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Efficacy and safety of the recombinant zoster vaccine: A systematic review and meta-analysis

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A B S T R A C T

In this systematic review with meta-analysis, the efficacy, effectiveness, and safety of the new GSK recombinant zoster vaccine (RZV) were assessed.

Twenty three publications reporting on 14 studies were selected, including 2 pivotal RCTs in older immunocompetent adults (ZOE-50 and ZOE-70), 4 RCTs on immunocompromised patients (haematopoietic stem cell transplantation (HSCT), haematological malignancies, solid tumour, and renal transplantation), and 8 observational studies. Vaccine efficacy of RZV against herpes zoster (HZ) and postherpetic neuralgia (PHN) was very high in immunocompetent older adults (respectively 94% and 91.2% in adults ≥50 years and 91.3% and 88.8% in adults ≥70 years). However, the number needed to vaccinate (NNV) was relatively high (between 32 and 36 for HZ and between 261 and 335 for PHN). Slow waning of the vaccine efficacy has been described after a median follow-up of 10 years after vaccination. In patients after HSCT, vaccine efficacy of RZV against HZ was lower compared to immunocompetent adults (68.2%), while vaccine efficacy of RZV against PHN was similar (89.3%). Higher incidences of HZ and PHN in patients after HSCT resulted in higher absolute reduction of cases and lower NNV (respectively 10 and 115). Observational studies confirmed a good vaccine effectiveness, albeit lower than in RCTs (ranging between 70% and 85%). No safety signal was identified neither in RCTs with immunocompetent or immunocompromised adults nor in observational studies and post-marketing surveillance. Increased reactogenicity after RZV vaccination, limited in extent and duration, did not result in low second dose compliance.

Conclusion: Although vaccine efficacy in RCTs and effectiveness in the real world has been reported to be good, it needs to be stressed that high numbers of immunocompetent adults need to be vaccinated to prevent HZ and PHN. Due to higher incidence, more acceptable NNVs were calculated in immunocompromised adults after HSCT.

Introduction

Herpes zoster (HZ, Shingles) is a vesicular and often painful dermatomal rash, resulting from the reactivation of latent varicella-zoster virus (VZV) in patients that have been infected with the virus previously. The primary infection, varicella, usually occurs in children, whereas herpes zoster usually develops in older adults [1]. The main risk factors include age-related decline in immunity (immunosenescense), and immunodepression from disease and/or its therapy, for example cancer [1,2]. HZ is mostly a self-limiting disease and the rash will heal within 2–4 weeks. The median duration of acute pain is 2 weeks, but in 60–70% of HZ cases, pain persists for 1 month [3,4]. Moreover, in 5–30% of HZ cases, severe pain persists at least 90 days after appearance of the rash and this is called 'postherpetic neuralgia', the most important complication of HZ [5,6]. Other complications are more rare but can be serious, for example the complications associated with herpes zoster ophthalmicus (HZO) (e.g. glaucoma and acute retinal necrosis), secondary bacterial infection and sepsis, neurological complications (e.g. encephalitis, Guillain-Barré syndrome) and cardiovascular disease [3–6]. In 2006, a live attenuated VZV vaccine (ZVL, Zostavax) to prevent HZ in individuals ≥50 years was granted market authorization by the European Medicines Agency (EMA). Unfortunately, the vaccine efficacy of ZVL against HZ declines with age from 70% in adults 50–59 years of age, to 64% in adults 60–69 years, and to 18% in adults ≥80 years [7–8]. Its efficacy also decreases over time, from 62% in the first year to 40% by the fifth year postvaccination [9]. Moreover, ZVL is contra-indicated in immunocompromised individuals [10]. The use of Zostavax in the US was therefore discontinued in November 2020 [11].

The recombinant zoster vaccine (RZV) is a new adjuvant recombinant subunit vaccine (Shingrix®, GSK) against herpes zoster, containing VZV glycoprotein E (gE) and the $AS01_B$ adjuvant system (GSK). The EMA granted RZV a marketing authorisation in March 2018 based on the

Abbreviations: EMA, European Medicines Agency; HM, haematological malignancies; HSCT, hematopoietic stem cell transplantation; HZ, herpes zoster; HZO, herpes zoster ophthalmicus; IBD, inflammatory bowel disease; KPH, Kaiser Permanente Hawaii; LTFU, long term follow-up; NNV, number needed to vaccinate; OLDW, OptmumLabs Data Warehouse; RCT, randomized controlled trial; RT, renal transplantation; RZV, recombinant zoster vaccine; SoT, solid tumour; VZV, varicella zoster virus; ZBPI, zoster brief pain inventory; ZVL, zoster vaccine live (attenuated VZV vaccine.

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results of two pivotal Phase III RCTs (ZOE-50 and ZOE-70) [12,13]. Over the next years, efficacy and safety have been studied in the ZOE-50/70 pooled participants, in subgroups of the ZOE-50/70 population [14–22], and in immunocompromised patients [23–27]. Different reports about real-world effectiveness have also been published [28–34].

The objective of this systematic review and meta-analysis is to consolidate the published evidence on safety and efficacy (and effectiveness when available) of RZV in different (sub)populations from RCTs and from real world data. The resulting information is needed by health care professionals and policy-makers on recommendations about vaccine use and reimbursement decisions.

Methodology

A protocol was written according to the Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA-P) guidelines. The final version of this protocol was registered in The International Prospective Register of Systematic Reviews (PROSPERO, REF CRD42022311749). No significant deviations from the protocol occurred.

A literature search was conducted in the following databases: OVID MEDLINE, Embase and Cochrane Central of Controlled Trials, to identify RCTs and observational studies, evaluating the efficacy, effectiveness, and safety of RZV in immunocompetent individuals above 50 years and immunocompromised patients above 18 years from inception data until 7 February 2022. Inclusion and exclusion criteria can be found in Table 1. Although RCTs are considered golden standard, observational studies were included for assessment of effectiveness and in-population safety. The search strategies per database can be found in supplementary material Fig. S1.

Additionally, we identified ongoing or recently completed trials on the International Clinical Trials Registry Platform Search Portal and ClinicalTrials.gov. Grey literature was searched on the websites of the International Network of Agencies for Health Technology (INAHTA), European network for Health Technology Assessment (EUnetHTA) and Google scholar using the keyword ‘zoster’ or ‘zoster vaccine’.

Publications were initially screened using title and abstract. If publications were considered potentially relevant, full-text articles were screened. The two first steps were achieved by one reviewer (RZ) and results were cross-checked by an independent group of 3 experts in the field (vaccine epidemiology, infectious diseases, health economics) to identify any missing publications. Additionally, relevant studies were identified by checking the citations of each selected publication. Data extraction was performed by one researcher (RZ) and checked against the original study by a second independent researcher (DR).

Information extracted included study methodology (study design, funding, setting, sample size, duration and follow-up), patient characteristics (mean age, age range, gender, inclusion and exclusion criteria), intervention and comparator, and (primary and secondary) outcomes.

Included primary outcomes were incidence of Herpes Zoster (HZ) infection, Post-Herpetic Neuralgia (PHN) and other complications (vasculitis, disseminated and/or visceral HZ, ophthalmic (HZO), cardiac or neurological complications including stroke). Other primary outcomes considered were hospitalization rates and quality of life. As secondary outcomes, we included measures of safety: proportion of all adverse events including total discontinuations, reactogenicity (injection site or local reactions like pain, redness and swelling, and systemic reactions including fatigue, fever, myalgia, gastro-intestinal symptoms and headache), as well as Guillain-Barré syndrome (GBS), potential immune-mediated disease (pIMD) and mortality.

