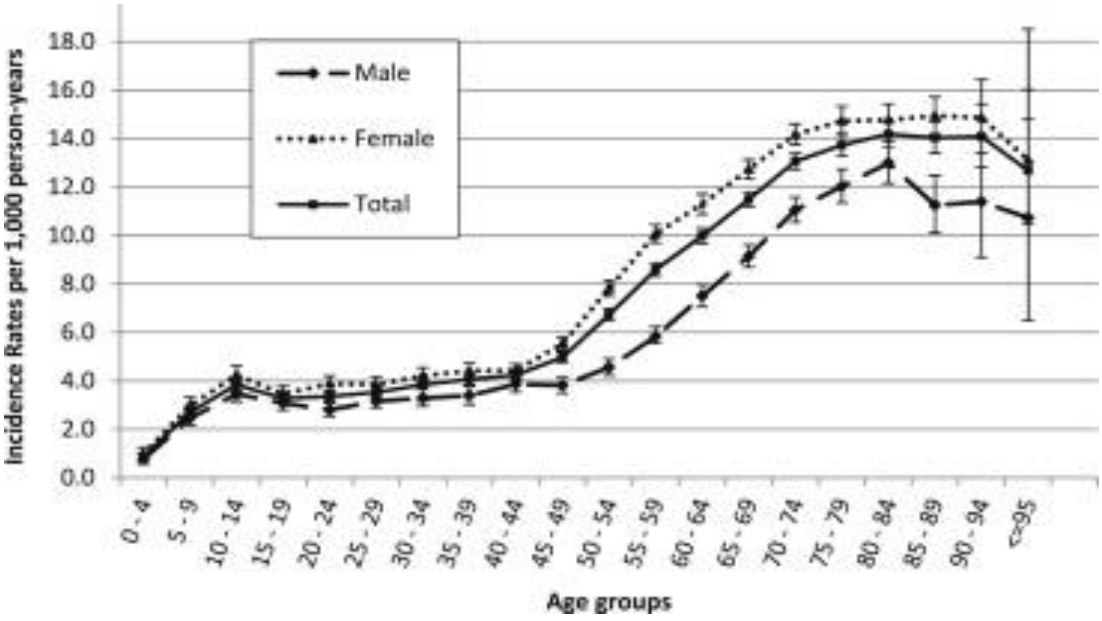
With regard to the proportion of Herpes zoster infected patients who develop PHN, there is clearly a linear increase in PHN with age, reaching more than 20% among HZ-patients 70 years-old or older (***Figure C***).

The **mortality rate** due to zoster in general is lower than 1%. Most VZV-related fatalities result from disseminated infection, (meningo)-encephalitis and pneumonia. [32] The latter two are responsible for about 80% of deaths from zoster. A study in the United States showed deaths ranged 0.19–0.51 per 1 million population and the rate of HZ as a contributing cause of death ranged 0.21–0.58 per 1 million population. [42]

Median age of the patients who died from HZ was 84 years (range, 50–99) and 60% had no contraindications for HZ vaccination.

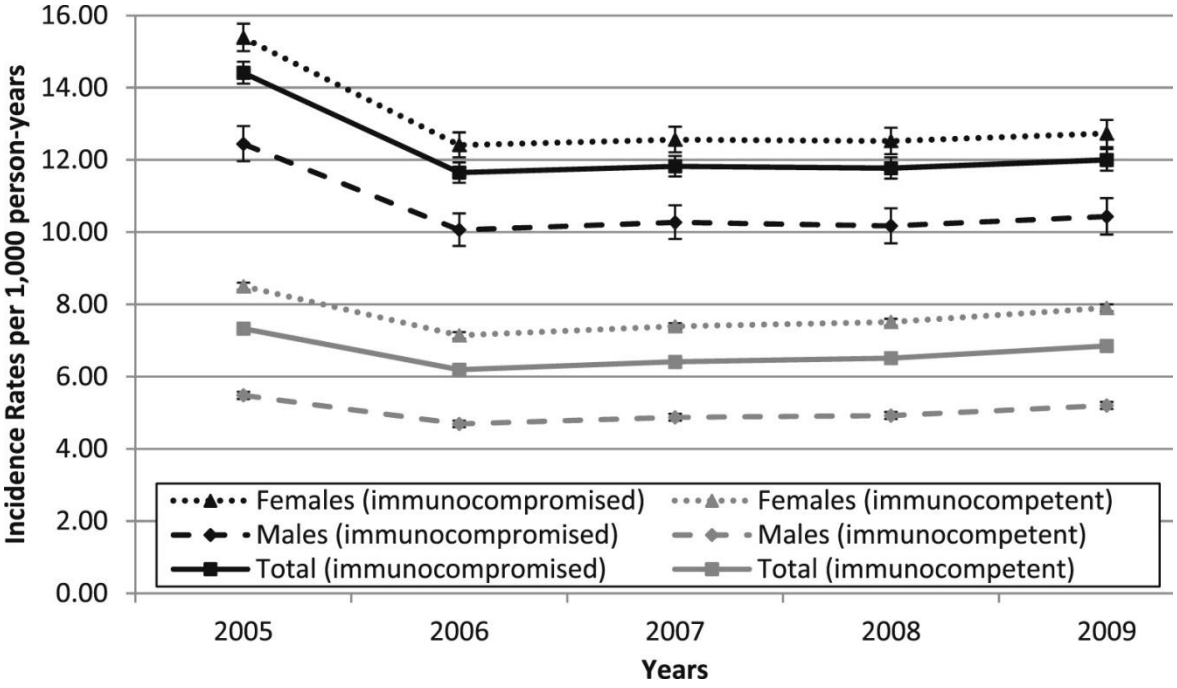
The same study estimated, that the HZ vaccination program in the U.S. could prevent 31% of all HZ deaths, though the true impact might be difficult to assess using national mortality data. [42]

