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A. Siedler[1] · J. Koch[1] · E. Garbe[2] · H. Hengel[3,9] · R. von Kries[4] · T. Ledig[5] · T. Mertens[6] · F. Zepp[7] · K. Überla[8]

[1] Immunization Unit, Robert Koch Institute, Berlin, Germany
[2] Bremen Institute for Prevention Research and Social Medicine, University of Bremen, Bremen, Germany
[3] Institute of Virology, Medical Center–University of Freiburg, Faculty of Medicine, Freiburg, Germany
[4] Institute of Social Paediatrics and Adolescent Medicine, Ludwig-Maximilians University of Munich, Munich, Germany
[5] General Practice, Ditzingen, Germany
[6] Institute of Virology, Ulm University Medical Center, Ulm, Germany
[7] Department of Pediatrics and Adolescent Medicine, University Medicine Mainz, Mainz, Germany
[8] Institute of Clinical and Molecular Virology, University of Erlangen-Nuernberg, Erlangen, Germany
[9] German Consulting Laboratory for HSV and VZV, Medical Center – University of Freiburg, Freiburg, Germany

Background paper to the decision to recommend the vaccination with the inactivated herpes zoster subunit vaccine

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

Electronic supplementary material

The online version of this article (https://doi.org/10.1007/s00103-019-02882-5) contains supplementary material, which is available to authorized users.

Summary

The STIKO recommends vaccination with the adjuvanted herpes zoster subunit (HZ/su) inactivated vaccine for the prevention of herpes zoster (HZ) and postherpetic neuralgia (PHN) for all people age 60 years and over (standard vaccination).

This recommendation takes into account the good efficacy of the vaccine, the anticipated period of protection it provides, and the increased risk of severe HZ disease and post-zoster pain in individuals age 60 years and over. Models of the epidemiological effects of vaccination show that administering the HZ/su vaccine at age 60 years has the greatest effect in preventing all HZ cases, and administering the vaccine at age 70 years showed the greatest effect in preventing PHN, in a vaccinated cohort. According to the results of a health economics model, the lowest cost per quality-adjusted life year (QALY) would be achieved with vaccination at age 65 years. The number of people who need to be vaccinated (number needed to vaccinate, NNV) to prevent one case of HZ is the same for both vaccination ages (60 and 65 years). In light of the fact that preventing HZ is the key prerequisite to preventing complications and late sequelae such as PHN, 60 years of age is considered the most favorable age for vaccination, to prevent both HZ and its complications.

The STIKO also recommends vaccination against HZ and PHN with the HZ/su inactivated vaccine for all people from the age of 50 years who have an elevated risk of HZ and PHN owing to increased health risks as a consequence of an underlying disease or immunosuppression (indication-based vaccination). This group includes e. g. people with congenital or acquired immunodeficiency or immunosuppression, HIV infection, rheumatoid arthritis, systemic lupus erythematosus, chronic inflammatory bowel disease, chronic obstructive pulmonary disease (COPD) or bronchial asthma, chronic renal disease, diabetes mellitus.

The efficacy and safety of the vaccine for patients with impaired immune systems have been demonstrated in numerous studies. Stratified data analyses on the efficacy of the vaccine have shown no difference in

A. Siedler and J. Koch have contributed equally to the publication.
E. Garbe, R. von Kries, T. Ledig, T. Mertens, F. Zepp, K. Überla, are members of the German Standing Committee on Vaccination (STIKO).
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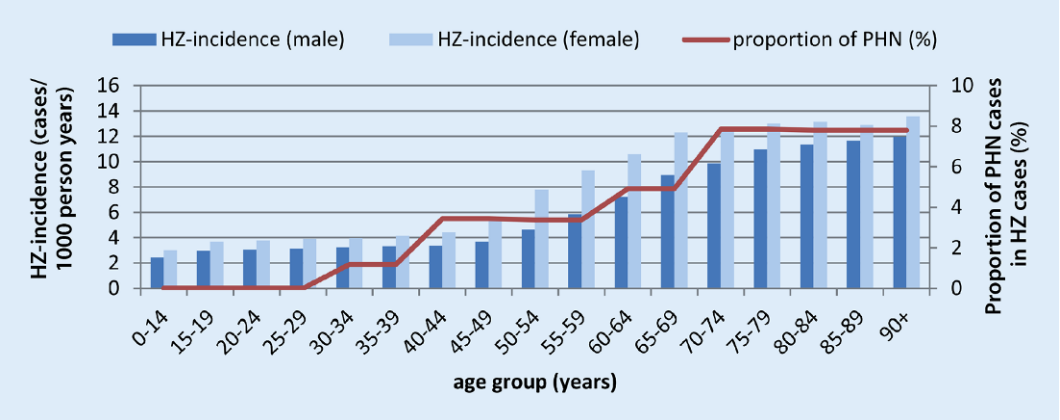

Fig. 1 ◀ Incidence of herpes zoster (*HZ*) by age and sex and proportion of postherpetic neuralgia (*PHN*) among HZ cases in Germany [5, 43]

comparison to overall efficacy for patients with an underlying disease, e. g., rheumatoid arthritis, chronic renal disease, COPD, or diabetes mellitus, who were enrolled in vaccine marketing authorization studies.

1 Introduction

Herpes zoster (HZ) and its most frequent complication, postherpetic neuralgia (PHN), place a large disease burden and limitations on the life quality of people affected in Germany. In March 2018, the European regulatory authority approved an adjuvanted HZ subunit (HZ/su) vaccine for the prevention of HZ and PHN from the age of 50 years (Shingrix®; Glaxo SmithKline (GSK), Rixensart, Belgium); this vaccine contains the adjuvant $AS01_B$ and recombinant varicella zoster virus (VZV) glycoprotein E (gE). This background paper summarizes the data basis used by the STIKO in its decision regarding standard vaccination and indication-based vaccination with the adjuvanted HZ/su inactivated vaccine. The present information is also based on the data already used in the STIKO decision on the live HZ vaccine in its 2017/2018 recommendations [1]. For example, the current disease burden of HZ in Germany had already been determined according to the STIKO standard operating procedure (SOP) [2]. This was followed by systematic reviews on the efficacy and safety of the HZ/su inactivated vaccine and evaluations of the data on the vaccine induced period of protection. A mathematical model of the potential epidemiological effects of HZ vaccination in Germany was conducted, which served as the basis for a health economics evaluation of potential vaccination strategies. This background paper includes a comprehensive appendix as electronic supplementary material containing further information on the systematic reviews conducted as well as on the decision process by the STIKO , which is available for download at https://link.springer.com/journal/volumesAndIssues/103.

2 Causes and symptoms

Detailed information on the etiology, symptoms, localization, complications, and risk factors of HZ was recently published in a STIKO background paper presenting the rationale of the STIKO decision against recommendation of the live HZ vaccine as a standard vaccination [1, 3]. For that reason a detailed description is not presented here.

3 Epidemiology

Data on the epidemiology of HZ were also published in the aforementioned background paper [1, 3]. These will be summarized again here, and complemented with data on the epidemiology of PHN and other complications of HZ, as well as a description of the risk factors of HZ and PHN.

In Germany, it is estimated that more than 300,000 people develop HZ each year, and that number is increasing. The risk of developing HZ is age dependent. From age 10 to 44 years, the incidence of HZ is 4/1000 person-years (PY) [4]; from age 50 years, the incidence rises steadily from around 6/1000 PY to more than 13/1000 PY from age 70 years [4, 5]. The incidence of HZ is higher among women than among men in every age group (**Fig. 1**).

Hospitalizations owing to HZ and its complications also increase with age. The reported incidence of HZ cases treated in the hospital is 0.13/1000 PY in the age group 50–54 years, and rises to around 1/1000 PY from the age of 80 years [5]. According to hospital diagnosis statistics, the annual number of HZ cases among people age >50 years treated in hospitals has approximately doubled in the past 10 years, with nearly 20,000 cases in 2015. Complications are recorded for more than 60% of patients hospitalized with HZ, the most frequent being HZ with clinical symptoms affecting the nervous system and herpes zoster ophthalmicus. The percentage of hospitalized patients with complications remains constant with increasing age in people age 50 years and older, but the number of patients treated in the hospital who develop complications rises with age (http://www.gbe-bund.de/gbe10/abrechnung.prc_abr_test_logon?p_uid=gast&p_aid=0&p_knoten=VR&p_sprache=D&p_suchstring=g%FCrtelrose). An analysis of data from insured individuals also showed an increase with age for all other HZ complications and multiple complications, except for HZ meningitis [4].

The risk of PHN following HZ rises steadily with age. In the aforementioned analysis of data from insured individuals, the percentage of PHN cases among all HZ cases in the age group 50–54 years was approximately 12%, and this increased to >20% with age until 80–84 years [4]. In a more conservative estimate based on out-

patient diagnosis invoicing, the percentage of PHN among people age 50–59 years was 3%, and around 8% in those age 70 years or more [5].

Immunosuppression and other underlying diseases have been described as additional risk factors for HZ and its complications. In an analysis of clinical data from Germany, the percentage of patients who developed PHN in all age groups was 36% higher among those with immunosuppression than among patients with a healthy immune system; in those age 50 years and over, this rate was 18% higher [4]. Patients with immunosuppression were defined in this study as those with HIV infection, malignant tumors, organ or stem-cell transplant recipients, and patients with other reasons for immunosuppression.

In a systematic review covering 84 mostly retrospective cohort studies conducted mainly in North America, Europe, and Asia from January 2003 to February 2017, the following comorbidities were identified as risk factors for HZ (RR, relative risk) [6]:

- Rheumatoid arthritis: RR 1.19–2.40
- Systemic lupus erythematosus: RR 1.29–4.11
- Inflammatory bowel disease: RR 1.26–1.50
- Chronic renal disease: RR 1.14–1.60
- COPD: RR 1.17–1.68
- Asthma: RR 1.11–1.70
- Diabetes mellitus: RR 1.02–1.68

In another systematic review, the risk of HZ was examined in patients with rheumatoid arthritis, psoriasis, SLE, or chronic inflammatory bowel diseases, as well as those who had received immunosuppressive therapy with biologics or with so-called non-biologic disease modifying anti-rheumatic drugs (nbDMARDS) [7]. During the time frame 1946–2016, a total of 40 randomized controlled trials (RCTs) including 20,136 patients and 19 observational studies with a total of 810,939 patients were identified. In the meta-analyses of both RCTs (odds ratio (OR) = 1.71, 95% confidence interval (CI) 1.11–2.64) and observational studies (OR = 1.58, 95% CI 1.39–1.81), an increased risk of HZ was found among patients who received biologics therapy, especially among those who had been treated with non-TNF-α antagonists (OR = 2.19, 95% CI 1.20–4.02). In contrast, patients who were treated with TNF-α antagonists did not have a significantly higher HZ risk. Patients who received high-dosage nbDMARDS or high-dose corticosteroids also showed an increased risk.

One study from the United Kingdom (UK) analyzed the risk of PHN using data from a routine database of patients with HZ in primary care [6]. The study findings showed that the incidence of PHN was markedly higher in the following risk groups: patients with leukemia (14.4%), lymphoma (12.1%), myeloma (17%), rheumatoid arthritis (9.1%), SLE (9.4%), COPD (13.2%), and chronic renal disease (10.6%), and patients who received high-dose corticosteroid therapy (14.5%) and homologous stem-cell therapy (29.4%).

Patients with immunosuppression and other severe underlying diseases (particularly autoimmune diseases) are at higher risk of developing HZ than those with healthy immune systems at any age. These individuals also more frequently experience severe progression or complications of HZ. For this reason, evidence on the efficacy and safety of vaccination with the HZ/su inactivated vaccine was systematically reviewed for these populations (see Sect. 11.6).

4 Herpes zoster subunit inactivated vaccine

An adjuvanted HZ/su inactivated vaccine (Shingrix®, manufactured by GSK, Belgium) was approved for use in Europe on 21 March 2018 by the European Medicines Agency [7]; the vaccine became available in Germany in May 2018. This immunogenic vaccine contains recombinant surface glycoprotein E (50 µg) of VZV. The HZ/su inactivated vaccine also contains the adjuvants $AS01_B$, consisting of monophosphoryl lipid A (MPL) from *Salmonella minnesota* and *Quillaja saponaria* Molina fraction 21 (QS-21), a surface-active substance from the South American soap bark tree.

The adjuvant contains elements that enhance the $CD4^+$ T cell and humoral immune response [8]. Thus, the vaccine can trigger a strong, cell-mediated immune response in individuals whose adaptive immune system is impaired, e. g., owing to immunosenescence or for other reasons of immunosuppression. The same adjuvant was used for the first time in a malaria candidate vaccine for children. There is no experience in using this adjuvant outside of clinical trials.

