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Background paper to the decision not to recommend a standard vaccination with the live attenuated herpes zoster vaccine for the elderly in Germany

Statement of the German Standing Committee on Vaccination (STIKO) at the Robert Koch Institute (RKI)

Electronic supplementary material

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Summary

A live attenuated vaccine (Zostavax®) against herpes zoster (HZ) and postherpetic neuralgia (PHN) was licensed for persons 50 years of age and older in 2006 and became available in Germany in September 2013. Based on the conclusion, that an effective and sustainable reduction of the HZ disease burden cannot be achieved with this vaccine, the STIKO decided against issuing a recommendation for routine HZ vaccination at this time. This decision is based on a systematic review of available data on the efficacy, duration of protection, and safety of the vaccine, and is supported by the results of health economic modelling. Both, the risk of developing HZ and the severity of the illness increase markedly with age. The efficacy of the vaccine, however, decreases with advancing age, from 70% for persons in their 50s to 41% for persons in their 70s to less than 20% for persons 80 years of age and older. The duration of vaccine related protection is limited to only a few years. The modelling results show only a slight, age-dependent reduction in the total number of HZ cases through vaccination with the live attenuated vaccine. The reduction ranged from 2.6% for persons vaccinated at the age of 50 to 0.6% for those vaccinated at the age of 80, based on assumed vaccine coverage of 35.5%. In addition to the vaccine's poor efficacy and duration of protection, HZ vaccination does not offer any added value in terms of herd immunity, since HZ is a disease of an endogenously reactivated pathogen with low transmission potential.

Finally, the live attenuated vaccine is often contraindicated in persons who are at greatest risk of HZ and its complications. Thus, in the overall appraisal, the epidemiological benefit-risk assessment of the HZ vaccination did not lead to a recommendation for routine vaccination with the live attenuated vaccine. An individual benefit-risk assessment may, however, lead to a different decision in individual patients.

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1. Introduction

In Germany, more than 300,000 persons over the age of 50 develop HZ every year [1]. HZ is caused by a reactivation of the varicella zoster virus (VZV) that remained latent in sensory ganglia after the primary infection. The primary VZV infection causes chicken pox, and usually occurs years to decades earlier. About 6–18% of HZ cases develop a postherpetic neuralgia (PHN) as the most frequent HZ complication [1]. The symptom of this is chronic pain that lasts months or years and significantly reduces quality of life. In May 2006, the European regulatory authority (European Medicines Agency, EMA) approved a live attenuated vaccine (Zostavax®; Merck) for the prevention of HZ and the PHN it causes for persons age 50 and over. This background paper summarizes the data basis the STIKO used to reach its decision on standard vaccination with the live attenuated vaccine. Based on the STIKO standard operating procedure (SOP) for the systematic development of vaccination recommendations, the disease burden of HZ in Germany was ascertained, systematic reviews of the efficacy and safety of the vaccine were conducted, and the data on the duration of protection of the vaccine evaluated. The potential epidemiological impact of a vaccination was modelled for different age groups, taking HZ epidemiology in Germany and other vaccine-specific input parameters into account. Based on this model, a health economics evaluation of the vaccination was conducted. This background paper includes an extensive appendix containing further information on the systematic reviews conducted. The appendix is available online as Electronic Supplementary Material (ESM_STIKO_Herpes_zoster_2017.pdf). Studies on the HZ subunit vaccine Shingrix® (GSK), currently in licensing process, were identified during the data processing. Since this vaccine is not approved yet, the STIKO did not take it into consideration for this decision.

2. Pathogenesis and clinical features of HZ

HZ, also known as shingles, is caused by a reactivation of the latent VZV infection. The clinical manifestation of this illness is normally a blister-like rash on one side, which is characteristically limited to one single dermatome or a few adjacent dermatomes. The illness is commonly accompanied by radicular radiating pain along the dermatomes affected. Patients frequently suffer significant pain that can last weeks to months, in some cases even years, and that considerably restricts quality of life [2–4].

2.1. Aetiology

VZV, an enveloped virus with double-stranded DNA from the family of human herpes viruses (HHV 3), causes varicella (chicken pox) in the primary infection. This highly contagious disease is transmitted through airborne droplets, or as a smear infection through chickenpox blisters [5]. Varicella-zoster virus seroprevalence in Germany was very high before the general varicella vaccination recommendation was issued in 2004: over 95% of people 14 years of age and older exhibited IgG antibodies to VZV [6, 7].

VZV persists latently after the primary exogenous infection (varicella) in the neurons of sensory spinal ganglia or the nerves of the brain [8]. In general, the latency phase lasts for several decades before the productive infection is reactivated and HZ occurs. HZ normally occurs only once, but second and third HZ episodes are possible and do happen occasionally. The frequency of repeated HZ increases with time after the first HZ illness in persons with a healthy immune system from 1.7% (95% CI 1.0–2.3) after 2 years to 3.2% (95% CI 2.3–4.2) after 4 years, then to 4.4% (95% CI 3.3–5.4) after 6 years and 5.7% (95% CI 4.4–6.9) after 8 years [9]. VZV replication can be reactivated, leading to HZ disease, in particular in cases of waning T-cell-specific immunity (e.g. with advancing age or on immunosuppressive therapy, see also risk factors), but also spontaneously in immunocompetent persons and in young adults, children, and adolescents [10]. HZ can occur only in persons who have previously had a primary VZV infection, including those who have been vaccinated with a live VZV vaccine. But the frequency of reactivation of the vaccine virus is significantly lower than that of the wild virus [11]. HZ is far less contagious than varicella: only 20% of persons susceptible to VZV developed chicken pox following contact to a HZ case in the household, whereas the rate of secondary varicella infections ranges from 61% to 100% after household contact to a varicella case [5]. Virus transmission occurs until lesons are crusted through aerosols or through smear infection with the contents of the blisters, and can be further reduced by covering the skin lesions [12].

2.2. Symptoms

VZV reactivation leads to inflammation of the sensitive spinal ganglia affected. Typically the virus spreads along the sensory nerves to the skin, where it causes the characteristic presentation of painful dermatomal HZ with erythema and clusters of papulovesicular, later papulous efflorescences. But it can also remain limited to the nerves, causing radicular pain in the absence of skin lesions (zoster sine herpete; [13]). Normally only one side of the body is affected by the zoster exanthem. [14]. In 70–80% of HZ cases, a promodal stage of 3–5 days precedes the disease, with varying symptoms [15]. Patients report general symptoms such as fever, fatigue, and exhaustion, as well as burning, paresthesia, or pain that is limited to the dermatome affected. After the skin lesions have healed and the acute pain symptoms have improved, chronic pain and allodynia, also described as postherpetic neuralgia (PHN), are observed [16].

2.3. Localization

The area served by the affected nerves determines the localization of HZ. Any dermatome can be affected. HZ occurs most frequently as zoster thoracicus in the area of the thoracic dermatomes and as zoster capitis in the head region. Around 50% to 56% of cases affect the thoracic dermatomes, and 20% the brain nerves [17, 18]. Less frequently affected, in descending order, are the cervical, lumbar, and sacral segments. If the trigeminal nerve is affected, zoster ophthalmicus can occur. It normally affects one eye, and can lead to vision loss or total blindness. Other zoster manifestations in the area of the trigem-

inal nerve are zoster maxillaris und zoster mandibularis. Zoster oticus and VZV vasculitis can manifest in the head region [8]. If the virus disseminates through the blood, it leads to a systemic syndrome (zoster disseminatus) that occurs very rarely in immunocompetent persons, but more frequently in persons with compromised immune systems [19, 20].

2.4. Complications

PHN is the most common complication of zoster. It is characterized by severe pain, often described as burning, and the allodynia that occurs or persists after acute skin symptoms fully abate [21, 22]. The risk of developing PHN increases with age. From a pathophysiological perspective, it seems this is due to inflammatory nerve damage involving the destruction of peripheral nerve structures and of neurons in the sensory ganglia [23]. Various definitions of PHN are used in scientific literature, taking varying durations of pain symptoms after the initial rash into account. PHN can last for weeks or months, and sometimes for many years [8, 24].

Other complications of HZ are acute or sustained damage to the eye caused by zoster ophthalmicus, bacterial superinfections of the skin lesions caused by staphylococcus or streptococcus infections (zoster gangraenosus), palsy of the brain and peripheral nerves, zoster meningitis, zoster encephalitis, zoster myelitis, zoster vasculitis with neurological damage including stroke, and visceral dissemination involving the internal organs (pneumonia, oesophagitis, myocarditis, enterocolitis, pancreatitis).

Immunocompromised persons or patients on immunosuppressive therapy are at greater risk of experiencing complications. The rash often covers a larger area and lasts longer [25]. The risk of disseminated HZ is also elevated in persons with immunosuppression [26].

2.5. Risk factors

Persons with pronounced immunosuppression, e. g. patients with cancer or HIV, persons who have had an organ or bone marrow transplant, and patients on immunosuppressive therapy, have the highest risk of developing HZ [27]. Diseases that are associated with a slightly elevated HZ risk include rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, chronic obstructive pulmonary disease, asthma, chronic kidney disease, and type-1 diabetes [27].

3. Epidemiology

The incidence for HZ is approximately 6 cases per 1,000 German population annually [28]. The incidence is higher among women than among men, and rises continuously from around the age of 50 years [28–30]. Based on statutory health insurance (SHI) data, the age-specific incidence of HZ ranges from 4 cases per 1,000 person-years (PY) among persons under the age of 50 to 14 cases per 1,000 PY among 80–89-year-olds [29]. Claims data from the associations of statutory health insurance physicians reveal similar findings, with the incidence of HZ at 6.2/1,000 PY among 50–54-year-olds rising to 13.2/1,000 PY among those 90 years of age and older [28]. Evaluations of hospitalization data also demonstrate a rise with increasing age from approx. 6.7/100,000 inhabitants between 20 and 49 years of age to 57.7/100,000 inhabitants 70 years of age and older (average of years 1995 to 2012; [30]). These data also show a continuous rise in age-adjusted hospitalizations from 9/100,000 inhabitants in 1995 to 17/100,000 in 2012.

