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Review

The comparative efficacy and safety of herpes zoster vaccines: A network meta-analysis ☆

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ABSTRACT

Background: We estimated the relative efficacy and safety of vaccines for prevention of herpes zoster (HZ) using network meta-analysis (NMA) based on evidence from randomized controlled trials.
Methods: A systematic literature review evaluated two different HZ vaccines: adjuvanted recombinant zoster vaccine (RZV) and zoster vaccine live (ZVL), with different formulations assessed. Detailed feasibility assessment indicated that a NMA was feasible for efficacy (incidence of HZ and postherpetic neuralgia [PHN]) and safety (serious adverse events [SAE] and reactogenicity [injection-site reactions, systemic reaction]) outcomes. Primary analyses included frequentist NMAs with fixed effects for efficacy outcomes, due to limited data availability, and both fixed and random effects for safety and reactogenicity outcomes. As age is a known effect modifier of vaccine efficacy (VE), VE analyses were stratified by age.
Results: RZV demonstrated significantly higher HZ efficacy than ZVL in adults ≥60 years of age (YOA) (VE_{RZV} = 0.92 (95% confidence interval [95%CI]: 0.88, 0.94), VE_{ZVL} = 0.51 (95%CI: 0.44, 0.57)) and adults ≥70 YOA (VE_{RZV} = 0.91 (95%CI: 0.87, 0.94), VE_{ZVL} = 0.37 (95%CI: 0.25, 0.48)). Similarly, RZV demonstrated significantly higher PHN efficacy than ZVL in adults ≥60 YOA (VE_{RZV} = 0.89 (95%CI: 0.70, 0.96), VE_{ZVL} = 0.66 (95%CI: 0.48, 0.78)) and adults ≥70 YOA (VE_{RZV} = 0.89 (95%CI: 0.69, 0.96), VE_{ZVL} = 0.67 (95%CI: 0.44, 0.80)). RZV was associated with significantly more injection-site and systemic reactions compared to most formulations of ZVL and placebo, however definitions and data collection procedures differed across the included studies. There were no statistically significant differences found between RZV and any formulation of ZVL or placebo for SAEs.
Conclusion: RZV is significantly more effective in reducing HZ and PHN incidence in adults ≥60 YOA, compared with ZVL. As anticipated with an adjuvanted vaccine, RZV results in more reactogenicity following immunization. No differences in SAEs were found between RZV and ZVL.

Abbreviations: ACIP, Advisory Committee on Immunization Practices; BIKEN, live attenuated Oka varicella vaccine manufactured by the Research Foundation for Microbial Diseases of Osaka University; CI, confidence interval; CIQ, Comité sur l'immunisation du Québec; FDA, Food and Drug Administration; HZ, herpes zoster; ID, intradermal; IM, intramuscular; IRR, incidence rate ratio; NACI, National Advisory Committee on Immunization; NMA, network meta-analysis; PHN, post-herpetic neuralgia; RCT, randomised controlled trial; RZV, recombinant zoster vaccine; SAE, serious adverse event; SC, subcutaneous; SLR, systematic literature review; SPS, Shingles Prevention Study; VE, vaccine efficacy; VZV, varicella zoster virus; ZEST, Zoster Efficacy and Safety Trial; ZVL, Zoster Vaccine Live.

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1. Introduction

Infection with varicella zoster virus (VZV) causes chickenpox in children, and can reappear in adults as herpes zoster (HZ), also known as shingles [1]. Post-herpetic neuralgia (PHN) is a common complication of HZ, characterised by constant, severe stabbing or burning pain [2] that adversely affects patients' quality of life [3].

Treatment for HZ is complex and only partially effective, while interventions to prevent HZ have potential to reduce the burden of HZ and PHN [3]. The administration of HZ vaccines to older individuals can boost VZV-specific immunological memory and in turn, prevent viral reactivation and HZ development. Two zoster vaccines are currently available in the United States (US) and Canada, Zoster Vaccine Live (ZVL) and adjuvanted Recombinant Zoster Vaccine (RZV). Other zoster vaccines are available elsewhere in the world. ZVL (*Zostavax* [frozen] originally licensed in Canada in September 2015 but no longer marketed in Canada and *Zostavax II* [refrigerated, available in Canada as of licence date May 2014], Merck Sharp and Dohme) is indicated for use in individuals aged 50 years or over and contraindicated for use in immunosuppressed or immunodeficient individuals in whom administration of ZVL may result in disseminated disease [4]. ZVL is administered as a single dose [4]. The efficacy and safety of the ZVL vaccine has been demonstrated in two phase III placebo-controlled randomised controlled trials (RCT). Firstly, the Shingles Prevention Study (SPS) which included over 38,000 subjects aged at least 60 years [5] and secondly the Zoster Efficacy and Safety Trial (ZEST) which included over 22,000 subjects aged 50–59 years [6]. RZV (*Shingrix*, GSK) was approved by the Food and Drug Administration (FDA) and Health Canada in October 2017 for prevention of HZ in adults aged 50 years and older [7,8]. It is a non-live adjuvanted subunit vaccine combining glycoprotein E, a protein found on the surface of VZV, with an adjuvant system $AS01_B$ that is intended to enhance the immunological response to the glycoprotein E antigen. The primary vaccination schedule for RZV consists of two doses, with the second dose administered at any time between 2 and 6 months after the first [8]. The efficacy and safety of the RZV vaccine has also been demonstrated in two phase III RCTs, ZOster Efficacy in adults aged 50 years and over (ZOE-50) and ZOster Efficacy in adults aged 70 years and over (ZOE-70), which together included approximately 30,000 subjects aged at least 50 years [9,10].

RCTs for ZVL and RZV have compared the efficacy and safety of the respective HZ vaccines versus placebo. To date there have been no head-to-head trials directly comparing the relative efficacy of the vaccines. A Cochrane systematic literature review (SLR) published in 2016 reviewed 13 RCTs comparing HZ vaccines with placebo or no vaccine, but did not compare the ZVL and RZV vaccines [11]. Further, this review was published before both the clinical efficacy studies for RZV were available. Preliminary data from one study, published as an abstract, compared the immunogenicity of the ZVL and RZV vaccines and reported higher cell-mediated immunity (CMI) responses for the RZV vaccine than the ZVL vaccine, but did not report on clinical efficacy or safety [12]. As such, there is a need for information on the relative efficacy and safety of available HZ vaccines to help support decision-makers and healthcare professionals selecting optimal ways to use the interventions.

In the absence of head-to-head clinical trials directly comparing the two interventions, relative efficacy can be investigated by using the technique of network meta-analysis (NMA), an extension of traditional pair-wise meta-analysis [13]. Provided that all the published trials have at least one intervention in common with another, a network can be constructed linking the interventions tested in each trial. Relative effects can then be estimated for all interventions included in the network. While NMAs have been frequently used in other therapeutic areas, the technique has not often been applied to vaccines. A recent NMA, published while this study was being conducted, compared the efficacy, effectiveness, and safety of HZ vaccines; however, they were not able to evaluate relative PHN efficacy (comparing RZV to ZVL) and did not stratify efficacy results by age which is a known effect modifier of vaccine efficacy (VE) [14]. The objective of the present study was to evaluate the relative efficacy and safety of HZ vaccines in adults aged 50 years or older using a NMA based on evidence from published RCTs.

2. Material and methods

2.1. Systematic literature review

A literature search was conducted to identify RCTs evaluating the efficacy and safety of HZ vaccines, using Population, Interventions, Comparators, Outcomes and Study Design (PICOS) criteria as follows:

- **Population:** Adults aged 50 years or older, with no history of prior HZ infection. Studies conducted in immunocompromised patients were excluded.
- **Interventions:** Interventions included all HZ vaccines, regardless of the dose, schedule, preparation, or route of administration.
- **Comparators:** Comparators included other HZ vaccines, placebo or no intervention (including studies evaluating different doses, schedules, preparations, or routes of administration).
- **Outcomes:** Efficacy outcomes included: incidence of HZ (full duration of follow-up or repeated measures); incidence of PHN (full duration of follow-up); incidence of other HZ complications such as HZ ophthalmicus, and visceral, dermatologic, neurologic/neurovascular conditions at last assessed follow-up; and HZ burden of illness mean score. Safety outcomes included total discontinuations, serious adverse events (SAEs), and reactogenicity (injection site/local reactions [pain, redness and swelling at injection site]; and systemic reactions [fatigue, fever, myalgia, gastrointestinal symptoms and headache]).
- **Study Design:** Full-text publications and conference abstracts showing results of phase II, III and IV RCTs were included.

Full details of the PICOS selection criteria used are provided in Supplementary File S1. There were no restrictions on publication date or language. Only human studies were included.

The primary search was conducted on 7 March 2017 in MEDLINE, MEDLINE in Process, EMBASE, and Cochrane Central Registry of Controlled Trials (CENTRAL) simultaneously, using Ovid and included studies published before 7 March 2017. Details of the search strategy are provided in Supplementary File S2. In addition, the Cochrane Database of Systematic Reviews was searched for existing SLRs related to clinical efficacy and/or safety and/or reactogenicity of RCTs for HZ vaccines. Conference abstracts from the 2016 ID Week (IDSA, SHEA, HIVMA, and PIDS joint meeting) [15] were also searched, as this is the major conference for presentation of new vaccine data and it was assumed that anything presented prior to 2016 would be available as a full-text publication.