One dose (0.5 mL) of the reconstituted HZ/su inactivated vaccine (powder and solvent for producing a suspension for injection) contains 50 µg VZV gE antigen, 50 µg MPL, and 50 µg QS-21. Additional ingredients in the vaccine are as follows. The powder (gE antigen) contains saccharose, polysorbate 80, sodium dihydrogen phosphate dihydrate, and dipotassium phosphate; the suspension ($AS01_B$ adjuvant system) contains dioleoylphosphatidylcholine, cholesterol, sodium chloride, disodium phosphate (anhydrous), potassium dihydrogenphosphate, and water for injection purposes. The vaccine does not contain any thimerosal or other preservatives. The HZ/su inactivated vaccine is approved for the prevention of HZ and HZ-attributable PHN in adults 50 years of age and older. The vaccination series consists of two vaccinations administered i. m. at least 2 months apart. The time frame for administration of the second dose can be extended up to 6 months after the first vaccine dose. The need for and optimal time frame of vaccination boosters after basic immunization is completed is not yet known. The safety and efficacy of the vaccine in children and adolescents is not yet known. Data are available on simultaneous administration with other vaccines, addressed in Sect. 10.2. Vaccination is contraindicated in cases of hypersensitivity to any of the ingredients in the vaccine. No data are available on the administration of the HZ/su inactivated vaccine to pregnant women. In several studies with patients receiving immunosuppressive therapy or patients with immunodeficiency disease, the vaccine has been demonstrated to be immunogenic and well tolerated [9].

5 Vaccination aims

The primary aims of vaccination with the adjuvanted HZ/su subunit vaccine are a reduction in the frequency of HZ and prevention of complications and HZ sequelae, such as PHN, in adults age 60

Table 1 Hierarchy of patient-relevant endpoints for the evaluation of efficacy and safety of the herpes zoster subunit inactivated vaccine

Type of endpoint	Population	Intervention	Comparator	Endpoints (outcomes)	Assessment of the significance of endpoints for a decision[a]
Efficacy	Adults ≥ 50 years[b]	Vaccination with HZ/su inactivated vaccine	No vaccination; Placebo vaccination; Other vaccination	Herpes zoster (HZ)	9
				Postherpetic neuralgia (PHN)	8
				Other complications (including death)	7
				Hospitalization	7
Safety	Adults ≥ 50 years[b]	Vaccination with HZ/su inactivated vaccine	No vaccination; Placebo vaccination; Other vaccination	Local reactions, not severe	3
				Severe local reactions	7
				Systemic reactions, not severe	5
				Severe systemic reactions	8

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

years and over. The longest possible protection for vaccinated individuals should be achieved.

The aim of indication-based vaccination is a reduction in the frequency of HZ and prevention of complications and HZ sequelae in populations with an elevated risk of HZ, according to the approved age at vaccination of 50 years or over.

6 Method of searching and assessing the quality of evidence

The evidence on efficacy and safety of the HZ/su inactivated vaccine was reviewed and assessed for quality according to the STIKO SOP for the systematic development of vaccination recommendations [2]. After the STIKO formulated the primary aims of HZ vaccination, and following the methods of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group, patient-relevant endpoints of HZ vaccination were defined. The endpoints HZ, PHN, other complications (including death), and hospitalization were selected for vaccine efficacy. The endpoints for vaccine safety were non-severe local reactions, severe local reactions, non-severe systemic reactions, and severe systemic reactions. All endpoints 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) in the decision on a vaccination recommendation by working group members (**Table 1**).

To identify clinical studies on vaccine safety and efficacy, systematic literature research following the requirements set forth in the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) was conducted using the following databases and taking patient-relevant endpoints into account: MEDLINE; EMBASE, BIOSIS Previews, SciSearch, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, GLOBAL Health [10]. The complete search strategies, flowcharts, and inclusion and exclusion criteria are provided in the appendix (last search date: 4 November 2017). Additionally, 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 (AS, JK). 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 was evaluated. Discrepancies between the two investigators were discussed until consensus was reached. The Cochrane risk of bias tool was used to assess the risk of bias in randomized controlled trials (RCTs) [11].

We entered the extracted data on patient-relevant endpoints from the included studies into RevMan (version 5.2) review management software, and RRs and corresponding 95% CIs of the vaccine group compared with the placebo group were calculated for the respective endpoints. If more than one study was available, a meta-analysis was conducted and the pooled estimates determined. If heterogeneity was present (assessed using the I^2 statistic), a random-effects model was used; otherwise, the data were summarized using a fixed-effects model. Using the pooled RR, the formula $((1 - RR) \cdot 100)$ was applied to calculate the vaccine efficacy or effectiveness or the risk of adverse side effects of vaccination.

To compile the GRADE evidence profile, pooled data from the endpoints defined as "critical" and "important" were entered into the GRADE profiler (version 3.6), and the quality of evidence in all included studies were assessed for each endpoint, according to the following aspects: study design, heterogeneity and precision, indirect evidence, effect size, and publication bias. Assessment of the overall quality of evidence across all endpoints was conducted using the lowest quality of evidence in those endpoints defined as "critical" [12, 13].

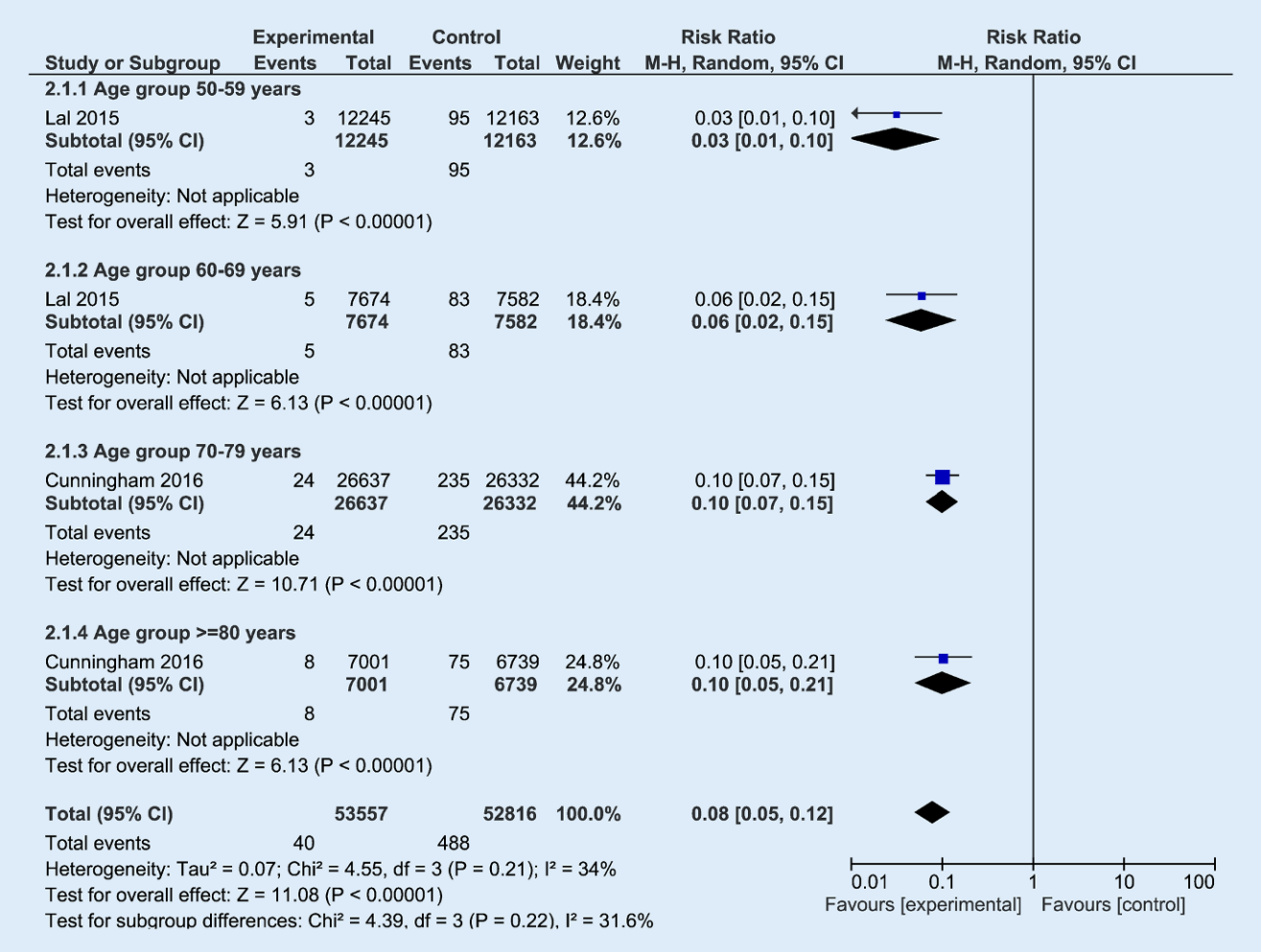

Fig. 2 ▲ Efficacy of HZ/su inactivated vaccine in preventing HZ in various age groups (≥50–59 years, ≥60–69 years, ≥70–79 years, ≥80 years); information from the cumulative follow-up periods (total) in person-years [14, 15]

7 Vaccine efficacy and period of protection

Vaccine efficacy (VE) is defined as the ability of a vaccine to prevent the incidence of a disease (e. g., HZ) or disease-related endpoints (such as PHN) in clinical studies under optimal and controlled conditions. These conditions are normally met in RCTs. Two RCTs were included in the systematic review on efficacy of the HZ/su inactivated vaccine; these are presented in greater detail below [14, 15]. The included RCTs had a low risk of bias.

7.1 Zoster efficacy study in persons ≥ 50 years (ZOE-50)

The ZOE-50 study (ClinicalTrials.gov, NCT01165177) was a double blind, placebo-controlled multicenter study to verify efficacy of the HZ/su inactivated vaccine in protecting adults age 50 years and above against HZ [15]. The study was conducted in 18 countries in Europe, North America, Latin America, and Asia/Australia. Participants age 50 years and older were recruited at a ratio of 1:1 for the vaccine and placebo arms. The following exclusion criteria were applied: a medical history of HZ, previous vaccination against VZV or HZ, immunosuppression owing to a disease (e. g., malignoma or HIV infection) or immunosuppressive therapy, allergy to one of the components of the vaccine, severe existing underlying disease with a survival time of <4 years, simultaneous participation in another clinical trial, administration of another study drug (medicinal product or vaccine) within 30 days before study initiation, administration of immunoglobulins or blood products within 90 days before study initiation, other planned vaccinations within 30 days before study initiation, and acute illness or fever at the time of recruitment. Female participants were excluded if they were pregnant or nursing or planning to become pregnant.

Each study participant received two doses of 0.5 mL HZ/su inactivated vaccine or placebo (0.9% saline solution) injected i. m. with an interval of 2 months. Because the solutions differed in appearance, the injection solution was prepared and administered by research assistants who were not involved in the assessment of the study results in any way. Study participants were monitored for a period of at least 30 months after receiving the second vaccine dose via monthly contacts and annual visits. The primary aim of the study was to investigate VE in protecting against

Table 2 Efficacy of the HZ/su inactivated vaccine against HZ and PHN in the ZOE-50 and ZOE-70 studies and in the pooled cohort, according to age groups (ITT and modified analysis) [14, 15]

Prevention of HZ (*n*)							
Age group, years	**Vaccine group**	**HZ cases**	**HZ incidence cases/1000 PY**	**Placebo arm**	**HZ cases**	**HZ incidence cases/1000 PY**	**HZ VE (95% CI), %**
ZOE-50 (ITT)							
50–59	3645	3	0.2	3644	95	7.8	96.9 (90.6–99.4)
60–69	2244	5	0.7	2246	83	10.9	94.1 (85.6–98.1)
≥70	1809	1	0.2	1823	57	10.2	98.3 (89.9–100)
Overall	7698	9	0.4	7713	235	9.3	96.2 (92.7–98.3)
ZOE-50 (modified analysis)							
50–59	3492	3	0.3	3525	87	7.8	96.6 (89.6–99.3)
60–69	2141	2	0.3	2166	75	10.8	97.4 (90.1–99.7)
≥70	1711	1	0.2	1724	48	9.4	97.9 (87.9–100.0)
Overall	7344	6	0.3	7415	210	9.1	97.2 (93.7–99.0)
ZOE-70 (ITT)							
70–79	5414	22	1.0	5420	181	8.7	88.0 (81.3–92.7)
≥80	1536	8	1.4	1530	59	10.9	86.9 (72.4–94.6)
Overall	6950	30	1.1	6950	240	9.1	87.7 (82.0–92.0)
ZOE-70 (modified analysis)							
70–79	5114	17	0.9	5189	169	8.8	90.0 (83.5–94.4)
≥80	1427	6	1.2	1433	54	11.0	89.1 (74.6–96.2)
Overall	6541	23	0.9	6622	223	9.2	89.8 (84.2–93.7)
Pooled analysis ZOE-50 + ZOE-70 (ITT)							
70–79	6837	24	0.9	6856	235	8.9	89.9 (84.6–93.7)
≥80	1921	8	1.1	1917	75	11.1	89.7 (78.6–95.8)
Overall	8758	32	1.0	8773	310	9.4	89.9 (85.4–93.2)
Pooled analysis ZOE-50 + ZOE-70 (modified analysis)							
70–79	6468	19	0.8	6554	216	8.9	91.3 (86.0–94.4)
≥80	1782	6	1.0	1792	68	11.1	91.4 (80.2–97.0)
Overall	8250	25	0.8	8346	284	9.3	91.3 (86.8–94.5)

Table continues at next page

HZ from the age of 50 years. The secondary aim was to show evidence of efficacy in the defined age groups. VE was identified as a reduction in the risk of developing HZ. Efflorescence suspected as attributable to HZ occurring after the second vaccine dose was examined by the study investigators. In each suspected case, swabs were taken from three lesions to verify the HZ diagnosis via PCR. The lower detection limit was 10 VZV DNA copies. If no examination material was available for laboratory diagnosis, HZ diagnosis was made by a five-member team of experts based on the clinical picture, photographs of the lesions, and disease progression.