Two researchers independently assessed the quality, level of evidence and risk of bias (RZ, DR). For RCTs we used version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2) and for primary observational studies the Cochrane Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I). Quality assessment of evidence was performed following the GRADE methods and evidence tables were made in GRADEproGDT.

Meta-analysis and production of forest plots were performed in Review manager 5.3. The pooled risk ratio’s (RR) and 95% confidence Intervals (CI) were calculated for dichotomous primary and secondary outcomes. When not reported, vaccine efficacy was calculated (1 minus risk ratio). Number needed to vaccinate (NNV) were calculated based on the absolute risk difference. We estimated the difference in means (MD) with 95% CI for continuous outcomes. The Higgins I^2 statistics was used to estimate the proportion of total variation in study estimates that is due to heterogeneity rather than sampling error. We assumed substantial heterogeneity when the I^2 statistic was >50%. We analysed data using a random-effects model. Results were considered statistically significant when p-value was <0.05. Subgroup analysis was done according to type of publication/setting (RCT or observational), immune status (immunocompetent and immunocompromised) and age range (18–49, 50–59, 60–69, 70–79, >80 year) to assess the potential effect of these factors on RZV efficacy and effectiveness. Sensitivity analysis was included removing either immunocompetent or immunocompromised individuals from the meta-analysis.

Table 1
Inclusion and exclusion criteria for systematic review.

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

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

Results

Literature search

The literature search yielded 1867 references, of which 54 were duplicates. Twenty three publications regarding 14 studies (6 RCTs and 8 observational studies) were selected after screening 66 full texts for eligibility criteria (Fig. 1). An overview of the study design and patient characteristics of the included studies can be found in Table 2. The studies excluded after full text screen and reasons for exclusion can be found in supplementary material Table S1. Six ongoing studies were identified on Clinicaltrials.gov (Indian population (NCT05219253), Chinese population (NCT04839982), population with prior episode of shingles (NCT04091451), with rheumatic disease (NCT04748939), with systemic lupus erythematosus (NCT04516408) and coadministration with influenza NCT05047770), but no results were available to include, and no additional data was identified from grey literature.

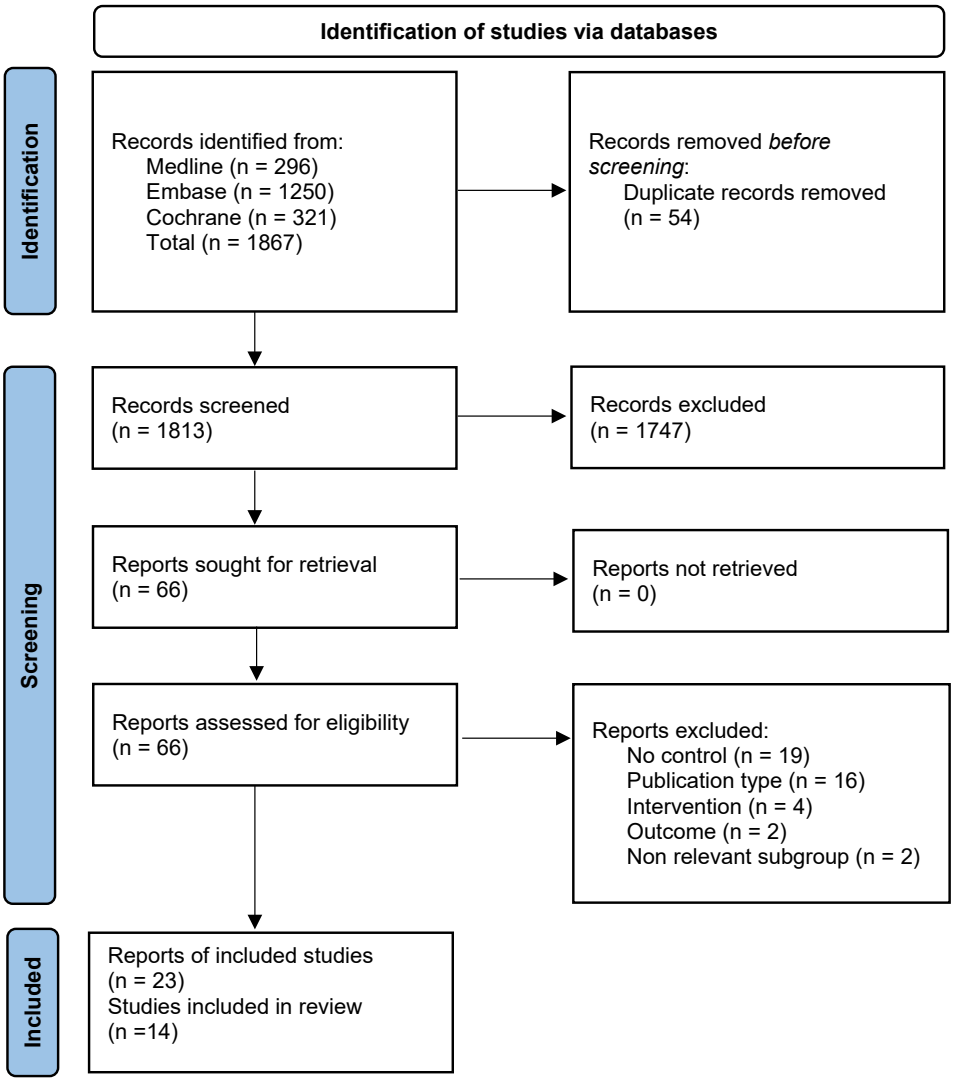

Fig. 1. Prisma Flow chart.

Study and patient characteristics

Two pivotal phase III RCTs (ZOE-50 and ZOE-70) on efficacy and safety of RZV were performed in older, immunocompetent individuals [12,13]. Eight further publications reported analysis of pooled data of these two studies, including sub-group analysis on patients with at least one potential immune mediated disease, at least one underlying medical condition, sex and frailty status [15–22] and one publication was an extension study, ZOE-LTFU [14]. Four phase III RCTs on safety (and immunogenicity) of RZV were performed in 4 different immunocompromised patient groups: patients who underwent a haematopoietic stem cell transplantation (ZOE-HSCT), patients with haematological malignancies (Zoster-039), renal transplant (Zoster-041) or a solid tumour (Zoster-028) [23,25–27]. Vaccine efficacy was only reported in Zoster-041 and Zoster-028 studies and quality of life was reported in an additional publication [24]. Finally, eight observational in-population studies on RZV were included from seven publications [28–34]. Five reported on effectiveness against HZ [33–34,29–31], one against PHN [29] and three against HZO [29,32,33]. Two studies, a cohort and a self-controlled case study reported in the same paper, assessed the occurrence of Guillain-Barré syndrome after vaccination [28]. Three observational studies reported on older, immunocompetent adults [32–34], while there was a mixed population of immunocompetent adults and immunocompromised patients in one study [29]. In the two studies by Goud et al. the population was also probably mixed, but this was not specified in the paper [28]. Finally, two studies were specifically on patients with inflammatory bowel disease [30,31]. The risk of bias results are summarized in Table 2. In general, the original RCTs were low risk of bias, the post-hoc analyses and long term follow-up study unclear risk of bias and the observational studies moderate risk of bias.

