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ORIGINAL RESEARCH ARTICLE

Differential Utility Losses in Herpes Zoster Cases Between Vaccinated and Unvaccinated Subjects: A Meta-analysis of Three Clinical Trials

Nikolaos Giannelos[1] · **Bernard Francq**[2] · **Desmond Curran**[1]

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Abstract

Background and Objective Recombinant zoster vaccine (RZV) is approved in adults for the prevention of herpes zoster. The effect of RZV in moderating the severity of breakthrough cases of herpes zoster has been noted but not explicitly quantified before. In this study, a meta-analysis was undertaken to estimate differential utility losses between unvaccinated (Placebo) and vaccinated (RZV) subjects in breakthrough cases of herpes zoster from three RZV clinical trials.

Methods Differential utility losses between the two groups were estimated in units of quality-adjusted life-years (QALYs), leveraging aggregate patient data from the ZOE-50 (NCT01165177), ZOE-70 (NCT01165229), and ZOE-HSCT (NCT01610414) clinical trials. Differential utility losses and the ratio of mean utility losses were analyzed using random-effects and fixed-effects meta-regression models.

Results The mean QALY loss differences between the unvaccinated (Placebo) and vaccinated (RZV) groups were 0.008, 0.004, and 0.011 in the ZOE-50, ZOE-70, and ZOE-HSCT studies, respectively, yielding an overall estimated difference of 0.007 (95% confidence interval 0.002–0.012) QALYs. Quality-adjusted life-year loss in the vaccinated group was estimated to be 35.5% of the value in the placebo group. A sensitivity analysis estimated an overall difference of 0.005 (95% confidence interval 0.001–0.009) QALYs, corresponding to 48.6% of the QALY loss value in the placebo group.

Conclusions Recombinant zoster vaccine is effective in alleviating disease severity in breakthrough cases of herpes zoster. The results may be useful in distinguishing QALY losses between vaccinated and unvaccinated cohorts in health economics studies, particularly cost-effectiveness analyses.

Plain Language Summary

Herpes zoster, also known as shingles, may cause painful rashes and persistent pain for months or even years after the initial episode. Recombinant zoster vaccine is approved for the prevention of shingles. Pivotal recombinant zoster vaccine clinical trials have reported data about the impact of shingles episodes on daily activities and overall health-related quality of life. In this work, we combined data from three recombinant zoster vaccine clinical trials and compared the loss in quality of life—measured in quality-adjusted life-years—incurred by vaccinated and unvaccinated subjects who experienced a shingles episode. We found that vaccinated patients experienced lower quality-adjusted life-year losses when they developed shingles compared with unvaccinated patients. Our results may be useful in assessing quality-adjusted life-year losses between vaccinated and unvaccinated cohorts in future herpes zoster vaccination health economics analyses.

1 Introduction

Herpes zoster, also known as shingles, results from a reactivation of latent varicella-zoster virus (VZV) infection. Herpes zoster often manifests as a painful vesicular rash within a dermatome. Most herpes zoster cases are accompanied by uncomplicated skin lesions and pain, which usually disappear within 2–4 weeks of rash onset. However, up to 30% of patients with herpes zoster develop postherpetic neuralgia, a

✉ Nikolaos Giannelos
NIKOLAOS.X.GIANNELOS@GSK.COM

[1] GSK, Wavre, Belgium

[2] GSK, Rixensart, Belgium

Key Points

Quality-of-life data from three recombinant zoster vaccine clinical trials were analyzed and the quality-adjusted life-years lost by vaccinated and unvaccinated patients who experienced a shingles episode were compared.

In addition to preventing herpes zoster, vaccinated patients experienced lower quality-adjusted life-year losses when they developed herpes zoster compared with unvaccinated patients.

These results may be useful in assessing quality-adjusted life-year losses in vaccinated and unvaccinated patients in future health economics analyses.

type of persistent neuropathic pain with a duration of several weeks to months (or even years) after rash onset, which is difficult to treat [1–3]. Patients' quality of life (QoL) during an episode of herpes zoster with or without postherpetic neuralgia may be significantly reduced as a consequence of enduring pain and discomfort affecting their activities of daily living at the physical, emotional, and social levels, in turn undermining their physical and mental health [4–7].