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



Source: Hillebrand et al. 2015 [31]

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



Source: Hillebrand et al. 2015 [31]

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

Age group (yrs)	Uncomplicated HZ	Zoster ophtalmicus	Zoster encephalitis	Zoster meningitis	HZ other nervous system involvement	Disseminated zoster	HZ w. other complications	Multiple zoster complications
<25	2.6	0.1	0.01	0	0.2	0.01	0.1	0.01
	(2.5-2.7)	*(0.1-0.1)*	*(0.01-0.02)*	*(0-0.01)*	*(0.2-0.2)*	*(0.01-0.02)*	*(0.1-0.1)*	*(0-0.02)*
25-44	3.1	0.2	0.03	0.01	0.4	0.03	0.2	0.04
	(3.0-3.2)	*(0.2-0.2)*	*(0.01-0.03)*	*(0-0.02)*	*(0.4-0.5)*	*(0.02-0.04)*	*(0.1-0.2)*	*(0.03-0.06)*
45-64	5.5	0.3	0.03	0	1.1	0.05	0.3	0.15
	(5.4-5.6)	*(0.3-0.4)*	*(0.02-0.03)*	*(0-0.01)*	*(1.1-1.2)*	*(0.04-0.06)*	*(0.3-0.3)*	*(0.13-0.17)*
65-84	8.7	0.7	0.05	0.01	2.4	0.07	0.5	0.39
	(8.6-8.9)	*(0.6-0.7)*	*(0.04-0.06)*	*(0-0.01)*	*(2.3-2.4)*	*(0.05-0.08)*	*(0.5-0.6)*	*(0.36-0.43)*
85+	9.4	0.7	0.09	0.01	2.6	0.1	0.6	0.41
	(9.0-9.9)	*(0.7-0.9)*	*(0.05-0.14)*	*(0-0.03)*	*(2.4-2.9)*	*(0.06-0.16)*	*(0.5-0.7)*	*(0.32-0.51)*
Total	**5.3**	**0.4**	**0.03**	**0.01**	**1.1**	**0.04**	**0.3**	**0.17**
	(5.2-5.4)	*(0.3-0.4)*	*(0.03-0.04)*	*(0-0.01)*	*(1.1-1.2)*	*(0.04-0.05)*	*(0.3-0.3)*	*(0.15-0.18)*

Source: Hillebrand et al. 2015 [31]

1.6.1 Epidemiological data from Switzerland

Swiss HZ sentinel data

In Switzerland a sentinel surveillance was established for four years from 1998 to 2001 in order to estimate yearly incidence of GP visits due to herpes zoster using the Swiss Sentinella surveillance system.

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 was reported in all age groups including patients younger than 50 years. However, the highest incidence was reported from persons aged 50 years or more (roughly two thirds of cases). In the age groups 50–59- and 60–69-years around 2700 cases per year were recorded; and 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 Sentinel data the incidence of HZ remains stable at a low level between age 0 to 40 years with around 120 cases per 100‘000 inhabitants and increases continually with increasing age to 410/100 000 among the 60- to 69-year olds and further to 760/100 000 in persons aged 80 years and older. In Europe and North America age specific incidence is comparable or slightly higher. [43] [44] [45] [46] [47] [48] [49]

HZ hospitalisation data provided by Federal Statistical Office (FSO)

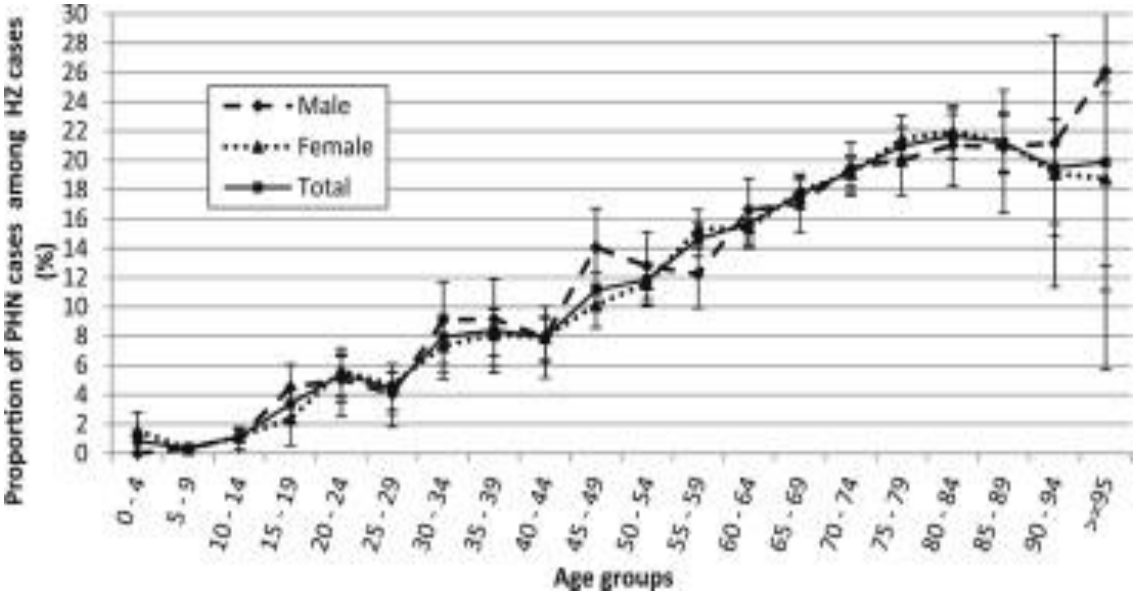
Table 3 shows numbers and average duration of hospitalisations due to herpes zoster, zoster ophthalmicus and their complications 2008-2013 in Switzerland, by age group and ICD-10 Diagnostic code (International Statistical Classification of Diseases and Related Health Problems). On average, **542 patients** had been hospitalised due to herpes zoster and its complications (main diagnosis).