Between August 2010 and July 2011, a total 16,160 study participants were recruited and stratified according to region and age (age groups: 50–59, 60–69, and ≥70 years). A total 749 participants were excluded from the study analysis, mostly owing to good clinical practice guideline violations. The remaining 15,411 study participants were included in the intention-to-treat (ITT) analysis, 7698 in the vaccine arm, and 7713 in the placebo arm. The percentage in each age group was identical in both arms: 47% of participants were 50–59 years old, 29% were age 60–69 years, and 23% were age 70 years and over. The mean age at study initiation was 62.3 years. Demographic characteristics were congruent between the two groups. Most participants were from Europe (51.2%), white (71.8%), and female (61.2%). The mean follow-up period was 3.2 years.

In the ITT analysis, VE in protecting against HZ from the age of 50 years was 96.2% (95% CI 93.0–98.0%). HZ incidence in the vaccine arm was 0.4 cases/1000 PY, vastly lower than in the placebo arm (09.3/1000 PY). The point estimates of age-specific VE in protecting against HZ were at a similarly high level, but the confidence intervals were broader. This is especially true for the two highest age groups, as the number of par-

Table 2 (continued)

Prevention of PHN (*n*)							
Age group, years	**Vaccine group**	**PHN cases**	**PHN incidence cases/1000 PY**	**Placebo arm**	**PHN cases**	**PHN incidence cases/1000 PY**	**PHN VE (95% CI), %**
Pooled analysis ZOE-50 + ZOE-70 (ITT)							
50–59	3644	0	0.0	3642	9	0.6	100 (49.1–100)
60–69	2243	0	0.0	2245	3	0.3	100 (–145.2–100)
70–79	6837	4	0.1	6856	31	1.2	87.0 (63.3–96.7)
≥80	1921	4	0.6	1917	7	1.0	43.0 (–124.3–87.8)
≥50 overall	14645	8	0.1	14660	50	0.9	83.9 (65.8–93.5)
≥70 overall	8758	8	0.2	8773	38	1.1	78.9 (54.0–91.5)
Pooled analysis ZOE-50 + ZOE-70 (modified)							
50–59	3491	0	0.0	3523	8	0.6	100 (40.8–100)
60–69	2140	0	0.0	2166	2	0.2	100 (–442.9–100)
70–79	6468	2	0.1	6554	29	1.2	93.0 (72.4–99.2)
≥80	1782	2	0.3	1792	7	1.1	71.6 (–51.6–97.1)
≥50 overall	13881	4	0.1	14035	46	0.9	91.2 (75.9–97.7)
≥70 overall	8250	4	0.1	8346	36	1.2	88.8 (68.7–97.1)

HZ herpes zoster, *PHN* postherpetic neuralgia, *PY* person-years, *VE* vaccine efficacy, *ITT* intention-to-treat, *CI* confidence interval. *ITT* all participants successfully recruited and included according to protocol, and received at least one vaccination. *Modified analysis* exclusion of participants who either did not receive a second vaccine dose or who received the wrong vaccine or a confirmed HZ diagnosis less than 30 days after the second vaccine dose.

ticipants was markedly lower (**Fig. 2**; **Table 2**).

In modified analyses, those study participants from the ITT group who did not receive a second vaccine dose or who received the wrong vaccine or an HZ diagnosis fewer than 30 days after the second vaccine were excluded. In these modified investigation cohorts, VE overall and for each age group was slightly higher than the levels in the ITT group (**Table 2**).

7.2 Zoster efficacy study in persons ≥ 70 years (ZOE-70)

The ZOE-70 study (ClinicalTrials.gov, NCT01165229) was initiated to examine the efficacy and safety of the HZ/su inactivated vaccine in protecting against HZ and PHN in adults age 70 years and older, and to conduct a pooled analysis with the results of the ZOE-50 study [14]. The ZOE-70 study was also a double-blind, placebo-controlled study conducted at the same study centers as the ZOE-50 trial and with a study design identical to that of ZOE-50 with regard to inclusion and exclusion criteria, randomization, blinding, stratification according to age and region, and vaccination regimen.

The primary aim of the ZOE-70 study was to investigate VE of the HZ/su inactivated vaccine in protecting against HZ in people age ≥ 70 years. The pooled analysis included study participants age ≥ 70 years from both studies (ZOE-50 + ZOE-70) and had the primary study aim to examine VE against both HZ and PHN in this age group. The secondary study aim of the pooled analysis was to determine VE against PHN in adults age ≥ 50 years and to evaluate reactogenicity and safety.

The criteria for suspicion and diagnosis of HZ were identical to those in the ZOE-50 study. To monitor the occurrence of PHN, all study participants with HZ were asked to report to the study center regularly for examination. In addition, they were asked to keep a pain diary every day for 28 days and weekly thereafter, in which they documented their pain score, from 0 (no pain) to 10 (severest pain). Entries were to be completed for at least 90 days after the occurrence of HZ efflorescence and until the patient was pain free for 4 weeks. PHN was defined as pain with a score ≥ 3 that continued or developed more than 90 days after the occurrence of rash.

A total of 14,816 study participants were recruited between August 2010 and July 2011. A total of 916 participants were excluded from the study analysis, mostly owing to good clinical practice guideline violations. The remaining 13,900 study participants were included in the (ITT) analysis, 6950 each in the vaccine and placebo arm. The demographic attributes between the vaccine and placebo arms of the ZOE-70 study corresponded roughly with one another. Most participants were from Europe (55%), white (76.9%), and female (54.9%). The mean age of participants in the ZOE-70 study at study initiation was 75.6 years (range: 62–96 years). In total, 3066 participants were ≥80 years old (22.1%) and 76 participants were ≥90 years old (0.5%). The mean follow-up period was 3.7 years.

In the ITT analysis of the ZOE-70 study, VE in protecting against HZ was 87.7% (95% CI 82.0%–92.0%). HZ incidence in the vaccine arm was 1.1 cases/1000 PY, vastly lower than in the placebo arm (09.1/1000 PY). VE in protecting against HZ was nearly the same in the different age groups (**Table 2**). Here as well, VE was somewhat higher in the modified cohorts than in the ITT group (**Table 2**).

In total, 17,531 participants from the ZOE-50 and ZOE-70 studies were includ-

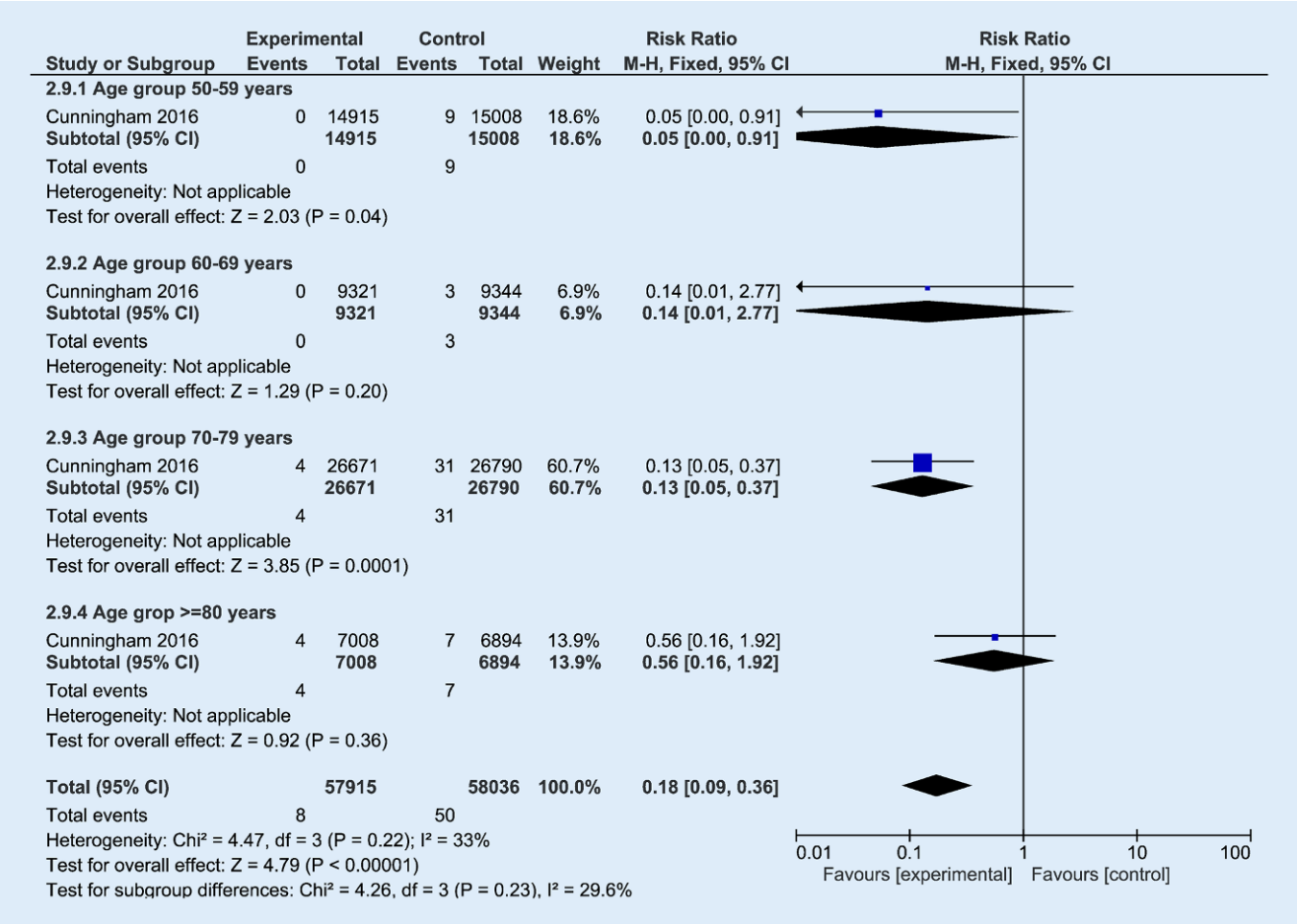

Fig. 3 ▲ Efficacy of HZ/su inactivated vaccine in preventing postherpetic neuralgia in various age groups (≥50–59, ≥60–69, ≥70–79, and ≥80 years); data from the cumulative follow-up periods (total) in person-years [14]

ed in the pooled analysis of participants age ≥70 years. In this population as well, the demographic attributes were similar in the comparison groups.

In the pooled ITT analysis from the ZOE-50 and ZOE-70 studies, VE in protecting against HZ for adults age ≥70 years was 89.9% (95% CI 85.4–93.2%); there was no difference between the age groups. In the modified analysis, VE for adults age ≥70 years was over 91.3% (95% CI 86.8–94.5%) (**Table 2**).

Over a period of 3.7 years after vaccination, VE in protecting against PHN in the pooled ITT analysis was 83.9% (95% CI 65.8–93.5%) for individuals age ≥50 years and 78.9% (95% CI 54.0–91.5%) for those age ≥70 years. Because of the low number of PHN cases observed in the individual age groups, the confidence intervals for the point estimates in the results of VE were very wide and/or included 1 (**Fig. 3**; **Table 2**).

7.3 Results of the meta-analysis of data from the ZOE-50 and ZOE-70 studies on the efficacy of the HZ/su inactivated vaccine in protecting from HZ and PHN

Data from the ITT groups were analyzed in the meta-analysis of age-specific efficacy against HZ of the HZ/su vaccine (**Fig. 2**). For the age groups ≥70 years, pooled results of the ZOE-50 and ZOE-70 studies were used for the analysis. The meta-analysis showed a VE across all age groups of 92.0% (95% CI 89.0–94.0%). The point estimates of VE declined somewhat with increasing age, from 97% in participants age 50–59 years to 94% in those age 60–69 years and 90% in the age groups 70 years and older; the confidence intervals around the point estimates were overlapped.

Based on the meta-analysis, the efficacy against PHN was 82.0% (95% CI 64.0–91.0%) across all age groups. Considering the efficacy in the various age groups, significant vaccine protection was seen only in those 70–79 years old, with 87.0% (95% CI 63.0–95.0%) (**Fig. 3**). In the younger age groups and in those over 80 years old, the study populations were too small for this rare event. No clear assessment was possible because of the low number of cases observed. The confidence intervals were wide in all age groups, and some included 1.