Publications were initially screened using title and abstract by two independent researchers. For publications assessed as potentially relevant, full-text articles were obtained and evaluated against the selection criteria. Full-text review was conducted by two independent researchers in a double-blind process and all discrepancies were judged by a third reviewer. A kappa statistic was calculated to assess the level of agreement during screening.

For each publication that met the selection criteria, data extraction was performed by one researcher and checked against the original study by an independent researcher. Data on study and patient characteristics were extracted in order to evaluate the comparability of the studies and patients. For outcomes, data were extracted from the text or tables in the publication where available.

Each study included was assessed for internal (amount of selection, information and confounding bias) and external (generalizability of study results) validity, using the Cochrane Risk of Bias Tool, which has been tested for internal consistency, reliability, and validity [16].

2.2. Network meta-analysis feasibility assessment

The feasibility of conducting a valid NMA was evaluated using a standardized approach [17], in order to determine if there were sufficient data for analysis and to ensure that the transitivity assumption held [18]. Transitivity implies that there are no systematic differences between the available comparisons other than the vaccines being examined (i.e. participants in the head-to-head studies included could have been randomized to any of the vaccines). As such, all included trials were examined in terms of covariates which could act as potential treatment effect modifiers. These were identified a priori and included age, sex, race, follow-up time, interventions and dose schedules, study design and quality, and outcome definitions. Due to the limited number of studies available, meta-regression could not be conducted for any of the covariates of interest. Differences in age were accounted for by splitting the data into age groups of ≥60 and ≥70 years of age, respectively. Differences in race were not relevant since the two studies on exclusively Japanese participants were excluded due to being disconnected from the network [19] or not approved for use in the population of interest [20]. We accounted for differences in follow-up time by suitable methodology (e.g. by considering person-years at risk and number of events in a model for count data) and conducted separate analyses for longer duration of follow-up in the safety analyses. Interventions were defined according to mode of application, dose and potential refrigeration. For both efficacy and safety outcomes, definitions over the included studies were deemed comparable. Of note, the degree of severity of the safety outcomes for reactogenicity was not included in the analysis, only the incidence. Overall, we ensured that only similar study data were pooled, applying the measures described above.

2.3. Network meta-analysis

In the absence of head-to-head clinical trials directly comparing the two interventions, relative efficacy was examined using NMAs. Efficacy outcomes were examined in terms of vaccine efficacy (VE) and incidence rate ratios (IRRs), and safety outcomes were examined as IRRs. NMAs were conducted using a frequentist approach based on weighted regression models whereby larger studies which have smaller standard errors are given more weight than the smaller ones [21]. In this type of analysis, the relative effects of each intervention is presented as a point estimate (e.g. VE, IRR) along with corresponding 95% confidence intervals (CI). For the efficacy outcomes, only fixed-effect frequentist NMA models were run due to the limited number of studies available. For the safety outcomes, slightly more data were available and therefore both fixed- and random-effects frequentist NMA models were used, with the final model selected based on model heterogeneity features. For frequentist analyses, point estimates reflect the average relative effect observed, while 95% CIs reflect the frequency (i.e., the proportion) of CIs that contain the true value in a hypothetical repeated experiment. The estimated p-scores (probability of an intervention being best) are used to rank all interventions. Frequentist results cannot be interpreted in terms of absolute expected results for each intervention. Heterogeneity features are demonstrated in terms of Cochran's Q-statistic and I^2, however, these should be interpreted with care when applied to small networks.

With regards to selection of comparator data, selection rules for including or excluding studies from the networks were developed in consultation with statistical and clinical experts, to ensure that patients were not double-counted in cases where multiple publications presented results for a single trial or where pooled data were available for age subgroups of interest. For RZV efficacy, as the vaccine was developed to be administered in a 2-dose schedule, the modified vaccinated cohort was preferred over the total vaccinated cohort, similar to the pre-specified primary endpoint population, to ensure the patients would have received both doses of vaccine. For safety of RZV, the total vaccinated cohort was used, as per ICH guidelines, so some patients had received only one dose [22]. The number of patients receiving only one dose was small; in the ZOE-50 trial, 95.6% of RZV recipients and 96.4% of placebo recipients received both doses, and in the ZOE-70 trial, 94.4% of RZV recipients and 95.6% of placebo recipients received both doses. For details of the decision rules applied in selecting studies for the analysis, see Supplementary File S3.

The frequentist NMA was conducted using the R package netmeta [23].

3. Results

3.1. Systematic literature review

A total of 1290 citations were identified from the literature searches, of which 89 were retrieved for full-text screening and 25 were included in the review (Fig. 1). The kappa statistic was 0.61 (good agreement) for the screening of studies from the databases, 0.88 (excellent agreement) for the conference abstracts, and 0.73 (good agreement) for the full-text screening. The 25 publications related to 21 trials, and included 21 full-text publications and 4 conference abstracts [5,6,9,10,19,20,24–42].

The key characteristics of the included studies are summarised in Table 1. Of the 21 trials, 18 were multi-centre and 3 were

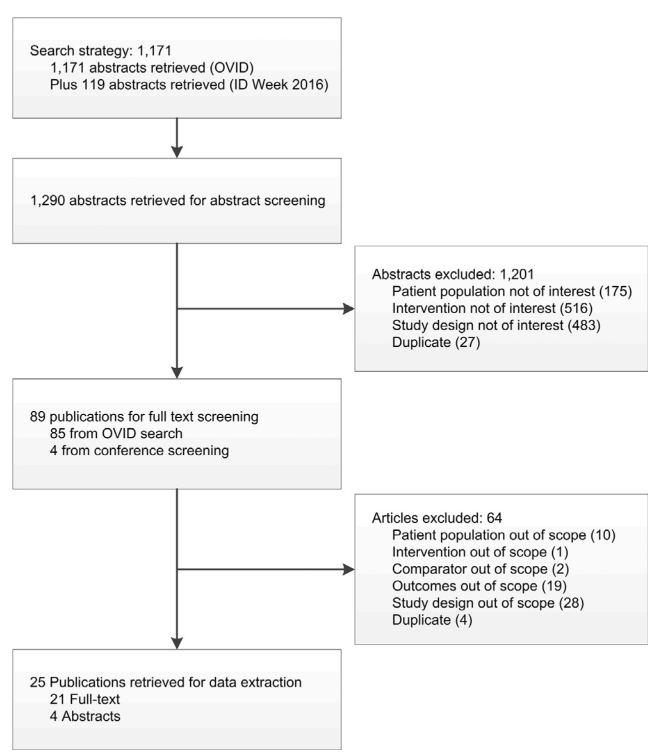

Fig. 1. Flow diagram of search results and study selection.

Table 1
Key study characteristics.