Approximately one in three people are expected to develop herpes zoster during their lifetime due to VZV reactivation. The risk of herpes zoster increases with advancing age, owing to an age-related decline in cell-mediated immunity against VZV [8]. For individuals living to the age of 85 years, the lifetime risk of shingles increases from one in three to one in two [9, 10].

The main treatment options available for herpes zoster and its complications include analgesics and antiviral agents; despite some efficacy recorded in clinical trials, these treatments have been shown to be suboptimal in clinical practice [10]. Herpes zoster is a vaccine-preventable disease, and the first herpes zoster vaccine, which contained live attenuated VZV (zoster vaccine live, ZVL; Zostavax; Merck Sharp & Dohme Co, Kenilworth, NJ, USA) [11], was licensed in the USA [12] and Europe in 2006 [13].

Adjuvanted recombinant zoster vaccine (RZV; Shingrix; GSK; Rixensart; Belgium) represents a more recent prophylactic vaccination option against herpes zoster. Recombinant zoster vaccine is a two-dose (non-live) recombinant subunit vaccine, combining VZV glycoprotein E with the $AS01_B$ adjuvant system. $AS01_B$ is an adjuvant system containing 3-*O*-desacyl-4′-monophosphoryl lipid A, QS-21 (*Quillaja saponaria* Molina, fraction 21, licensed by GSK from Antigenics LLC, a wholly owned subsidiary of Agenus Inc., a Delaware, USA corporation) and liposome (50 mg of 3-*O*-desacyl-4′-monophosphoryl lipid A and 50 µg of QS-21).

Clinical trials evaluating the efficacy, safety, immunogenicity, and impact on health-related QoL of RZV were recently reviewed [14]. Efficacy was assessed in two multinational, phase III randomized, observer-blinded, placebo-controlled clinical trials, which were conducted concurrently at the same study sites using the same methods, albeit in two different immunocompetent adult populations: the ZOE-50 study (NCT01165177) recruited 15,411 patients (7698 vaccinated; 7713 placebo) aged 50 years and older [15], whereas the ZOE-70 study (NCT01165229) recruited 13,900 patients (6950 vaccinated; 6950 placebo) aged 70 years and older [16]. A third clinical trial, ZOE-HSCT (NCT01610414), examined the efficacy of RZV in 1846 adults (922 vaccinated; 924 placebo) aged 18 years and older recovering from an autologous hematopoietic stem-cell transplant [17].

The aforementioned trials also collected data on the herpes zoster burden of illness and interference with activities of daily living assessed by the Zoster Brief Pain Inventory instrument [18], as well as the herpes zoster impact on health-related QoL, assessed with the aid of the EuroQol 5-Dimension utility index [19] and the SF-36 health survey [20]. Comparisons between the vaccinated and unvaccinated arms suggested that RZV mitigates the severity of pain in breakthrough cases of herpes zoster, limiting QoL losses [21, 22]. No quantitative outcomes on the exact QoL losses by breakthrough episode of the disease were shown. It is the purpose of this work to estimate differential utility (QoL) losses between unvaccinated (Placebo) and vaccinated subjects in breakthrough cases of herpes zoster from readily available QoL outcomes of RZV clinical trials.

2 Methods

2.1 Study Selection

ZOE-50 (NCT01165177) [15], ZOE-70 (NCT01165229) [16], and ZOE-HSCT (NCT01610414) [17] were included in the present analysis based on herpes zoster case detection defined as the primary endpoint of data collection in the trial (with availability of vaccine efficacy outcomes) and additional availability of health-related QoL results. The selection was validated by recently published medical literature reviews [14, 23], as well as a non-systematic database search for herpes zoster and RZV-related (code GSK1437173A) clinical trials within ClinicalTrials.gov, the results of which are summarized as Electronic Supplementary Material (ESM), including a modified PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [24] flowchart (Fig. S-1 of the ESM)

for registry searches further corroborating the selection of NCT01165177, NCT01165229, and NCT01610414 into the present analysis.

2.2 Data Sources

To estimate differential utility losses between unvaccinated and vaccinated subjects per breakthrough episode of herpes zoster, published aggregate patient data (APD) were employed to analyze the ZOE-50 [15], ZOE-70 [16], and ZOE-HSCT [17] clinical trial QoL outcomes. A subset of the relevant datasets has been reported previously [21, 22].