7.4 Duration of protection from HZ provided by the HZ/su inactivated vaccine (results of the pooled analysis of the ZOE-50 and ZOE-70 studies)

Because the incidence of HZ increases with age, long-term protection provided by the vaccine is especially important. For the duration of vaccine protection against HZ, only data for adults age ≥70 years

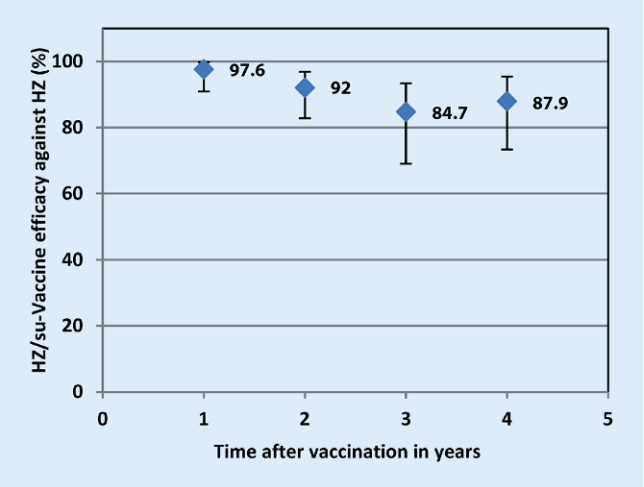

Fig. 4 ◀ Duration of efficacy of the HZ/su inactivated vaccine in preventing HZ in adults ≥70 years old (ZOE50 + ZOE70) [14]

from the pooled analysis of the ZOE-50 and ZOE-70 studies over a time frame of 4 years were available [14]. The data were from the modified analysis, i. e., participants who did not receive the second vaccine dose or who developed HZ within 30 days after the second vaccine dose were excluded. Based on the pooled analysis, VE in protecting against HZ dropped after administration of the second vaccine dose, from 97.6% (95% CI 90.9–99.8%) in the first year to <90% from the third year after vaccination (**Fig. 4**). The data from years 3 and 4 after vaccination suggest that VE reaches a constant plateau as time progresses. A clear interpretation based on clinical data is not possible at this time. No data have been published on the duration of action of the HZ/su inactivated vaccine in protecting against PHN.

7.5 Long-term immunogenicity of the HZ/su inactivated vaccine

Because the duration of vaccine efficacy could be examined for only a short period of time in the RCTs, data from a single-arm phase II multicenter study were referenced in addition to the systematic review. In that study, the immune response of participants age ≥60 years who had received two HZ/su vaccinations at a 2-month interval was examined [16, 17]. A total of 129 participants from Czech Republic, Germany, and the Netherlands were enrolled. The cellular and humoral immune responses induced by vaccination were examined annually over a period of 6 years. The frequency of gE-specific CD4⁺ T cells with at least two expressed activation markers and the geometric mean values of the serum concentration (GMC) of anti-gE antibodies (mIU/mL) were determined using an ELISA developed by the vaccine manufacturer (cut-off: 18 mIU/mL). The subgroup of participants from Czech Republic ($n = 68$) was followed up for a period of 9 years [18]. The median frequency of gE-specific CD4⁺ T cells was highest 3 months after the second vaccine dose (1800/10^6 cells). This proportion dropped to 415/10^6 cells during the 9 years after vaccination, but at that point it was still more than three times higher than pre-vaccination levels (119/10^6) (**Fig. 5**). The data indicate that the duration of vaccine-induced protection may be even longer than that confirmed to date in RCTs.

The highest mean concentration of anti-gE antibodies was also measured 3 months after administration of the second vaccine dose (43,100 mIU/mL), which declined as time progressed. However, in year 9 after the second vaccine dose, it was still seven times higher than pre-vaccination levels (**Fig. 6**). From the year 4 after completing the vaccination series, the frequency of gE-specific CD4⁺ T cells and the concentration of anti-gE antibodies remained at constant high levels. This observation fit with the VE findings according to clinical endpoints, which remained at a steady level 3 and 4 years after vaccination.

7.6 Conclusions on the efficacy and effectiveness of the HZ vaccination

The HZ/su inactivated vaccine can effectively prevent HZ in people >50 years; efficacy is 92% across all age groups. Protection against HZ falls slightly with increasing age but remains over 90% in adults 70 years and over. Thus, the HZ/su inactivated vaccine confers a high level of protection at all ages and also in older people with the highest risk of HZ. This is an advantage compared with the live attenuated vaccine, which has a markedly lower VE in older age groups. Protection drops from 98% in the first year to 85% in the third year after vaccination and remains at 88% in the fourth year after vaccination. Further conclusions on the duration of protection for the clinical endpoint HZ are not yet possible. Based on immunological data available for a period of 9 years after vaccination, the immune response remains at a level that is multiple times higher than before vaccination. This might indicate a prolonged duration of vaccine-induced protection. The HZ/su inactivated vaccine can prevent the occurrence of PHN. This effect is derived from the effective prevention of HZ as a precondition for the prevention of its sequelae. Because of the rarity of this event, significant results on protection against PHN are available only for the entire cohort, and age-related results are available only for the largest cohort recruited, participants age 70–79 years. Overall, VE is 82%, and it is 87% among 70- to 79-year-olds.

8 Vaccine reactogenicity and safety

8.1 Approach and studies considered

The STIKO working group assessed severe adverse drug reactions (8 points) and severe pain at the point of injection (7 points) as essential endpoints. Fever as a systemic reaction was classified as an important endpoint (5 points); swelling and other local reactions were considered less important endpoints (3 points) (**Table 1**).

Results from three RCTs that recorded the abovementioned endpoints were

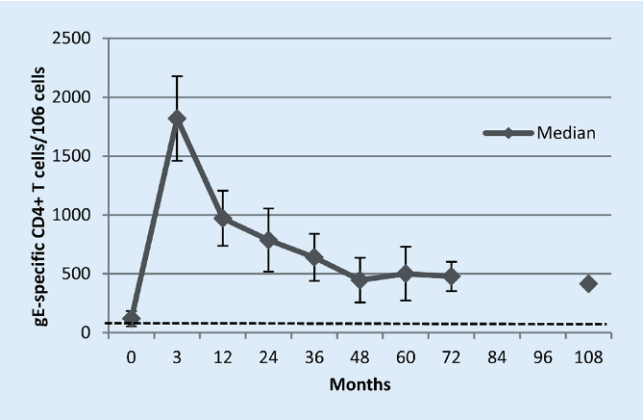

Fig. 5 ◀ Median and 95% confidence intervals of the frequency of VZV glycoprotein E (gE)-specific CD4+ T cells over 108 months [16–18]

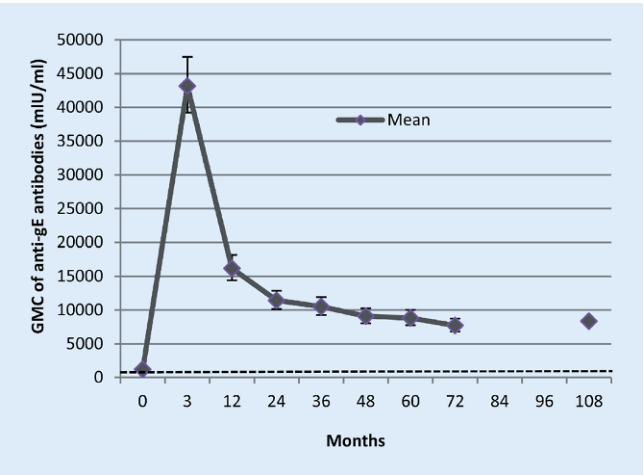

Fig. 6 ◀ Geometric mean values of serum concentration (GMC) of anti-gE antibodies (mIU/mL) with 95% confidence intervals over 108 months [16–18]

included in the safety evaluation. These RCTs were the ZOE-50 [15] and ZOE-70 studies [14], described in subsections 7.1 and 7.2 above, and results from two study arms of a phase II study [19]. The included RCTs had a low risk of bias. Details on the studies and results of the aggregate evaluation are presented hereinafter.

One subgroup of participants from the ZOE-50 study was asked to document local reactions at the site of injection (pain, redness, and swelling) and systemic reactions (fatigue, fever, headache, and myalgia) in a diary for 7 days [15]. This subgroup included all participants age ≥70 years and selected randomized participants from younger age groups. Redness and swelling at the injection site were assessed using diameter on a scale from 0 (<20 mm) to 3 (>100 mm). Fever, preferably measured orally, was also assessed using a 4-point scale from 0 (<37.5 °C) to 3 (>39.0 °C). For other side effects intensity was classified on a scale from 0 (none) to 3 (common everyday activities are impossible). Other adverse side effects were registered as spontaneous reports for a period of 30 days after every vaccine dose. Other severe side effects were measured for a period of at least 12 months after administration of the second dose. All health complaints with any link to the study, all deaths, and all potentially immune-mediated discomfort were evaluated for the entire study duration of 3.5 years. A total of 8926 participants were included in the subgroup for safety evaluation of the HZ/su inactivated vaccine (4460 from the vaccine and 4466 from the placebo arms).

In the ZOE-70 study, a random sample group of 1025 participants (7.4% of the total study population; 512 from the vaccine arm and 513 from the placebo arm) was recruited from among the study participants in the safety evaluation [14]. The evaluation procedure was identical to that of the ZOE-50 study; the study duration was 4 years.

In a multi-arm, phase II multicenter study, the safety of the HZ/su inactivated vaccine in various doses was tested among participants age ≥50 years [19]. The study included a total of 410 participants from Czech Republic, Spain, and the United States (US). Data from the placebo arm ($n = 38$) and the arm with a later vaccine concentration ($n = 150$) were extracted. The safety evaluation was identical to that of the ZOE-50 and ZOE-70 studies. Every major event over a time frame of 14 months was evaluated.

8.2 Local reactions after the HZ/su inactivated vaccine

In clinical studies of the safety of the HZ/su inactivated vaccine, participants in the vaccine arm reported local reactions at the site of injection significantly more frequently than participants in the placebo arm (81% vs. 12%). Pain was the most frequent local reaction. Local reactions of the highest intensity (grade 3) occurred in 9.4% versus 0.3% of participants (**Fig. 7**). The frequency of vaccine reactions was not significantly increased after administration of the second vaccine dose [14]. Vaccine reactions were independent of age; 53% of participants age ≥80 years and 55% of those age 70–79 years reported vaccine reactions [14]. All reactions were temporary and lasted a median of 2–3 days.

8.3 Systemic reactions after the HZ/su inactivated vaccine

Systemic side effects associated with the vaccine were also more frequent in the intervention arm (65%) than in the placebo arm (29%). Systemic reactions of the highest intensity (grade 3) occurred in 10.6% of participants in the vaccine arm and 2.4% of those in the placebo arm (**Fig. 8**). The frequency of the systemic reactions fever, fatigue, myalgia, and headache were described in the ZOE-70 study, each with regard to intensity and for grade 3 (see the appendix).

8.4 Severe adverse events caused by the vaccine (SAE)

In the three clinical trials examining the safety of the HZ/su inactivated vaccine, 24 of 29,499 participants experienced SAEs in connection with the vaccine, of which

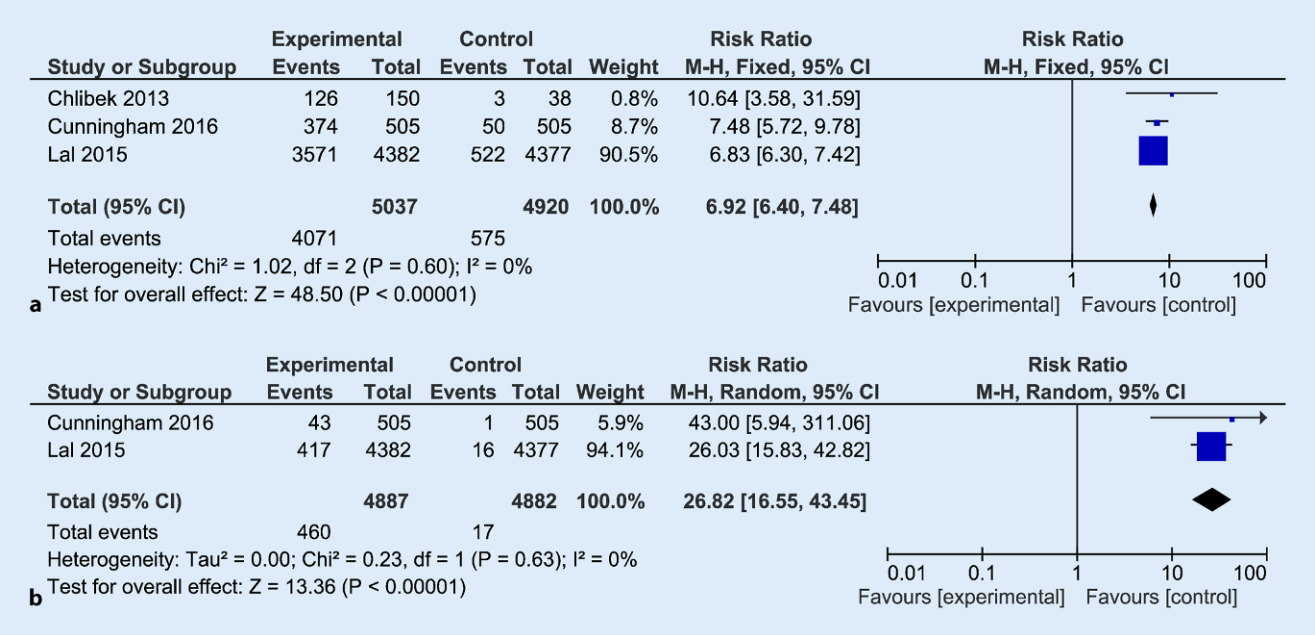

Fig. 7 ▲ Forest plots of relative risks (RR) of local reactions to the HZ/su inactivated vaccine (all degrees and grade 3). **a** Local reactions at the injection site (all degrees), **b** Local reactions at the injection site (grade 3)

13 occurred in the vaccine arm and 11 in the placebo arm (**Fig. 8**). The following syndromes were recorded as SAEs in the vaccine arm: hypotension with syncope, lymphadenitis, myocardial infarction, ulcerative colitis, pancreatitis, erythema and pain at the injection site, shivering, fever, allergic granulomatous vasculitis, bacterial joint inflammation, erysipelas, HZ oticus, eczema, neutropenic sepsis, and acute myeloid leukemia (for details, see appendix).