Author(s), Year	Study Acronym or NCT number	Investigational Interventions (route of administration)	Study design	# Centres/ location (Study start - Study end date)	Planned study duration (Mean/Median follow-up duration)	Summary of inclusion/exclusion criteria
Lal 2015* [9] McElhaney 2016a [32] Curran 2016a [27]	ZOE-50	RZV (IM) Placebo	Phase 3, DB, MC, RCT	18/Multi (Enrollment: Aug 2010 - Jul 2011)	ND (Mean: 3.5 yrs)	**Included:** ≥50 years old **Excluded:** immunocompromised from disease; Active neoplastic disease; prior HZ; previously vaccinated against varicella or HZ
Cunningham 2016* [10] Cunningham 2016 McElhaney 2016b [32] Curran 2016b [27]	ZOE-70	RZV (IM) Placebo	Phase 3, DB, MC, RCT	18/Multi (Enrollment: Aug 2010 - Jul 2011; Last study visit: Jul 2015)	ND (Mean: 3.7 yrs)	**Included:** ≥70 years old **Excluded:** immunocompromised from disease; Active neoplastic disease; prior HZ; previously vaccinated against varicella or HZ
Vink 2017 [20]	NCT01777321	RZV (SC) RZV (IM)	Phase 3, OL, single centre RCT	1/Japan (Jun 2013 - Nov 2014)	12 months + post-dose #2 = 14 months total	**Included:** ≥50 years old, Japanese, healthy **Excluded**: prior HZ episode, prior VZV or HZ vaccination
Poder 2016 [35]	NCT01751165	RZV (IM); RZV (IM), 0,6-mo, RZV (IM), 0,12-mo	Phase 3, OL, MC RCT	NR/US, Estonia (ND)	1 month post dose 2 for immunogenicity; up to 12 months post dose 2 for safety and reactogenicity	**Included:** ≥50 years old, US and Estonia **Excluded**: history of HZ, prior HZ or VZV vaccination, administration of immune-modifying drugs, immunosuppressants
Chlibek 2013 [26]	NCT00802464	RZV (IM) RZV (IM), $AS01_E$ Placebo (unadjuvant gE/ saline) Placebo (saline)	Phase 2, OB, MC RCT	12/Czech Republic, Spain, US (Jan 2010 - Jul 2010)	3 months for primary CMI endpoint; 1 month safety	**Included:** ≥50 years old **Excluded**: history of HZ, prior HZ or VZV vaccination, confirmed or suspected immunosuppressive or immunodeficient condition
Schwarz 2016 [38]	NCT01954251	RZV (IM) + IIV4 (IM); IIV4 (IM)	Phase 3, OL, MC RCT	NR/Canada, Germany, US (ND)	21 days after dose 1 and 1 month after dose 2 for CMI; 30 days for safety and 12 months for SAEs	**Included:** ≥50 years old **Excluded**: ND
Oxman 2005* [5] Oxman 2008 [34] Simberkoff 2010 [39]	SPS	ZVL (SC); Placebo	Phase 3, DB MC RCT	22/US (Nov 1998 - Sep 2001)	(Mean: 3.13 yrs; Median: 3.12 yrs)	**Included:** ≥60 years old, VZV history **Excluded:** immunocompromised from disease; Active neoplastic disease; prior HZ
Schmader 2012b [37]	STPS	ZVL (SC); Placebo	DB MC RCT	12/US (Oct 2005 - Mar 2006)	ND	**Same as SPS study**
Beals 2016 [24]	NCT01385566	ZVL (SC) Full-dose; ZVL (SC) 1/3-dose; ZVL (ID) Full-dose; ZVL (ID) 1/3-dose; ZVL (ID) 1/10-dose; ZVL (ID) 1/27-dose	RCT, partly blinded, MC	3/US (Sep 2011 - Jan 2012)	6 weeks	**Included:** ≥50 years old, VZV history **Excluded:** immunocompromised from disease; prior HZ
Berger 1998 [25]	Berger 1998	ZVL (SC) 3200 pfu; ZVL (SC) 8500 pfu; ZVL (SC) 41,650 pfu; PPV23 (SC)	DB, single centre, RCT (PPV23 arm was SB)	1/Switzerland (ND)	42 days	**Included:** ≥55 years old, VZV history, immunocompetent **Excluded:** prior HZ episode, immunosuppressive condition, prior VZV or HZ vaccination
DiezDomingo 2015 [28]	NCT01391546; 2009-012458-19	ZVL (IM); ZVL (SC)	MC, non-inferiority RCT	7/Germany; 3/ Spain (Jun 2011 - Sep 2012)	35 days	**Included:** healthy subjects ≥50 years old, VZV history **Excluded:** prior HZ; immunocompromised from disease.
Gilderman 2008 [29]	Protocol010	ZVL (SC) Refrigerated ZVL (SC) Frozen	DB, MC, RCT	US (Jul 2005 - Oct 2005)	28 days	**Included:** Immunocompetent subjects; ≥50 years old; with a history of varicella. **Excluded:** prior HZ; immunocompromised from disease.
Hata 2016 [19]	UMIN000004771	BIKEN/Oka vaccine + PPV23 (SC); Placebo + PPV23 (SC)	DB, single centre, RCT	1/Japan (Mar 2011 - Jan 2014)	3 months for primary CMI endpoint; 42 days for safety	**Included**: Diabetes mellitus patients had HbA1c levels within the range 6–9.5% (Japan Diabetes Society) or 6.4– 9.9% (National Glycohaemoglobin Standardization Program), aged 60–70 years, without moderate or severe acute illness. **Excluded: I**mmunocompromised patients

(*continued on next page*)

Table 1 (*continued*)

Author(s), Year	Study Acronym or NCT number	Investigational Interventions (route of administration)	Study design	# Centres/ location (Study start - Study end date)	Planned study duration (Mean/Median follow-up duration)	Summary of inclusion/exclusion criteria
Kerzner 2007 [30]	Protocol 011	ZVL (SC) + IVV (SC); Placebo + IVV (SC)	Blinded (subject, investigator, and sponsor), MC, RCT	13/US; 7/ Europe: UK, Germany, Netherlands and Italy. (Sep 2005 - Mar 2006)	4 weeks	**Included:** ≥50 years old **Excluded:** prior HZ
MacIntyre 2010 [31]	Protocol 012	VZV (SC) + PPV23 (IM); Placebo + PPV23 (IM)	RCT, blinded (subject, investigator and Sponsor), MC	18/Australia, Canada, Germany, Italy, Spain & the UK (Jun 2007 - Feb 2008)	8 weeks	**Included:** ≥60 years old, no history of invasive pneumococcal disease **Excluded:** prior HZ, immunocompromised from disease
Murray 2011 [33]	Protocol 020	ZVL (SC); Placebo	DB, MC, RCT	46/Canada, Germany, Spain, the UK and the US (Sep 2007 - Jan 2009)	6 months	**Included:** ≥60 years old **Excluded:** prior HZ
Russell 2015 [36]	NCT00546819	ZVL (SC); Placebo	Phase 2b, DB, MC, RCT	45/North American & Europe (Oct 2007 - Aug 2010)	182 days	**Included:** ≥60 years old; individuals receiving chronic/maintenance systemic corticosteroid therapy **Excluded:** Prior HZ; patients receiving other concomitant immunosuppressive therapies
Schmader 2012a [6]	ZEST	ZVL (SC); Placebo	Event-driven, DB, MC, RCT	105/North America & Europe (Oct 2007 - Jan 2010)	(Mean: 1.3 years)	**Included:** Healthy subjects aged 50–59 years, VZV history **Excluded:** immunocompromised from disease
Tyring 2007 [40]	Protocol 009	ZVL (SC) higher potency; ZVL (SC) lower potency;	RCT, blinded (subject, investigator and Sponsor), MC	18/US, Canada, UK, Germany & Belgium (Oct 2003 - Jun 2004)	42 days	**Included:** ≥50 years old, VZV history **Excluded:** immunocompromised from disease; prior HZ
Vermeulen 2012 [41]	Protocol 007	ZVL (SC), 0, 6-wk Placebo	RCT, DB, MC	5/US & 1/ Netherlands (Nov 2001 - Feb 2003)	6 months	**Included:** Healthy subjects ≥60 years old, VZV history **Excluded:** immunocompromised from disease; active neoplastic disease; prior HZ
Vesikari 2013 [42]	NCT00561080; EUCTR identifier 2007-000744-28	ZVL (SC) single-dose; ZVL (SC), 0, 1-mo; ZVL (SC), 0, 3-mo	Phase 3, RCT, MC	Europe: Finland, Germany, Italy, Spain, and The Netherlands (ND)	4 weeks after each dose received	**Included:** ≥70 years old **Excluded:** prior HZ

BIKEN/Oka vaccine, Live attenuated Oka varicella vaccine manufactured by the Research Foundation for Microbial Diseases of Osaka University (BIKEN); CMI, cell mediated immunity; DB, double blind; HZ, herpes zoster; ID, intradermal; IM, intramuscular; IIV4, inactivated influenza vaccine; IVV, influenza virus vaccine; MC, multicentre; mo, month; ND, not documented; NR, not reported; OB, observer blind; OL, open label; pfu, plaque-forming unit; PPV23, 23-valent pneumococcal polysaccharide vaccine; RCT, randomised controlled trial; RZV, recombinant zoster vaccine; SAE, serious adverse event; SB, single blind; SC, subcutaneous; SPS, Shingles Prevention Study; STPS, Short-Term Persistence Substudy; UK, United Kingdom; US, United States; VZV, varicella zoster virus; ZEST, Zoster Efficacy and Safety Trial; ZVL, Zoster vaccine live.

* Key reference sourced.

single-centre. The only HZ vaccines evaluated were RZV (n = 6), ZVL (n = 14), and the live attenuated Oka varicella vaccine manufactured by the Research Foundation for Microbial Diseases of Osaka University (BIKEN) (n = 1), although different formulations and routes of administration were included. Among the 6 trials that evaluated RZV, ZOE-50 and ZOE-70 were phase III trials and had the longest study durations (over 3 years). Study duration or planned follow-up time in the other 4 studies ranged from 3 to 14 months. Of the 14 trials on ZVL, the SPS study also had the longest duration (over 3 years) followed by the ZEST trial (mean of 1.3 years). Study duration in the other trials ranged from 1 month to 3 months, mainly for safety outcomes.

Key patient and intervention characteristics for each trial are summarised in Table 2.

Results from the assessment of risk of bias are presented in Supplementary File S4.

3.2. NMA feasibility assessment

The feasibility assessment concluded that NMA was feasible for efficacy outcomes (incidence of HZ and PHN, stratified into age ≥60 years and age ≥70 years subgroups), SAEs and reactogenicity (injection-site reactions, systemic reactions) (each in the population aged ≥50 years). The NMA was not found to be feasible for the efficacy outcomes in the ≥50 years old population because age is an effect modifier, age was imbalanced between the studies, and the limited number of available studies made it impractical to control for age. Additionally, a number of key decisions were made at this stage including: excluding trials that were not connected to the network or not approved for use in the population of interest; pooling age subgroups for the SAE and reactogenicity outcomes; and pooling safety outcomes on the basis of follow-up duration. As the study examining the BIKEN vaccine was not connected to

Table 2
Key patient and intervention characteristics.