Statistical analysis results

Efficacy and effectiveness against herpes zoster

Meta-analysis on all studies with HZ as outcome showed vaccine efficacy of about 75%. The forest plot is available in Fig. 2 and the combination of the summary of findings and GRADE quality of evidence in Table 3. Because so many papers referred to the initial 2 studies, inclusion of their data in the meta-analysis was not always relevant. The data is also very heterogeneous. Sensitivity analysis on either immunocompetent or immunocompromised adults are available in the supplementary material Figs. S2 and S3 and show vaccine efficacy of respectively 80% for immunocompetent and 66% for immunocompromised. The data from observational studies could not be controlled for confounding in the meta-analysis. As this was the combination of data from RCTs and observational studies we discuss the data also separately in the following sections. Results on vaccine efficacy against HZ in the overall population and different age categories of ZOE-50, pooled ZOE-

Table 2
Overview of included publications.

Reference	Study design	Patients inclusion and exclusion criteria	n patients Mean age (±SD) Gender Race	Intervention	Outcome	Risk of Bias
Randomized controlled trials and related papers						
1. ZOE-50 (1)	**Phase 3 RCT** 1:1 randomized Placebo-controlled Triple blind Multicentre 18 countries Funded by industry Mean FU 3.2y	**Inclusion criteria:** ≥50 years **Exclusion criteria:** History of HZ HZ or varicella vaccine Immunosuppressive condition	15 411 TVC 14 759 mTVC 62.3y (±9.0) Female 61.2% White 71.8%	RZV IM versus placebo 2 doses (0, 2m)	Efficacy against HZ Secondary outcomes: Efficacy by age group Safety	Low
2a. ZOE-70 (2)	**Phase 3 RCT** 1:1 randomized Placebo-controlled Triple blind Multicentre 18 countries Funded by industryMean FU 3.7y	**Inclusion criteria:** ≥70 years **Exclusion criteria:** History of HZ HZ or varicella vaccine Immunosuppressive condition	13 900 TVC 13 163 mTVC 75.5y (±4.7) Female 54.9% White 76.9%	RZV IM versus placebo 2 doses (0, 2m)	Efficacy against HZ ≥70y Secondary outcome: Safety	Low
2b. ZOE-50/70 (2) HZ and PHN	**ZOE-50 and ZOE-70** Funded by industry Mean FU 3.8y	ZOE-50 and ZOE-70 All patients ≥70y Analysis against PHN all patients ≥50y	≥70: 17 531 TVC 16 596 mTVC ≥50: 29 305 TVC 27 916 mTVC	RZV IM versus placebo 2 doses (0, 2m)	Efficacy against HZ and PHN ≥70y Secondary outcomes: Efficacy against PHN ≥50y	Low
3. ZOE-50/70 Complications (not PHN) (3)	**ZOE-50 and ZOE-70** Funded by industry Mean FU 3.9 ± 0.7y (ZOE-50) 3.7y ± 0.8y (ZOE-70)	ZOE-50 and ZOE-70 All patients ≥50y	27 916 mTVC	RZV IM versus placebo 2 doses (0, 2m)	Secondary outcomes: Efficacy against HZ-complications (not-PHN) HZ-related mortality and HZ-related hospitalisation	Low
4. ZOE-50/70 Safety (4)	**ZOE-50 and ZOE-70** Funded by industry Mean FU 4.4y	ZOE-50 and ZOE-70 All patients ≥50y	29 305 TVC 68.6y Female 59.2% White 73.7%	RZV IM versus placebo 2 doses (0, 2m)	Safety	Low
5. ZOE-50/70 Underlying conditions (5)	**ZOE-50 and ZOE-70** Post hoc analysis Funded by industry	ZOE-50 and ZOE-70 Patients ≥50y with at least one of 15 selected medical conditions at enrolment[1] Excluded: patients with none of the 15 selected medical conditions	23 035 mTVC (82.5 % of ZOE-50/70) 68.5y (±9,8) Female 58.2% White 73.7%	RZV IM versus placebo 2 doses (0, 2m)	Efficacy and safety according to number and type of selected medical conditions present at enrolment	Unclear because of post-hoc analysis
6. ZOE-50/70 Quality of life (6)	**ZOE-50 and ZOE-70** Funded by industry	ZOE-50 and ZOE-70 All patients ≥50 from ZOE-50 All patients ≥70y from ZOE-50/70	ZOE-50 14 753 mTVC ZOE-50/70 ≥ 70y 16 596 mTVC	RZV IM versus placebo 2 doses (0, 2m)	Least, worst and average pain HZ Burden of illness HZ Burden of interference Quality of life	Unclear because number of cases is different from origignal ZOE-50
7. ZOE-50/70 Frailty study (7)	**ZOE-50 and ZOE-70** Funded by industry Mean FU 4 years	Centres willing to participate ZOE-50 and ZOE-70 patients ≥50y	26 976 (92 % of TVC ZOE-50/70 68.8y Female 58.1% White 74.6%	RZV IM versus placebo 2 doses (0, 2m)	Frailty status Secondary outcomes: efficacy against HZ, efficacy against HZ burden of illness, immunogenicity, reactogenicity and safety by frailty status	Unclear because of post-hoc analysis
8. ZOE-50/70 ≥1 pIMD (8)	**ZOE-50 and ZOE-70** Post hoc analysis Funded by industry Mean FU 4.4y	ZOE-50 and ZOE-70 patients ≥50y with at least one pIMD, at enrolment (not-immunocompromised) exclusion: patients ≥50y with no pIMD at enrolment	1943 (6.6% of pooled ZOE-50/70) RZV 68.8 (± 9.6) Placebo 69.4y (± 9.5) Female 60.4% White 85.4%	RZV IM versus placebo 2 doses (0, 2m)	Efficacy and safety	Unclear because of post-hoc analysis
9. ZOE-50/70 Sex, geographic area and ethnicity/ ancestry (9)	**ZOE-50 and ZOE-70** Post hoc analysis Funded by industry	All patients ≥50 from ZOE-50 All patients ≥70y from ZOE-50/70	14 753 mTVC RZV 62.3y Placebo 62.2% Female 61.2% 16 596 mTVC RZV 75.5y Placebo 75.5y Female 54.9%	RZV IM versus placebo 2 doses (0, 2m)	Efficacy against HZ and PHN according to sex, geographic area, ethnicity/ancestry	Unclear because of post-hoc analysis

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Table 2 (*continued*)