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)*

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



Source: Hillebrand et al. 2015 [31]

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). [50]

Costs of medicaments' treatment of HZ (antivirals and analgesics) vary slightly on the drugs that will be used.

Table 3. Yearly average number of **Hospitalisations due to herpes zoster (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 encephalitis (B020) Total: 23	00-59	2.7	1	5	21.4
	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) Total: 7	00-59	2.5	1	5	7.1
	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
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 generalisatus (B027) Total: 24	00-59	2.2	1	3	8.1
	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 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 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

Source: Federal Statistical Office (FSO), Neuchâtel, Switzerland; 2015

2 Vaccine characteristics

2.1. Nature and characteristics of the vaccine

The vaccine against HZ (Zostavax®) is a live attenuated vaccine administered as a single dose subcutaneously, containing the Oka/Merck strain of varicella virus.
Unlike the vaccines against chickenpox (Varilix® and Varivax®) which contain only about 2000 and 1350, respectively PFU (plaque forming units) of the same viral strain, one dose (0,65 ml) of Zostavax® contains a viral titer 14 times higher (over 19'400 UFP).
Excipients are: water, saccharose, gelatine, potassium chloride, potassium dihydrogen phosphate, sodium chloride, sodium glutamate, sodium hydrogen phosphate, urea and traces of Neomycin. (Documed).

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

Zostavax® was approved by Swissmedic in February 2007 for use in adults 50 years of age or more. The vaccine is currently available in Switzerland.

2.3. Administration schedule and number of doses

Only one vaccine dose is recommended by the manufacturer and the duration of protection is considered as 3 years, starting from age 50 years upwards (Documed).
The vaccine can be administered at the same time as other live vaccines, but an interval of 1 month is recommended if not administered at the same time.

2.4. Immunogenicity, persistence of immunity and vaccine efficacy (short and long-term) incl. reduction of disease and death risks in different population groups

2.5. Effectiveness in the population (short and long-term), incl. impact on reduction of burden of disease, including herd immunity).

The effectiveness of the vaccine in the prevention of HZ and PHN was demonstrated by two large Phase III clinical studies:
The **"Shingles Prevention Study" (SPS)** [16] 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® can significantly reduce the incidence of zoster 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, [51] 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 zoster 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. [51]
The **"Zostavax® efficacy and safety trial" (ZEST)** [52] 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 herpes zoster 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)** [53] and the **"Long-term persistence substudy" (LTPS)** [54] 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 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.
For this reason a follow-up study with subjects from the SPS 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. (*Preaud E, Baron-Paillon F*, SPMSD Zostavax® duration of protection 16)
However vaccination schedules of booster in subjects ≥ 70 at one month or 3 months did not increase VZV antibody response comparing to a single dose vaccination and antibody persistence after 12 months was similar regardless of boosters. [55]

***Table 4*. Persistence of vaccine efficacy by age group according to SPS, STPS and LTPS studies**

	Mean age at enrolment into SPS	**VE HZ** (95% CI)	**VE PHN** (95% CI)
SPS	**≥ 60 overall**	**51.3%**	**66.5%**
0.0 – 4.0 yrs		(44.2 – 57.6)	(66.5 – 79.2)
	60 – 69	**63.9%**	**65.7%**
		(56 – 71)	(20 – 87)
	≥ 70	**37.6%**	**66.8%**
		(25 – 48)	(43 – 81)
STPS	**≥ 60 overall**	**39.6%**	**60.1%**
4.0 – 7.0 yrs		(18.2 – 55.5)	(<0 – 86.7)
	60 – 69	**44.2%**	**80.6%**
		(16.2 – 63.0)	(<0 – 98.0)
	≥ 70	**33.1%**	**31.3%**
		(<0 – 58.3)	(<0 –84.2)
LTPS	**≥ 60 overall**	**21.1%**	**35.4**
7.0 – 10.0 yrs		(10.9 – 30.4)	(8.8 – 55.8)
	60 – 69	**20.2%**	**17.1%**
		(6.7 – 32.2)	(<0 – 48.0)
	≥ 70	**22.4%**	**49.7%**
		(6.0 – 36.6)	(15.6 – 72.5)

Sources: Shingles Prevention Study (SPS) [16] ; Short-term persistence substudy (STPS) [53] ; Long-term persistence substudy (LTPS) [54]

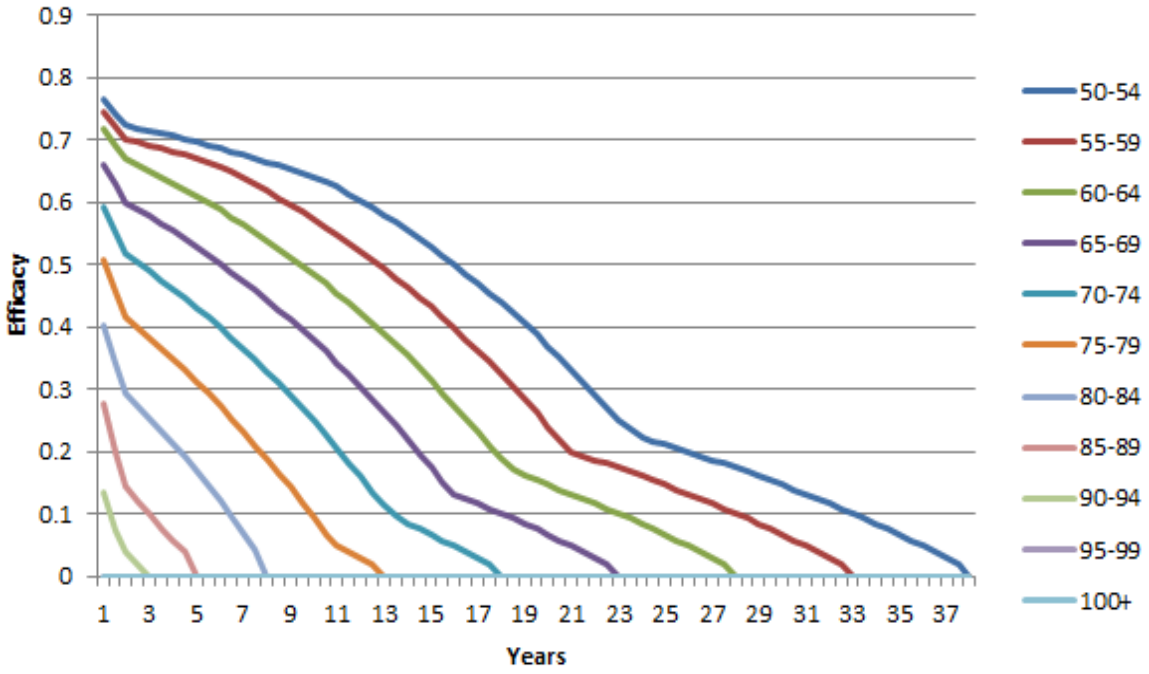
The effectiveness of vaccination against HZ was also demonstrated by **Tseng et al.** in general medical practices, in patients aged over 60 years of age. [56] This retrospective cohort study showed a 55% reduction in incidence of zoster, regardless of age at vaccination, sex, race or the presence of comorbidities.