The HZ incidence in persons with immunosuppression was around twice as high as in immunocompetent persons (12 vs. 6/1,000 PY; [29]).

HZ-related mortality appears to be low. According to causes of death statistics (link to www.gbe-bund.de), the median annual number of deaths among persons at age 50 and over caused by HZ was around 75 between the years 2005 and 2014. Claims data from the association of statutory health insurance physicians confirm the low mortality of 0.21 per 100,000 inhabitants aged ≥50 years [28]. According to that data, mortality exceeding one death caused by HZ per 100,000 inhabitants does not occur until the age of >85 years.

The most frequent complications (besides PHN) are further involvement of the nervous system (15.5% of cases), zoster ophthalmicus (4.8%), disseminated zoster (0.6%), zoster encephalitis (0.4%), and zoster meningitis (0.1%). A total of approx. 28% of HZ cases led to one or more complications [29]. The risk of complicated disease progression increased with age, and was slightly higher among persons with immunosuppression than among immunocompetent persons with HZ.

4. Live attenuated herpes zoster vaccine

A live attenuated HZ vaccine, Zostavax® (manufacturer: Merck Sharp & Dohme; market authorization holder (until 31. 12. 2016): Sanofi Pasteur MSD), was licensed for Europe on 19 May 2006 by the European Medicines Agency (EMA; [31]). The initial registration in 2006 applied to the deep-frozen formulation; the lyophilized formulation was approved in January 2007. The lyophilized formulation of the vaccine has been available in Germany since September 2013. One dose (0.65 ml) of the reconstituted live HZ vaccine (powder plus solvent for the reconstitution to a suspension) contains at least 19,400 plaque-forming units (PFU) of the attenuated varicella zoster virus of the Oka/Merck strain. Additional ingredients in the vaccine are: saccharose, hydrolyzed gelatine, sodium chloride, potassium dihydrogen orthophosphate, potassium chloride, sodium L-glutamate monohydrate, disodium hydrogen phosphate, sodium hydroxide (for pH adjustment), and urea. The vaccine does not contain any thimerosal or other preservatives. The Oka strain, which is also contained in varicella vaccines for the prevention of chicken pox, was isolated in Japan in the 1970s from samples taken from a three-year-old boy who was ill with chicken pox [32]. The virus concentration is different in the vaccines. It is 14 times higher in the HZ vaccine than in the varicella vaccine [32]. The strain was attenuated through repeated cultivation in human embryonic lung cells, then passaged in embryonic guinea pig embryo fibroblasts. The virus is cultivated in human diploid cells [33]. The HZ vaccine is approved for the prevention of HZ and PHN caused by HZ with a single dose in persons age 50 and

Table 1 Hierarchy of patient-relevant outcomes for the evaluation of the efficacy and safety of the live attenuated herpes zoster vaccine

Focus of the systematic review	Population	Intervention	Comparator	Outcomes	Assessment of the significance of outcomes for a decision#
Efficacy	Adults ≥50y; (or other age groups)[1]	Vaccination with live HZ vaccine	No vaccination Placebo vaccination Other vaccination Antiviral therapy	HZ incidence	**5**
				PHN	**9**
				Other complications (incl. death)	**9**
				Hospitalization	**7**
Safety	Adults ≥50y; (or other age groups)[1]	Vaccination with live HZ vaccine	No vaccination Placebo vaccination Other vaccination Antiviral therapy	Local reactions, not serious	**3**
				Severe local reactions	**7**
				Systemic reactions, not serious	**4**
				Severe systemic reactions	**7**

Scale from 1–9: "critical" (7–9 points), "important" (4–6 points), or "of limited significance" (1–3 points). Each endpoint is to be assessed on its own. The same score can be assigned to multiple endpoints, as different endpoints can be equally significant.
[1]Age group should be selected according to the modelling results

over. The necessity and timing of a booster dose have not yet been determined. The vaccine can be administered as a subcutaneous (s. c.) or intramuscular (i. m.) injection. It should be administered s. c. in patients with severe thrombocytopenia or coagulopathy.

The vaccine is contraindicated for persons with congenital or acquired immunodeficiency (e. g. resulting from acute or chronic leukemia, lymphoma, other bone marrow or lymphatic diseases, or HIV/AIDS), on immunosuppressive therapy (including high doses of corticosteroids), with active, untreated tuberculosis, who are pregnant, or who have known hypersensitivity to ingredients in the vaccine. The vaccine can be administered simultaneously with an inactivated influenza vaccine to different body sites. The live HZ vaccine and the 23-valent pneumococci polysaccharide vaccine Pneumovax® must not be administered simultaneously, as this would negatively impact the immunogenicity of the live HZ vaccine. No data are available on the simultaneous administration with other vaccines.

5. Goal of vaccination

The STIKO has defined the reduction of HZ illnesses, their complications, and the long-term consequences caused by HZ in persons ≥50 as the primary goal of the vaccination. This aim should be specified according to other age groups, taking the results of the systematic review on vaccine efficacy, the duration of vaccine induced protection for different age groups, and the results of the modelling and the health economics evaluation into account.

6. Method of searching and assessing the quality of evidence

A working group of the STIKO processed the evidence on efficacy and safety of the live zoster vaccine and assessed the quality of the evidence according to the STIKO standard operating procedure (SOP) for the systematic development of evidence-based recommendations on immunization [34]. After the STIKO formulated the primary goal of the HZ vaccination, and following the GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology, patient-relevant outcomes of the HZ vaccination were defined and classified according to their importance for decision-making. The outcomes were assessed on a scale of 1–9 as essential/critical (7–9 points), important (4–6 points), or of limited significance (1–3 points) for the decision by the working group members (**Table 1**).

In order to identify clinical studies on vaccine safety and efficacy, the systematic literature research was carried out in accordance with the requirements of the PRISMA statement (preferred reporting items for systematic reviews and meta-analyses). The following databases were searched taking patient-relevant outcomes into account: MEDLINE; EMBASE, BIOSIS Preview, SciSearch, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, GLOBAL Health [35]. The complete search strategies, flowcharts, and inclusion and exclusion criteria are shown in the appendix (ESM_STIKO_Herpes_zoster_2017.pdf). Additionally, the reference lists of the studies included and the reviews identified were screened for other potentially relevant studies. No limitations were placed on publication status or language.

The literature research and data extraction were conducted by two independent investigators. The relevant study characteristics of the original studies that fulfilled the inclusion criteria were recorded using a standardized extraction form, and their internal and external validity were evaluated. Discrepancies between the two investigators were discussed until they reached consensus.

The data extracted on patient-relevant endpoints from the studies included were entered into the review management software RevMan (version 5.2), and the relative risk (RR) and corresponding 95% confidence intervals (95% CI) of the vaccine group compared to the placebo group were calculated for the relevant outcome. If more than one study was available, a meta-analysis was conducted in which individual results were summarized into an overall result and the pooled point estimates determined. If heterogeneity was present (assessed using I^2 statistics), a random effects model was used, otherwise the data were summarized using a fixed-ef-

Table 2 Age distribution and inclusion and exclusion criteria of the SPS study

Age (years)	Intervention (*n*)	Placebo (*n*)	Inclusion criteria	Exclusion criteria
60–69	10,370	10,356	Age ≥60 (years) and medical history of varicella or ≥30 years residency in the USA	Immunosuppression of any type, recipient of blood products, acute illnesses such as influenza or urinary tract infection, recipient of antiviral therapy, severe underlying diseases, etc.
70–79	7,621	7,559		
80+	1,263	1,332		
Total Ø 68.3	**19,254**	**19,247**		

fects model. Using the RR, the formula ([1-RR]*100) was applied to calculate the vaccine efficacy or effectiveness, or the risk of adverse side effects of the vaccination.

To compile the GRADE evidence profile, data from the outcomes defined as "critical" and "important" were entered into the GRADEprofiler (version 3.6) and the quality of evidence in all studies involved was assessed for each outcome according to the following aspects: study design, heterogeneity and precision, indirect evidence, effect size, and publication bias. The assessment of the overall quality of evidence across all endpoints was conducted using the lowest quality of evidence in the endpoints defined as "critical".

7. Vaccine efficacy

The STIKO working group defined and assessed the following outcomes with regard to vaccine efficacy (see table 1): HZ incidence (5 points), PHN (9 points), HZ-associated hospitalization (7 points), other complications (e.g. death [9 points]). Because the incidence of HZ increases with age, long-term protection provided by the vaccine is especially important.

Vaccine efficacy (VE) is the percentage reduction of disease (e.g. HZ), or disease-related complications (e.g. PHN) in a vaccinated group of people compared to an unvaccinated group that is achieved under standardized conditions. The data used were collected in randomized clinical trials (RCTs). If no data could be extracted from the RCTs included, data from cohort studies or the results of observational studies were also used (see section 8: vaccine efficacy, in particular for duration of vaccine protection). Two RCTs were included in the systematic review on the efficacy of the live HZ vaccine; which are presented in more detail below [36, 37].

7.1. Shingles prevention study (SPS)

The SPS is the first randomized, double-blind, placebo-controlled multicentre study to confirm that the live zoster vaccine is effective in preventing HZ and PHN [36]. Patient recruitment was conducted between November 1998 and September 2001 at 22 study centres in the USA at a ratio of 1:1 for the vaccine and placebo groups. It included 38,546 patients aged ≥60 years with a known medical history of chicken pox or with residency in the USA for ≥30 years (**Table 2**). The follow-up was completed in April 2004. 95% of the study participants were white, and 59% were men. The mean duration of observation was 3.13 years (median: 3.12 years; range: 0.0–4.9). 95.3% of the subjects completed the study. 1% were lost to follow-up, and 4% died. Only 7% of the subjects ($n = 2{,}595$) were ≥80 years old, hence the statistical power for assessing vaccine efficacy for this age group is limited.