SAEs that were considered by the responsible reviewers to be related to intervention, potentially immune-mediated diseases, and deaths occurred with comparable frequency in the study arms (vaccine and placebo arm) of the ZOE-50 and ZOE-70 studies (**Fig. 9**).

The reviewers initially classified one death in the HZ/su arm of the ZOE-70 study as associated with the vaccine. This case occurred in a 90-year-old participant with preexisting thrombocytopenia who was diagnosed with acute myeloid leukemia (AML) 75 days after the first dose of HZ/su and died from neutropenic sepsis 97 days after vaccination, without having received the second dose. The CHMP (Committee for Medicinal Products for Human Use) considered a relationship between vaccination and AML to be highly unlikely as the neutropenic sepsis and subsequent events were considered most likely side effects of ongoing therapy with azacitidine [20].

8.5 Conclusions on the safety of the HZ/su inactivated vaccine

The HZ/su inactivated vaccine is exceptionally reactogenic. Local reactions and grade 3 systemic reactions occurred in roughly every 10th vaccinated person. However, the vaccine reactions do not last long (1 to 2 days for reactions of the highest degree). In marketing authorization studies, there were no warnings about severe side effects or potentially immune-mediated diseases. The frequency of SAEs was the same in the vaccine group and in the placebo group. SAEs considered to be vaccine related mainly included health conditions or diseases that are generally not rare in the investigated age groups. One fatal case was initially regarded as vaccine related, but the CHMP deemed a causal relationship to be unlikely.

9 Evidence profile of the efficacy and safety of the HZ/su inactivated vaccine

To assess the quality of available evidence for the efficacy and safety of the HZ/su inactivated vaccine, an evidence profile was drawn up of pre-defined PICO questions using GRADEprofiler software. Relevant effect estimates observed for each endpoint and the quality of evidence for these estimators have been compiled in this profile (**Table 3**).

The quality of evidence for efficacy of the HZ/su inactivated vaccine in preventing HZ is classified as high; the quality of evidence for efficacy against PHN is classified as low, and the quality of evidence for the safety of the vaccine is estimated as moderate.

10 Implementing the HZ/su vaccination

10.1 Dose, type, and duration of administration

The HZ/su vaccine is approved for use in adults age 50 years and older. The vaccination scheme is two i. m. vaccinations at least 2 months apart. In addition to the vaccination interval of 2 months, immunogenicity studies have also examined vaccination intervals of 6 and 12 months and determined the vaccine response rates 1 month after administering the second dose in each case [21]. It was shown that the immune response to vaccination on a

Table 3 GRADE evidence profile on the quality of systematic reviews on the efficacy and safety of the HZ/su inactivated 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	Adjuvanted recombinant VZV subunit zoster vaccine	Placebo	Relative risk (RR) (95% CI)	Absolute		
Herpes zoster, age: 50–59 years (ZOE 50 + ZOE 70) (ITT-analysis) (mean follow-up 3.2 years)												
1[a]	Randomized trial	No serious risk of bias[b]	No serious inconsistency	No serious indirectness	No serious imprecision	None	3/12,245(0.02%)	95/12,163 (0.78%)	RR 0.03 (0.01 to 0.1)	8 fewer per 1000 (from 7 fewer to 8 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0.6%[c]		6 fewer per 1000 (from 5 fewer to 6 fewer)		
								0.9%[c]		9 fewer per 1000 (from 8 fewer to 9 fewer)		
Herpes zoster, age: 60–69 years (ZOE 50 + ZOE 70) (ITT-analysis) (mean follow-up 3.2 years)												
1[a]	Randomized trial	No serious risk of bias[b]	No serious inconsistency	No serious indirectness	No serious imprecision	None	5/7674 (0.07%)	83/7582 (1.1%)	RR 0.06 (0.02 to 0.15)	10 fewer per 1000 (from 9 fewer to 11 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0.92%[c]		9 fewer per 1000 (from 8 fewer to 9 fewer)		
								1.2%[c]		11 fewer per 1000 (from 10 fewer to 12 fewer)		
Herpes zoster, age: 70–79 years (ZOE 50 + ZOE 70) (ITT-analysis) (mean follow-up 3.7 years)												
1[a]	Randomized trial[d]	No serious risk of bias[b]	No serious inconsistency	No serious indirectness	No serious imprecision	None	24/26,637 (0.09%)	235/26,332 (0.89%)	RR 0.1 (0.07 to 0.15)	8 fewer per 1000 (from 8 fewer to 8 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								1.1%[c]		10 fewer per 1000 (from 9 fewer to 10 fewer)		
								1.3%[c]		12 fewer per 1000 (from 11 fewer to 12 fewer)		

Table 3 (continued)

Quality assessment							No. of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Adjuvanted recombinant VZV subunit zoster vaccine	Placebo	Relative risk (RR) (95% CI)	Absolute		
Herpes zoster, age: ≥80 years (ZOE 50 + ZOE 70) (ITT-analysis) (mean follow-up 3.7 years)												
1[a]	Randomized trial[d]	No serious risk of bias[b]	No serious inconsistency	No serious indirectness	No serious imprecision	None	8/7001 (0.11%)	75/6739 (1.1%)	RR 0.1 (0.05 to 0.21)	10 fewer per 1000 (from 9 fewer to 11 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								1.27%[c]		11 fewer per 1000 (from 10 fewer to 12 fewer)		
								1.4%[c]		13 fewer per 1000 (from 11 fewer to 13 fewer)		
Postherpetic neuralgia, age: 50–59 years (ZOE 50 + ZOE 70) (ITT-analysis) (mean follow-up 3.7 years)												
1[e]	Randomized trial	No serious risk of bias[b]	No serious inconsistency	No serious indirectness	Serious[f]	None	0/14,915 (0%)	9/15,008 (0.06%)	RR 0.05 (0 to 0.91)	1 fewer per 1000 (from 0 fewer to 1 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0.005%[g]		0 fewer per 1000 (from 0 fewer to 0 fewer)		
								0.76%[g]		1 fewer per 1000 (from 0 fewer to 1 fewer)		
Postherpetic neuralgia, age: 60–69 years (ZOE 50 + ZOE 70) (ITT-analysis) (mean follow-up 3.7 years)												
1[e]	Randomized trial[d]	No serious risk of bias[b]	No serious inconsistency	No serious indirectness	Very Serious[h]	None	0/9321 (0%)	3/9344 (0.03%)	RR 0.14 (0.01 to 2.77)	0 fewer per 1000 (from 0 fewer to 1 more)	⊕⊕OO LOW	CRITICAL
								0.003%[g]		0 fewer per 1000 (from 0 fewer to 0 more)		
								0.14%[g]		1 fewer per 1000 (from 1 fewer to 2 more)		

Table 3 (continued)

Quality assessment							No. of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Adjuvanted recombinant VZV subunit zoster vaccine	Placebo	Relative risk (RR) (95% CI)	Absolute		
Postherpetic neuralgia, age: 70–79 years (ZOE 50 + ZOE 70) (ITT-analysis) (mean follow-up 3.7 years)												
1[e]	Randomized trial[d]	No serious risk of bias[b]	No serious inconsistency	No serious indirectness	No serious imprecision	None	4/26,671 (0.01%)	31/26,790 (0.12%)	RR 0.13 (0.05 to 0.37)	1 fewer per 1000 (from 1 fewer to 1 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								0.04%[g]		0 fewer per 1000 (from 0 fewer to 0 fewer)		
								0.22%[g]		2 fewer per 1000 (from 1 fewer to 2 fewer)		
Postherpetic neuralgia, age: ≥80 years (ZOE 50 + ZOE 70) (ITT-analysis) (mean follow-up 3.7 years)												
1[e]	Randomized trial[d]	No serious risk of bias[b]	No serious inconsistency	No serious indirectness	Very Serious[h]	None	4/7008 (0.06%)	7/6894 (0.1%)	RR 0.56 (0.16 to 1.92)	0 fewer per 1000 (from 1 fewer to 1 more)	⊕⊕OO LOW	CRITICAL
								0.1%[g]		0 fewer per 1000 (from 1 fewer to 1 more)		
								0.26%[g]		1 fewer per 1000 (from 2 fewer to 2 more)		
Safety–adverse effects at injection site (follow-up 1–7 days)												
3	Randomized trial	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	4071/5037 (80.8%)	575/4920 (11.7%)	RR 6.92 (6.4 to 7.48)	692 more per 1000 (from 631 fewer to 757 more)	⊕⊕⊕⊕ HIGH	NOT IMPORTANT
								9.9%		586 more per 1000 (from 535 fewer to 642 more)		
Safety–erythema (follow-up 1–7 days)												
3	Randomized trial	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	1906/4889 (39%)	64/4920 (1.3%)	RR 29.06 (22.73 to 37.17)	365 more per 1000 (from 283 fewer to 471 more)	⊕⊕⊕⊕ HIGH	NOT IMPORTANT
								1%		281 more per 1000 (from 217 fewer to 362 more)		

Table 3 (continued)

Quality assessment							No. of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Adjuvanted recombinant VZV subunit zoster vaccine	Placebo	Relative risk (RR) (95% CI)	Absolute		
Safety–pain (follow-up 1–7 days)												
3	Randomized trial	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	3936/5037 (78.1%)	536/4920 (10.9%)	RR 7.17 (6.61 to 7.78)	672 more per 1000 (from 611 fewer to 739 more)	⊕⊕⊕⊕ HIGH	CRITICAL
								8.5%		524 more per 1000 (from 477 fewer to 576 more)		
Safety–swelling (mean follow-up 1–7 days)												
3	Randomized trial	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	1290/5037 (25.6%)	48/4920 (1%)	RR 26.14 (19.68 to 34.71)	245 more per 1000 (from 182 fewer to 329 more)	⊕⊕⊕⊕ HIGH	CRITICAL
								0.4%		101 more per 1000 (from 75 fewer to 135 more)		
Safety–vaccine-related systemic adverse effects (mean follow-up 1–7 days)												
3	Randomized trial	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	3256/5029 (64.7%)	1427/4921 (29%)	RR 2.24 (2.13 to 2.35)	360 more per 1000 (from 328 fewer to 391 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
								25.2%		312 more per 1000 (from 285 fewer to 340 more)		
Safety–swelling (follow-up 1– days)												
3	Randomized trial	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	1026/5029 (20.4%)	146/4921 (3%)	RR 6.9 (5.83 to 8.17)	175 more per 1000 (from 143 fewer to 213 more)	⊕⊕⊕⊕ HIGH	CRITICAL
								2.6%		153 more per 1000 (from 126 fewer to 186 more)		
Safety–myalgia (mean follow-up 1–7 days)												
3	Randomized trial	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	2244/5029 (44.6%)	573/4921 (11.6%)	RR 3.85 (3.54 to 4.18)	332 more per 1000 (from 296 fewer to 370 more)	⊕⊕⊕⊕ HIGH	CRITICAL
								8.1%		231 more per 1000 (from 206 fewer to 258 more)		

Table 3 (continued)

Quality assessment							No. of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Adjuvanted recombinant VZV subunit zoster vaccine	Placebo	Relative risk (RR) (95% CI)	Absolute		
Safety–headache (mean follow-up 1–7 days)												
3	Randomized trial	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	1896/5029 (37.7%)	759/4921 (15.4%)	RR 2.45 (2.27 to 2.64)	224 more per 1000 (from 196 fewer to 253 more)	⊕⊕⊕⊕ HIGH	CRITICAL
								10.9%		158 more per 1000 (from 138 fewer to 179 more)		
Safety–vaccine-related serious adverse effects (follow-up 3.5–4.0 years)												
3	Randomized trial	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[i]	None	13/11475 (0.1%)	11/11366 (0.1%)	RR 1.18 (0.53 to 2.64)	0 more per 1000 (from 0 fewer to 2 more)	⊕⊕⊕O MODERATE	CRITICAL
								0.1%		0 more per 1000 (from 0 fewer to 2 more)		
Safety–Potential immune-mediated disease (follow-up 3.5–4.0 years)												
2	Randomized trial	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[i]	None	170/14,648 (1.2%)	194/14663 (1.3%)	RR 0.88 (0.71 to 1.08)	2 fewer per 1000 (from 4 fewer to 1 more)	⊕⊕⊕O MODERATE	CRITICAL
								1.3%		2 fewer per 1000 (from 4 fewer to 1 more)		

ITT intention-to-treat, *VZV* varicella zoster virus

[a]Participants were instructed in the signs and symptoms of herpes zoster (HZ) and to contact their study site immediately if any developed. Starting 1 month after the second dose, participants were followed for at least 30 months via monthly contacts and annual visits

[b]Allocation concealment unclear, but age and sex distribution bias seem unlikely causes

[c]Average annual HZ incidence for Germany (minimum and maximum) from publications of Ultsch and Hillebrand

[d]Pooled analysis of data from the ZOE-50 and ZOE-70 studies for the age groups 70–79 years and ≥80 years are considered for vaccine efficacy (VE)

[e]Postherpetic neuralgia (PHN) was defined as worst pain score of 3 and higher on a scale of 0 to 10 for pain that persisted or developed more than 90 days after the onset of HZ

[f]Number of events in control and placebo groups too small

[g]Average annual PHN incidence for Germany (minimum and maximum) from Ultsch et al.