Quality-of-life aggregate patient data retrieved by trial were: (a) annual baseline utility scores from day 0 (vaccination) to 38 (13) months post-vaccination in ZOE-50/70 (ZOE-HSCT) for the vaccinated (RZV) and unvaccinated (Placebo) groups and (b) weekly utility scores for confirmed breakthrough herpes zoster cases from day 0 (herpes zoster case onset) to 4 weeks follow-up for the vaccinated (RZV) and unvaccinated (Placebo) groups. Weekly utility scores were adjusted for response shift bias [25], ensuring that no average weekly utility score exceeded the average baseline utility score for the respective group and study. The complete dataset is provided as Appendix A of the ESM.

2.3 Tools and Implementation

The statistical analysis package metafor [26], written in R [27], was deployed to synthesize individual trial outcomes into an aggregate differential quality-adjusted life-year (QALY)-loss metric. For each study, i, a two-group comparison using continuous (quantitative) data was employed, as outlined in Table 1. Differential utility losses per breakthrough episode of herpes zoster between Group 1 (Placebo) and Group 2 (RZV) were estimated in units of QALYs.

The ratio of means (ROM), mean difference, and standardized mean difference (SMD) were estimated as outcome measures. A SMD with heteroscedastic population variances between the two groups was also calculated as a sensitivity analysis on SMD.

The ratio of means (log-transformed) was defined as:

$$\mathrm{ROM}_i = \ln\left(\frac{\mathrm{M1}_i}{\mathrm{M2}_i}\right).$$

Mean difference was defined as:

$$\mathrm{MD}_i = \mathrm{M1}_i - \mathrm{M2}_i.$$

Standardized mean difference was defined as:

Table 1 Two-group comparison inputs for the meta-analysis

Group	Outcome measure	Standard deviation	Group size
Group 1 (Placebo)	M1[i]	SD1[i]	N1[i]
Group 2 (RZV)	M2[i]	SD2[i]	N2[i]

M outcome measure, *N* group size, *RZV* recombinant zoster vaccine, *SD* standard deviation

$$\mathrm{SMD}_i = \frac{\left(\mathrm{M1}_i - \mathrm{M2}_i\right)}{\mathrm{SDP}_i},$$

with SDP_i denoting the pooled standard deviation (SD) between the two groups:

$$\mathrm{SDP}_i = \sqrt{\frac{\left(\mathrm{N1}_i - 1\right) \times \mathrm{SD1}_i^2 + \left(\mathrm{N2}_i - 1\right) \times \mathrm{SD2}_i^2}{\mathrm{N1}_i + \mathrm{N2}_i - 2}}.$$

Standardized mean difference with heteroscedastic population variances between the two groups was defined in a similar way to SMD, with SDP_i denoting the square root of the average variance between the two groups:

$$\mathrm{SDP}_i = \sqrt{\frac{\mathrm{SD1}_i^2 + \mathrm{SD2}_i^2}{2}}.$$

Detailed formulas for estimating *M* and SD for each group are documented in Appendix B of the ESM.

2.4 Meta-analysis

The meta-analysis was performed within a random-effects (RE) model and a fixed-effects (FE) model for comparison [28]. Some methodological differences between the two are noted below, in the context of interpreting results.

In the FE model, the true effect/outcome $\theta[i]$ from each study i with sampling variance $v[i]$ is related to the observed effect/outcome $y[i]$ as $y[i] = \theta[i] + \varepsilon[i]$, where epsilon denotes the sampling error. An average (weighted) effect/outcome for all studies can be estimated from: $\theta w = \mathrm{sum}(w[i] \times \theta[i])/\mathrm{sum}(w[i])$, where $w[i]$ denotes the weight of each study, estimated as the inverse of the study variance: $w[i] = 1/v[i]$.

In the RE model, the true effect/outcome of study i, $\theta[i]$, is assumed to be distributed (usually normally) as $\theta[i] \sim N(\mu, \tau^2)$, where μ denotes the true effect/outcome in the population and τ^2 the variance of the true/effect outcome in the population, sometimes referred to as the amount of heterogeneity in the true effects/outcomes. The observed effect/

outcome $y[i]$ is given by: $y[i] = \mu + u[i] + \varepsilon[i]$, where $u[i] \sim N(0, \tau^2)$ and $\varepsilon[i] \sim N(0, v[i])$.