Another cohort study by **Tseng et al.** [26] shows a decreased risk (adj. HR: 0.58; 95% CI 0.46–0.73) of ophthalmic zoster and hospitalisation due to herpes zoster among previously vaccinated ≥60 year old patients treated with chemotherapy. This retrospective study showed that HZ vaccine continues to protect against HZ if recipients later undergo chemotherapy. However, one of its limitations is that the cohort consisted of a population of fully insured patients, from a single region of the United States (southern California) and had a short follow-up period.

In addition to data from the literature, the company SPMSD on 1st of June 2015 provided a model to estimate effects on burden of disease and costs in Switzerland with different vaccination strategies. Figure D of the modelling report shows data on efficacy against HZ and its duration of Zostavax® protection by 5-years age groups.

Figure D. Data on efficacy against HZ and its duration of Zostavax® vaccination by age group

(source: Merck durability model, Sanofi Pasteur MSD, 2015)



For the immunogenicity of Zostavax® 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 4 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. No vaccine-related serious adverse events were reported in this study. [57]

In a 2006 study, *Diaz et al*. tested 647 healthy subjects 13 to 69 years old (median age: 22 years) with two-dose regimen of an experimental "high-titered varicella vaccine" (~50,000 PFU). No vaccine-related clinical serious adverse experience were reported in the "high-titered" vaccine group. Immunogenicity was similar compared to a matched group of seronegative subjects who received standard varicella vaccine. [58]

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).

N/A; see also point 3.3. “Alternative strategies”

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

2.7.1 Safety: rates and severity adverse events

The vaccine against HZ is generally well tolerated. The study population (n = 38'546) in the Shingle Prevention Study [16] was also subject to a safety study. [59]

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).

2.7.2 Contraindications, precautions

Given the above considerations, this live attenuated vaccine is in principle contra-indicated in various situations, namely in:

1) Patients with moderate to severe primary or acquired immunodeficiency (including patients with leukaemia, lymphoma or other haematological malignancies, patients with AIDS or immunosuppressive 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, for women in childbearing age, the vaccine HZ cannot administered if a pregnancy has not been excluded (pregnancy test). Nevertheless, the risk from accidental vaccination seems low. Indeed, VZV wild-type only exposes the foetus to a low risk. It is therefore likely that the foetal risk following a live attenuated vaccination is probably even lower. In addition, mothers receiving the vaccine are very likely to have a pre-existing immunity against VZV, which is supposed to limit viral replication and subsequently to reduce the foetal risk. However, an interval of 4 weeks is suggested between vaccination and the beginning of a pregnancy. [60]
4) Patients with active (symptomatic) untreated tuberculosis[2]

Zostavax® should **not** be used for the prevention of primary VZV infections (chickenpox).

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

Immunocompromised patients

The situation of immunocompromised patients is problematic. As mentioned above, this is a population at risk of developing severe HZ, subject to higher morbidity and mortality, comparable to non-immunocompromised 70

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

years old and more. However, the administration of a live attenuated vaccine is contraindicated and should be planned at least one month prior to therapeutic immunosuppression.

The review of the vaccination certificate represents an essential step in the medical evaluation of immunocompetent patients who may receive immunosuppressive therapy when affected by a disease that can lead to immunodeficiency. Whenever possible, vaccination of these patients should be recommended before initiation of immunosuppressive therapy, when immunity is still intact (e.g. patients undergoing organ transplantation), in principle 4 weeks before initiation of immunosuppression. [60] [61] (52, 53).

In studies of unvaccinated patients with immune-mediated diseases, the use of immunosuppressant drugs has been associated with an increased risk of herpes zoster. [23]

Cheetham et al. [62] recently 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[3] (adj. O.R. 2.99; 95% CI 1.58-5.70).

This is the first published study that has specifically evaluated the risk associated with immunosuppressant drug use at the time of vaccination. Furthermore, the results show that patients taking low-dose corticosteroids have an increased risk for herpes zoster, 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. Patients with "remote use" of immunosuppressant agents represented 3.5% of the total eligible zoster-vaccinated population (9'728 of 277'358) for this study. Patients with "current use" represented 1.7% (4'826 of 277'358). 550 of them, representing 0.2% were "currently" using high-dose corticosteroids, i.e. less than 4 weeks before or at the time of vaccination. [62]

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 herpes zoster rash within 42 days. Therefore, other mechanisms are likely at work. However, given the limited data available on the safety of live virus vaccines in immunosuppressant drug users, this study provides some information about the incidence of adverse events after zoster vaccination while receiving immunosuppressant medications. [62]

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 suggests thus 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. But it seems that this protection is not provided to subjects who underwent chemotherapy early after vaccination (within 60 days), although the selection of this group was strongly biased. 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. [26].