Study	Intervention name	Description of dose	Route of administration	Administration frequency	Number of subjects	Mean age (years)	% male	Race (% white)
Lal 2015 (ZOE-50) [9]	RZV (IM)	Each 0.5mLdose contained 50 µg VZV glycoprotein E and the liposome-based $AS01_B$ adjuvant system containing 50 µg of 3-*O*-desacyl-4′-monophosphoryl lipid A (MPL) and 50 µg of *Quillaja saponaria* Molina, fraction 21 (QS-21, Licensed by GSK from Antigenics LLC, a wholly owned subsidiary of Agenus Inc., a Delaware, USA corporation)	Intramuscular	Twice (at month 0 and month 2)	7698	62.4	38.8%	71.9%
	Placebo	0.9% NaCl solution	Intramuscular	Twice (at month 0 and month 2)	7713	62.3	39%	72%
Cunningham 2016 (ZOE-70) [10]	RZV (IM)	Each 0.5 mL dose contained 50 µg VZV glycoprotein E and the liposome-based $AS01_B$ adjuvant system containing 50 µg of MPL and 50 µg of QS-21	Intramuscular	Twice (at month 0 and month 2)	6950	75.6	45.50%	76.90%
	Placebo	0.9% NaCl solution	Intramuscular	Twice (at month 0 and month 2)	6950	75.6	44.80%	76.90%
Vink 2017 [20]	RZV (SC)	Each 0.5 mL dose contained 50 mg of recombinant VZV gE combined with the $AS01_B$ Adjuvant System (liposome, 50 µg MPL, 50 µg of QS-21	Subcutaneous	Twice (at month 0 and month 2)	30	61.9	50%	ND
	RZV (IM)		Intramuscular	Twice (at month 0 and month 2)	30	61.9	50%	ND
Poder 2016 [35]	RZV (IM)	50 µg of VZV gE and $AS01_B$ Adjuvant System (containing 50 µg of MPL and 50 µg of QS-21	Intramuscular	Twice (at month 0 and month 2)	119	64.5	24.4%	97.5%
	RZV (IM) 0, 6 mo		Intramuscular	Twice (at month 0 and month 6)	119	64.0	35.3%	99.2%
	RZV (IM) 0, 12 mo		Intramuscular	Twice (at month 0 and month 12)	116	64.1	31.9%	100%
Chlibek 2013 [26]	RZV (IM)	50 µg gE, $AS01_B$: 1 mg dioleoyl phosphatidylcholine, 250 µg cholesterol, 50 µg MPL, and 50 µg QS-21	Intramuscular	Twice (at month 0 and month 2)	150	65	46.0%	64.0%
	RZV (IM), $AS01_E$	50 µg gE, $AS01_E$: 500 µg dioleoyl phosphatidylcholine, 125 µg cholesterol, 25 µg MPL, and 25 µg QS-21	Intramuscular	Twice (at month 0 and month 2)	149	65	40.3%	97.3%
	Placebo (unadjuvant gE/ saline)	unadjuvanted gE (100 g gE/saline)	Intramuscular	Twice (at month 0 and month 2)	73	65	45.2%	98.6%
	Placebo (saline)	saline	Intramuscular	Twice (at month 0 and month 2)	38	65	42.1%	100%
Schwarz 2016 [38]	RZV (IM) + IIV4 (IM)	50 µg of VZV gE and $AS01_B$ Adjuvant System (50 µg MPL, 50 µg QS-21 and liposome)	Intramuscular	Twice (both at month 0, RZV at month 2)	413	63.4	48.9%	92.3%
	IIV4 (IM)	15 µg hemagglutinin of each: A/Christchurch/16/2010 (H1N1), A/Texas/50/2012 (H3N2)	Intramuscular	Once (month 0)	415	63.4	47.5%	91.8%
Oxman 2005 (SPS) [5]	ZVL (SC)	Contained virus stabilizers and trace quantities of neomycin.	Subcutaneous	Once	19,270	ND	59.2%	95.4%
	Placebo	Contained the same stabilizers, but no virus or neomycin	NA	Once	19,276	ND	58.9%	95.4%
Schmader 2012b (STPS) [37]	ZVL (SC)	ND	ND	ND	7320	73.3	ND	ND
	Placebo	ND	ND	ND	6950	73.3	ND	ND
Beals 2016 [24]	ZVL (SC) Full-dose	Lyophilised preparation (*Zostavax*, Merck & Co Inc, Kenilworth, NJ, US) of live, attenuated varicella-zoster virus (Oka/Merck) stored frozen before reconstitution. Intradermal injection used the NanoPass MicronJet600 device (NanoPass, Nes Ziona, Israel)	Subcutaneous	Once	VZV: 52; Concomitant Placebo: 9	60	40%	ND
	ZVL (SC) 1/3-dose		Subcutaneous	Once	VZV: 34; Concomitant Placebo: 6	61	42%	ND
	ZVL (ID) Full-dose		Intradermal	Once	VZV: 34; Concomitant Placebo: 6	62	50%	ND

(*continued on next page*)

Table 2 (*continued*)

Study	Intervention name	Description of dose	Route of administration	Administration frequency	Number of subjects	Mean age (years)	% male	Race (% white)
	ZVL (ID) 1/3-dose		Intradermal	Once	VZV: 35; Concomitant Placebo: 6	61	51%	ND
	ZVL (ID) 1/10-dose		Intradermal	Once	VZV: 34; Concomitant Placebo: 6	62	53%	ND
	ZVL (ID) 1/27-dose		Intradermal	Once	VZV: 34; Concomitant Placebo: 6	60	29%	ND
Berger 1998 [25]	ZVL (SC) 3200pfu;	ND	Subcutaneous	Once	ND (200*)	67.7	59%	ND
	ZVL (SC) 8500pfu;	ND	Subcutaneous	Once	ND (200*)	ND	59%	ND
	ZVL (SC) 41,650pfu;	ND	Subcutaneous	Once	ND (200*)	ND	59%	ND
	PPV23 (SC);	ND	Subcutaneous	Once	ND (200*)	ND	59.0%	ND
DiezDomingo 2015 [28]	ZVL (IM)	Each dose of 0.65 mL contained ≥19,400pfu of varicella-zoster virus, Oka/Merck strain (live, attenuated) (Lot Numbers: WL00040507; WL00046785).	Intramuscular	Once	177	62.6	44.6%	100%
	ZVL (SC)		Subcutaneous	Once	177	62.6	45.2%	100%
Protocol 010 (Gilderman 2008) [29]	ZVL (SC) Refrigerated	*Zostavax* (zoster vaccine live; Oka/Merck) is a single- dose, sterile, lyophilized, preservative-free, live attenuated virus vaccine manufactured by Merck & Co., Inc., West Point, PA	Subcutaneous	Once	182	63.4	46.7%	68.1%
	ZVL (SC) Frozen		Subcutaneous	Once	185	63.2	42.7%	68.1%
Hata 2016 [19]	BIKEN/Oka vaccine + PPV23 (SC)	ND	VZV: Subcutaneous; PPV23: Subcutaneous	VZV: Once; PPV23: Once	27	66.70	48.2%	0%
	Placebo + PPV23 (SC)	ND	PPV23: Subcutaneous	Placebo: Once; PPV23: Once	27	65.78	63.0%	0%
Protocol 011 (Kerzner 2007) [30]	ZVL (SC) + IVV (SC)	The potency of *Zostavax* used in this study (~58,000 pfu/dose) was similar to *Zostavax* potencies studied in the SPS. The lyophilized *Zostavax* and placebo were supplied to the study centres in 0.7-mL single-dose vials and stored at – 15 °C or colder. The *Zostavax* and placebo were reconstituted with sterile diluent immediately before administration and were indistinguishable from each other in appearance. Both inactivated influenza virus vaccines (*Fluzone* and *Vaxigrip*) used in this study target three influenza prototype strains each year from the A(H1N1), A(H3N2), and B families. The 2005/06 influenza vaccine includes: A/New Caledonia/20/99(H1N1)- like strain, A/California/7/2004(H3N2)-like strain, and B/Shanghai/361/2002-like strain. Influenza vaccine was administered using a 0.5-mL single-dose syringe	Subcutaneous	Once	382	63.4	43.7%	67.5%
	Placebo + IVV (SC)		Subcutaneous	Once	380	63.6	44.2%	68.7%
Protocol 012 (MacIntyre 2010) [31]	VZV (SC) + PPV23 (IM)	Zoster vaccine: 0.7 mL single- dose vials of lyophilized ZV and placebo to be stored between 2 and 8 °C. Sterile diluent was used to reconstitute ZV and placebo immediately prior to administration. ZV and placebo were indistinguishable from each other in appearance. All subjects received a single subcutaneous injection of either ZV or placebo.	VZV: Subcutaneous; PPV23: Intramuscular	VZV: Once; PPV23: Once	235	66.3	41.3%	98.7%
	Placebo + PPV23 (IM)	PPV23 consists of a mixture of highly purified capsular polysaccharides from 23 of the most prevalent pneumococcal types that cause invasive disease. PPV23 was shipped refrigerated as a liquid vaccine in a sterile vial, ready for use and did not require reconstitution. The vaccine was required to be stored between 2 and 8 °C. All subjects received a single intramuscular injection of PPV23.	PPV23: Intramuscular	Placebo: Once; PPV23: Once	236	66.0	42.8%	99.2%