Reference	Study design	Patients inclusion and exclusion criteria	n patients Mean age (±SD) Gender Race	Intervention	Outcome	Risk of Bias
10. ZOE-50/70 Reactogenicity trends (10)	**ZOE-50 and ZOE-70** Post hoc analysis Funded by industry	ZOE-50 and ZOE-70 All patients ≥50y	29 305 TVC	RZV IM versus placebo 2 doses (0, 2m)	Reactogenicity trends: the intensity of each solicited injection site and general event after dose 1 was compared to the intensity of the same event reported after dose 2.	Unclear because of post-hoc analyses
11. Zoster-049 ZOE-LTFU (long term follow-up) (11)	Phase 3b open label **Extension ZOE-50 and ZOE-70** Funded by industry	**Inclusion criteria:** At least 1 RZV dose in ZOE-50 or ZOE-70 **Exclusion criteria:** immunosuppressive or immune modifying treatments Other VZV or HZ vaccines	7413 TVC 7277 mTVC 67.2y (± 9.4) Female 60.7% White 76.5%	RZV IM versus historic control/placebo group in ZOE-50/70	Efficacy against HZ from 5.1 years to 7.1 years after vaccination (2y) Secondary outcome: Efficacy against HZ from 1 month post-dose 2 until 7.1 years (7y) Immunogenicity Safety	Unclear because of potential selection bias
12. Zoster-002 ZOE-HSCT (Haematopoeitic stem cell transplantation) (12) 13. ZOE-HSCT Zoster-002 (13)	**Phase 3 RCT** 1:1 randomized Placebo controlled Triple blinded Multicentre 28 countries Funded by industry Median FU 21m	**Inclusion criteria:** ≥18 years Autologous HSCT in previous 50-70d **Exclusion criteria** Anti-VZV prophylaxis >6m History of vaccination varicella or HZ (1y) HIV infection	1846 TVC 1721 mTVC 54.9y Female 37.0% White 78.4%	RZV IM versus placebo (0 and 1–2m)	Efficacy against HZ Secondary outcome: Efficacy against HZ-related complications (hospitalisation, PHN and other complications) Immunogenicity QoL ZBPI burden of illness ZBPI burden of interference	Low
14. Zoster-028 Solid tumour (14)	**Phase 2/3 RCT** 1:1 randomized Placebo controlled Triple blinded Multicentre 6 countries Funded by industry Mean FU 12m	**Inclusion criteria:** ≥18 years ≥1 solid tumour and receiving or scheduled to receive cytotoxic or immunosuppressive chemotherapy **Exclusion criteria:** History of vaccination varicella or HZ History of HZ Systemic GC > 14d	232 TVC 57.8y (±11.2) Female 60.0% White 83.7%	RZV IM versus placebo (0 and 1–2m)	Immunogenicity Safety	Low
15. Zoster-039 Haematological Malignancies (15)	**Phase 3 RCT** 1:1 randomized Placebo controlled Triple blinded Multicentre (77) Funded by industry Mean FU 12.1m	**Inclusion criteria:** ≥18 years Haematological malignancy Life expectancy ≥12m Immune-suppressive cancer treatment Antiviral prophylaxis was permitted **Exclusion criteria:** CLL on oral chemo or HSCT vaccination for VZV or HZ History of HZ or HIV infection	562 TVC 57.3y (±15.2) Female 40.6% White 71.1%	RZV IM versus placebo (0 and 1–2m)	Immunogenicity Safety Efficacy against HZ (post-hoc analysis)	Low
16. Zoster-041 Renal Transplant (16)	**Phase 3 RCT** 1:1 randomized Placebo-controlled Triple blinded Multicentre 9 countries Funded by industry Mean FU 12m	**Inclusion criteria:** ≥18 years 4–18 mpost Renal transplant Bloodgroup compatible allograft Daily immunosuppressive therapy Stable renal function Free of rejection 3m before vaccination **Exclusion criteria:** PKD with high incidence of recurrence or previous allograft loss due to recurrence multiple organ transplant systemic AI or pIMD, HZ/varicella vaccination 12m prior first dose History of HZ or varicella	264 TVC 52.4y (± 12.6) Female 29.9% White 70.1%	RZV IM versus placebo (0 and 1–2m)	Immunogenicity Safety	Low
Observational studies						
17. Sun 2021 (a) (17)	**Retrospective cohort** OptmumLabs Data Warehouse (OLDW)[2], USA Median FU: 7m	**Inclusion criteria**: ≥50y, ≥ 365d of continuous enrolment in OLDW diagnosis of HZ before vaccination is accepted **Exclusion criteria:** Immunocompromised patients, HZ	4 769 819 adults 7 300 036 PY V2: 173 745 (3.6%) 65.0y (IQR 56–73)	Vaccinated with two doses (V2) versus Unvaccinated	Effectiveness against HZ First diagnosis of HZ during follow-up	Moderate

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Table 2 (*continued*)

Reference	Study design	Patients inclusion and exclusion criteria	n patients Mean age (±SD) Gender Race	Intervention	Outcome	Risk of Bias
	(IQR 2.8–13m)	diagnosis between 2 doses and up to 30d after second dose, single dose RZV, second dose < 30d or > 210d after first dose	Female: 52.2% White: 65.4% **Unvaccinated** 64.0y (IQR 56–73) Female 52% White 5.1% **Vaccinated (V2)** 72.0y (IQR 69–77) Female 58% White 74.3%			
18. Sun2021 (b) (18)	**Retrospective cohort** Electronic health records from Kaiser Permanente Hawaii (KPH), USA 1/2018–31/12/2019 Median FU: 730d	**Inclusion criteria:** ≥50y, ≥365d continuous enrolment **Exclusion criteria**: Immunocompromised patients, first dose RZV prior to index data, HZ diagnosis 1 year prior to index date, between 2 doses or up to 30d after second dose, single dose RZV, second dose <30d or >210d after first dose	78 356 adults 128 010 PY V2: 11 864 (15.1%) 61y (IQR 54–69) Female: 51.5% White: 30.0% Asian: 37.1% **Unvaccinated** 59y (IQR 53–65) **Vaccinated (V2)** 74y (IQR 70–80)	Vaccinated with two doses (V2) versus Unvaccinated (U)	Effectiveness against HZ Effectiveness against HZO	Moderate
19. Izurieta 2021 (19)	**Prospective cohort** USA, Medicare Median FU 2.9m (V1) 7.1m (V2)	**Inclusion criteria:** ≥65y, Medicare part D ≥ 12 m continuously, Medicare part A and B and not C at least 15 m, with and without influenza vaccine, including an auto-immune population[3] **Exclusion criteria:** nursing home, skilled nursing facility or hospice; HZ diagnosis 1 year prior	15 589 546 adults V1: 1 498 275 (9.6%) V2**:** 1 006 446 (6.5%) Female: 58.9% White: 88.0% U: 74.6y (± 6.7) V1: 73.8y (± 5.9) V2:74.0y (± 5.9)	Vaccinated (V) with one dose (V1) with two doses (V2) versus Unvaccinated (U)	Effectiveness against HZ Secondary outcomes: PHN and HZO	Moderate Unclear adjustment for confounding
20. Kochar 2021 (20)	**Retrospective cohort** USA, Explorys Health record database 10/2017–4/2020 Median FU: >9m	**Inclusion criteria:** ≥50y, with and without Inflammatory bowel disease (IBD) **Exclusion criteria:** Control: no IBD or other autoimmune disease (RA, SLE, psoriasis, ankylosing spondylitis)	**IBD** 95 070 adults V2: 1180 (1.2%) U ≥ 65y: 49% V2 ≥ 65y: 56% Female: 50.5% White: 72% **Control** 18 564 400 adults V2: 14 180 (0.1%) U ≥ 65y: 49% V2 ≥ 65y: 48% Female: 53% White U: 51% White V2:81%	Vaccinated with two doses (V2) versus Unvaccinated (U) and IBD population versus Control	Effectiveness against HZ	High because no adjustment for confounding
21. Khan 2021(21)	**Retrospective cohort study** US National Veterans Affairs Healthcare system 3/1/2018–31/10/2020 Mean FU: 1.13y	**Inclusion criteria:** ≥50y, diagnosis of inflammatory bowel disease (IBD) **Exclusion criteria:** Control: no IBD or other autoimmune disease (RA, SLE, psoriasis, ankylosing spondylitis)	33 000 adults V2 50-60y: 764 (10.9%) 50-60y Female: 17% White: 71% ≥60y Female: 4.5% White: 89%	Vaccinated with one dose (V1) with two doses (V2) versus Unvaccinated	Effectiveness against HZ	Moderate
22. Lu 2021 (22)	Retrospective observational cohort USA; OptmumLabs	**Inclusion criteria**: ≥50y, ≥ 365d of continuous enrolment in OLDW	4 842 579 adults 7 491 570 PY V2: 177 289	Vaccinated with 2 doses (V2) versus Unvaccinated (U)	Effectiveness against HZO	Moderate