The RE model estimates μ, τ^2. The average effect/outcome for all studies is computed as: $\theta w = \text{sum}(w[i] \times \theta[i])/\text{sum}(w[i])$, with $w[i] = 1/(\tau^2 + v[i])$.

The default estimator applied to the RE model was the restricted maximum likelihood (REML) one [29]. Simulation studies have indicated that REML estimation tends to provide approximately unbiased estimates of the degree of heterogeneity [30].

The maximum likelihood and Paule–Mandel estimators [31, 32] were employed for the sensitivity analysis. The Paule–Mandel estimator has been considered optimal in several investigations [33, 34]. Heterogeneity was explored by reporting τ^2, I^2 (total heterogeneity over total variability), H^2 (total variability over sampling variability), and Cochran's Q statistic [35].

3 Results

Making use of the formulas outlined in Appendix B of the ESM, differential QALY losses between Group 1 (Placebo) and Group 2 (RZV), as well as QALY loss ratios between the two groups, are shown in Table 2. The mean QALY loss differences between the unvaccinated (Placebo) and vaccinated (RZV) groups were 0.008, 0.004, and 0.011 in the ZOE-50, ZOE-70, and ZOE-HSCT studies, respectively.

Aggregate outcome measures taking into account study weights estimated by the RE model (with the REML, ML, and Paule-Mandel estimators) as well as the FE model are summarized in Table 3. The overall estimated difference between the unvaccinated (Placebo) and vaccinated (RZV) groups was 0.007 (95% confidence interval [CI] 0.002–0.012) QALYs. Quality-adjusted life-year loss in the vaccinated group was estimated to be 35.5% of the value in the placebo group. Further details can be found in Appendix C of the ESM.

The forest plot of MD (ROM) corresponding to the RE model with the REML estimator is shown in Figs. 1 and 2. The analysis revealed low (4.88%) to moderate (37.19%) across-study heterogeneity as reflected in the I^2 index, depending on model selection (ML vs REML, see Table C-1 of the ESM). Note that the p value (0.24574) in Cochran's Q test was higher than the value of 0.1 usually employed as the threshold of study homogeneity in meta-analyses, something to be expected given the small number of studies employed [36]. Detailed summary statistics by model type for MD (ROM) are shown in Table C-1 (C-2) of the ESM.

Table 3 ROM, MD, SMD, and SMDH from random-effects and FE models

Outcome measure type	Random effects (REML)	Random effects (ML)	Random effects (PM)	FE
ROM	1.03463	1.03463	1.03463	1.03463
MD	0.00722	0.00715	0.00714	0.00714
SMD	0.42020	0.42319	0.42319	0.42319
SMDH	0.43516	0.43634	0.43634	0.43634

FE fixed-effects, *MD* mean difference, *ML* maximum likelihood, *PM* Paule-Mandel, *REML* restricted maximum likelihood, *ROM* ratio of means, *SMD* standardized mean difference, *SMDH* heteroscedastic standardized mean difference

3.1 Sensitivity Analysis

A sensitivity analysis was performed using common baseline utility values for the two groups, determined as the simple mean of their pooled average values. Making use of the formulas outlined in Appendix B, differential QALY losses between Group 1 (Placebo) and Group 2 (RZV), as well as QALY-loss ratios between the two groups, are shown in Table 4. The mean QALY loss differences between the unvaccinated (Placebo) and vaccinated (RZV) groups were 0.006, 0.002, and 0.008 in the ZOE-50, ZOE-70, and ZOE-HSCT studies, respectively.

Aggregate outcome measures taking into account study weights estimated by the RE model (with the REML, ML, and Paule-Mandel estimators) as well as the FE model are summarized in Table 5. The overall estimated difference between the unvaccinated (Placebo) and vaccinated

Table 2 Differentials and ratios of QALY losses between Group 1 (Placebo) and Group 2 (RZV) by trial

Study/RCT	Group 1 (Placebo)	Group 2 (RZV)	Differential QALY loss (Group 1 – Group 2)	QALY loss ratio (Group 1/Group 2)
ZOE-50	0.010271	0.002543	0.007728	4.038930
ZOE-70	0.007286	0.003771	0.003514	1.932113
ZOE-HSCT	0.012913	0.002149	0.010764	6.008841