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

Another retrospective cohort study among ≥ 60 year-old subjects suffering from various immune mediated diseases, some of them under biological agents 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 [63]. Therefore these results suggest that the current approach not to vaccinate already immunocompromised subjects may need to be revaluated as they might benefit from vaccination without severe adverse events (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. [60]
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. [57]
The 2006 study by Diaz et al. testing 647 healthy adults 13 to 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. [58]
Finally, the development of an **inactivated vaccine** against HZ for the immunocompromised population remains of importance. *(see **point 8** “open issues & questions” on **new vaccine developments**).*

2.9. Potential interactions with other vaccines.

Though it has been shown that concomitant vaccination with **23-valent pneumococcal polysaccharide vaccine PPV23** lead to lower antibody titers protection to HZ doesn’t seem to be compromised, probably due to the fact that protection is mediated by cellular immunity. Concomitant administration of zoster vaccine and PPV23 is advocated by the CDC and FDA to improve immunization rates among vaccine-eligible individuals. [44] [45]
Even if PPV23 is currently *(2015)* not recommended in Switzerland, in Australia simultaneous administration of Zostavax® with pneumococcal polysaccharide vaccine is not routinely recommended; if possible the two vaccines should be given at least 4 weeks apart. Nevertheless, inadvertent administration of Zostavax® and pneumococcal polysaccharide vaccine at the same time or at an interval of less than 4 weeks does not require revaccination [64] (www.health.gov.au/internet/immunise/publishing.nsf/Content/Handbook10-home~handbook10part4~handbook10-4-24)

Administration of **DTPa** at the same time has not been investigated.
Simultaneous administration with **influenza vaccine** at different injection sites is possible.
Except the above mentioned, literature regarding concomitant administration of zoster vaccine with other vaccines is nearly inexistent.

3 Vaccination strategy

3.1. Existing recommendations and guidelines; by Dec. 2015 (e.g. ACIP, WHO, CCMP, AAP, recommendations of other countries, consensus conferences, monograph of the product).

Country	Authorised age	Recommendation		Reimbursed?
		Y/N	Age / risk groups	Y/N
Austria	≥ 50	yes	≥ 50	?
Belgium + Netherlands		**no**	--	--
Germany (only 3 Bundesländer: Sachsen, Mecklenburg-Vorp., Thüringen)		(yes)	(≥ 50))	3 Bundesländer: Voluntary (depending on health insurance)
France[4]		yes	65 - 74 (1st year: catch-up for 75-79	Decision ongoing
Greece		yes	≥ 60	yes
Italy (only in 4 Regioni: Liguria, Sicilia, Friuli-Venezia-Giulia and Veneto)		(yes)	Liguria ≥65, Sicilia risk patients 50-65 + 1 cohort among 65-75, Friuli-Venezia-Giulia & Veneto: "risk patients" ≥50 (?)	(yes)
Portugal		**no**	--	--
Sweden		yes	≥ 50	yes
Rest of Scandinavia		**no**	--	--
Spain (only as pilot programme in 1 Region: Castilla y Léon)		(yes)	COPD-patients 60-64 yrs.	(?)
U.K.[5]		yes	Recommended: 70-79	yes: Funding by cohorts at 70, and catch-up: 78 & 79 yrs.
Australia	≥ 50	yes	61-79	yes
Canada		yes	≥ 60	yes
USA[6]		yes	≥ 60	yes
Israel	?	yes	≥ 60	no
Korea		yes	≥ 60	no
Japan		?	?	?

[4] France : adultes âgés de 65 à 74 ans révolus avec un schéma vaccinal à une dose. Durant la première année suivant l'inscription du vaccin au calendrier vaccinal, les personnes âgées de 75 à 79 ans révolus pourront être vaccinées dans le cadre d'un rattrapage.

[5] U.K. Recommendations and information for health care professionals: www.gov.uk/government/uploads/system/uploads/attachment_data/file/357164/PHE_Shingles_advice_for_health_professionals_2014_15_v2_FINAL_approved.pdf

[6] USA: The ACIP reviewed the cost-effectiveness of the vaccine in August 2014. Models assumed that vaccination at the age of 60 would prevent the most shingle cases (followed by vaccination at 70 then at 50) but vaccination at 70 would prevent most cases of PHN (followed by 60 and by 50)

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

The aim of a vaccine recommendation in Switzerland would be the reduction of burden of disease in the population(s) that are the most at risk of getting HZ and its major complications.

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

The aim in Switzerland will be to selectively vaccinate according to **age group** (**complementary** recommendation category) 65 to 79 year-old persons and according to **immune status** (**risk group** recommendation category).

To reduce the risk of HZ in elderly persons (65-79 yrs.) 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. The proposal for the age group defined complementary recommendation is largely backed by results from a modelling study performed in April and May 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). The modelling study aimed to evaluate reduction of HZ and PHN-cases as well as the cost-effectiveness of this HZ vaccine for Switzerland. The model adapted a previous Swiss model from Szucs et al. (2011) [50], with a methodological update (table 5) including a new application of the vaccine efficacy duration based on long-term efficacy data, and new input parameters (demographics, hospitalisation costs, coverage assumption). The model includes information from a variety of sources: Swiss Sentinel Surveillance Network, Swiss Federal Statistical Office and a Swiss burden of illness study. A Markov model was used, simulating the lifetime effects of vaccination in the current aged 50+ Swiss population. A sensitivity analysis with varying input parameter sizes was performed. Main results are included in the present document in **chapter 4.**

Table 5: Comparison between the present 2015 model with the model study by Szucs et al. 2011 [50]