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Table 2 (*continued*)

Reference	Study design	Patients inclusion and exclusion criteria	n patients Mean age (±SD) Gender Race	Intervention	Outcome	Risk of Bias
	Data warehouse (OLDW) 1/1/2018–31/12/2019 Median FU: 2y	**Exclusion criteria:** Immunocompromised patients	(3.7%) U: 64y (IQR 56–73) V2: 72y (IQR 69–77) Majority female and white			
23a. Goud 2021 (23)	Retrospective observational cohort USA, Medicare 1/10/2017–31/3/2019 Median FU: 42d	**Inclusion criteria** ≥65 years, Medicare beneficiaries **Exclusion criteria:** Long term daily therapy, admitted to nursing home, skilled nursing facility or in hospice at any point during study period, GBS diagnosis within 6 m prior to vaccination, RZV inconsistent with recommended dosing	**RZV** 849 397 adults 74.8y Female 58% **ZVL** 1 871 099 adults 74.3y Female 60%	RZV versus ZVL	Guillain-Barré syndrome (GBS)	Moderate
23b. Goud 2021 (23)	Self-controlled case series (SCCS) USA, Medicare 1/10/2017–31/3/2019 Median FU: 189d	**idem**	**RZV** 849 397 adults 74.8y Female 58%	RZV self controlled	Guillain-Barré syndrome (GBS)	Moderate

AI: auto-immune, CLL: chronic lymphocytic leukemia, d: days, FU: follow-up, HIV: human immunodeficiency virus, GBS: Guillain-Barré syndrome, HZ: herpes zoster, HZO: herpes zoster ophthalmicus, IM: intramuscular, m: months, mTVC: modified (total) vaccinated cohort, n: number, PHN: postherpetic neuralgia, pIMD: potential immune-mediated disease, PKD: polycystic kidney disease, PY: person-years, RA: rheumatoid arthritis, RZV: recombinant zoster vaccine, SD: standard deviation, SLE: systemic lupus erythematosus, TVC: total vaccinated cohort, U: unvaccinated, USA: United States of America, V: vaccinated, V1: vaccinated with one dose, V2: vaccinated with two doses, y: years, ZBPI: Zoster Brief Pain Inventory, ZVL: zoster vaccine life.

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

[2] OLDW Healthcare claims administrative database: commercial insurance, Medicare advantage or Medicare part D.

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

50/70 and the long term follow-up, and associated number needed to vaccine (NNV) are summarized in the supplementary material Table S2.

Data for immunocompetent individuals from RCTs. High quality data showed a very good vaccine efficacy against herpes zoster in older immunocompetent individuals (pooled ZOE-50 and ZOE-70), estimated at 94% (95%CI: 79–98, $p < 0.001$) overall (50 years and older) and at 91.3 % (95%CI: 86.8–94.5; $p < 0.001$) in individuals of 70 years and older during a follow-up period between 3.2 and 3.8 years [12–13]. In order to prevent 1 case of herpes zoster over respectively 3.2 years and 3.8 years, 36 individuals ≥50 years and 23 individuals ≥70 years needed to be vaccinated. There was no significant difference in vaccine efficacy between different age groups. Different subgroups were evaluated by post-hoc analysis using the pooled data from ZOE-50 and ZOE-70, including adults with at least one specific medical condition at enrolment, at least one potential immune mediated disorder (e.g. psoriasis, spondyloarthropathy) or the frailty status [35]. Overall the vaccine efficacy was high in all different subgroups, with only small differences noticed between subgroups [16,18,21]. Vaccine efficacy was also similar in males and females [22].

An overall vaccine efficacy of 90.9% (95%CI: 88.2–93.2) against HZ was reported in immunocompetent individuals ≥50y in the long-term follow-up study of ZOE-50/70 (ZOE-LTFU) during a mean follow-up of 7.1 years, resulting in an NNV of 23 [14]. The vaccine efficacy gradually declined from 97.7% (95%CI: 93.1–99.5) in the first year to about 85% in year 6 and 7. The monitoring of participants is still ongoing until 10 years after vaccination [14].

Data for immunocompetent individuals from observational studies. Vaccine effectiveness against HZ in immunocompetent individuals observed in 3 observational studies of moderate quality was lower than in the pivotal trials (between 70% and 85%) and the follow-up time was shorter (7 to 24months) [29,33,34]. Considering similar age groups, results were significantly better in ZOE-50 compared to the two observational studies in patients ≥50y (but not in ZOE-70 and combined ZOE-50/70). The two studies on individuals ≥50y that adjusted their vaccine effectiveness results for confounding [33,34] had significantly better results (85.5%, 95%CI: 83.5–87.3 and 83.5%, 95%CI: 74.9–89.2) than the study on patients ≥65y with non-adjusted results [29] (70.5%, 95%CI: 69.0–72.0). The adjusted results could not be considered in the meta-analysis with RevMan. Thus, the pooled estimates combining RCT and observational studies might be conservative.

Data for immuncompromised patients from RCTs. Good quality data (RCT) showed an adequate vaccine efficacy against herpes zoster in patients ≥18 years who underwent a hematopoietic stem cell transplantation (68.2%; 95% CI: 55.6–77.5) [23] and by post-hoc analysis in patients with haematological malignancies (80.4%; 95% CI: 73.1–86.5) [25]. The latter must be interpreted with caution because of post-hoc analysis of vaccine efficacy [25]. The pooled results of both studies showed that although the relative reduction was smaller compared to immunocompetent individuals (vaccine efficacy 70% compared to 94%) (Fig. 2), the number of cases prevented for a given number of vaccinees was much higher because the higher baseline risk. Per 10 000 person-years, there was a reduction of 618 cases in the immunocompromised patients studied, compared to a reduction of 86 cases in the older, immunocompetent adults ≥50 years (Table 3). The separately calculated NNVs for patients with HSCT and haematological malignancies,