QALY quality-adjusted life-year, *RCT* randomized controlled trial, *RZV* recombinant zoster vaccine

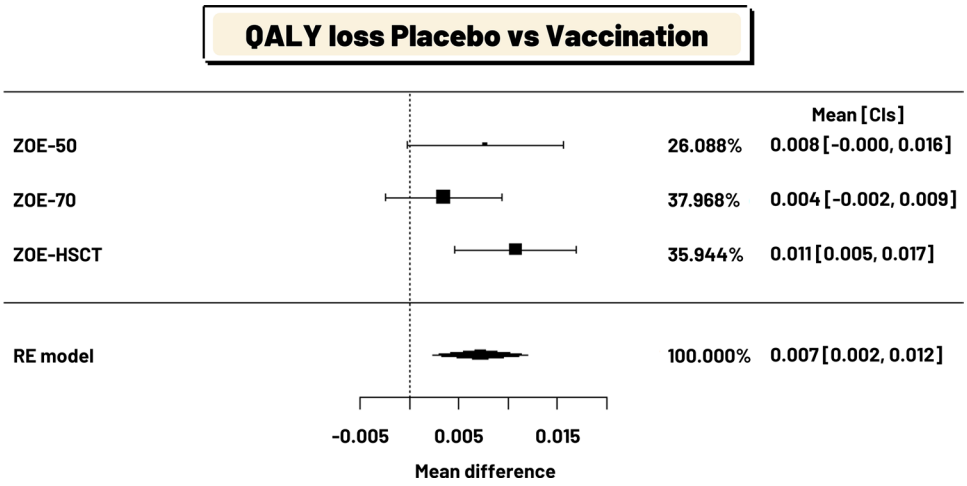

Fig. 1 Forest plot of mean differences indicating study weights, mean effects, and mean effect 95% confidence intervals (CIs) with the random-effects (RE) [restricted maximum likelihood estimator] model. *QALY* quality-adjusted life-year

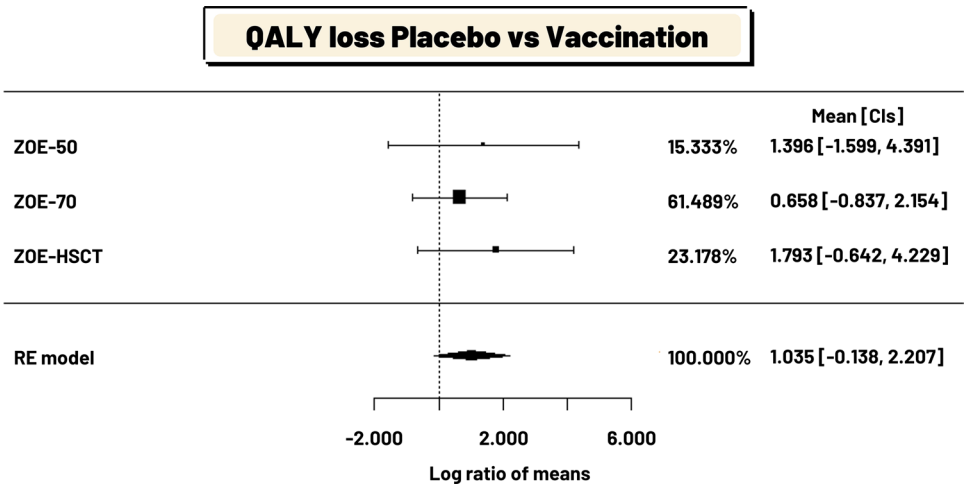

Fig. 2 Forest plot of the log transformed ratio of means indicating study weights, mean effects, and mean effect 95% confidence intervals (CIs) with the random-effects (RE) [restricted maximum likelihood estimator] model. *QALY* quality-adjusted life-year

Table 4 Sensitivity analysis using common baseline utility values for the two groups: differentials and ratios of QALY losses between Group 1 (Placebo) and Group 2 (RZV) by trial

Study/RCT	Group 1 (Placebo)	Group 2 (RZV)	Differential QALY loss (Group 1–Group 2)	QALY loss ratio (Group 1/Group 2)
ZOE-50	0.008899	0.003057	0.005842	2.910668
ZOE-70	0.006443	0.004614	0.001830	1.396562
ZOE-HSCT	0.011277	0.003403	0.007874	3.314188

QALY quality-adjusted life-year, *RCT* randomized controlled trial, *RZV* recombinant zoster vaccine

(RZV) groups was 0.005 (95% CI 0.001–0.009) QALYs. Quality-adjusted life-year loss in the vaccinated group was estimated to be 48.6% of the value in the placebo group. The forest plot of MD (ROM) corresponding to the RE model with the REML estimator is shown in Figs. 3 and 4. Summary statistics by model type for MD (ROM) are shown in Table C-3 (C-4) in the ESM.