Subcutaneous injections with either 0.5 ml live attenuated zoster vaccine or placebo solution were administered. The appearance of the two solutions was different. The frozen vaccine was used in 12 different concentrations ranging from 18,700 to 60,000 PBE (median: 24,600 PBE). More than 90% of those vaccinated received doses with <32,300 PBE (concentration in the final HZ live vaccine product approved: 19,400 PBE).

A burden of illness (BOI) score was defined as the primary endpoint for vaccine efficacy; it consisted of the incidence of HZ and the duration and intensity of zoster pain. The individual severity of HZ pain and associated limitations in the daily routine were recorded on a scale of 0–10 for an observation period of 6 months. PHN was selected as the secondary endpoint. PHN was defined as pain caused by HZ with a score of ≥3 on the pain scale, and which occurred or continued over certain periods of time (30, 60, 90, 120 and 182 days) after the initial occurrence of the HZ rash. The follow-up for PHN was limited to 182 days after the start of the rash. The tertiary endpoint was defined as the occurrence of HZ.

Skin rashes looking suspicious for HZ were examined by study investigators. HZ diagnoses were performed using PCR (93%) or virus culture (1%). If no material was available for a laboratory diagnosis, a 5-member expert team (6%) performed the HZ diagnosis based on the clinical picture. Participants who developed HZ in the first 30 days following vaccination were excluded from the analysis.

VE against HZ was 51.3% (5.42 cases/1,000 person-years (PY) in the intervention group vs. 11.12 cases/1,000 PY in the placebo group; $p < 0.001$), and VE against PHN was 66.5% (0.46/1,000 PY vs. 1.38/1,000 PY). The vaccination significantly reduced the RR of developing HZ (RR: 0.49 (95% CI 0.43–0.56) and later PHN (RR: 0.34 [95% CI 0.22–0.52]).

The VE against HZ declined with increasing age (**Fig. 1**) from 64% among 60 to 69-year-olds to 41% among 70 to 79-year-olds and 17% among those over the age of 80. The efficacy in the highest age group was not significant, as the confidence interval (CI) of the RR included 1 (RR: 0.83 [95% CI 0.54–1.27]). The analysis in this group did not deliver statistical significant value due to the low number of participants. A total of approx. 9,000 subjects aged ≥80 years would have been neccessary for a statistically valid analysis. The VE against PHN among 60 to 69-year-olds (65% [95% KI 22–84%]) and 70 to 79-year-olds (74% [95% KI 50–86%]) was constant, but the results are highly imprecise (**Fig. 2**). Taking the limitations given above into account no reliable proof of protection against PHN among ≥80-year-

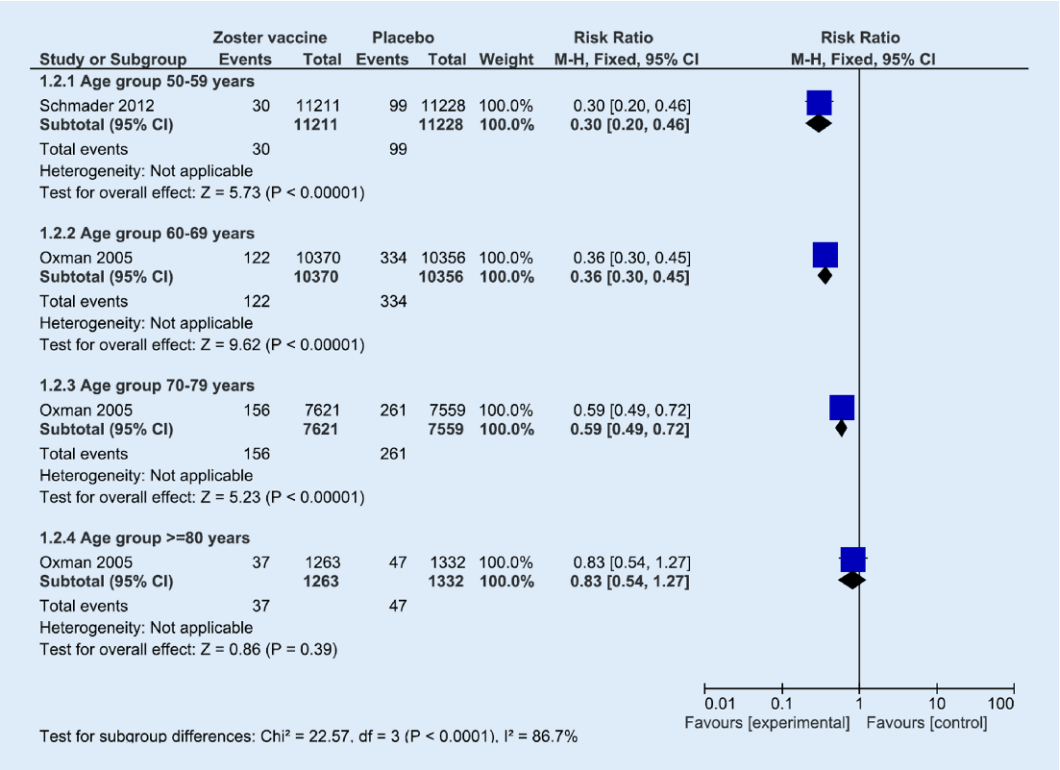

Fig. 1 ◀ Efficacy of live attenuated HZ vaccine in preventing HZ in different age groups (≥50–59 years, ≥60–69 years, ≥70–79 years, ≥80 years; [36, 37])

olds (RR: 0.62 [95% CI 0.24–1.56]) could be proved.

7.2. Zostavax efficacy and safety trial (ZEST)

The ZEST study is also a randomized, double-blind, placebo-controlled multicentre study (ratio: 1:1) conducted to prove the efficacy of the live zoster vaccine in protecting from HZ at 105 study centres in North America and Europe between October 2007 and January 2010 [37]. 22,439 subjects at the age of 50–59 years with a known medical history of chicken pox or ≥30 years of residency in an area in which varicella was endemic were included (intervention arm: 11,211 persons, placebo arm: 11,228 persons). 94.4% of the study participants were white, and 62% were women. The mean duration of observation was 1.3 years (range: 0 days to 2 years). 94% of the subjects completed the study; 3% were lost to follow-up.

The subjects were administered either 0.65 ml of the approved live HZ vaccine (19,400 PBE) or the identical quantity of a placebo solution subcutaneously. The primary endpoint of the study was the reduction in HZ incidence. Inclusion and exclusion criteria and the algorithm for diagnosing HZ were identical to those in the SPS study. The incidence of PHN was not investigated in this study.

The VE in protecting from HZ was 69.8% (1.99 cases/1,000 PY in the vaccine arm vs. 6.57 cases/1,000 PY in the placebo arm; $p < 0.001$; **Fig. 1**). The vaccination significantly reduced the relative risk of developing HZ (RR: 0.30 [95% CI 0.20–0.46]).

8. Duration of protection provided by the live attenuated HZ vaccine

In the RCTs described above, the observation period was too short to reach conclusions on the duration of protection from HZ or PHN [36, 37]. The subjects from the SPS study continued to be observed in two subsequent studies with partial temporal overlap. But the blinding was lifted, the vaccine was offered to all placebo recipients, meaning the studies were conducted in part without a comparison group. Thus they no longer fulfilled the quality criteria of an RCT. Unlike vaccine efficacy under controlled conditions in a specifically defined population, vaccine effectiveness is determined in post-marketing studies under everyday conditions in the normal population. Hereinafter the results of retrospective cohort studies are shown in addition to the results of the SPS follow-up studies. The study results are especially important because they deliver information on long-term protection after vaccination. The data were extracted from the studies included in the same manner as described above.

8.1. Short-term persistence substudy (STPS)

The STPS study [38] is a continuation of the SPS study. It was initiated to investigate the duration of efficacy of the HZ vaccination over a longer period of time. A total of 14,700 former SPS study participants (intervention arm: 7,320 persons, placebo arm: 6,950 persons) from 12 of the original 24 SPS sites were included in the STPS study. The study was conducted from December 2004 to March 2006. Between the end of the SPS study and the start of the STPS study, ongoing surveillance of the participants was interrupted for a period of 15 months. The average age of partic-

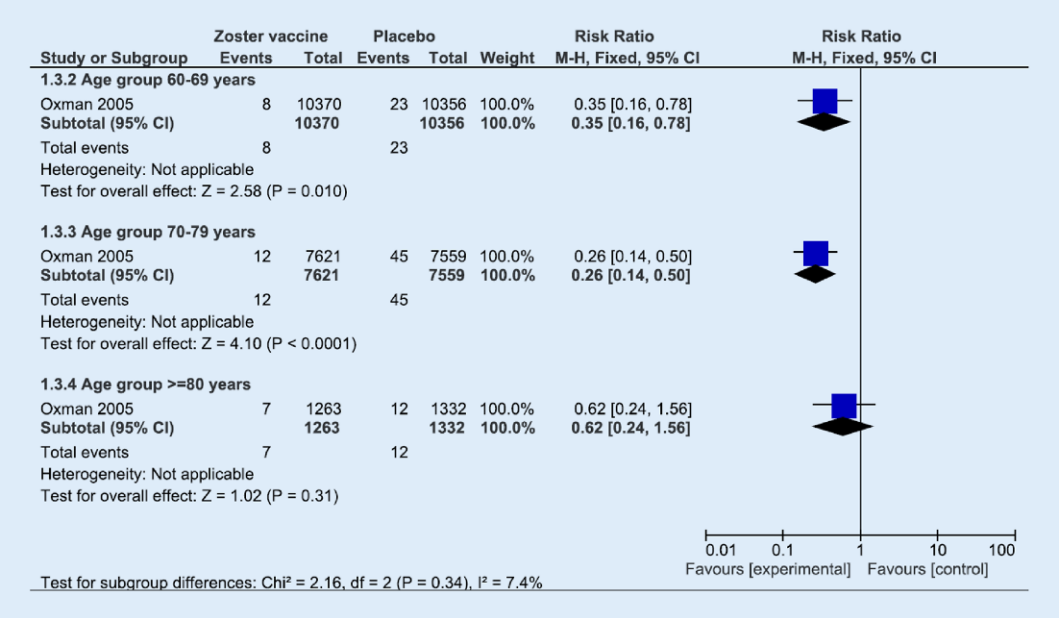

Fig. 2 ◀ Efficacy of live attenuated HZ vaccine in preventing postherpetic neuralgia in different age groups (≥60–69 years, ≥70–79 years, ≥80 years; [36])