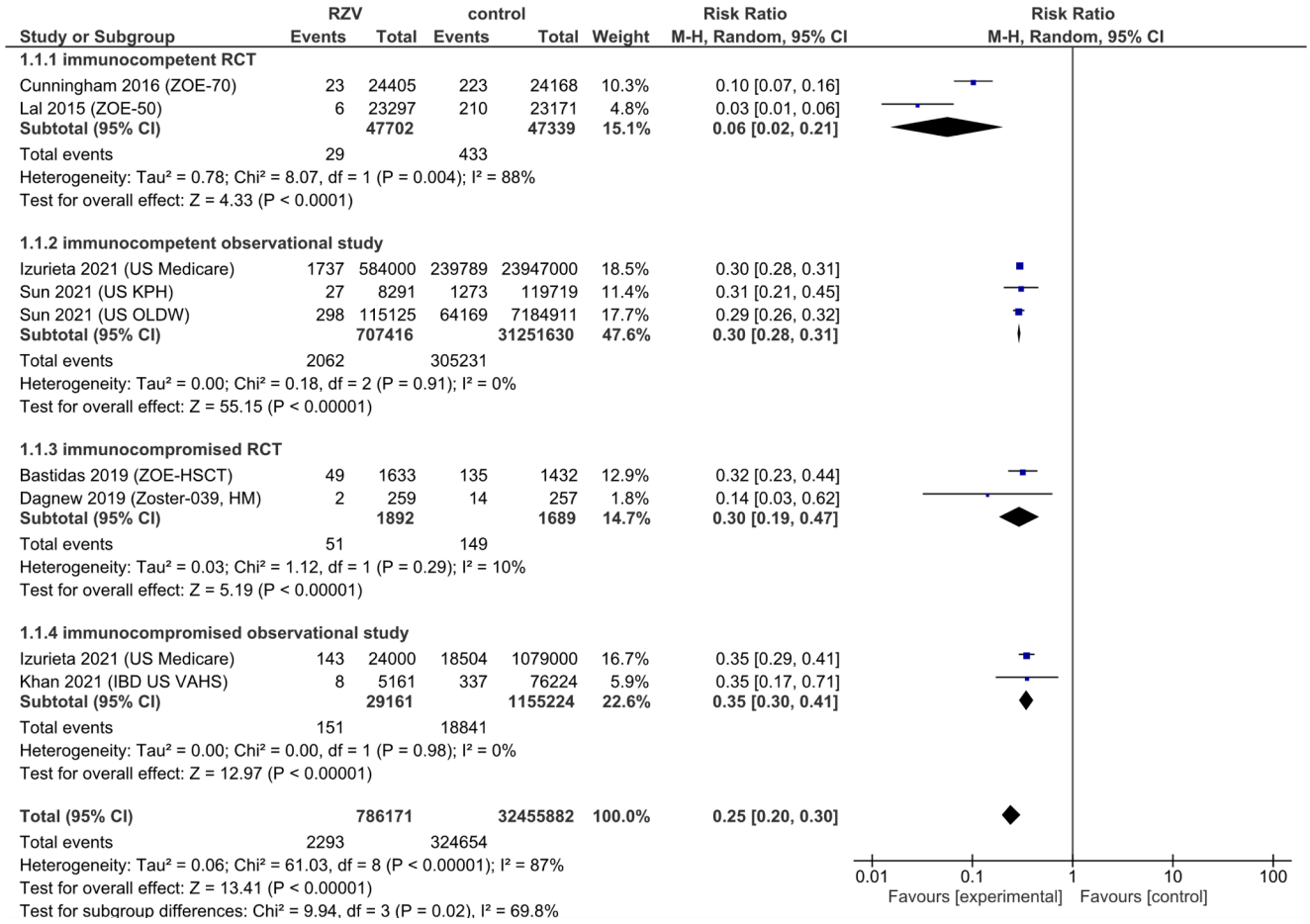

Fig. 2. Meta-analysis results on efficacy/effectiveness against HZ. References: Bastidas 2019 (1); Cunningham 2016 (2); Dagnew 2019 (3); Izurieta 2021 (4), Khan 2021 (5), Lal 2015 (6), Sun 2021 (US KPH) (7); Sun 2021 (US OLDW) (8). CI: confidence interval, HSCT: hematopoietic stem cell transplantation, HM: haematological malignancies, IBD: inflammatory bowel disease, KPH: Kaiser Permanente Hawaii, OLDW: OptmumLabs Data Warehouse, Total: total follow-up time in person-years.

were respectively about 10 and 21 (supplementary material Table S2).

Data for immunocompromised patients from observational studies. Vaccine effectiveness in the immunocompromised patients in 2 observational studies of moderate quality was similar to the efficacy in ZOE-HSCT and the RCT in patients with haematological malignancies (vaccine efficacy 65% (unadjusted) versus 70%), but the anticipated absolute effects were smaller in the real world (reduction of 106 per 10 000 person-years) [29,30] than the ones estimated in patients from ZOE-HSCT and the RCT on patients with haematological malignancies (reduction of 618 cases per 10 000 person-years [23,25]. The big difference in baseline risk might be due to the type of immunocompromised patients that were included (HSCT and HM in the RCTs compared to inflammatory bowel disease and a more heterogeneous population in observational studies (including patients with HIV/AIDS, HM, treatment-dependent and treatment independent immune deficiencies, solid malignancy, transplantation, rheumatological/inflammatory, dialysis and intermediate conditions in observational studies) [29,30]. The risk ratio (Table 3) is very similar in immunocompromised patients from RCTs and in patients (both immunocompromised an immunocompetent) from observational studies. However the results from observational studies were not adjusted to confounding, which would result in lower risk ratio's and thus real vaccine efficacy is probably higher.

Efficacy/effectiveness against PHN

Results on vaccine efficacy against PHN in RCTs can be found in Table 3 and in the supplementary material Table S2 and Fig. S4. The vaccine efficacy against PHN in older, immunocompetent individuals (ZOE-50 and ZOE-70, high quality data) was estimated at 91.2% (95% CI: 75.9–97.7; $p < 0.001$) in individuals 50 years and older and at 88.8% (95%CI: 68.7–97.1; $p < 0.001$) in individuals 70 years and older during a follow-up period of 3.8 years [12]. The number of cases prevented for a given number of vaccinations (8 per 10 000 person-years) was much lower than for HZ (86 per 10 000 person-years). The NNV over a period of 3.8 years is almost 335 for individuals ≥50 years and 261 for individuals ≥70 years. Prevention of PHN during long-term follow-up (ZOE-LTFU) was not reported so far. A big size cohort study in a population of mostly immunocompetent adults ≥65 years reported a lower vaccine effectiveness (76%; 95%CI: 68–82), but similar absolute risk reduction during a limited follow-up of 7 months [29]. When we combine the results of RCTs and observational study, there is a risk reduction of 16% (95%CI: 6–41%) resulting in a vaccine efficacy of 84%. Of note heterogeneity between studies was high ($I^2 = 70\%$), a result which was not unexpected given different age ranges are considered. The vaccine efficacy against PHN in immunocompromised patients with HSCT was estimated at 89.3% (95%CI: 22.5–99.8) during 21 months of follow-up [23] and the NNV was calculated at 115. The results were thus similar to immunocompetent adults, but imprecise because of a low number of events and relatively low number of participants. Per 10 000 person-years, there was a reduction of 44 cases in the immunocompromised patients studied, compared to a reduction of 8 cases in the older, immunocompetent adults.

Table 3
Quality of evidence and summary of findings.