[h]Number of events in control and placebo groups too small and 95% confidence intervals (CIs) extremely wide

[i]Imprecision for this crucial endpoint is inacceptable

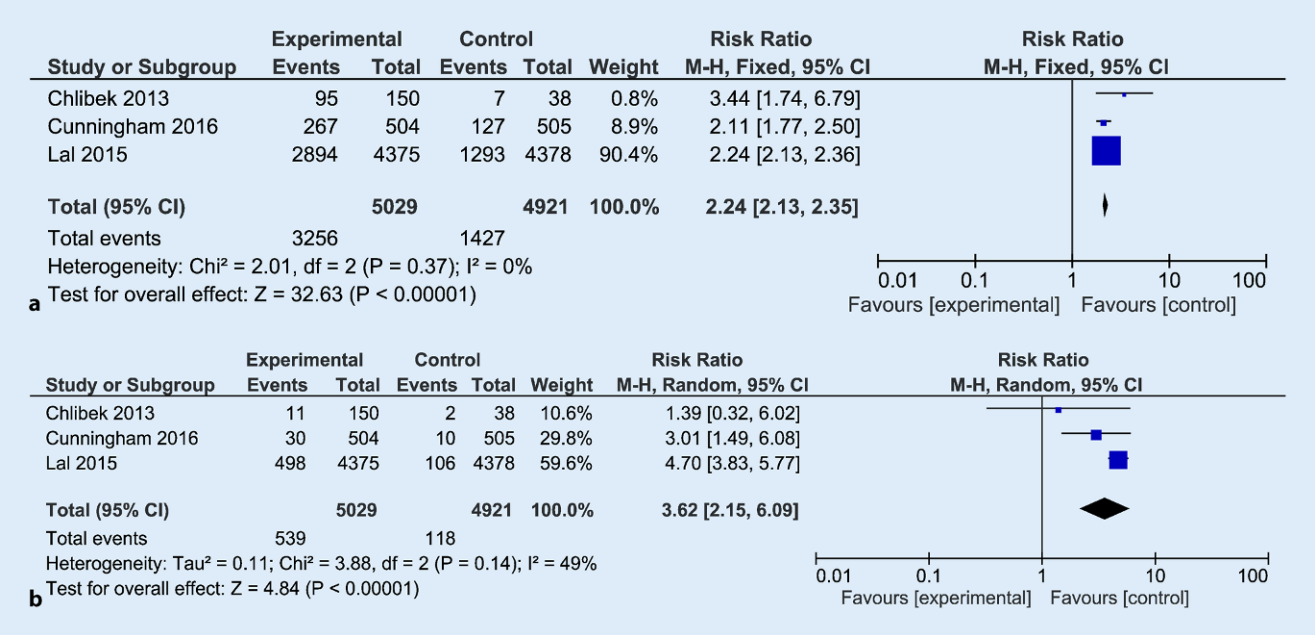

Fig. 8 ▲ Forest plots of the relative risks (RR) of adverse systemic side effects to the HZ/su inactivated vaccine (all degrees and grade 3). **a** Systemic adverse side effects (all degrees), **b** Systemic adverse side effects (grade 3)

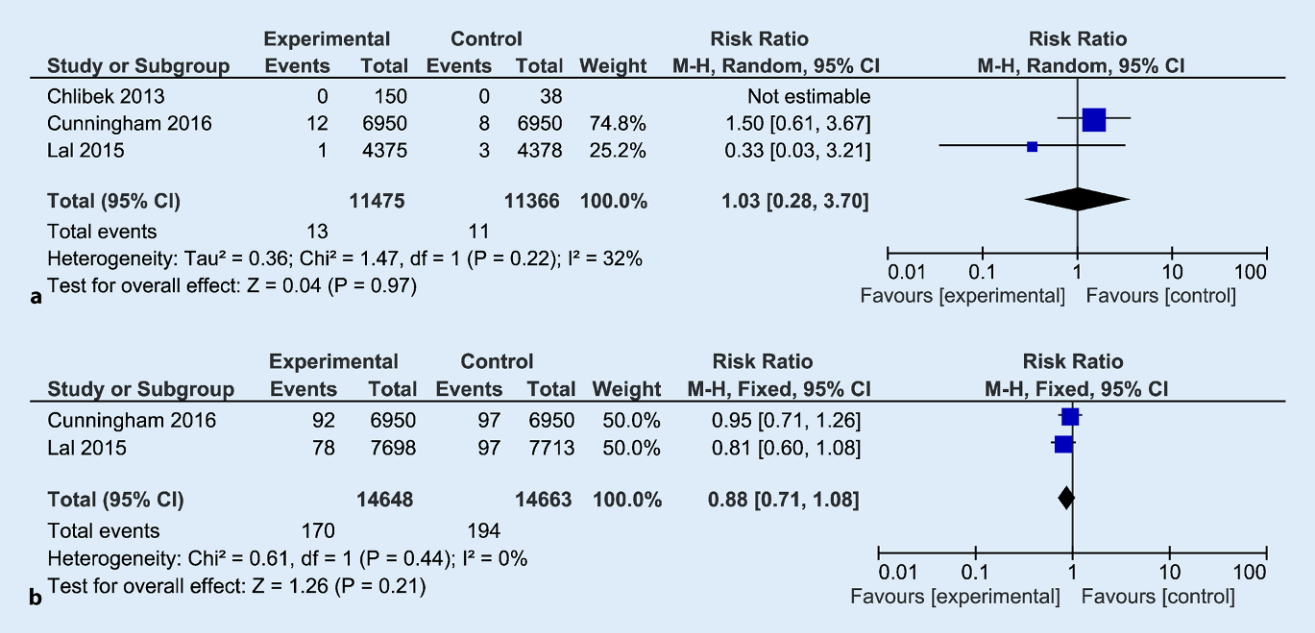

Fig. 9 ▲ Forest plots of the relative risks (RR) for severe adverse effects of the HZ/su inactivated vaccine and possible immune-mediated diseases. **a** Possible vaccination-related severe adverse effects, **b** Possible immune-mediated diseases

0–6 month schedule was the only one not inferior to the 0–2 month schedule. Based on these findings, administration of the second vaccine dose can be delayed for up to 6 months without concern about a loss in the target immune response. If administration of the second vaccine dose is delayed for more than 6 months, the immune response appears to be somewhat reduced, but study data show that anti-gE antibody concentrations are more than 11 times higher than pre-vaccination levels. No study data are available regarding the need for booster doses or repeated vaccinations. Results from long-term observations on the duration of protection after vaccination are required, ideally with the clinical endpoint of HZ.

10.2 Coadministration with other vaccines

The immunogenicity and safety of the HZ/su inactivated vaccine with simultaneous administration of a quadrivalent seasonal influenza vaccine (QIV) were studied in an open, randomized phase III trial in adults age ≥50 years. Participants ($n = 828$)

were allocated to one of two groups at a ratio of 1:1. Participants received the first HZ/su inactivated vaccine dose together with the QIV dose, followed by a second HZ/su dose 2 months later (intervention arm), or the QIV first and the two HZ/su inactivated vaccine doses 2 and 4 months later (control arm). According to measured anti-gE concentrations (cut-off: 97 mIU/mL), a similar number of participants in the intervention arm (95.8%, 95% CI 93.3–97.6%) and the control arm (97.9%, 95% CI 96.0–99.1%) responded to the HZ/su inactivated vaccine. At the same time, it could be demonstrated that the antibody concentrations to the HZ/su and QIV vaccines were not inferior to those in the control arm. Safety concerns regarding simultaneous administration were not observed [22]. Simultaneous administration of the HZ/su inactivated vaccine and a non-adjuvanted, inactivated, seasonal influenza vaccine on different limbs is possible, according to the product information.

Simultaneous administration of the HZ/su inactivated vaccine with the 23-valent pneumococcal polysaccharide vaccine (PPSV23) was studied in 865 adult participants age 50 years and older (average age 63.2 years) in an open randomized trial [23]. Here as well, participants were assigned to the coadministration or control arm at a ratio of 1:1, and the vaccination scheme in both arms corresponded to that of the study on the simultaneous administration of QIV. In total, 98% of participants in both arms responded to the HZ/su inactivated vaccine, and similar antibody concentrations were measured. No safety concerns arose in this study either. The study results were not taken into account in the current valid version of the product information (last updated in March 2018), and coadministration is not yet covered by marketing authorization.

10.3 HZ/su vaccination after prior HZ disease

The immunogenicity and safety of the HZ/su inactivated vaccine in patients ≥50 years after prior HZ disease were studied in a non-randomized, open, multicenter trial in Canada and Russia between June 2013 and November 2014 [24]. Among participants in the study ($n = 96$), 68% ($n = 65$) had developed HZ within the past 4 years and none had ongoing active symptoms; in 19% ($n = 18$) of participants, the HZ episode occurred 5–9 years earlier and in 14% ($n = 13$), it was 10 or more years earlier. The median participant age was 64 years (range: 50–89 years). Participants received two doses of HZ/su at an interval of 2 months and were observed for a follow-up period of 12 months. Immunogenicity of the vaccine was measured as the rise in titer of anti-gE antibodies 1 month after the second vaccination. The primary goal of the study was a fourfold increase in titer over baseline before vaccination; this was achieved in 90.2% (95% CI 81.7–95.7%) of participants. Local and systemic side effects were documented for 7 days and adverse events for 30 days after each vaccination. Severe side effects occurring at any time during the study were recorded. The results confirmed the findings of the marketing authorization studies. With nine HZ episodes reported by six participants over a period of 12 months after vaccination, more recurrent episodes occurred than expected based on observational studies in unvaccinated people with anamnestic HZ. However, the HZ diagnoses were not confirmed by laboratory investigation and three patients had not consulted a physician. In summary, it can be stated that the HZ/su inactivated vaccine disease is sufficiently immunogenic in adults age ≥50 years with prior HZ, and no safety concerns have been identified.

10.4 HZ/su vaccination after prior HZ live vaccine

An open, multicenter phase III study was conducted to investigate whether the immune response to the HZ/su inactivated vaccine in adults age ≥65 years who had been vaccinated with the live HZ vaccine 5 or more years previously is comparable to that in previously naive individuals [25]. The study was conducted in the US between March and August 2016, with 430 study participants allocated to one of the two groups at a ratio of 1:1. In parallel, the tolerability of HZ/su vaccination after prior HZ live vaccine was studied; safety monitoring was conducted through August 2017. The aim of the study was to compare the humoral immune response to the two vaccination regimens 1 month after the second vaccine dose using the GMC of anti-gE antibodies, and to demonstrate non-inferiority of the previously vaccinated group to the naive group. Among participants previously vaccinated with the live vaccine, the humoral immune response to the HZ/su inactivated vaccine was not worse than the response among those not previously vaccinated. There was also no difference between the groups in cellular immunogenicity, reactogenicity, or safety [25]. Based on these findings, there are no objections to use of the HZ/su inactivated vaccine in people previously vaccinated with the live vaccine, as long as there is an interval of at least 5 years between the two vaccinations.

10.5 HZ/su vaccination in patients with bleeding tendency

The HZ/su inactivated vaccine is approved for i. m. injection. In an open, randomized phase III trial (participant ratio 1:1), the safety and immunogenicity of subcutaneous (s. c.) injection were compared to that of i. m. injection in two vaccinations (at 0 and 2 months) [26]. A total of 60 participants from Japan age ≥50 years were included. The age distribution was identical in the two groups, with mean age 61.9 years; 50% of participants were female. Anticipated and unanticipated reactions after administration of the vaccine were documented for 7 and 30 days after vaccination, and their severity was assessed according to grades 1 to 3. Although the immune response after vaccination was equally high in both groups, the reactogenicity of the vaccine in the s. c.-vaccinated group was markedly stronger than that in the i. m. group. According to the product information, the HZ/su inactivated vaccine is approved only for i. m. administration.