Table 2 (*continued*)

Study	Intervention name	Description of dose	Route of administration	Administration frequency	Number of subjects	Mean age (years)	% male	Race (% white)
Protocol 020 (Murray 2011) [33]	ZVL (SC)	The lyophilized ZVL and placebo were supplied to the study centres in 0.7-mL single-dose vials and stored between 2 and 8 °C. The ZVL and placebo were reconstituted with sterile diluent immediately prior to administration, and were indistinguishable from each other in appearance. Placebo was the vaccine stabilizer of ZVL with no live virus.	Subcutaneous	Once	5983	70.5	41.3%	96.3%
	Placebo		Subcutaneous	Once	5997	70.4	41.2%	96.2%
Russell 2015 [36]	ZVL (SC)	The lyophilized ZVL (lots WL00010964, WL00027069, WL00030806, WL00031970, and WL00032884) and placebo (lots WL00018605 and WL00026615) were supplied in 0.7 mL single-dose vials and stored at colder. The placebo contained the same stabilizers as the ZVL but no live virus or virus components. ZVL and placebo were reconstituted with sterile diluent immediately prior to administration. All subjects received a single 0.65 mL subcutaneous injection of either ZVL or placebo in the deltoid area.	Subcutaneous	Once	207	69.8	32.4%	94.7%
	Placebo		NA	Once	102	69.9	21.6%	94.1%
Schmader 2012a (ZEST) [6]	ZVL (SC)	The lyophilized ZVL and placebo were supplied in 0.7-mL single-dose vials and stored at 2–15 °C or colder. ZVL and placebo were reconstituted with sterile diluent immediately prior to administration. All subjects received a single 0.65-mL subcutaneous injection of either ZVL or placebo in the deltoid area.	Subcutaneous	Once	11,211	54.9	38.3%	94.4%
	Placebo	The placebo contained the same stabilizers as the ZVL but no live virus or virus components. ZVL and placebo were reconstituted with sterile diluent immediately prior to administration. All subjects received a single 0.65-mL subcutaneous injection of either ZVL or placebo in the deltoid area.	NA	Once	11,228	54.8	37.9%	94.4%
Protocol 009 (Tyring 2007) [40]	ZVL (SC) higher potency	The lyophilized vaccines were supplied to the study centres in 0.7-mL single-dose vials and stored at −15 °C or colder. The vaccines were reconstituted with sterile diluent immediately prior to administration. The two potency formulations were indistinguishable in appearance. All subjects received a single 0.65-mL subcutaneous injection of either the higher potency zoster vaccine or the lower potency zoster vaccine.	Subcutaneous	Once	461	65.2	38.8%	93.7%
	ZVL (SC) lower potency		Subcutaneous	Once	234	65.6	42.7%	91.5%
Protocol 007 (Vermeulen 2012) [41]	ZVL (SC), 0, 6-wk	The ZVL and placebo were reconstituted with sterile diluent immediately prior to administration. The first and second doses were administered 42 days apart subcutaneously within 30 min after ZVL reconstitution.	Subcutaneous	Twice	105	68.7	39.4%	97.1%
	Placebo		NA	Twice	105	70.7	34.3%	97.1%
Vesikari 2013 [42]	ZVL (SC) single-dose	ND	Subcutaneous	Once	253	76.1*	44.4%*	ND
	ZVL (SC), 0, 1-mo	ND	Subcutaneous	Twice	255	76.1*	44.4%*	ND
	ZVL (SC), 0, 3-mo	ND	Subcutaneous	Twice	251	76.1*	44.4%*	ND

BIKEN/Oka vaccine, Live attenuated Oka varicella vaccine manufactured by the Research Foundation for Microbial Diseases of Osaka University (BIKEN); gE, glycoprotein E; ID, intradermal; IM, intramuscular; IVV, influenza virus vaccine; MPL, 3-*O*-desacyl-4′-monophosphoryl lipid A; mo, month; NA, not applicable; ND, not documented; pfu, plaque-forming units; PPV23, 23-valent pneumococcal polysaccharide vaccine; RZV, recombinant zoster vaccine; SC, subcutaneous; SPS, Shingles Prevention Study; STPS, Short-Term Persistence Substudy; US, United States; VZV, varicella zoster virus; wk, week; ZVL, Zoster Vaccine Live

* Data are for the whole population. For the specific subgroup, data are not reported.

the network, it was removed at this stage and no analyses were conducted using its data. Expert opinion considered placebo to be an appropriate common comparator despite differences in the route of administration. Details of the feasibility assessment are provided in Supplementary File S5.

3.3. NMA results

3.3.1. Networks and input data

The networks and input data for each outcome analysed in the NMA are shown in Supplementary File S6.

3.3.2. Efficacy outcomes

For efficacy outcomes, evidence was only available to compare two vaccines, intramuscular (IM) RZV and subcutaneous (SC) ZVL. Fig. 2 shows the NMA results for VE against HZ in subjects aged ≥60 years (Fig. 2a) and aged ≥70 years (Fig. 2b). RZV (IM) had a higher VE than ZVL (SC) in both age groups. The difference between the VE of RZV (IM) and the VE of ZVL (SC) was 0.41 (95% CI 0.34, 0.47) in subjects aged ≥60 years and 0.54 (95% CI 0.43, 0.65) in subjects aged ≥70 years, indicating that the VE of RZV (IM) was 41 percentage points and 54 percentage points higher than the VE of ZVL (SC) in subjects aged ≥60 years and ≥70 years, respectively. The VE was statistically significantly different between the two vaccines in both age groups as the CI did not include zero.

Fig. 2 also shows the results for VE against PHN in subjects aged ≥60 years (Fig. 2c) and aged ≥70 years (Fig. 2d). In both age groups, RZV (IM) had higher VE than ZVL (SC). The difference between the VE of RZV (IM) and the VE of ZVL (SC) was 0.23 (95% CI 0.09, 0.37) and 0.22 (95% CI 0.07, 0.37), respectively, indicating that VE for RZV (IM) was 23 percentage points and 22 percentage points higher than the VE for ZVL (SC) in subjects aged ≥60 years and ≥70 years, respectively. The VE was statistically significantly different between the two vaccines in both age groups.

Fig. 3 shows the efficacy results for HZ and PHN in both age groups presented in terms of the IRR. For HZ in subjects aged ≥60 years, RZV (IM) was statistically significantly better than ZVL (SC) (IRR:0.17; 95% CI 0.11, 0.25) and placebo (IRR:0.08; 95% CI 0.06, 0.12) (Fig. 3a). Similar results were found for HZ in the group aged ≥70 years, with RZV (IM) also significantly superior to ZVL (SC) (IRR: 0.14; 95% CI 0.09, 0.22) and placebo (IRR:0.09; 95% CI 0.06, 0.13) (Fig. 3b).

RZV (IM) was also statistically significantly better than ZVL (SC) (IRR:0.32; 95% CI 0.10, 0.97) and placebo (IRR:0.11; 95% CI 0.04, 0.30) against PHN in subjects aged ≥60 years (Fig. 3c). In subjects aged ≥70 years, the IRR for PHN for RZV (IM) was statistically significantly better than placebo (IRR:0.11; 95% CI 0.04, 0.31), but was not statistically significantly different from ZVL (SC) (IRR:0.34; 95% CI 0.11, 1.06) (Fig. 3d).