Input parameters	New model 2015 – Base case	Szucs et al. 2011
Demographics	Swiss official BFS data, updated	Swiss official BFS data
HZ & PHN incidence	Swiss sentinel surveilance	Swiss sentinel surveilance
HZ & PHN pain split	Gauthier et al.	Gauthier et al.
Quality of life	Oster et al.	Oster et al.
Management costs	Michel et al., inflated plus: Inpatient costs from CHUV	Michel et al.
Vaccine efficacy	Oxman et al.	Oxman et al.
Vaccine efficacy duration	Merck durability model (includes V.E. results on long-term data)	Lifetime (simple assumption)
Vaccination coverage	15%	20%

Source: Model from CEA Zostavax® report by Sanofi Pasteur MSD, 28 May, 2015

For the **risk group recommendation**, physicians should identify patients **50 to 79 years old** with a moderate to severe immunosuppression in the foreseeable future and actively recommend HZ (**Zostavax®**) vaccination >4

weeks prior to immunosuppression. This will in principle target patients who are facing an immunosuppressive therapy at short term or presenting with a “light” immunodeficiency which can be assumed to deteriorate into “severe” in the future (limitations for use of Zostavax®; see future „official FOPH / EKIF recommendations“).
This may also target future immunocompromised patients **18 to 49 years old**, but in this age group **Zostavax®** would have to be used **“off-label”.** As detailed in chapter 1.4, future immunocompromised patients have a high risk for HZ complications and will most probably benefit from HZ vaccination. On the other hand, as described in chapters 2.5 and 2.8., available evidence on immunogenicity, safety and tolerability is scarce in this age group, even if the results of two rather small studies are supportive. Instead, in non-VZV-immune 18 to 49 year old individuals with a future immunosuppression risk, vaccination with **varicella vaccine** may be considered. This alternative might seem reasonable, since a few epidemiological studies show slightly lower incidence rates of HZ in the population vaccinated with varicella vaccine [65], although more studies are needed to confirm these initial observations.

Table 6 shows the expected number of HZ and PHN cases avoided when the vaccination strategy is selected for the age group 65-74 and 70-79 respectively, based on 5, 10, 20 and lifetime analyses. These same results are also presented graphically in figures E and F below.

Table 6. Number of HZ and PHN cases avoided

	HZ cases avoided	PHN1 cases avoided	PHN3 cases avoided
Age 65-74			
5 years	1,415	383	343
10 years	2,478	884	819
20 years	2,978	1,025	957
Lifetime	2,930	1,012	946
Age 70-79			
5 years	1,092	449	412
10 years	1,623	787	739
20 years	1,714	815	768
Lifetime	1,700	811	765

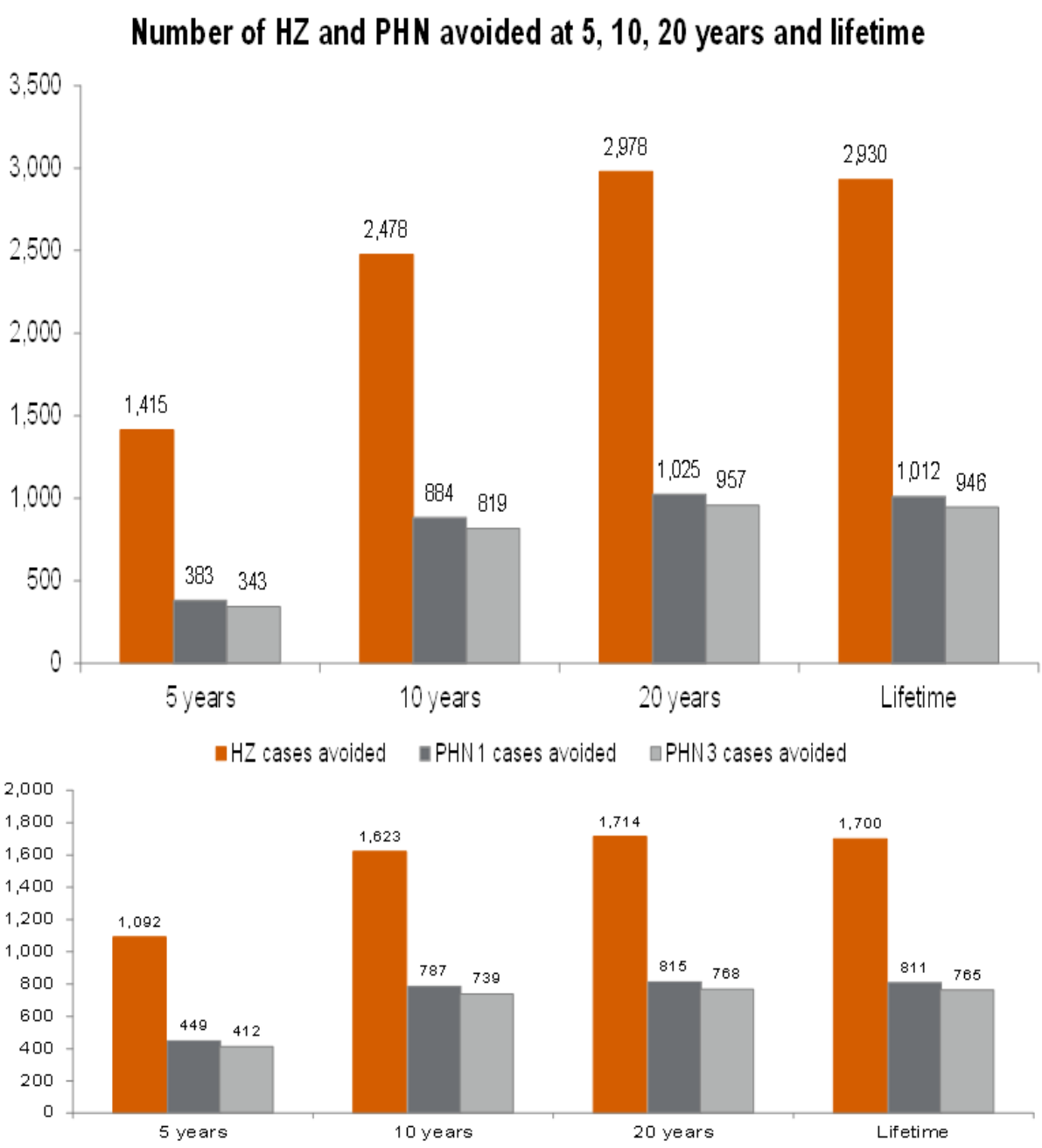
Table 7 shows numbers needed to vaccinate (NNV) to avoid one case of Herpes Zoster or one case of PHN3 with 3 different vaccination strategies: for two age groups 65 to 74 and 70 to 79 years old.