10.6 HZ/su vaccination in patients with immunosuppression and other underlying diseases

10.6.1 Patients after autologous stem-cell transplantation

In the first year after hematopoietic stem-cell transplantation (HSCT), the risk of developing HZ is markedly higher [27] and HZ disease can be complicated by visceral dissemination [28]. The safety and immunogenicity of the HZ/su inactivated vaccine were studied in an observer-blinded, placebo-controlled phase 1/2a trial between 2009 and 2012 in the US among individuals who had received an autologous stem-cell transplant 50–70 days previously [29]. The 121 study participants were randomized at a ratio of 1:1:1:1 and received either three doses gE/$ASO1_B$ (later vaccine), or three doses gE/$ASO1_E$, or one dose physiological saline solution and two doses gE/$AS01_B$, or three doses physiological saline solution, at months 0, 1, and 3. Regardless of the vaccine formula, the gE-specific $CD4^+$ cell counts and anti-gE serum antibody titers 1 month after the last vaccine dose were both higher than those in the placebo arm, and titer levels remained constantly high for 1 year. Both vaccine formulas were well tolerated and triggered a satisfactory immune response that remained for a period of 1 year.

The efficacy and safety of the HZ/su inactivated vaccine in patients after autologous HSCT were also studied for 21 months in a randomized, observer-blinded, placebo-controlled phase 3 trial stratified into two age groups (18–49 years and ≥50 years) [30]. In total, 1721 (93.2%) of the 1846 participants vaccinated after HSCT were included in the analysis. The efficacy against HZ was 68%, and 89% against PHN; this was the same for both age groups. There were no safety concerns.

HZ and PHN can be effectively prevented with the HZ/su inactivated vaccine in patients after autologous HSCT, regardless of age.

10.6.2 Persons with HIV

People with HIV have a markedly higher risk of developing HZ [31, 32]. Antiretroviral therapy (ART) clearly reduces the risk of HZ, but it is still 3–5 times higher than in people with healthy immune systems [33]. The safety and immunogenicity of the HZ/su inactivated vaccine were studied in an observer-blinded, placebo-controlled phase 1/2a trial in Germany, the US, and the UK between September 2010 and May 2013 [34]. The following three groups of patients with HIV were studied; participants differed with regard to immune status ($CD4^+$ cell count) and ART: (i) ART and $CD4^+$ cell count ≥ 200 cells/mm^3 ($n = 95$); (ii) ART and $CD4^+$ cell count < 200 cells/mm^3 ($n = 14$), (iii) no ART and $CD4^+$ cell count ≥ 500 cells/mm^3 ($n = 15$). The groups were randomized at a ratio of 3:2 and received the HZ/su inactivated vaccine or saline solution at months 0, 2, and 6. Of the 123 enrolled participants (average age 46 years), 112 (91.1%) completed the study. Local and systemic reactions occurred in the vaccine arm more frequently than in the placebo arm, but generally did not last long (median: 1–3 days) and were mild to moderate in intensity. Up to 16.4% of participants in the vaccine arm and 8.3% of those in the placebo arm complained of severe (grade 3) local or general reactions. SAEs were not observed. Over a follow-up period of 18 months, the vaccine showed no sustained negative effects on HIV viral load or immune status (measured by $CD4^+$ cell count). One month after the third vaccine dose, the gE-specific cell-mediated immune response and anti-gE serum antibody titer were significantly higher in the verum group than in the placebo group, and remained higher than pre-vaccination titers for a period of 12 months. Based on the study results, the HZ/su vaccine is sufficiently immunogenic in people with HIV and has an acceptable safety profile. Because the gE-specific, cell-mediated immune response barely increases after the third vaccine dose, a two-dose scheme is deemed sufficient for successful vaccination.

10.6.3 Patients with tumors

Patients with solid tumors who are receiving immunosuppressive therapy have a fourfold greater risk of developing HZ. In a randomized, observer-blinded, placebo-controlled phase 2/3 study, the immunogenicity and safety of the HZ/su inactivated vaccine were studied in patients 18 years and over ($n = 347$) receiving immunosuppressive therapy for a tumor disease in Canada, Czech Republic, Korea, France, the UK, and Spain [35]. Participants in the vaccine and placebo arms (1:1) were allocated into two further subgroups (each at a ratio of 4:1) who received two vaccine doses i. m. at an interval of 1–2 months. The first dose was administered either 8–30 days before starting the chemotherapy cycle (group A, pre-chemo) or at the start of the chemotherapy cycle (group B, on chemo). One month after the second vaccine dose, the vaccine induced a robust immune response regardless of whether vaccination started before or at the same time as the chemotherapy cycle. The immune response persisted for up to 12 months after the second dose. The vaccine was well tolerated, and there were no safety concerns.

In another 1:1 randomized, placebo-controlled, observer-blinded phase 3 trial, the safety and immunogenicity of the HZ/su inactivated vaccine were studied in patients ≥18 years ($n = 562$) with tumors of the lymphatic system (multiple myeloma, Hodgkin lymphoma, chronic lymphocytic leukemia, non-Hodgkin lymphoma) [36]. Participants received two doses at an interval of 1–2 months ≥ 10 days before or after chemotherapy. A total of 562 participants were included (HZ/su group: 283; placebo group: 279). The preliminary results showed that vaccination induces robust humoral (anti-gE antibodies) and cellular (gE-specific $CD4^+$ T cells) immunity. No safety concerns arose up to 6 months after administration of the second dose in an ongoing study with blinding maintained.

10.6.4 Patients after kidney transplant

As a result of lifelong immunosuppressive therapy, people who have received a kidney transplant have a sevenfold higher risk of developing HZ. In a randomized, double-blind, placebo-controlled phase 3 trial, the immunogenicity and safety of the HZ/su inactivated vaccine were studied in individuals who had received a kidney transplant in Belgium, Canada, Czech Republic, Finland, Italy, Panama, Korea, Spain, and Taiwan

in two different age cohorts (18–49 years and 50+ years) [37]. Participants ($n = 123$ in the vaccine arm and $n = 132$ in the placebo arm) received two vaccinations i. m. at an interval of 1–2 months, administered 4–8 months after transplantation. Preliminary data showed that the HZ/su inactivated vaccine induces a robust humoral and cell-mediated immune response up to 1 month after the second vaccination. The humoral immune response was higher in the younger age cohort than in the cohort age 50 years and over. There were no safety concerns up to 1 month after administration of the second dose.

10.6.5 Summary of HZ/su vaccination in patients with immunosuppression and underlying diseases

Depending on their underlying disease and/or therapy, patients with immunosuppression have a markedly increased risk of HZ and subsequent PHN. In vaccine studies, the efficacy, immunogenicity, and safety of the HZ/su inactivated vaccine have been examined in the following risk groups: patients after HSCT, people infected with HIV, kidney transplant recipients, patients with tumors of the lymphatic system before or after immunosuppressive chemotherapy, and patients with solid tumors before or after immunosuppressive chemotherapy. In patients after HSCT, the HZ/su inactivated vaccine demonstrated efficacy of 64–69% in protecting against HZ and 84–90% in protecting against PHN. In other patient groups, vaccination induced robust humoral and cellular immune responses that lasted more than 12 months. The vaccine is reactogenic, generally well tolerated, and there is no evidence of SAEs in this patient group. According to the product information, the vaccine is not contraindicated for patients with immunosuppression. It must be noted that, as with other vaccines, it is possible that these patients may not achieve a sufficient immune response. An individual risk-benefit assessment before vaccination is advised [9].

In light of the examined efficacy and safety of the HZ/su inactivated vaccine in particularly vulnerable groups of patients with an impaired immune system, it can be assumed that the vaccine is safe and effective for people with chronic underlying diseases who also have an increased risk of HZ disease and complications. This is supported by the results of a post-hoc analysis using data of the pooled ZOE-50 and ZOE-70 trials conducted in patients with underlying diseases such as arthritis, chronic renal disease, chronic obstructive pulmonary disease, coronary disease, and diabetes mellitus. In these patients, the analysis showed an efficacy level of the vaccine that corresponds to the overall efficacy against HZ [9, 20].

11 Acceptance and feasibility of the HZ/su vaccination

Acceptance of a vaccine in the target population is an important prerequisite for the successful implementation of a new vaccination recommendation. For an individual decision on HZ vaccination, it is necessary to be aware of HZ disease, to be able to estimate the severity of the disease, and to know that there is a vaccine that can provide protection from the disease. A survey was conducted among people age over 50 years ($n = 1001$) in Italy from October 2014 to April 2015 [38]. A total of 95% of participants said they were aware of HZ disease. Most respondents (80%) knew a person who had had HZ in the past, and 22% had already had HZ themselves. A total 91% did not know that there is a vaccine to prevent HZ, and 85% said that they were generally in favor of HZ vaccination. This study proved the decisive role of primary care physicians in the decision-making process for HZ vaccination; 83% of survey respondents said they would receive vaccination if their primary care physician recommended it. The authors of a systematic review on the acceptance of HZ vaccination came to a similar conclusion [39]. According to the review, recommendation by a primary care physician is the decisive factor in high acceptance of a vaccine. Additional factors identified for successful vaccine implementation were cost reimbursement and awareness about HZ in the target population.

To estimate the implementation of vaccination recommendation in the target group of adults age 60 years and over in Germany, data were referenced on seasonal influenza vaccination coverage from invoicing data by the associations of statutory health insurance physicians [40] as well as data on the use of pneumococcal vaccines for older adults from the German health interview and examination survey for adults (DEGS) [41]. According to these data, nationwide influenza vaccination coverage has fallen from around 48% among people age ≥ 60 years during the 2008/09 and 2009/10 seasons to less than 35% in the 2016/17 season. Vaccination coverage appears to have stagnated since the 2012/2013 season at around one-third of all adults age 60 years and older who are vaccinated for seasonal influenza. The large spread among the federal states was also noteworthy (2016/17: 19.9% in Baden-Württemberg to 55.2% in Saxony-Anhalt). Based on the DEGS survey, 31.4% of people age 65–79 years were vaccinated against pneumococcal disease in 2008–2011, women (33.2%) somewhat more frequently than men (29.3%). However, it remains unclear at this time whether these utilization data can be applied to HZ vaccination.

12 Modelling the influence of the vaccination on HZ and PHN epidemiology in Germany

12.1 Methods

A static Markov cohort model was used for analysis [42], updated specifically with regard to data on vaccine efficacy and vaccine-induced period of protection [43]. The model follows a simulated cohort of one million 50-year-olds to the end of their lives. It covers five conditions (health, death, HZ, PHN, and health after illness), and calculates a cycle length of 3 months based on duration of HZ illness and PHN definition. The age at vaccination was varied between 50 and 80 years in 5 year steps. In addition to the number of HZ (PHN) cases prevented by vaccination and the number needed to vaccinate (NNV) to prevent one HZ (PHN) case, health economics analyses were also conducted. Incremental cost-effectiveness ra-

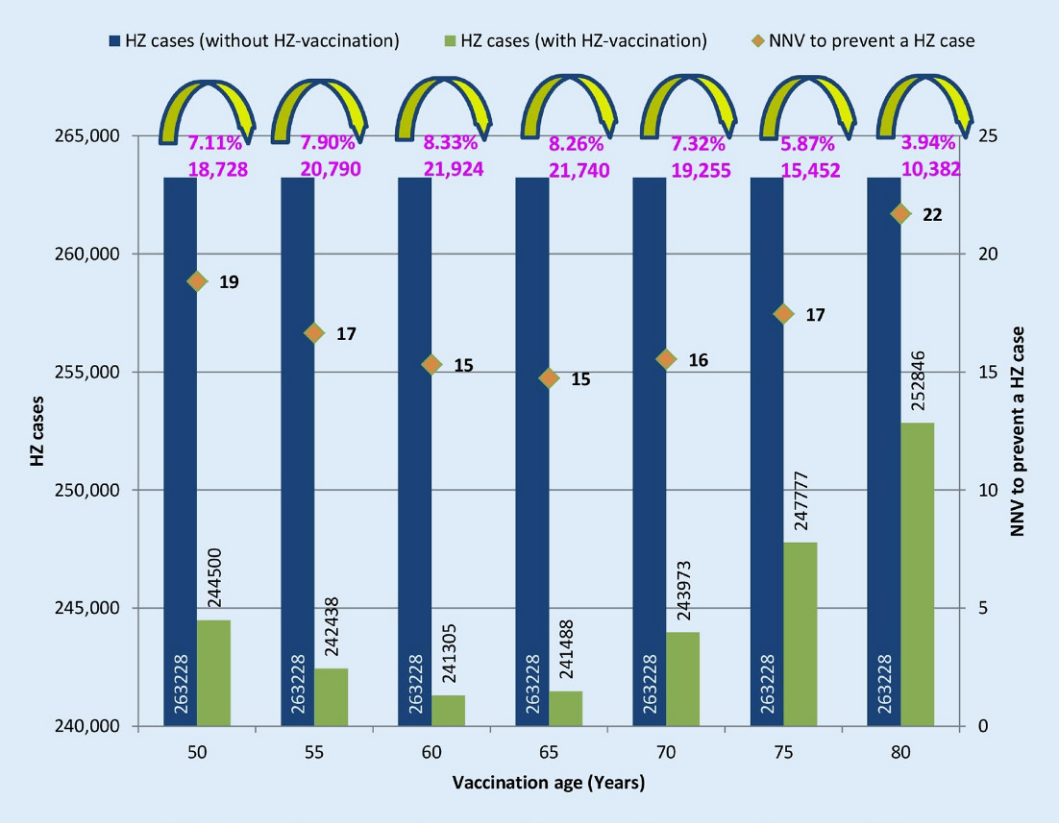

Fig. 10 ◄ Number of HZ cases with and without vaccination with the HZ/su inactivated vaccine and number needed to vaccinate (*NNV*) according to age at vaccination (vaccination coverage 35.5%, cohort size 1,000,000, undiscounted)

tios (ICER), with € per HZ case prevented (€/HZ) and € per QALY gained (€/QALY), were calculated. All analyses were calculated from a societal perspective, i. e., including costs for absenteeism from work. In addition to a base-case analysis (vaccination at age 60 years, assumed 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 were conducted, to identify the impact of uncertain input factors. The model was developed using the programming language R (The R Project for Statistical Computing, Vienna, Austria).