3.3.3. Safety outcomes: Serious adverse events

Evidence was available to compare safety outcomes for RZV (IM) and several formulations and routes of ZVL. RZV (IM) was compared with placebo [9,10]. Four studies compared ZVL (SC) with placebo [5,6,33,36], one study compared ZVL (SC) to an alter-

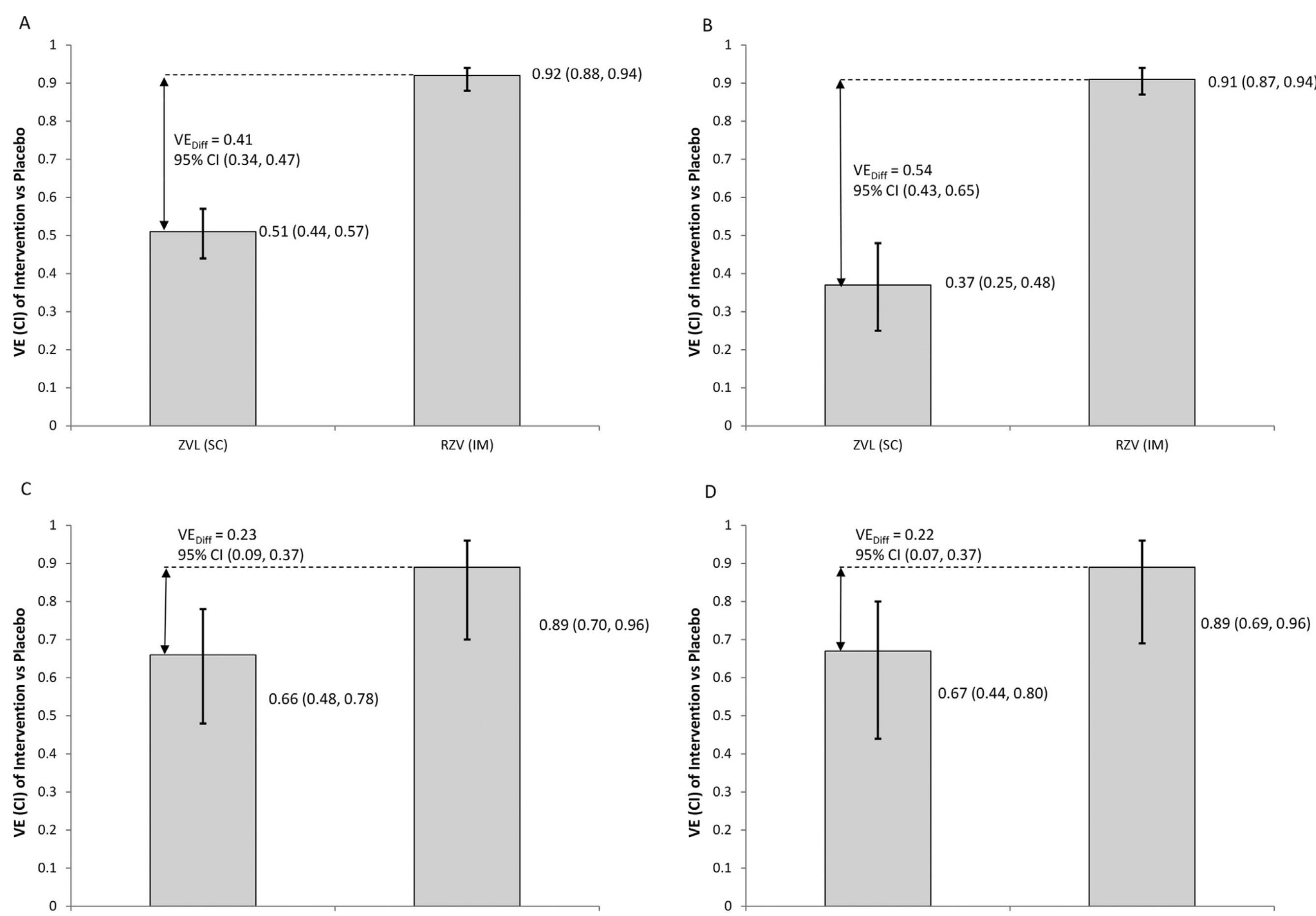

Fig. 2. Vaccine efficacy (a) against HZ in subjects aged ≥60 years, (b) against HZ in subjects aged ≥70 years, (c) against PHN in subjects aged ≥60 years, (d) against PHN in subjects aged ≥70 years. CI, confidence interval; HZ, herpes zoster; IM, intramuscular; PHN, post-herpetic neuralgia; RZV, recombinant zoster vaccine; SC, subcutaneous; VE, vaccine efficacy; YOA, years of age; ZVL, Zoster Vaccine Live.

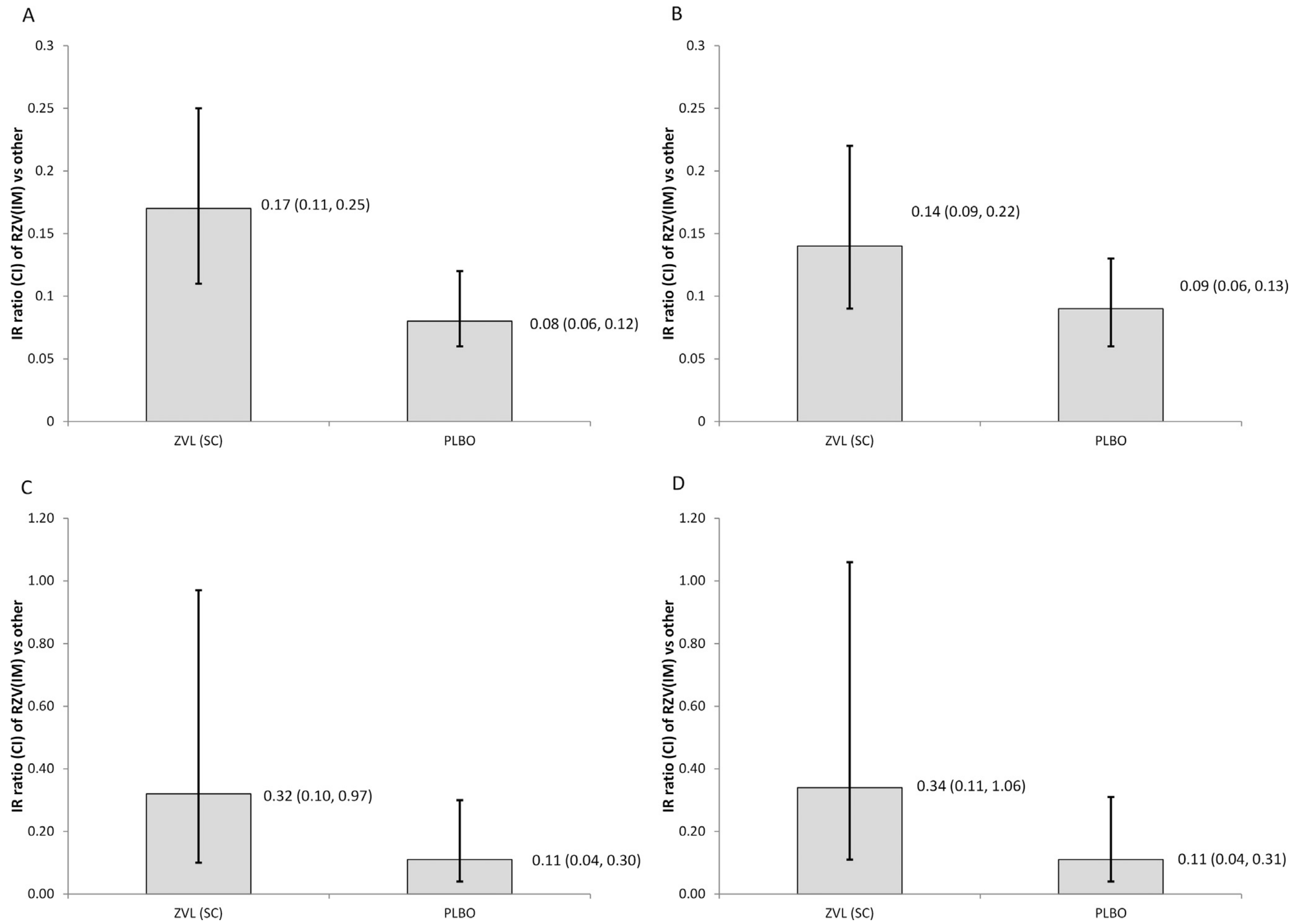

Fig. 3. Incidence rate ratio (a) for HZ in subjects aged ≥60 years, (b) for HZ in subjects aged ≥70 years, (c) for PHN in subjects aged ≥60 years, (d) for PHN in subjects aged ≥70 years. CI, confidence interval; HZ, herpes zoster; IM, intramuscular; IR, incidence rate; PHN, post-herpetic neuralgia; PBLO, placebo; RZV, recombinant zoster vaccine; SC, subcutaneous; ZVL, Zoster Vaccine Live.

native dose of ZVL (SC) [42], one study compared an alternative dose of ZVL (SC) with placebo [41], one study compared ZVL (SC) with ZVL (IM) [28], one study compared ZVL (SC) to high potency ZVL (SC) [40], and one study compared ZVL (SC) with refrigerated ZVL (SC) [29]. Details of the preparations used in each study are summarised in Table 1. One study compared ZVL (SC) with refrigerated ZVL (SC) (available in Canada).

Fig. 4 and Table 3 show the NMA results for the analysis of SAEs over ≤42 days of follow-up (Fig. 4a) and SAEs over the longest duration of follow-up (Fig. 4b). The NMA for safety outcomes used count data in the regression analyses, so the number of events and the total person-time of follow-up are accounted for in the model. There were no statistically significant differences between any of the interventions.