Outcomes		N° of person-years (studies)Follow-up	Certainty of the evidence(GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
					Risk with placebo or no vaccination	Risk difference with RZV
Herpes zoster	**Immunocompetent adults ≥50y**	95,041 (2 RCTs) (1, 2) FU 3.2–3.8 y	⊕⊕⊕⊕ High	**RR 0.06** (0.02 to 0.21)	91 per 10,000 PY	**86 fewer per 10,000 PY** (90 fewer to 72 fewer)
		31,959,046 (3 observational studies) (3–5) FU 7 m-2y	⊕⊕⊕∩ Moderate§	**RR 0.30** (0.28 to 0.31)	98 per 10,000 PY	**68 fewer per 10,000 PY** (70 fewer to 67 fewer)
	Immunocompromised adults ≥18y	3581 (≥18y) (2 RCTs) (6, 7) FU 12.1 m-21m	⊕⊕⊕∩ Moderate[a]	**RR 0.30** (0.19 to 0.47)	882 per 10,000 PY	**618 fewer per 10,000 PY** (715 fewer to 468 fewer)
		1,184,385 (≥50y) (2 observational studies) (3, 8) FU 7.1–1.13y	⊕⊕⊕∩ Moderate§	**RR 0.35** (0.30 to 0.41)	163 per 10,000 PY	**106 fewer per 10,000 PY** (114 fewer to 96 fewer)
PHN	**Immunocompetent adults ≥50y**	106,717 (2 RCTs) (1, 2) FU 3.7–3.9y	⊕⊕⊕⊕ High	**RR 0.09** (0.03 to 0.24)	9 per 10,000 PY	**8 fewer per 10,000 PY** (8 fewer to 7 fewer)
	Mixed population, mostly immunocompetent ≥65y	20,097,000 (1 observational study) (3) FU median 7.1m	⊕⊕⊕∩ Moderate§	**RR 0.23** (0.18 to 0.30)	10 per 10,000 PY	**8 fewer per 10,000 PY** (8 fewer to 7 fewer)
	Immunocompromised adults ≥18y	3731 (1 RCT) (6) FU 21m	⊕⊕∩∩ Low[a,b]	**RR 0.11** (0.01 to 0.85)	49 per 10,000 PY	**44 fewer per 10,000 PY** (49 fewer to 7 fewer)
HZO	**Immunocompetent adults ≥50y**	106,755 (2 RCTs) (9) FU 3.7–3.9y	⊕⊕⊕∩ Moderate[b]	**RR 0.04** (0.00 to 0.31)	1 per 10,000 PY	**1 fewer per 10,000 PY** (1 fewer to 1 fewer)
	Mixed population, mostly immunocompetent ≥50y	33,473,713 (3 observational studies) (3, 4, 10) FU 7.1 m-2y	⊕⊕⊕∩ Moderate§	**RR 0.33** (0.29 to 0.38)	8 per 10,000 PY	**5 fewer per 10,000 PY** (5 fewer to 5 fewer)
Hospitalisation	**Immunocompetent adults ≥50y**	106,755 (2 RCTs) (9) FU 3.7–3.9y	⊕⊕∩∩ Low[b]	**RR 0.09** (0.01 to 1.66)	1 per 10,000 PY	**1 fewer per 10,000 PY** (1 fewer to 1 more)
	Immunocompromised adults ≥18y	3713.3 (1 RCT) (6) FU 21m	⊕⊕∩∩ Low[a,b]	**RR 0.15** (0.03 to 0.66)	71 per 10,000 PY	**61 fewer per 10,000 PY** (69 fewer to 24 fewer)

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; FU: follow-up, HZO: herpes zoster ophtalmicus; m: months, PHN: post-herpetic neuralgia, RR: rate ratio, y: years; PY: person-years
GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.
Following GRADE methodology, the quality of evidence was one level downgraded in case of serious imprecision and by 2 levels in case of very serious imprecision. Reason for imprecision was (a) low number of participant and/or (b) low number of events. (§)The quality of evidence was upgraded by one level when a large effect was reported.

Efficacy/Effectiveness against other complications of HZ and hospitalisation

Results on vaccine efficacy against HZO and hospitalisation in RCTs are summarized in Table 3 and more details can be found in the supplementary material (Table S2, Fig. S5 and S6). There was low quality of evidence from clinical studies on the protection of older, immunocompetent adults against other complications including herpes zoster ophtalmicus and hospitalisation [19]. There was moderate quality of evidence based on three observational studies that RZV is effective against HZO (67%; 95%CI: 62–71) in mostly immunocompetent adults ≥50 years [29,32,33], but the absolute risk reduction was small (5 cases per 10000 person-years, unadjusted data). This kind of data was not available for hospitalisation in the real world. For immunocompromised adults who underwent HSCT, there was also low quality evidence that RZV would significantly reduce the number of hospitalisations and other complications [23].

Quality of life

Two papers evaluated the effect of vaccination on quality of life using SF-36 health survey, EuroQol-5 Dimension (EQ-5D) utility index, the burden of illness score and burden of interference with activities of daily living score. These last two scores were calculated from the area under the curve (d0-d182) of the Zoster Brief Pain inventory (ZBPI) worst pain

and ZBPI activities of daily living scores, reflecting incidence of HZ on the one hand and duration and intensity of pain or duration and degree of interference with activities of daily living on the other hand. A score of 0 was given to patients without confirmed HZ [17,24]. The results for immunocompetent adults were not always very clear, but there was a significant reduction in maximum worst pain score ($p = 0.032$) in the pooled ZOE-70 population after vaccination. However, the significant reduction in burden of illness (vaccine efficacy of 92.1% in pooled ZOE-70 (95%CI: 90.4–93.8) and 98.4% in ZOE-50 (95%CI: 92.2–97.7)), was mostly explained by the high efficacy of preventing HZ [17]. For patients after HSCT there was also a significant reduction in maximum worst pain score from 7.1 to 5.8 ($p = 0.011$) and vaccine efficacies against burden of illness of 82.5% (95%CI: 73.6–91.4) and against burden of interference of 82.8% (95%CI: 73.3–92.3), which were higher than its efficacy against HZ (68%) [24]. Data were considered not suitable for meta-analysis.

Reactogenicity

In the pivotal trials on older, immunocompetent adults, local reactions (including pain, redness and swelling) occurred more frequently in individuals vaccinated with RZV (between 74% and 82%) compared to placebo (between 10% and 12%). Local reactions occurred more frequently in the ZOE-50 trial, compared to the ZOE-70 trial, suggesting that reactions diminish with age (supplementary material Table S4). This was shown in the ZOE-70 trial, where patients 70–79 years had more reactions than patients ≥80 years. The same was true for systemic reactions like headache, fatigue, gastrointestinal symptoms, myalgia, shivering and fever. The frequency of severe, grade 3 reactions varied around 9% for local reactions (similar in ZOE-50 and ZOE-70) and between 6% and 11% for systemic reactions [12,13]. Frail individuals also had lower reactogenicity compared to pre-frail and non-frail individuals [16]. Median duration of local symptoms were 2 days and of systemic reactions 3 days.

In the trials on immunocompromised adults [23,25–27], the frequency of local reactions (any or grade 3) largely overlapped with immunocompetent adults (somehow higher for patients after HSCT). The frequency of systemic reactions was higher in immunocompromised compared to immunocompetent adults (except for patients with renal transplant), both after RZV and placebo [27]. For solid tumour and renal transplant patients, there was no significant difference between the occurrence of systemic grade 3 reactions between RZV and placebo. The higher frequency of systemic reactions is probably linked to the underlying disease and/or treatment in this immunocompromised population.