4 Discussion

The present analysis was conducted using aggregate patient QoL data sourced from three pivotal RZV clinical trials. The results indicate a mean difference in QALY losses between unvaccinated (Placebo) and vaccinated (RZV) subjects of 0.007 QALYs for each breakthrough case of herpes zoster,

Table 5 Sensitivity analysis using common baseline utility values for the two groups: ROM, MD, SMD, and SMDH from random and FE models

Outcome measure type	Random effects (REML)	Random effects (ML)	Random effects (PM)	FE
ROM	0.72181	0.72181	0.72181	0.72181
MD	0.00500	0.00497	0.00497	0.00497
SMD	0.29646	0.29646	0.29646	0.29646
SMDH	0.30506	0.30506	0.30506	0.30506

FE fixed effects, *MD* mean difference, *ML* maximum likelihood, *PM* Paule-Mandel, *REML* restricted maximum likelihood, *ROM* ratio of means, *SMD* standardized mean difference, *SMDH* heteroscedastic standardized mean difference

amounting to QALY losses in the vaccinated group equal to 35.5% of those in the placebo. A sensitivity analysis performed with common baseline utility values for the two groups yielded slightly more conservative results: the mean difference in QALY losses for the two groups was estimated to be 0.005 QALYs, and the (logarithmic) ratio of means between the two groups indicated that the QALY losses in the vaccinated group were 48.6% of those in the placebo group.

To place these results into perspective, QALYs can be recast into quality-adjusted life-days, indicating that over 2.5 (1.8 for the sensitivity analysis) quality-adjusted life-days would be gained per vaccinated subject and episode of breakthrough herpes zoster infection. The results indicate that, in addition to preventing herpes zoster, vaccination with RZV reduces the impact of herpes zoster on QALY losses. Because the analysis was limited to the first 4 weeks post breakthrough herpes zoster case detection, the mean QALY loss difference estimated in the present study poses a

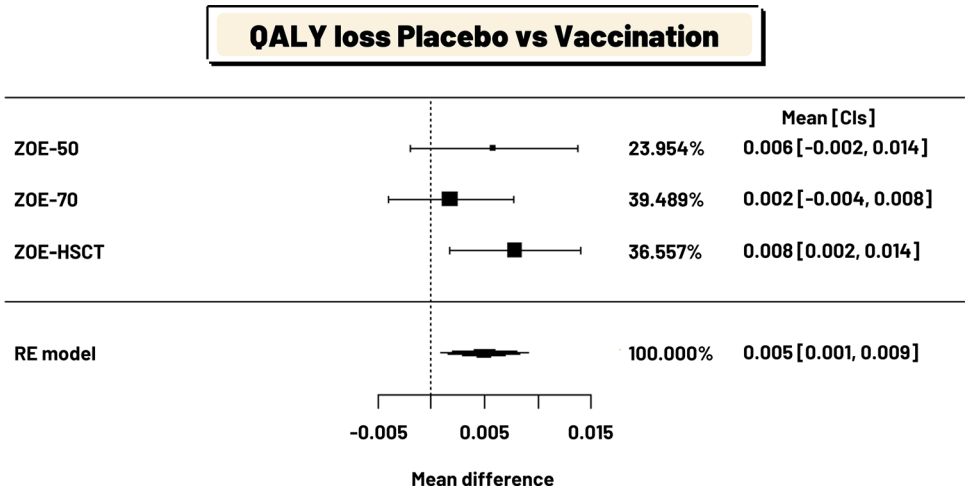

Fig. 3 Supplementary analysis using common baseline utility values for the two groups: forest plot of mean differences indicating study weights, mean effects, and mean effect 95% confidence intervals (CIs) with the random-effects (RE) [restricted maximum likelihood estimator] model. *QALY* quality-adjusted life-year