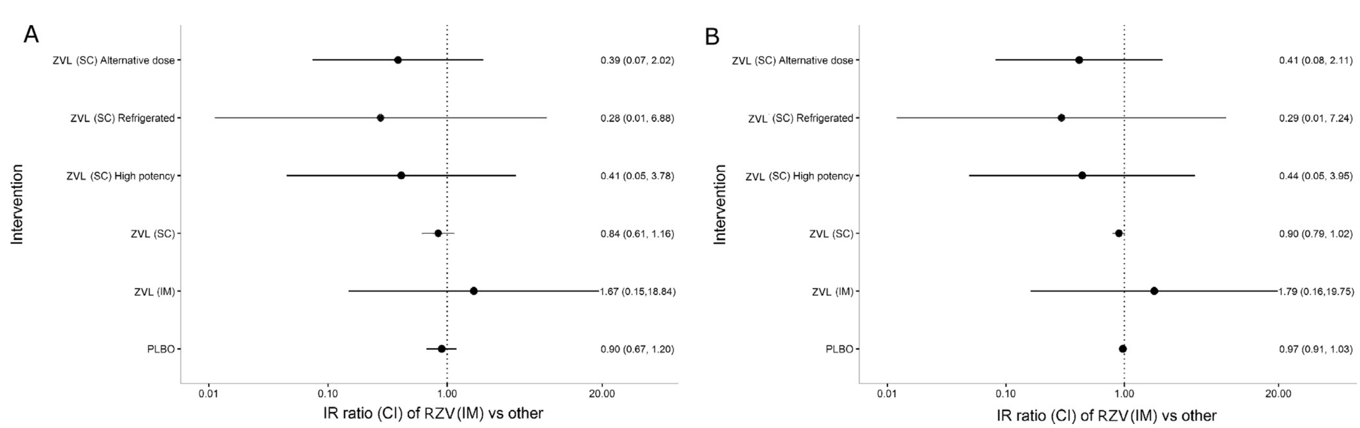

Fig. 4. Serious adverse events in subjects aged ≥50 years, fixed-effects model (a) duration of follow-up ≤ 42 days, (b) longest duration of follow-up. CI, confidence interval; IM, intramuscular; IR, incidence rate; PBLO, placebo; RZV, recombinant zoster vaccine; SC, subcutaneous; ZVL, Zoster Vaccine Live.

Table 3
P-score, rank and summary statistics for serious adverse events in subjects aged ≥50 years, fixed-effects model.

Follow-up ≤ 42 days Treatment	P-score	Rank
ZVL (IM)	0.753095	1
RZV (IM)	0.732787	2
Placebo	0.622524	3
ZVL (SC)	0.486776	4
ZVL (SC) High potency	0.336619	5
ZVL (SC) Refrigerated	0.288799	6
ZVL (SC) Alternative dose	0.279402	7
Summary statistics:		
Q statistic 3.39; t^2: 0.00; P-value: 0.4950; I^2: 0%		
Follow-up longest duration		
Treatment	**P-score**	**Rank**
ZVL (IM)	0.755881	1
RZV (IM)	0.748449	2
Placebo	0.630028	3
ZVL (SC)	0.455078	4
ZVL (SC) High potency	0.338465	5
ZVL (SC) Refrigerated	0.290128	6
ZVL (SC) Alternative dose	0.281971	7
Summary statistics:		
Q statistic 3.69; t^2: 0.00; P-value: 0.595285; I^2: 0%		

IM, intramuscular; RZV, recombinant zoster vaccine; SC, subcutaneous; ZVL, Zoster Vaccine Live.

Table 4
P-score, rank and summary statistics for injection-site reactions (random-effects model) and systemic reactions (fixed-effects model) in subjects aged ≥50 years.

Injection-site reactions Treatment	P-score	Rank
Placebo	0.98385	1
ZVL (IM)	0.789074	2
ZVL (SC) refrigerated	0.605628	3
ZVL (SC) Alternative dose	0.441013	4
ZVL (SC)	0.431557	5
ZVL (ID) Full-dose	0.206225	6
RZV (IM)	0.042652	7
Summary statistics:		
Q statistic 62.18; t^2: 0.08; P-value: <0.0001; I^2: 95.18%		
Systemic reactions		
ZVL (SC) Alternative dose	0.864041	1
ZVL (SC) Refrigerated	0.655998	2
Placebo	0.63555	3
ZVL (IM)	0.453254	4
ZVL (SC)	0.390979	5
RZV (IM)	0.000178	6
Summary statistics:		
Q statistic 0.49; t^2: 0.00; P-value: 0.9221; I^2: 0%		

ID, intradermal; IM, intramuscular; RZV, recombinant zoster vaccine; SC, subcutaneous; ZVL, Zoster Vaccine Live.

3.3.4. Safety outcomes: Reactogenicity

Evidence was available to compare reactogenicity outcomes for RZV (IM) and several formulations and routes of ZVL. For injection site reactions, two studies compared RZV (IM) with placebo [9,10], three studies compared ZVL (SC) with placebo [5,6,36], one study compared ZVL (SC) to an alternative dose of ZVL (SC) [42], one study compared ZVL (SC) with ZVL (IM) [28], one study compared ZVL (SC) to a full dose of ZVL (intradermal [ID]) [24], and one study compared frozen ZVL (SC) with refrigerated ZVL (SC) [29]. Details of the preparations used in each study are summarised in Table 1. For systemic reactions, data were available for the same formulations from the same studies, except ZVL (ID) for which there were no data. Results from the network meta-analysis are shown in Fig. 5 and Table 4.

There was a statistically significantly higher incidence of injection-site reactions comparing RZV (IM) to refrigerated ZVL (SC) (IRR:2.93; 95% CI 1.24, 6.93), ZVL (SC) (IRR:2.24; 95% CI 1.28, 3.93), ZVL (IM) (IRR:4.23; 95% CI 1.80, 9.98) and placebo (IRR:7.11; 95% CI 4.65, 10.89)). RZV (IM) had slightly higher numerical incidence of injection-site reactions than full-dose ZVL (ID) (IRR:1.47, 95% CI 0.56, 3.83) and an alternative dose of ZVL (SC) (IRR:2.25; 95% CI 0.97, 5.25) but the differences were not statistically significant (Fig. 5a).

Comparing RZV to placebo (IRR:2.23, 95% CI 2.09, 2.37), ZVL (IM) (IRR:2.05, 95% CI 1.31, 3.18), ZVL (SC) (IRR:2.11, 95% CI 1.96, 2.27), refrigerated ZVL (SC) (IRR:2.38, 95% CI 1.49, 3.79), and an alternative dose of ZVL (SC) (IRR:2.84, 95% CI 1.82, 4.43), there was a statistically significantly higher incidence of systemic reactions (Fig. 5b).

4. Discussion

A total of 25 publications relating to 21 RCTs were identified by a SLR and included in the review. Of these, 18 publications relating to 14 trials were included in the NMA. NMA was conducted on networks for efficacy and safety outcomes for which evidence was available, using a frequentist approach. The results of the analysis showed that RZV (IM) had statistically significantly higher VE than ZVL (SC) against HZ and PHN in subjects aged ≥60 years and subjects aged ≥70 years. The VE against HZ of RZV (IM) was 41 percentage points and 54 percentage points higher than the VE of ZVL (SC) in subjects aged ≥60 years and subjects aged ≥70 years,

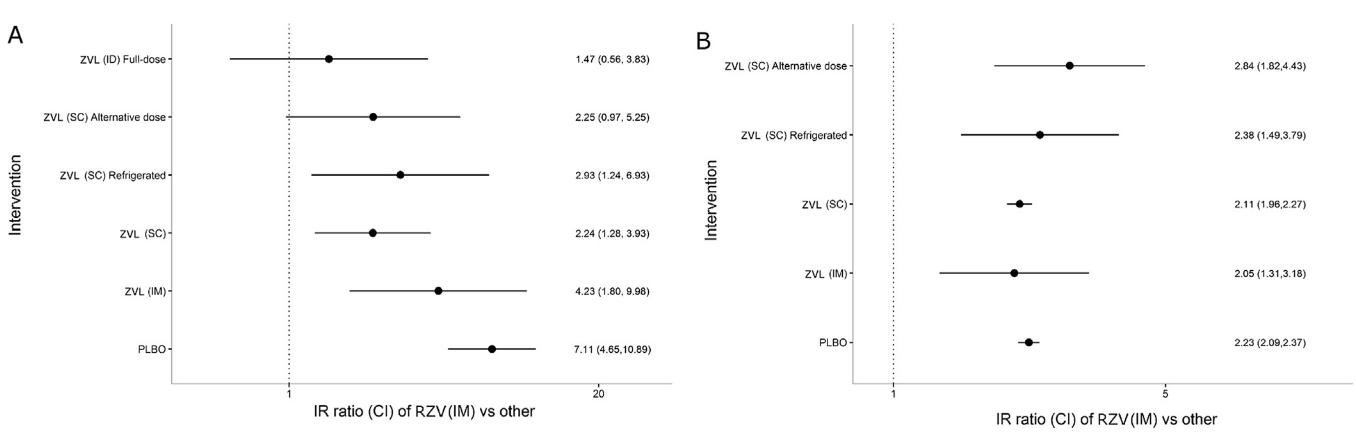

Fig. 5. Reactogenicity in subjects aged ≥50 years (a) injection-site reactions, random-effects model, (b) systemic reactions, fixed-effects model. CI, confidence interval; ID, intradermal; IM, intramuscular; IR, incidence rate; PBLO, placebo; RZV, recombinant zoster vaccine; SC, subcutaneous; ZVL, Zoster Vaccine Live.

respectively. Against PHN, VE for RZV (IM) was 23 percentage points and 22 percentage points, respectively, higher than the VE for ZVL (SC) in the previously mentioned age groups.