12.2 Input data

Data on epidemiology and on direct and indirect treatment costs of HZ and PHN were taken from invoicing data by the associations of statutory health insurance (SHI) physicians (KV) and from SHI funds in Germany ([5, 44], Damm et al. (not yet published)). The costs for a complete vaccination series (two vaccine doses plus administration) were assumed to be € 182 (https://www.rki.de/zoster-impfung). The theoretical price per dose (no information was available from the manufacturer at the time of modeling) was € 84 and administration costs were € 7. The data on vaccine effectiveness and vaccine-induced period of protection have been described above. Quality-of-life data for calculating QALYs were taken from patients with HZ or PHN disease in Canada [45].

12.3 Results

Of one million 50-year-olds without HZ vaccination in the model cohort, 260,000 will develop HZ in the remaining course of their lives (cf. 263,228/1,000,000 = 26.3%), and 15,000 will develop PHN (cf. 15,325/1,000,000 = 1.5%). In the base-case scenario, 21,924 HZ cases (NNV = 15), i. e., 8.33% of HZ cases that would occur without vaccination, could be prevented with the HZ/su inactivated vaccine (**Fig. 10**). A higher vaccination rate of e. g. 60% (80%) could prevent 24,843 (37,264) HZ cases. The potential reduction in HZ cases varies according to age at vaccination. It is highest with vaccination at age 60 years (8.3%) and lowest with vaccination at age 80 years (3.9%) (**Fig. 10**). The lowest NNV was achieved with vaccination at the ages of 60 and 65 years, with 15 for each. According to the model, the most PHN cases can be prevented with vaccination at the age of 70 years (9.9%), followed by 9.8% for vaccination at age 65 years and 9% for vaccination at age 60 years (**Fig. 11**). The NNV to prevent one PHN case also varies according to age at vaccination, and ranges from 421 for vaccination at age 50 years to 197 for vaccination at age 70 years (**Fig. 11**).

Vaccination with the HZ/su inactivated vaccine leads to ICERs of € 1774/HZ and € 23,934/QALY in the base-case scenario. Vaccination at age 65 years appears to be the most cost-effective, but the difference between vaccination at age 60 years is small (**Fig. 12**).

In other sensitivity analyses, it was shown that especially the vaccine-induced period of protection, price of the vaccine, and recurrence rate of HZ have the greatest impact on base-case results. If theoretical lifelong vaccine protection is

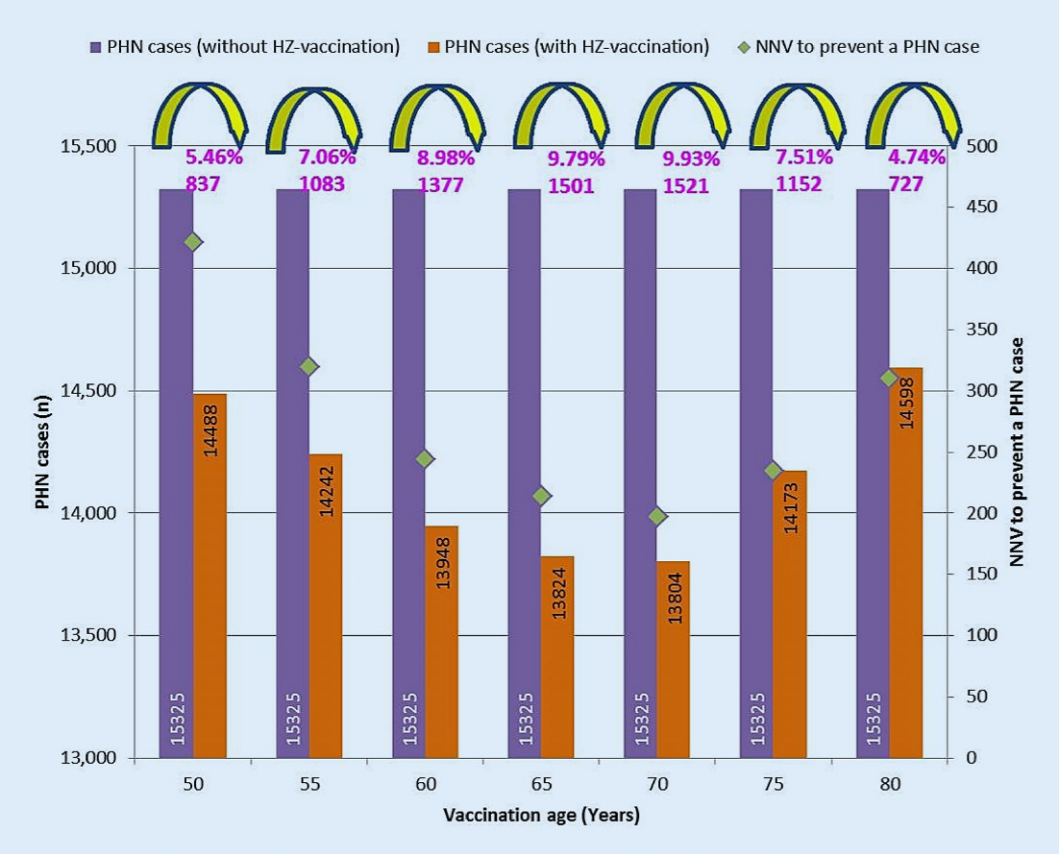

Fig. 11 ◄ Number of PHN cases with and without vaccination with the HZ/su inactivated vaccine and NNV according to age at vaccination (vaccination coverage 35.5%, cohort size 1,000,000, undiscounted)

assumed, the ICER falls to € 8523/QALY for vaccination at age 60 years. Assuming a period of protection of only 5 years leads to an ICER of € 86,678/QALY, if the immunization costs fall from € 182 to € 100, the resulting ICER is € 11,437/QALY; if these costs rise to € 282, the ICER is then € 39,173/QALY (**Fig. 12**).

12.4 Conclusions from modelling

In a cohort of one million 50-year-olds that were followed up until the end of their life, modeling the epidemiological effects of HZ vaccination revealed that vaccination at age 60 would prevent most HZ cases and vaccination at age 70 would prevent most PHN cases. The health economic model showed the best cost-effectiveness with vaccination at age 65 years, which was only slightly better than vaccination at 60 years of age. NNV was lowest for vaccination at ages 60 and 65 years, with the same values. As results on VE against PHN are based on very few cases (see **Table 2**) and prevention of HZ is the precondition for preventing PHN, and because vaccination at age 60 years would prevent most HZ cases according to the model, 60 years of age seem to be the best age for vaccination, from an epidemiologic point of view.

13 Evaluation of the vaccination recommendation

13.1 Epidemiology monitoring

From invoicing data of the associations of SHI physicians, diagnostic data are available for monitoring the epidemiology of HZ and PHN in individuals insured under SHI [5]. Information on HZ and PHN epidemiology before the introduction of vaccination is available from the same data source, such that a potential effect of vaccination at population level can be assessed very well using the same data source. Furthermore, HZ is a notifiable disease in the federal states of Brandenburg and Saxony, according to state regulations; thus, further population-based epidemiological data are available for the comparison of age specific HZ-incidences in periods pre- and post-introduction of vaccination.

13.2 Monitoring of adverse drug reactions

Surveillance systems have been established in Germany at the Paul Ehrlich Institute for Vaccines and Biomedicines (PEI) for the spontaneous recording of suspected cases of possible adverse events after vaccination. According to the German Medicines Act (*Arzneimittelgesetz*, AMG), possible side effects of vaccines must be reported by the marketing authorization holder and/or pharmaceutical company. Doctors are also required to report suspected cases of vaccine complications in accordance with the Protection Against Infection Act (IfSG) [46, 47]. Examples of how these data can be used include conducting observed versus expected analyses and examination of whether certain events occur more frequently among those recently vaccinated than would be expected, compared with background incidence for the age group;

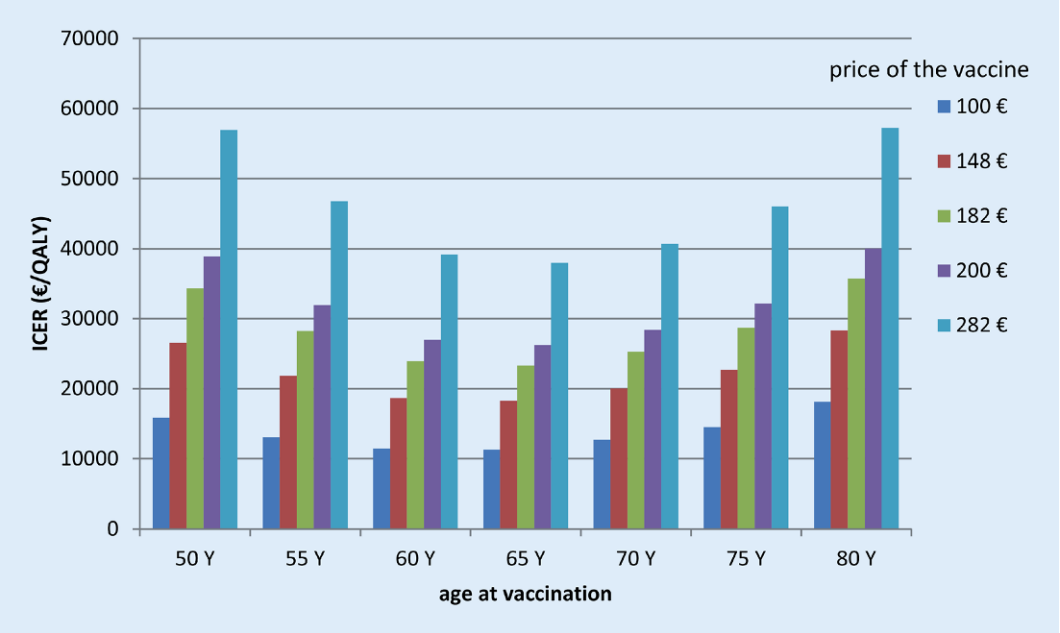

Fig. 12 ◂ Costs per quality-adjusted life year (QALY) gained according to vaccine price and age at vaccination

in addition, the data can be used in quantitative methods, such as the proportional reporting ratio (PRR).

If illnesses occur in temporal correlation to vaccinations, it is important to distinguish between a causal link and coincidental events. For that reason, researchers at the Robert Koch Institute (RKI) and PEI are conducting a joint project to determine estimators of the background incidence in selected immune-mediated diseases, orthostatic hypotension, myocardial infarction, stroke, and sudden death in adults age ≥ 50 years in Germany. Based on these estimators, the expected number of newly occurring diseases in a certain time interval, independent of vaccination with the HZ/su inactivated vaccine, can be calculated. This can be used in a comparison with the observed number of these diseases after introduction of the HZ/su inactivated vaccine, to generate warnings should the comparison point to an elevated number of rare adverse side effects.

13.3. Vaccination coverage monitoring

The aforementioned invoicing data from the associations of SHI physicians on vaccinations and relevant diagnoses (HZ, PHN) can be used and analyzed [48]. This facilitates the determination of nationwide vaccination coverage among people insured under SHI (around 85% of the population). These data are available with a 6-month delay. In addition, incidences of the target diseases can be determined according to age and risk group by the same data source, such that the implementation of HZ vaccination recommendations and their impact can be evaluated using this system.

13.4 Summary evaluation of the vaccination recommendation

For the ongoing evaluation of HZ vaccination recommendations, various surveillance and monitoring systems have been implemented that permit the continuous recording of data on HZ and PHN epidemiology, the occurrence of adverse effects of vaccination, and HZ vaccination coverage. Data collection via these systems was in place prior to the introduction of HZ vaccination. Thus, reliable evaluation of the vaccination recommendation is possible by comparing data between the pre- and post-vaccination phases. Using the available data, it is possible to assess vaccine effectiveness after vaccination by age and risk groups as well as over time. In addition, international publications are continuously reviewed, which report on vaccine effectiveness, duration of vaccine-induced protection, and vaccine safety; the results will be analyzed and compared with the data from Germany. This will contribute to answering any remaining questions, such as how long the vaccine will protect against HZ as a clinical endpoint.

Corresponding address

A. Siedler
Immunization Unit, Robert Koch Institute
Berlin, Germany
SiedlerA@rki.de

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