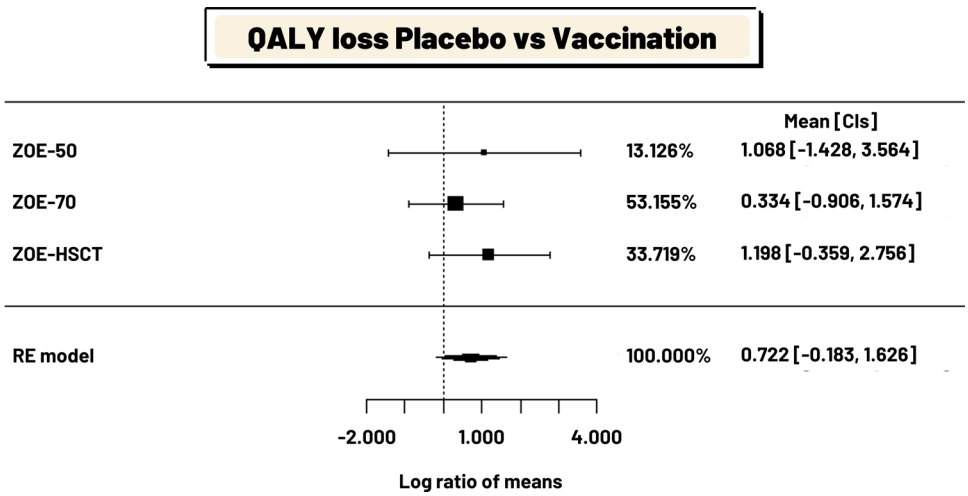

Fig. 4 Supplementary analysis using common baseline utility values for the two groups: forest plot of the log-transformed ratio of means indicating study weights, mean effects, and mean effect 95% confidence intervals (CIs) with the random-effects (RE) [restricted maximum likelihood estimator] model. *QALY* quality-adjusted life-year

conservative limit on the differential QALY losses in breakthrough cases of herpes zoster between unvaccinated and vaccinated individuals, i.e., the actual QoL gains for vaccinated subjects, taking into account the sub-acute and chronic pain herpes zoster phases [37], may in fact be higher.

A limitation of the analysis lies in the use of aggregate patient data. Meta-analyses based on individual patient data may offer advantages over meta-analyses conducted using APD. Nevertheless, APD meta-analyses are utilized by the US Preventive Services Task Force, the Cochrane Collaboration, and many professional societies, in support of clinical practice guidelines [38]. The use of APD in meta-analyses frequently produces results equivalent to those of meta-analyses based on individual patient data and should always be explored first [39].

Practical applications of the present work can be foreseen in health economics and outcomes research. The cost benefits of vaccination interventions against herpes zoster have been reviewed extensively [40–44] and QALY losses have been identified as significant sources of outcome variability in cost-effectiveness analyses. While differentiation of QALY losses per episode of herpes zoster between vaccinated and unvaccinated cohorts has been performed for ZVL [45], based on primary pain and QoL outcomes reported elsewhere [1, 11, 46], the equivalent analysis for RZV was until now missing.

5 Conclusions

Recombinant zoster vaccine has been shown to reduce QoL losses in breakthrough cases of herpes zoster. This result should influence the way new cost-effectiveness analyses of herpes zoster vaccination with RZV are designed, by differentiating between QoL losses in vaccinated and unvaccinated cohorts accordingly.

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Authors' contributions All authors were involved in the design of the study, collected or generated the data, analyzed and/or interpreted the data, and participated in the development of this manuscript and in its critical review, providing substantial intellectual contributions. All authors had full access to the data and gave approval of the final manuscript before submission. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The work described was carried out in accordance with ICMJE recommendations for the conduct, reporting, editing, and publishing of scholarly work in medical journals. The corresponding author had the final responsibility to submit the manuscript for publication.

Declarations

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Conflict of interest Nikolaos Giannelos, Bernard Francq, and Desmond Curran are employed by and hold shares in GSK. The authors declare no other financial and non-financial relationships and activities.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and material The authors confirm that the data supporting the findings of this study are available within the article and its supplementary information.

Code availability Not applicable.

Trademarks Shingrix is a trademark owned by or licensed to GSK. Zostavax is a trademark of Merck Sharp & Dohme Corp. AS01 is a trademark owned by or licensed to GSK.

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