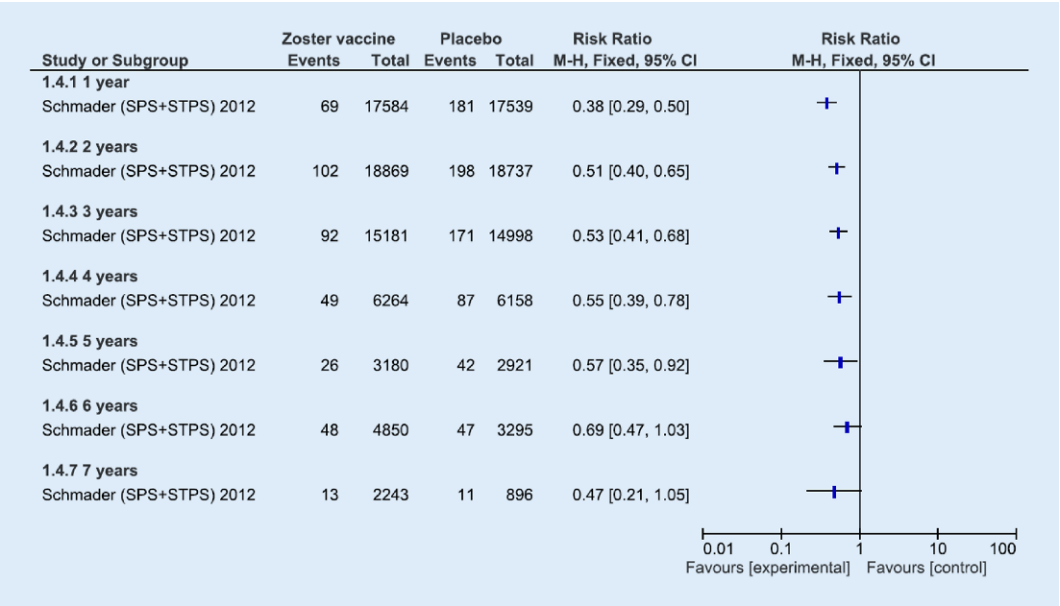

Fig. 3 ▲ Duration of efficacy and effectiveness of the live HZ vaccine in preventing HZ in persons aged ≥60 years, shown in years after vaccination (reference value: person-years); [38]. (The number of HZ cases and person-years in the follow-up of the SPS and STPS studies were aggregated to calculate the efficacy and effectiveness of the live HZ vaccine. 100% of the data were generated from the SPS study for the first 3 years, 97% from the SPS study and 3% from the STPS study for year 4, 16% from the SPS study and 84% from the STPS study for year 5, and 100% from the STPS study for years 6 and 7.)

ipants was 73.3 years. The inclusion and exclusion criteria of the STPS were identical to those of the SPS, as were the contact management, the three endpoints, case definition criteria (HZ and PHN), and diagnostic follow-up. Everyone who had received placebo in the SPS study was offered the live HZ vaccine; $n = 6{,}194$ subjects from the placebo arm were given the vaccination during the STPS study. That led to more follow-up years per subject for the intervention arm than for the placebo arm (9,967 PY vs. 6,802 PY) in the STPS study.

Thus randomization and blinding were partially lifted in the STPS study, giving it more the character of an observational study.

The STPS study lasted between 3.3 and 7.8 years after the initial vaccination in the SPS study. Aggregating the results of the SPS and STPS studies, findings on the period of protection provided by the vaccination are available for 0–7.8 years.

The effectiveness of the HZ vaccination in protecting against HZ (**Fig. 3**) decreased continuously over time from 62% in post-vaccination year 1 to 49% in year 2, 47% in year 3, 45% in year 4, and 43% in year 5. From year 6 onwards, no

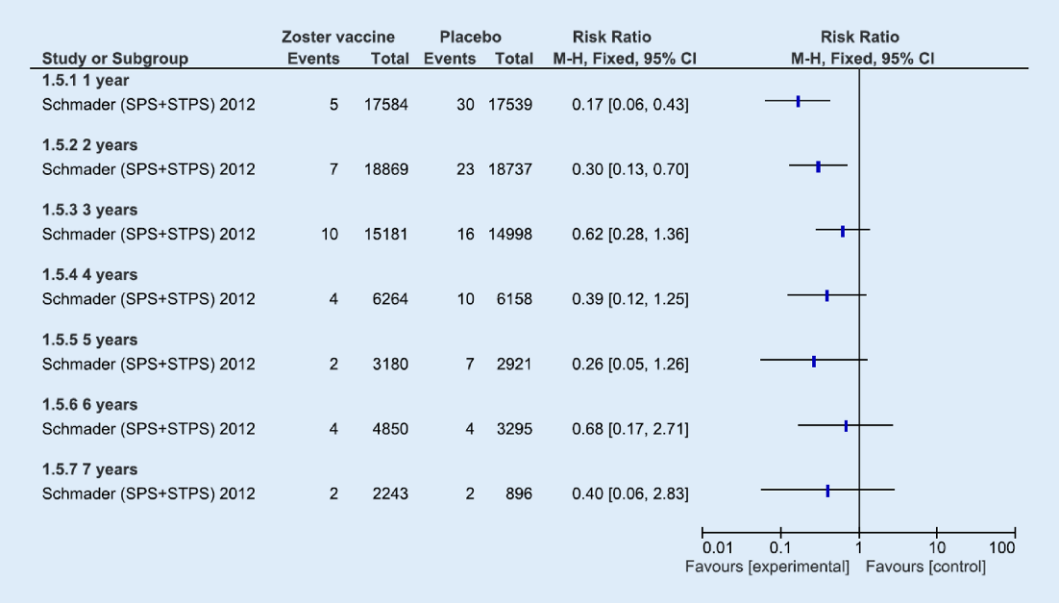

Fig. 4 ▲ Duration of efficacy and effectiveness of the live HZ vaccine in preventing PHN in persons aged ≥60 years, shown in years after vaccination (reference value: person-years); [38]. (The number of HZ cases and person-years in the follow-up of the SPS and STPS studies were aggregated to calculate the efficacy and effectiveness of the live HZ vaccine. 100% of the data were generated from the SPS study for the first 3 years, 97% from the SPS study and 3% from the STPS study for year 4, 16% from the SPS study and 84% from the STPS study for year 5, and 100% from the STPS study for years 6 and 7.)

significant protection could be proved, but the number of observations was low, and the resulting confidence interval was very broad and included "1".

The effectiveness of the HZ vaccination in protecting from PHN (**Fig. 4**) decreased from 83% in the first post-vaccination year to 70% in year 2. From year 3 onwards, no significant protection from PHN can be proved.

8.2. Long-term persistence substudy (LTPS)

In the LTPS study, parts of the cohort of the SPS and STPS studies were followed up for a period of up to 11 years after vaccination [39]. The study was conducted from March 2006 to December 2010. The aim was to determine the level of protection in each year from years 7 to 11 after the vaccination. The methods used were identical to those in the preceding studies. Because no placebo group was available as a comparison, historical control data were used. Vaccinated subjects in the LTPS study were compared to subjects of the same age from the SPS and STPS study, taking the increasing incidence of HZ with advancing age into account. 6,867 subjects from the intervention arm of the SPS study were included in the LTPS study, and 25,250 person-years recorded. The average age was 74.5 years.

In the first year of observation, year 7 after vaccination, VE in preventing HZ was found to be 46.0% (95% CI 28.4–60.2) in the LTPS study. The level of protection continued to fall over time, and in years 9 to 11 after vaccination, no significant protection against HZ could be proved (**Fig. 5**).

8.3. Retrospective cohort studies for the evaluation of the live HZ vaccine under everyday conditions in the post-marketing phase

After the HZ vaccination was recommended for adults aged ≥60 years in the US in 2006, a retrospective cohort study of members of the Kayser Permanente in southern California was conducted from January 2007 to December 2009 to evaluate the live HZ vaccine [40]. Participants were immunocompetent adults aged ≥60 years. At a ratio of 1:3, the incidence of HZ among 75,761 persons vaccinated at the age of ≥60 years was compared to that of 227,283 non-vaccinated persons of comparable age (+/– 1 year). The mean follow-up was 1.6 years for non-vaccinated persons and 1.7 years for vaccinated persons. Over a period of 1.7 years, the VE in preventing HZ was 55% (95% CI 52–58) with no difference in efficacy according to age at time of vaccination, gender, race, or underlying diseases. The effectiveness in protecting from HZ-associated hospitalization was 65% (95% CI: 49–67).