Table 7. Number needed to vaccinate (NNV) to avoid one case

Age group and case avoided	**NNV - Lifetime horizon**
Age 65-74	
HZ	39
PHN3	122
Age 70-79	
HZ	54
PHN3	119

Source: CEA Zostavax® report by Sanofi Pasteur MSD, May 2015

Figures E+F. HZ and PHN cases avoided: age 65-74 (above) and age 70-79 (below), respectively
Source of fig. E, F and tab. 6: CEA Zostavax® report by Sanofi Pasteur MSD, May 2015



However, the current level of knowledge on the safety as well as on the efficacy of Zostavax® in immunocompromised individuals, and epidemiology of HZ and its complications in these risk groups (18-49 years old) is rather low. Therefore, Zostavax® "off label" **cannot** be recommended in the current absence of solid evidence-based arguments (i.e. notably in the absence of controlled efficacy trials). This underlines the need for further clinical trials in the risks groups aged <50 years.

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 vaccine Zostavax®, 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 immunodepressed patients with an increased risk for HZ and HZ-complications **(risk group recommendation)**.

The reasons for a complementary vaccine recommendation for 65-79 year old persons are explained in chapter 3.3. As an alternative, also a universal vaccine recommendation ("Basisimpfung" / "vaccination de base") might be considered, but HZ incidence is neither affecting the majority of the population, nor does the disease and its complications frequently lead to severe sequelae or death and therapeutic options exist. In addition, VZV circulation in the population cannot be influenced substantially by a universal vaccine recommendation.

The question of **booster** doses against HZ is under investigation, 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 **universal childhood vaccine recommendation against varicella virus** ("Basisimpfung") for toddlers in Switzerland. Theoretically, if vaccine coverage would be very high in the long-term, VZV-transmission would decrease. This might not only reduce varicella- and HZ-incidence in Varicella vaccine responders, but because of herd immunity also in those not vaccinated or in vaccine non-responders. On the other hand, such a strategy might pose risks, since a decrease in VZV-circulation would reduce "natural boosting" and thus might actually increase HZ-incidence in some population groups or overall, and in practice it remains questionable if herd protection and thus the goals are attainable with such a strategy, despite an effectiveness of varicella vaccination well over 80% in healthy children and adults below 40 years. With a basic reproductive number R_0 of around 3-7, VZV is highly transmissible [66]. Furthermore, the goals could be reached only in the long-term, and only if other countries - in Europe - would adopt a similar strategy.

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 or specialists should inform their patients aged 50 to 79 about the complementary vaccination recommendation (age group 65-79 years) and risk group recommendation (age 50-79 years) 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, in principle at least 4 weeks prior to treatment with immunosuppressors and according to the recommendations and preconditions listed by CDC; see future „official FOPH / EKIF recommendations"). This will in principle target individuals 50 years and above who are facing an immunosuppressive therapy at short term and have not been vaccinated previously.

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

The objective of the strategy would be the optimal reduction of burden of disease, i.e. about 50% decrease of HZ cases and 60% PHN for the complementary recommendation according to age group.

The same applies for the risk group recommendation (see table 2.5 from SPS) although there is yet no large studies allowing to establish these postulates in the immunocompromised individuals. Tseng et al. (2014) report a 42% protection against HZ in an immunocompromised cohort [26].

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.

4 Cost-effectiveness of strategies

4.1. 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.

An English cost-effectiveness analysis from 2010 showed that a vaccination programme preventing HZ and PHN would be most cost effective in the UK in the age groups of 60-64 and 65-69years. In the immunocompetent population aged 50 years and more the same effectiveness would not be achieved. Interestingly this analysis does not include common ocular and neurological complications other than PHN because of lack of data [67]. In 2013 a German model testing different scenarios showed that vaccinating individuals at 60 years of age seemed the most cost effective [68]. In the Netherlands a model from 2010 stated that cost effectiveness was narrowly achieved by vaccinating the population at 70 years [69].

Pharmacoeconomic evaluation of the vaccine for the prevention of HZ and PHN in Switzerland was published in 2011 [50] 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, and a vaccination strategy to vaccinate elderly persons of 70-79 years was estimated to be cost-effective in Switzerland.

Szucs et al. [50] 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 herpes zoster and PHN and the effects of vaccination. It distinguishes between different health states: full health, HZ, PHN and deaths. Pain is subclassified 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 3'412 cases of HZ less, 1,460 cases of PHN less 3 months after disease outbreak and 885 additional QALY in the Swiss population. 31 respectively 73 people should be vaccinated to prevent one case of HZ or PHN. In summary, this study suggests that the cost-benefit of such a vaccination strategy would just be cost effective in people 70 years of age or over in Switzerland [70]. 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. [70]

A cost efficacy model evaluation for Switzerland by Sanofi Pasteur MSD In 2015 took into account costs of therapy (incl. hospitalisation costs) for HZ and PHN cases and the results by age groups show that ICER varied according to vaccination age, with an optimal vaccination age between 65 and 79 years.