Similar results were reported for IRR in three of the four efficacy outcomes (HZ in both age groups and PHN in subjects aged ≥60 years). For one of the efficacy outcomes, PHN in subjects aged ≥70 years, the difference in IRR was not statistically significantly different between RZV (IM) and ZVL (SC). There were no statistically significant differences between RZV (IM), placebo or any of the ZVL formulations in SAEs (with ≤42 days or longest duration of follow-up). RZV (IM) was associated with a statistically significantly higher incidence of injection-site reactions and systemic reactions compared with placebo or most formulations of ZVL. In terms of comparisons with formulations available in Canada and the US, RZV (IM) was found to have higher efficacy than ZVL, higher reactogenicity than ZVL and ZVL refrigerated, and safety outcomes comparable with ZVL and ZVL refrigerated.

The assessment of statistical significance for the difference between RZV (IM) and ZVL (SC) for PHN in subjects aged ≥70 years resulted in different conclusions for the VE analysis (statistically significant difference, as the 95% CI did not include zero) compared with the IRR analysis (difference did not reach statistical significance). This may reflect standard error approximation assuming normally distributed data, and the use of direct rather than indirect comparisons for VE when compared to IRR. Additionally, this could be due to the small sample size of patients who developed PHN in the clinical trials, limiting the power to detect differences especially in sub-populations. However, the upper bound of the CI for the IRR analysis was 1.06, only a little above the threshold for statistical significance of 1.0, and the results should be interpreted with caution. We were not able to perform NMA for the efficacy outcomes in the ≥50 years old population because age is an effect modifier, age was imbalanced between the studies, and the limited number of available studies made it impractical to control for age.

Reactogenicity, as assessed by local injection-site reactions and systemic reactions, was statistically significantly higher with RZV (IM) compared with placebo and most of the ZVL formulations analysed. The results of the NMA showed a statistically significantly lower incidence of injection-site reactions for refrigerated ZVL (SC), ZVL (SC), ZVL (IM) and placebo, compared with RZV (IM), and there was a statistically significantly lower incidence of systemic reactions for placebo, ZVL (IM), ZVL (SC), refrigerated ZVL (SC), and an alternative dose of ZVL (SC), compared with RZV (IM).

The increased reactogenicity is thought to be associated with the adjuvant, which increases the overall immune response to the antigen [43,44]. Both higher immunogenicity and more frequent injection-site pain have been associated with this adjuvant type in previous research [45]. A recent study of RZV demonstrated that no clinically meaningful reductions in overall mean Short Form 36 (SF-36) Physical Functioning scores were observed after RZV dose 1. However, grade 3 reactogenicity, which occurred in 9.5% of participants, was associated with a transient clinically important decrease in SF-36 Physical Functioning score (affecting activities such as walking, carrying groceries or climbing stairs) on days 1–2 after first vaccination [46]. Patient counselling to advise of the anticipated short-term effects of the vaccine may help inform the patient. There were no differences in SAEs between the vaccines.

The US Advisory Committee on Immunization Practices (ACIP) meeting in October 2017 recommended the use of RZV for the prevention of HZ in adults aged ≥50 years, including in people who had previously received ZVL, and recommended RZV for preferential use over ZVL owing to its higher efficacy [47]. Additionally, the Canadian National Advisory Committee on Immunization (NACI) provided a strong recommendation that RZV should be offered to populations ≥50 years of age without contraindications as well as to populations ≥50 years of age without contraindications who have previously received ZVL [44]. The Comité sur l'immunisation du Québec (CIQ) recommended that RZV be used preferentially over ZVL [48]. The results of the present analysis are in line with the recommendations by ACIP, NACI, and the CIQ as the benefit-risk profile appears more favourable for RZV compared with ZVL. Similarly, the German Standing Committee on Vaccination (STIKO) did not recommend ZVL as a standard vaccine [49] but did recommend RZV in adults ≥60 years of age [50].

Additionally, the results of the present analysis are aligned with the results from a recently published NMA on the efficacy, effectiveness, and safety of HZ vaccines [14]. In the NMA by Tricco et al., RZV was found to be statistically superior compared to ZVL (VE = 85%, 95% credible interval (CrI): 31%, 98%) in terms of protection against laboratory-confirmed HZ. The NMA also found RZV to be associated with more adverse events at the injection site compared to ZVL (Relative Risk (RR) = 1.79, 95%CrI: 1.05, 2.34) and more systemic adverse events (RR = 2.28, 95%CrI: 1.45, 3.65). However, the methodology between these two NMAs are slightly different with Tricco et al. utilizing a Bayesian approach and the present analysis using a frequentist approach. The present analysis also differs by evaluating relative PHN efficacy and presenting results stratified by age. Tricco et al. indicated that the results comparing PHN efficacy for RZV and ZVL were inconclusive owing to a lack of data; however, in the current frequentist analysis stratified by age, there was enough data to evaluate VE for PHN in all age groups, and IRR for PHN in the ≥60 years of age group. Despite these differences, the overall results of the two NMAs have very similar findings.

This study was based on a SLR conducted according to PRISMA and Cochrane Collaboration guidelines and recommendations, which provided a robust evidence base for the analysis. The largest studies in the analysis were RCTs comparing RZV or ZVL with placebo [5,6,9,10]. These larger studies provided a substantial sample size with tens of thousands of patients, resulting in sufficient statistical power to detect possible differences between interventions.

However, the study has some limitations that should be taken into account when considering the findings. The number of studies for each outcome of interest was relatively small, so the results are limited by the generalizability of the included studies and thus should be interpreted with caution. The small number of studies may also have had an impact on the estimates generated by the NMA (for example, the different results for PHN in people aged ≥70 years for VE compared with IRR). A further limitation is that the 95% CIs were quite wide for some of the safety outcomes analysed. This was mainly a consequence of substantial between-study heterogeneity, which was taken into account in the random effects models (e.g. in the NMA of injection-site reactions). This tended to increase the corresponding standard errors and therefore the width of the CIs in the random effects models.

The underlying studies also have some limitations, as populations recruited for the RCTs may under-represent certain population groups, for example non-white participants. This is a common issue with RCTs, and is not specifically related to the present analysis. The need for data from a larger population collected outside a research setting, particularly for ethnic minorities, was discussed at ACIP [43]. While there have been 7 studies examining the real world effectiveness of ZVL, future research evaluating the real world effectiveness of RZV is needed [51]. While high compliance was observed in the phase III clinical trials (~95%), data will also be needed on real-world patient adherence with two doses of RZV in routine practice, as distinct from the controlled setting of RCTs.

5. Conclusion

In the absence of head-to-head clinical studies, NMA provides a unique opportunity to evaluate evidence for the comparative efficacy and safety of RZV compared with ZVL, based on currently available published RCTs on the individual vaccines. The results of this analysis suggested that RZV had significantly higher VE against HZ and PHN in both age groups studied (aged ≥60 years and ≥70 years). There were no differences in safety between the two vaccines. As may be anticipated for an adjuvanted vaccine, RZV was associated with significantly higher reactogenicity than ZVL. This analysis should further help policy-makers and public health officials to evaluate the different vaccines available for HZ in order to support evidence-based decisions. Although some of the individual studies in the analysis were quite large, the networks for individual outcomes were small, and the results should therefore be interpreted with caution. These results should be confirmed in the future as further data, such as studies conducted in real-life settings, become available. This NMA approach could also be applied to the evaluation of other vaccines in the future.

Conflict of Interest

AMG, RW, DC, EE, and TM are employees of the GSK group of companies. BS and LO were employed by the GSK group of companies at the time the study was conducted. LO is now employed by CureVac AG. DC, EE, TM and LO also hold shares in the GSK group of companies. JEM reports personal fees from the GSK group of companies, during the conduct of the study; and personal fees from Sanofi, Pfizer, Novovax, Medicago and Merck, outside the submitted work. AT, KH, XW and RN are employees of ICON Plc, previously Mapi BV, which received payment from the GSK group of companies to conduct this research. At the time the study was conducted, HB was also an employee of Mapi BV and is now an employee of Evidera.

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Author contributions

AT, KH, HB, and RN contributed to the design and concept of the study, conduct of the analyses, and writing of the original report and manuscript. XW contributed to the study design, data acquisition and quality control of data and algorithms, writing of original report, manuscript editing and review. JEM contributed to the concept of the study, conduct of the analyses and reviewed the original report and manuscript. AMG, DC and RW contributed to the design and concept of the study, data collection, interpretation of the results, the review of the report, and writing of the manuscript. EE, LO, and BS contributed to the study design and the original report and manuscript review. TM contributed to the interpretation of the results and the review of the manuscript.

Trademark statement

Shingrix is a trade mark owned by or licensed to the GSK group of companies.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.04.014.

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