To examine the long-term protection provided by the vaccine, a follow-up study was initiated with the same study cohort, using the identical study design for a period of 8 years [40, 41]. 176,078 subjects who received the vaccination between January 2007 and December 2014 at the age of ≥60 years were compared to 528,234 non-vaccinated persons at a ratio of 1:3. The effectiveness of the vaccination decreased continuously over the observation period of 8 years after vaccination from 69% (95% CI 66–71) in year 1 to 50% (95% CI46–53) in year 2, between 39% (95% CI 34–44) and 33% (95% CI 23–42) in years 3–6, 17% (95% CI 1–29) in year 7, and 4% (95% CI -24–26) in year 8. No significant vaccine protection was detectable in year 8 after vaccination (**Fig. 6**).

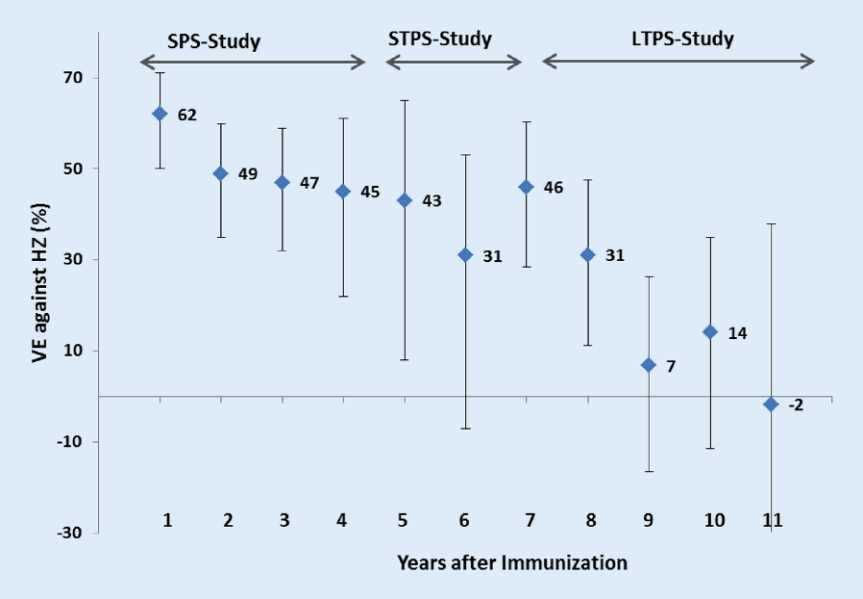

Fig. 5 ▲ Duration of efficacy and effectiveness of the live HZ vaccine in preventing HZ in persons aged ≥60 years, shown in years after vaccination [36–38]. (The number of HZ cases and person-years in the follow-up of the SPS and STPS studies were aggregated to calculate the efficacy and effectiveness of the live HZ vaccine in years 4 and 5 after vaccination. 97% are from the SPS study and 3% from the STPS study for year 4, 16% from the SPS study and 84% from the STPS study for year 5, and 100% from the STPS study for years 6 and 7. The number of HZ cases and person-years in the follow-up of the STPS and LTPS studies were aggregated to calculate the efficacy and effectiveness of the live HZ vaccine in years 7 and 8 after vaccination. 31% of the data for year 7 are from the STPS study and 69% from the LTPS study; 8% of the data for year 8 are from the STPS study and 92% from the LTPS study.)

9. Conclusions on the efficacy and effectiveness of the HZ vaccination

The two RCTs identified show that the live HZ vaccine can prevent HZ in persons aged ≥50 years [36, 37]. Because VE is strongly age-dependent and decreases with increasing age, pooled results over all age groups are not presented. VE is shown separately for every age group in the GRADE evidence profile. VE in preventing HZ falls from 70% among 50 to 59-year-olds to 41% among 70 to 79-year-olds. VE among ≥80-year-olds is even lower, less than 20%. The CI of the point estimator is broad and includes the no-effect line. A precise statement is not possible due to the low number of participants in this age group.

The vaccine can also prevent PHN after an HZ illness. Its efficacy is also age-dependent. VE is 65% among 60 to 69-year-olds, and 74% among 70 to 79-year-olds (with overlapping confidence intervals). VE in preventing PHN is markedly lower among ≥80-year-olds, but a solid statement is not possible due to the low number of participants in this age group. The CI of the point estimator is broad and includes the no-effect line. No data are available to investigate the efficacy of protection from PHN among 50 to 59-year-olds.

The RCTs included in the review do provide data on the efficacy of the vaccine in different age groups. However, it had been neglected to include enough participants from the age group with the highest risk for HZ to be able to draw a clear conclusion on the protection by the vaccine provided at this age. The quality of evidence was therefore downgraded in the GRADE evidence profile due to the lack of precision (**Table 3**).

Another reason for criticism is the fact that 12 vaccine batches were used in the STP study with varying levels of virus concentration (18,700–60,000 PBE). The approved product contains 19,400 PBE. The quality of evidence was therefore downgraded due to indirect evidence with regard to the intervention. Overall, the quality of evidence was "low" to determine that the live HZ vaccine is effective in preventing HZ and PHN in all age groups with regard to the outcomes in the evidence profile. The actual effect of the vaccine could vary substantially from the calculated effect estimates.

Both RCTs have a short observation period of 1.3 years (ZEST) and 3.1 years (SPS); for that reason it is not possible to provide data on the duration of vaccine protection. For this issue it was therefore necessary to combine the results from the SPS study and its follow-up studies (STPS and LTPS) (36, 38, 39) and to take into account the results of the post-marketing study with members of the Kayser Permanente [41]. The results of the long-term observations show, that the HZ vaccine provides only short term protection against HZ. These studies deliver data over a period of 8 to 11 years after vaccination. Both studies show a marked reduction in VE in protecting against HZ from >60% to <50% in year 2 after vaccination (**Figs. 5 and 6**). That is followed by a plateau phase of several years with slightly declining protection rates: 40% to 50% in the SPS study and its follow-up studies, and 30% to 40% in the Kayser Permanente study. But unlike the Kayser Permanente study, the SPS/STPS/LTPS studies show widening confidence intervals for the point estimates from year to year, and the uncertainty of the point estimates increases with time. In the Kayser Permanente study, the VE in year 7 after vaccination was 16.5%, and vaccine effectiveness from year 8 onwards was not demonstrated.

The results of the SPS study show that the efficacy in protecting from PHN is brief and lasts only up to 2 years after vaccination. The live HZ vaccine provides protection from PHN by preventing HZ disease in the first place. If HZ disease can be prevented, no HZ-associated PHN can occur. If the vaccine induced protection from zoster wanes over time, its effectiveness in preventing PHN is questionable.

In summary, the live HZ vaccine does protect from HZ and PHN, but the results are unsatisfactory with regard to older age groups and with regard to the duration of protection. To provide protection at the age at which the risk of disease is greatest, the individual must be vaccinated as late as possible. But this is not very promising, as the vaccine does not demonstrate efficacy in older age groups.

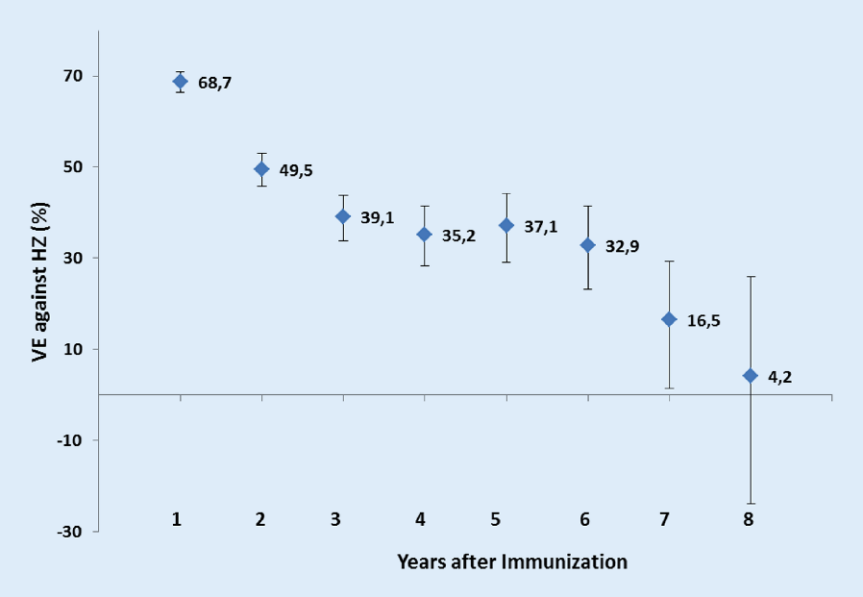

Fig. 6 ▲ Duration of effectiveness of the live HZ vaccine in preventing HZ in persons aged ≥60 years, shown in years after vaccination [40, 41]

10. Vaccine safety

The STIKO working group defined and evaluated the following endpoints as relevant for the assessment of vaccine safety: non-severe local reactions (erythema, swelling, reactions at the point of injection; 3 points), severe local reactions (pain, 7 points), non-severe systemic reactions (fever; 4 points), severe systemic reactions and severe adverse events following immunization (SAE; 7 points; **Table 1**).

A total of 5 RCTs were included to assess the safety of the live HZ vaccine [36, 37, 42–45]. They vary widely with regard to their consideration of the relevant endpoints and participant numbers. In **Table 4** the study duration, participant numbers, duration of follow-up, and the endpoints considered in the studies included are listed.

10.1. Local reactions after vaccination with the live HZ vaccine

In the clinical safety studies, persons vaccinated with the HZ live attenuated vaccine reported local reactions at the injection site significantly more frequently than participants in the placebo group. Based on the analysis of the aggregated data, local reactions at the injection site occurred in 60% of the subjects in the intervention group vs. 15% of the subjects in the placebo group. Swelling occurred in 26% vs. 4.5%, erythema in 36% vs. 7%, and pain in 34% vs. 8% (**Fig. 7**). The risk of local reactions was higher among participants aged 60–69 years (56.6%) than among subjects aged ≥70 years (39.2%; [45]). Most local reactions were minor and disappeared within 4 days [36].