Safety

No differences were observed in severe adverse events between RZV and placebo. This was the case fordifferent patient populations including immunocompetent [12,13,20] and immunocompromised adults [23,25–27], adults with at least one medical condition at enrolment [21], with different frailty status [16] and with at least one potential immune-mediated disorder at enrolment [18].

The reported frequency of potential immune-mediated disorders was low and balanced between RZV and placebo recipients, and similar in immunocompetent [23,25–27] and immunocompromised adults [23,25–27].

A publication by Goud et al. reported on the risk for Guillain-Barré syndrome in a cohort study and in a self-controlled case study among community-dwelling Medicare beneficiaries of 65 years or older. The cohort study showed a relative risk for GBS in the RZV group compared to the ZVL group of 2.34 (95%CI: 1.001–5.41; $p = 0.047$). The self-controlled case series showed an increased risk for GBS in the risk window (42 days) compared to the control window ($RR = 2.84$; 95%CI: 1.53–5.27; $p = 0.001$), resulting in an attributable risk of 3 per million RZV doses (95%CI: 0.62–5.64) [28]. However, this was not confirmed in post-licensure safety surveillance. The number of observed cases of GBS was lower than the number of expected cases, concluding insufficient evidence of a causal relationship between RZV and GBS [36,37].

No other unexpected patterns for (serious) adverse events were detected in post-licensure safety surveillance, confirming findings from early monitoring of RZV [36–38]. After 9.3 million doses were administrated, 168 adverse events per 100 000 doses were reported of which 4.7% were serious including 9 deaths. Reports were linked to reactogenicity in 49.8 per 100 000 doses and to pIMD in 1.1 per 100 000 doses. The reports also documented 837 herpes zoster events, 25 cases of HZO (0.3 per 100 000 doses) and 21 cases of PHN (0.2 per 100 000 doses) after vaccination [37].

Discussion

In the two pivotal RCTs, vaccine efficacy of RZV against HZ and PHN was very high in immunocompetent older adults, respectively about 94% and 91% ≥50y, and 91% and 89% ≥70y, and remained very good against HZ after 7 years follow-up (91%). Also in immunocompromised patients, like patients with HSCT, the vaccine efficacy was very acceptable at 68% against HZ and 89.3% against PHN. Finally, observational studies confirmed a good vaccine effectiveness, albeit lower than in RCTs, ranging between 70% and 85%. Two previously performed network meta-analyses reported a significantly higher vaccine efficacy against herpes zoster of RZV (intramuscular (IM)) compared to ZVL (subcutaneous (sc)) [39,40].

Despite a high vaccine efficacy in immunocompetent populations demonstrated in pivotal RCTs, high numbers of persons are needed to be vaccinated to prevent a relatively low number of events, especially for PHN. For a follow-up of 7.1 years, the NNV to prevent a case of herpes zoster was calculated to be 23. Thus even after a follow-up of 15 years, assuming no further waning, the NNV will still be higher than 10. Vaccine efficacy was slightly lower in immunocompromised patients, probably reflecting a weaker immune response due to underlying disease and/or medication. However the absolute reduction in the number of cases was higher because of a higher baseline risk of HZ and its complications in this population. The vaccine effectiveness in the real world was also lower compared to vaccine efficacy in the pivotal trials (significant only compared to ZOE-50), even in studies with adjustment for confounding factors [33,34]. This can be expected due to the inclusion of patients with comorbidities, diseases and medication, that have been excluded from participation in RCTs, for example individuals with ‘significant underlying illness that (in the opinion of the investigator) would be expected to prevent completion of the study’ or ‘chronic administration of immunosuppressants are other immune-modifying drugs within 6 months prior to the first vaccine dose (corticosteroids > 20 mg/d) or ‘any other condition that (in the opinion of the investigator) might interfere with the evaluations required by the study’ [13].

In the Belgian population ≥50 years, nearly 32 000 cases of HZ are diagnosed every year, of which 4800 develop into PHN. About 900 persons are hospitalised with HZ as major diagnosis and 11 patients die every year [41]. Belgium is counting 4.6 million people ≥50y and 3 million people ≥60y. Thus preventing HZ would require vaccinating huge populations. In the pivotal tirals, the NNV for prevention against HZ was 36 (individuals ≥50y during 3.2 years) and 32 (individuals ≥70y during 3.8 years). Taking into account the actual Belgian incidence rates, vaccinating 10 000 persons of 50 years and older would prevent 64 cases of herpes zoster, 8–10 cases of PHN and<2 hospitalisations every year. Vaccinating 10 000 persons of 60 years and older would prevent 77 cases of herpes zoster, 10–12 cases of PHN and 2–3 hospitalisations every year..

No relevant safety signals have been identified so far. Despite the high reactogenicity of the RZV vaccine, which was generally limited in extent and duration, the second dose compliance both in immunocompetent and immunocompromised participants was very good and ranging between 90% and almost 100% [12,13,23,25–27]. To enhance shared decision-making, individuals must be informed before vaccination of the efficacy and side-effects of the vaccine.

The main strengths of this systematic review is its full compliance with PRISMA requirements, meta-analysis of results for both immunocompetent and immunocompromised patients, and the inclusion of real world population studies which permit an appraisal of vaccine effectiveness and safety.

However, including observational studies in meta-analysis has also drawbacks. In particular, including results adjusted for confounders in the meta-analysis is challenging [42]. Moreover, substantial differences in study populations increase the heterogeneity of results. The same problem is apparent when combining immunocompetent and immunocompromised populations.

Another limitation was that studies in immunocompromised patients included often only small number of patients and efficacy was only estimated in patients after HSCT and with HM, and the latter was performed post-hoc. Studies on other immunocompromised patients did not include data on efficacy, but only on immunogenicity. This is a difficulty as the threshold of cell-mediated immunity ensuring protection is unknown, and the humoral immunity does not play an important role in HZ protection. Moreover, all studies in immunocompromised patients were short term (not >2 years) and the waning over a longer time span is still unknown.

During the reviewing process of this manuscript, interim results 10 years after vaccination (ZOE-LTFU) were published [43]. They included overall vaccine efficacy against HZ for immunocompetent individuals ≥50y of 89.0% (95%CI: 85.6–91.3) during a mean follow up of 9.6 years. The vaccine efficacy gradually declined from 97.7% (95%CI: 93.1–99.5) in the first year to about 73% in year 9 and 10. The published interim results did no yet include data on PHN and the effect of additional RZV doses [43]. Additional randomized controlled trials on vaccine efficacy in patients with various immunocompromising conditions, and longer term real world and post-surveillance data can further consolidate our findings. Of note, trials on patients with systemic lupus erythematosus (SLE) (NCT04516408), rheumatic disease (NCT04748939), and patients who had previously had an episode of herpes zoster (NCT04091451) are on-going.

Conclusion

Although vaccine efficacy in RCTs and effectiveness in the real world has been reported to be good, it needs to be stressed that high numbers of immunocompetent adults need to be vaccinated to prevent low number of cases of RZV and its complications. Due to higher incidence of HZ andits complications in immunocompromised patients, lower NNVs were calculated in that specific population compared to immunocompetent adults. However, efficacy beyond two years in this vulnerable population is still unknown. Vaccinated adults should be informed about the high incidence of, albeit mostly mild to moderate, reactogenicity of the vaccine to ensure uptake of the 2 doses of the vaccine.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jvacx.2023.100397.

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