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 is not perceived as a major health issue neither by the population nor by GPs in the outpatient setting. [49] However, the perception of the vaccine may have changed or may change rapidly with a growing population of senior citizen and the quest for an optimal quality of life in this population.

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.

As mentioned in paragraph 5.1 HZ is not perceived as a major health issue neither by the population nor by GPs in the outpatient setting. 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 did not specify the perception of the disease in well informed individuals in process to be immunosuppressed due to a specific medical condition and speciality physicians in charge, but for that population it can be assumed that acceptance of a vaccine would be reasonably high.

In England, where HZ vaccination is recommended for 70 year old persons (and one age year of catch-up in every of the following years) www.nhs.uk/Conditions/vaccinations/Pages/who-can-have-shingles-vaccine.asp the PHE-report (Public Health England) “Herpes zoster (shingles) immunisation programme 2014/15” indicates a **59%** vaccine **coverage** for those aged =70 years in 2014 [71].

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

Low

6 Feasibility of the recommendations

6.1. Availability of vaccine and long-term supply.

According to the manufacturer the vaccine is available since October 2015. Availability and supply of the vaccine will not be an issue if there is a recommendation (also see point 2.2.).

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 (flu for instance for 65+) or follow up visits (future immunocompromised patients) at the GPs or medical specialist the implementation of the recommendation should be of acceptable difficulty.

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 65 years two vaccinations are recommended, a dT booster dose and the vaccination against seasonal influenza: this represents a favourable occasion to inform about the complementary HZ vaccination. For future immunocompromised patients however, the treating physicians must think about and actively recommend HZ vaccination.

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 expected work load is expected to be low as information about the vaccine and its administration would be integrated in an otherwise planned medical visit.

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 risk group recommendation (“future immunocompromised patients) is considered as essential. 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.

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 herpes zoster 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.

Neither cases of herpes zoster nor its complications or zoster ophtalmicus must be mandatorily reported in Switzerland. Since 2002, there is no Sentinella surveillance for HZ cases. However, 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.
Using the **Swiss Sentinella surveillance system**, in context with a new surveillance project beginning January 2016, the following data will be collected:
a) GP visits due to HZ;
b) first consultation for post-herpetic neuralgia and;
c) for Zoster ophthalmicus.
Hospitalisation data can be obtained from the FOS.
However, these two sources will not provide data on future 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.

8 Open questions

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

Current data suggest that protection is limited depending on age of administration and time since vaccination (table 4), and there are no manufacturer’s recommendations concerning a booster vaccination, though this issue is currently being investigated. [72]
The rather limited acceptance in the previous evaluation (2010) from the dispensing physician might not have been changed and appropriate information might be needed to raise awareness of the benefits of the vaccine.
Some open questions remain with regard to future immunocompromised patients (including those patients younger than 50 years), notably the definition of groups at risk of adverse events post vaccination with a live vaccine. According to CDC, a number of patients with immunocompromised conditions have been considered as potential targets because of acceptable safety (see future „official FOPH / EKIF recommendations“).

Furthermore, 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. Therefore, the current approach not to vaccinate already immunocompromised subjects may need to be revaluated. This may become particularly true when the inactivated vaccine will be available commercially (see below point 8.2). So far no clinical studies with this candidate vaccine have been performed in immunocompromised patients.
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 [57, 58], the same also applies to safety and long-term efficacy.

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

The University of Colorado, Denver, is currently 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 randomized, double-blind, placebo-controlled study 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 herpes zoster (HZ) in adults with STM or HM, as compared to placebo by Merck Sharp & Dohme Corp. is currently 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 HZ vaccine as a potential trigger for natural VZV-reactivation remained unclear. [62]

New (inactivated) HZ subunit vaccine by GSK:
A controlled phase I / II study, showed good tolerance, a clinically acceptable safety profile and good immunogenicity for an AS01B-adjuvanted vaccine containing the recombinant glycoprotein E subunit in an immunocompetent population of older adults [57].
In 2015, Lal H et al. published the results of a phase 3 RCT conducted in 18 countries among older adults (≥50 years of age). Participants received two intramuscular doses of the subunit vaccine or placebo 2 months apart. Overall vaccine efficacy against HZ after a mean follow-up of 3.2 years was 97.2% (95% confidence interval [CI], 93.7 to 99.0; P<0.001). It was between 96.6% and 97.9% for all age groups (50-59, 60-69, ≥70 years) [73].
As this vaccine is inactivated, safety can be presumed also for (future) immunocompromised patients, but it has not been tested in that group yet.

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

9 Equity of the recommendation

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

According to the current licensure by Swissmedic, only individuals over 50 can be immunized with Zostavax®. Therefore patients <50 years old in process of undergoing immunosuppressive treatment, should not be vaccinated with this product in principle.

Likewise, even if it is approved by Swissmedic, the vaccine will not be recommended to persons aged 80 years or older. For these reasons, the proposed recommendations may thus eventually be perceived by some patients as "unfair".

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.

10 Legal considerations

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

Fachinformation zu Zostavax® im Arzneimittel-Kompendium der Schweiz®: http://compendium.ch/mpro/mnr/19160/html/de

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.

Implementation of a vaccine recommendation for **future immunocompromised patients below the age of 50** could be effective to reduce the burden of disease (and possibly costs) in that specific population, but one might assume potential problems of legal action in the case of vaccine failures and/or severe AE's.

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" [74].

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.

11 Conformity of Recommendation

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

Though recommendations vary slightly in different countries (age group) conformity for the proposed recommendation for elderly persons is given.

Currently there are no national recommendations for “future immunocompromised patients” or other risk groups other than defined by age. In 3 regions of Italy (Sicilia, Friuli-Venezia-Giulia, Veneto) HZ vaccine is recommended for “risk patients” aged 50-65 years and in Spain, as a pilot program in 1 Region (Castilla y Léon) for COPD-patients 60-64 years of age.

See table in point 3.1. (Existing recommendations and guidelines)

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