10.2. Systemic reactions after vaccination with the live HZ vaccine

Systemic reactions associated with the vaccination (headache, fatigue, pain in the extremities) were also more common in the intervention group than in the placebo group (RR 1.41; 95% CI 1.28–1.55) (**Fig. 8**). Based on the analysis of the aggregated data, systemic adverse side effects occurred in 6.6% of the intervention group and 4.7% of the placebo participants. Fever (>38.3 °C, oral) occurred at the same rate in both comparison groups. 27 subjects (0.8%) in each of the intervention and placebo group of the SPS substudy reported that they experienced fever after the vaccination.

10.3. Severe adverse events following vaccination

In the 5 clinical studies that examined the safety of the live HZ vaccine, nine out of a total of 65,175 participants experienced severe adverse events (SAE) which were considered to be caused by the live attenuated HZ vaccine or the placebo vaccination. There were 5 cases in the verum group and 4 cases in the placebo group (see appendix (ESM_STIKO_Herpes_zoster_2017.pdf)). The verum group cases included a 46-year-old woman with asthma exacerbation, an 80-year-old man with a new case of polymyalgia rheumatica, one subject with an anaphylactic reaction 30 minutes after the vaccination, one subject who developed uveitis, and one who developed sciatica.

10.4. Varicella zoster and herpes zoster-like efflorescence, virus transmission after live HZ vaccination

As the results of the SPS study and its safety substudy showed, varicella-like exanthem within 42 days after vaccination at the injection site occurred significantly more frequently in the intervention group (0.11%) than in the placebo group (0.04%; [36, 45]). It consisted of small, transient (5–7 days) vesicles that did not spread. Neither the wild-type virus nor the vaccine virus (Oka strain) could be verified in the lesions by culture or PCR. Varicella-like exanthem occurred at the same rate on other parts of the body (0.1% vs. 0.1%; [36]). HZ-like efflorescence, i. e. vesicles that do not extend beyond the boundaries of one dermatome, occurred more frequently within the first 42 days after vaccination in the placebo group than in the intervention group. HZ was diagnosed in 24 participants from the placebo group and 7 participants from the intervention group. Examination samples to verify the virus were present for all but one of those participants. The wild-type virus was verified in all of them; none of the sample contained the vaccine virus (Oka strain, [45]). Transmission of the vaccine virus was not observed in the clinical studies. But findings from the post-marketing phase of the varicella vaccines do hint that the vaccine

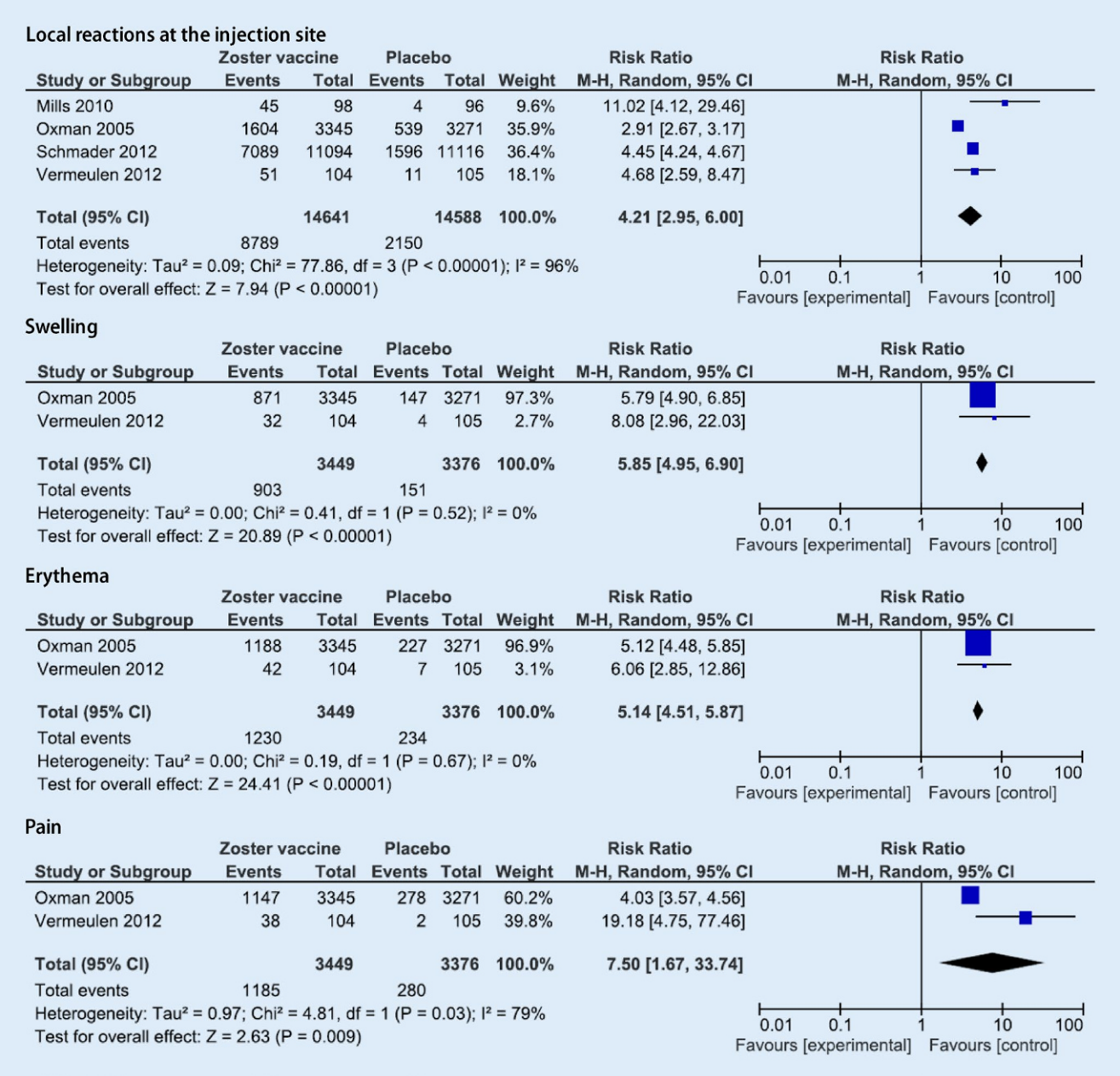

Fig. 7 ▲ Forest plots of the relative risk (RR) of reactogenicity endpoints of the live HZ vaccine

virus may be transmitted to susceptible persons in rare cases by vaccinated persons who developed varicella-like exanthem after vaccination [46]. This risk of transmission is also plausible after administration of the live attenuated HZ vaccine. But the possibility of transmission of an attenuated vaccine virus must be balanced with the risk of transmitting the VZ wild-type virus to a susceptible person during a natural HZ illness.

10.5. Live HZ vaccine after prior HZ disease

The live attenuated HZ vaccine can also be administered to persons who already have a medical history of HZ disease. A crossover, placebo-controlled study of 101 subjects aged ≥50 years showed that no serious adverse side effects occurred within 28 days after vaccination. Reactions at the injection site were considerably more frequent following the live attenuated HZ vaccine (45.9%) than the administration of placebo (4.2%). The percentage of subjects who experienced systemic adverse side effects was similar in the verum group (15.3%) and the placebo group (13.5%; [42]).

10.6. Summary assessment of the safety of the live HZ vaccine

Based on the results of clinical studies, the administration of the live HZ vaccine to persons at 50 years and older is safe and generally well tolerated. Although local

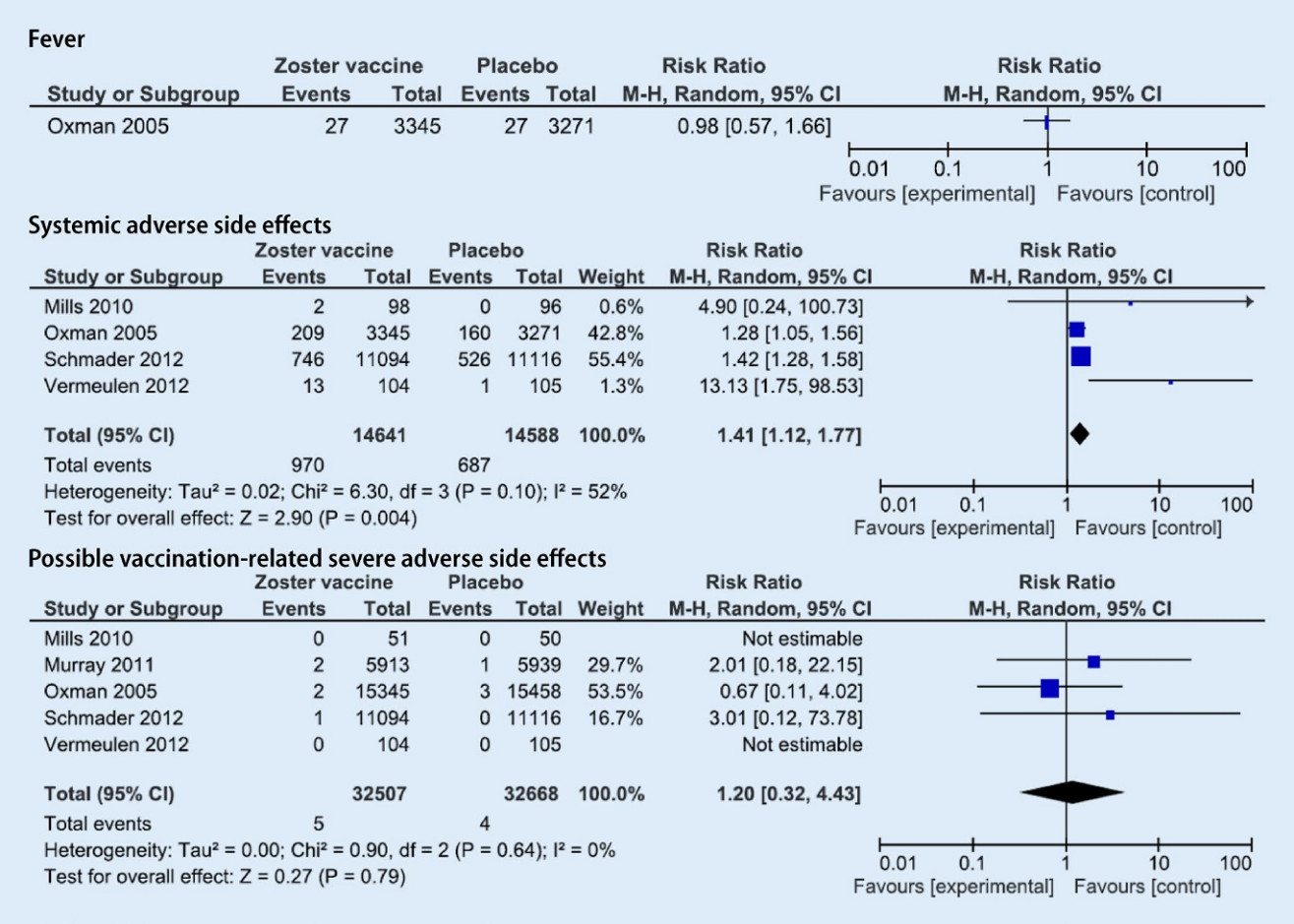

Fig. 8 ▲ Forest plots of the relative risk (RR) of systemic and severe adverse reactions

reactions at the injection site (swelling, pain, and redness) occurred more frequently in vaccinated persons, they were mostly mild and transient (<4 days). The risk of local reactions is higher among 60 to 69-year-olds than among older persons. The frequency of systemic adverse side effects was somewhat higher in the verum group than in the placebo group (6.3% vs. 4.9%), most frequently headache and fatigue. Fever (>38.3 °C) occurred with similar frequency in the two groups, in less than 1% of the study participants. The incidence of vaccine-associated SAEs was very low (<0.02%); there was no difference between the vaccination group and the placebo group. Varicella-like efflorescence at the injection site was rare overall, but occurred significantly more frequently in those who received the vaccine than in those who received placebo. No vaccination virus could be verified in the vesicles. Transmission of the vaccination virus was not observed in the clinical studies. The live attenuated HZ vaccine can also be administered to persons who have already had a zoster episode. The quality of evidence for the endpoints assessed for safety is generally considered high (**Table 3**). Only the quality of data on pain at the injection site is seen as critical. It is considered objectionable that the confidence intervals of the two studies included do not overlap, and that vaccines with differing virus concentration were used.

11. Vaccination strategy

The primary aim of HZ vaccination was considered by STIKO in reducing disease burden caused by HZ in persons aged 50 years and over. It was specified as follows, taking into account data on HZ epidemiology in Germany, results of systematic reviews on vaccination efficacy, the period of protection provided by the vaccine in different age groups, and the results of the model and the health economics evaluation: In recommending a zoster vaccination, the STIKO aims to substantially reduce the frequency and severity of HZ in older adults (≥70 years). The immunity of persons with existing VZV immunity should be boosted with the HZ vaccine to reduce permanently the incidence of HZ, its complications, and the HZ sequela PHN.

12. Administration and contraindications

12.1. Dose and method of administration

The live attenuated HZ vaccine is administered after reconstitution of powder and solvent for injection. The vaccine can be injected subcutaneously or intramuscularly as a single dose (0.65 ml), preferably

Table 3 Evidence profile of the quality of the systematic review of the safety and efficacy of the live herpes zoster vaccine: (important and critical endpoints)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Live attenuated VZV vaccine		Relative (95% CI)	Absolute		
Herpes zoster at the age of 50–59 years (modified ITT) (follow-up mean 1.3 years)												
1[1]	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	30/11.211 (0.27%)	99/11.228 (0.88%)	RR 0.3 (0.2 to 0.46)	fewer per 1000 (from 5 fewer to 7 fewer)	⊕⊕⊕⊕ HIGH	IMPORTANT
								0.6%[2]		fewer per 1000 (from 3 fewer to 5 fewer)		
								0.9%[2]		fewer per 1000 (from 5 fewer to 7 fewer)		
Herpes zoster at the age of 60–69 years (modified ITT) (follow-up mean 3.13 years)												
1[1]	Randomized trials	No serious risk of bias[3]	No serious inconsistency	Serious[4]	No serious imprecision	None	122/10.370 (1.2%)	334/10.356 (3.2%)	RR 0.36 (0.3 to 0.45)	21 fewer per 1000 (from 18 fewer to 23 fewer)	⊕⊕⊕O MODERATE	IMPORTANT
								0.92%[2]		fewer per 1000 (from 5 fewer to 6 fewer)		
								1.1%[2]		fewer per 1000 (from 6 fewer to 8 fewer)		
Herpes zoster at the age of 70–79 years (modified ITT) (follow-up mean 3.13 years)												
1[1]	Randomized trials	No serious risk of bias[3]	No serious inconsistency	Serious[4]	No serious imprecision	None	156/7621 (2%)	261/7559 (3.5%)	RR 0.59 (0.49 to 0.72)	14 fewer per 1000 (from 10 fewer to 18 fewer)	⊕O MODERATE	IMPORTANT
								1.1%[2]		fewer per 1000 (from 3 fewer to 6 fewer)		
								1.3%[2]		fewer per 1000 (from 4 fewer to 7 fewer)		
Herpes zoster at the age of >=80 years (modified ITT) (follow-up mean 3.13 years)												
1[1]	Randomized trials	No serious risk of bias[3]	No serious inconsistency	Serious[4]	Serious[5]	None	37/1263 (2.9%)	47/1332 (3.5%)	HR 0.83 (0.54 to 1.27)	fewer per 1000 (from 16 fewer to 9 more)	⊕⊕OO LOW	IMPORTANT
								1.27%[2]		fewer per 1000 (from 6 fewer to 3 more)		
								1.4%[2]		fewer per 1000 (from 6 fewer to 4 more)		

Table 3 (Fortsetzung)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Live attenuated VZV vaccine		Relative (95% CI)	Absolute		
PHN at the age of 60–69 years (modified ITT) (follow-up mean 3.13 years)												
1	Randomized trials	No serious risk of bias[3]	No serious inconsistency	Serious[4]	Serious[6]	None	8/10.370 (0.08%)	23/10.356 (0.22%)	RR 0.35 (0.16 to 0.78)	fewer per 1000 (from 0 fewer to 2 fewer)	⊕⊕OO LOW	CRITICAL
								0.03%[7]		fewer per 1000 (from 0 fewer to 0 fewer)		
								0.14%[7]		fewer per 1000 (from 0 fewer to 1 fewer)		
PHN at the age of 70–79 years (modified ITT) (follow-up mean 3.13 years)												
1	Randomized trials	No serious risk of bias[3]	No serious inconsistency	Serious[4]	No serious imprecision	None	12/7621 (0.16%)	45/7559 (0.6%)	RR 0.26 (0.14 to 0.5)	fewer per 1000 (from 3 fewer to 5 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0.04%[7]		fewer per 1000 (from 0 fewer to 0 fewer)		
								0.22%[7]		fewer per 1000 (from 1 fewer to 2 fewer)		
PHN at the age of >=80 years (modified ITT) (follow-up mean 3.13 years)												
1	Randomized trials	No serious risk of bias[3]	No serious inconsistency	Serious[4]	Serious[5]	None	7/1263 (0.55%)	12/1332 (0.9%)	RR 0.62 (0.24 to 1.56)	fewer per 1000 (from 7 fewer to 5 more)	⊕⊕OO LOW	CRITICAL
								0.1%[7]		fewer per 1000 (from 1 fewer to 1 more)		
								0.26%[7]		fewer per 1000 (from 2 fewer to 1 more)		
Safety—pain—(follow-up 1–42 days)												
2	Randomized trials	No serious risk of bias	Serious[8]	Serious[4]	No serious imprecision	None	1185/3449 (34.4%)	280/3376 (8.3%)	RR 4.14 (3.67 to 4.68)	260 more per 1,000 (from 221 fewer to 305 more)	⊕⊕OO LOW	CRITICAL
Safety—vaccine-related systemic AE—(follow-up 1–28 + 1–42 days)												
4	Randomized trials	No serious risk of bias[9]	No serious inconsistency	No serious indirectness	No serious imprecision	None	970/14.641 (6.6%)	687/14.588 (4.7%)	RR 1.41 (1.12 to 1.77)	19 more per 1,000 (from 6 fewer to 36 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Safety—fever—(follow-up 1–42 days)												
1	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	27/3345 (0.81%)	24/3271 (0.73%)	RR 0.98 (0.57 to 1.66)	fewer per 1000 (from 3 fewer to 5 more)	⊕⊕⊕⊕ HIGH	CRITICAL

Table 3 (Fortsetzung)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Live attenuated VZV vaccine		Relative (95% CI)	Absolute		
Safety—vaccine-related serious AE—(follow-up 1 day to 3.13 years[10])												
5	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	5/32.507 (0.02%)	4/32.668 (0.01%)	RR 1.23 (0.35 to 4.27)	more per 1000 (from 0 fewer to 0 more)	⊕⊕⊕⊕ HIGH	CRITICAL
								0%		–		

[1]Subjects educated about signs and symptoms of HZ and instructed to call study site if HZ symptoms appear. Monthly contacts were made to ensure that symptoms suggestive of HZ were reported.
[2]Average annual HZ incidence for Germany (minimum and maximum) from publications by Ultsch and Hillebrand
[3]Sequence generation not described
[4]12 different vaccine lots used in the study (range:18,700–60,000 plaque-forming units (PFU) per dose; median: 24,600 PFU (>90% of vaccinated subjects received doses < 32,300 PFU); (19.400 PFU in final product)
[5]95% confidence interval around the best estimate of effect includes no effect.
[6]95% confidence interval is wide.
[7]Average annual PHN-incidence for Germany (Minimum and Maximum) from publication of Ultsch et al.
[8]Widely differing confidence intervals in included studies; partly not overlapping.
[9]Sequence generation, randomization and blinding in one of the four included studies not described (weight of the respective study: 0.6%)
[10]Different length of follow-up

Table 4 Description of studies considered in the systematic review on the safety of the live HZ vaccine

Study	Design	Study period	Age group (years)	Participants (*n*)		Follow-up (reactogenicity + systemic reactions, days after vaccination	Follow-up on severe adverse events (SAE) after vaccination	Reactions at point of injection	Erythema	Swelling	Pain	Fever	Systemic AEs	SAE
				Intervention	Placebo									
Schmader [37]	Multicentre RCT	10/2007–01/2010	50–59	11,094	11,116	1–42	43–182 days	X					X	X
Oxman [35], **Simberkoff**[a] [44] [36, 45]	Multicentre RCT	11/1998–09/2001	60–69 70	1,732 1,613	1,727 1,544	1–42	3.4 years (1 day -5.4 years)	X	X	X	X	X	X	X
Murray [43]	Multicentre RCT	09/2007–01/2009	60	5,913	5,939	1–42								X
Mills[b] [42]	Multicentre RCT	05/2006–07/2007	50	51	50	1–28 days	1–182 days	X					X	X
Vermeulen [44]	Multicentre RCT	11/2001–02/2003	60	104	105	1–42	1–42 days	X	X	X	X		X	X

[a]Safety substudy of non-randomized subpopulation from the SPS study;
[b]Subjects with a medical history of HZ

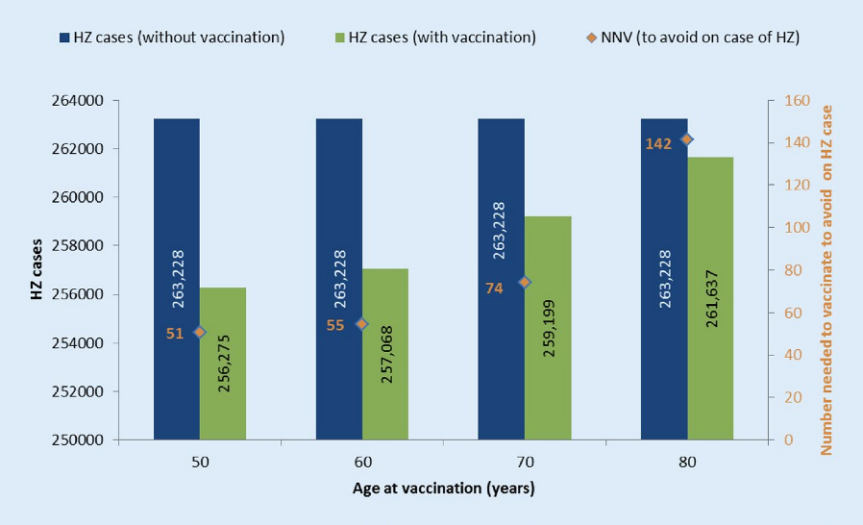

Fig. 9 ▲ Number of HZ cases with and without vaccination with the live HZ vaccine, NNV according to age at vaccination

in the deltoid region. The vaccine should be administered in patients with severe thrombocytopenia or any coagulation disorder subcutaneously. A booster vaccination is not yet approved [47].

12.2. Coadministration with other vaccines

The live attenuated HZ vaccine can be administered concomitantly with inactivated influenza vaccine as a separate injection at different body sites. This was tested in an RCT in which 762 adults ≥ 50 years received a single dose of live HZ vaccine, either concomitantly ($n = 382$) or not ($n = 380$), with an inactivated split influenza vaccine [48]. The virus-specific immune responses 4 weeks after vaccination were comparable for both vaccines, regardless of whether the vaccines were administered concomitantly or not.

The live HZ vaccine and the 23-valent pneumococcal polysaccharide vaccine Pneumovax® should not be administered concomitantly. Findings from one RCT show that simultaneous administration of the vaccines resulted in reduced immunogenicity of the live attenuated HZ vaccine. In a clinical study, 473 adults ≥ 60 years received one dose of live HZ vaccine, either simultaneously ($n = 237$) or not ($n = 236$), with the 23-valent pneumococcal polysaccharide vaccine [49]. The VZV-specific immune responses after simultaneous administration, measured 4 weeks after vaccination, did not correspond to the VZV-specific immune responses after non-simultaneous administration. Therefore, administration of the two vaccines should be considered to be separated by at least 4 weeks.

No data are available at this time on the simultaneous administration with other vaccines.

12.3. Contraindications

The live HZ vaccine is contraindicated for persons with a known hypersensitivity to one of the substances contained in the vaccine (e. g. neomycin).

It is also contraindicated under the following conditions or in the presence of one of the following diseases:

- Congenital or acquired immunodeficiency as a consequence of acute or chronic leukaemia, lymphoma, or any other disease of the bone marrow or the lymphatic system; immunodeficiency as a consequence of HIV/AIDS; immunosuppressive therapy including high doses of corticosteroids
- Active, untreated tuberculosis
- Pregnancy

13. Health economic evaluation of HZ vaccination in Germany

13.1. Methods

An existing static Markov cohort model was developed for this analysis [50] and updated by implementing recent data specifically with regard to vaccine efficacy and duration of vaccine-induced protection. The model follows a simulated cohort of 1 million 50-year-olds to the end of their lives. It includes five conditions (health, death, HZ, PHN, and health after illnesses), and calculates with a cycle length of three months based on duration of HZ. The age at vaccination was varied between 50, 60, and 70 years. In addition to the number needed to vaccinate (NNV) in order to prevent one HZ (PHN) case, the incremental cost-effectiveness ratios (ICER) €/HZ case prevented (€/HZ) and €/quality adjusted life-year gained (€/QALY) were calculated. All analyses were calculated from a societal perspective, i. e. including costs for disease-related sick leave. In addition to a base case analysis (vaccination at age 60, immunization costs of € 182 per person vaccinated, 35.3% vaccination coverage, and 3% annual discount rate of costs and benefits), descriptive univariate and probabilistic sensitivity analyses (PSA) were conducted in order to analyze the impact of input data uncertainty. The model was developed using the programming language R.

13.2. Input data

The input data for the model were partially updated and their impact on results investigated in sensitivity analyses. The data on epidemiology and the direct and indirect treatment costs of HZ and PHN were taken from SHI billing data in Germany [1, 28]. The vaccination costs consist of € 175 per vaccine dose (rote-liste.de, effective: 27 February 2017) and € 7 administration costs (assumption). The data on vaccine efficacy and vaccine-induced duration of protection have already been described above. Quality of life data to calculate QALYs were taken from persons with HZ or PHN disease in Canada [51].

13.3. Results

In the base case, 6,161 HZ cases (NNV = 55), i. e. 2.34% of HZ cases, could be prevented with the live HZ vaccine (**Fig. 9**). A higher vaccination coverage of 60% (80%) could prevent 10,471 (13,962) HZ cases. The lowest NNV is 51, and is achieved with vaccination at age 50. The NNV is 74 with vaccination at age 70. Depending on the age at vaccination, the relative reduction in HZ cases within one cohort ranges from 2.64% (age at vaccination: 50) and 1.53% (age at vaccination: 70). The NNVs to prevent one PHN case at ages 50, 60, and 70 years are 23,435, 2,216, and 907, respectively.

Vaccination with the live HZ vaccine leads to ICERs of € 7,006/HZ and € 88,357/QALY from societal perspective. Overall, vaccination in the base case leads to >€ 60 million in vaccination costs and a reduction in treatment costs of approx. € 2.5 million. The most cost-effective age at vaccination appears to be 60 years. At a vaccination age of 50 and 70 years, the relevant ICERs are € 104,845 and € 114,858/QALY respectively.

In sensitivity analyses it was shown that especially the vaccine-induced duration of protection, the price of the vaccine, and an assumed recurrence of HZ have the greatest impact on results. If theoretical lifelong vaccine protection is assumed, the ICER falls to € 9,242/QALY. Assuming a period of protection of only 5 years leads to an ICER of € 151,909/QALY. If the immunization costs fall from € 182 to € 82, the resulting ICER is € 37,665/QALY. If they rise to € 282, the ICER is then € 139,049/QALY. If the model takes into account that a person can have HZ disease more than once, the ICER is then € 70,933/QALY. A lower discount rate for effects or an assumed higher probability of developing PHN also reduces the ICER. By contrast, the ICER rises consistently if one takes the SHI (payer) perspective. In the PSA (10,000 Monte Carlo simulations), in which input data such as QALYs, treatment costs, epidemiology, and vaccine efficacy were varied within their confidence intervals based on likelihood distributions, 90% of the ICERs were between € 54,000 and € 107,000/QALY.

14. Conclusion and Recommendation

The German Standing Committee on Vaccination (STIKO) does not recommend the administration of the live attenuated herpes zoster (HZ) vaccine as a standard vaccination for the prevention of herpes zoster and its complications in the elderly. The STIKO based this decision on the results of a systematic review of the data on the safety and efficacy of the live attenuated herpes zoster vaccine in accordance with its standard operating procedure (SOP). Available data on the epidemiology of HZ in Germany and results of modelling the epidemiological and health economic effects of this vaccination were also taken into account.

An individual benefit-risk assessment may, however, lead to a different decision in individual patients.

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