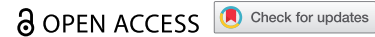


RESEARCH ARTICLE



## Effectiveness and safety of the recombinant zoster vaccine in adults aged $\geq 50$ years with inflammatory bowel disease

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### ABSTRACT

Adults with inflammatory bowel disease (IBD) face a higher risk of herpes zoster (HZ). We assessed the vaccine effectiveness (VE) of the recombinant zoster vaccine (RZV) in preventing HZ and the risk of flares post-immunization in adults aged  $\geq 50$  years with IBD. We conducted a matched cohort analysis at Kaiser Permanente Southern California. To evaluate VE, we included individuals aged  $\geq 50$  years with IBD who received 2 doses of RZV between 04/01/2018–12/31/2021 and followed them through 12/31/2022. These individuals were matched up to 1:3 to RZV-unvaccinated individuals on age, sex, race/ethnicity, condition (ulcerative colitis, Crohn's disease), IBD medication type, and index date (date of second dose among vaccinated individuals; same date assigned to unvaccinated match). Cox proportional hazards regression was used to estimate VE. To evaluate safety, we used self-controlled case series analysis (SCCS). The relative risk (RR) of flare was estimated using conditional Poisson regression, comparing the incidence of chart-confirmed IBD new-onset flares in the risk (30 days after each dose) versus comparison periods among individuals with  $\geq 1$  dose. In the VE evaluation cohort (2-dose vaccinated: N = 872, unvaccinated: N = 2,550), overall adjusted VE in preventing HZ was 65.1% (95% CI, 24.8–83.8). In SCCS analysis, among 1,199 individuals who received  $\geq 1$  dose of RZV, there was no increased risk of IBD flare observed within 30 days after vaccination (RR: 0.80; 95% CI, 0.47–1.35). In adults aged  $\geq 50$  with IBD, 2 doses of RZV effectively prevented HZ without increasing flare risk. These findings support current vaccination recommendations to prevent HZ in adults  $\geq 50$  years, including individuals with immunodeficiency or immunosuppression.

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Inflammatory bowel disease; ulcerative colitis; Crohn's disease; herpes zoster; recombinant zoster vaccine; vaccination

## Introduction

Herpes zoster (HZ), commonly known as shingles, is a painful, vesicular rash that is caused by the reactivation of the latent varicella-zoster virus.<sup>1,2</sup> Adults with inflammatory bowel disease (IBD), a chronic inflammatory autoimmune disease that encompasses ulcerative colitis (UC) and Crohn's disease (CD), have been shown to have a higher risk of HZ compared to immunocompetent adults.<sup>3–6</sup> The risk of HZ may be further increased by immunosuppressive therapy, especially with Janus kinase -inhibitors.<sup>7–11</sup>

An adjuvanted recombinant zoster vaccine (RZV; *Shingrix*, GSK, Rixensart, Belgium) consisting of lyophilized glycoprotein E antigen and the adjuvant system AS01<sub>B</sub><sup>12</sup> was approved in 2017 by the United States (US) Food and Drug Administration (FDA) for the prevention of HZ in adults aged  $\geq 50$  years,<sup>13</sup> and recommended by the Advisory Committee on Immunization Practices (ACIP) in immunocompetent individuals aged  $\geq 50$  years.<sup>14</sup> In July 2021, the FDA approved the use of RZV in individuals aged  $\geq 18$  years who are or will be at increased risk of HZ due to immunodeficiency or immunosuppression caused by known disease or therapy.<sup>15,16</sup> In October 2021, ACIP also recommended 2 RZV doses to individuals  $\geq 19$  years who are or will be immunodeficient or immunosuppressed because of disease or therapy.<sup>16</sup> This

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expansion in recommendations addressed an unmet need for vaccination against HZ in immunocompromised adults.

Pre-licensure studies were not conducted specifically in populations with autoimmune disease.<sup>17–20</sup> However, a post-hoc analysis of 2 parallel randomized clinical trials of RZV showed a 90.5% vaccine efficacy against HZ in individuals with pre-existing potential immune-mediated diseases, but these trials excluded those who were considered immunocompromised or were receiving immunosuppressive treatments.<sup>21</sup> A retrospective cohort study from the Veterans Affairs Healthcare System showed that RZV vaccination was associated with decreased risk of HZ disease among individuals aged  $\geq 50$  years with IBD.<sup>22</sup>

Assessing the safety of RZV in individuals with IBD is necessary because there are concerns that adjuvanted vaccines might trigger a disease flare in individuals with autoimmune conditions.<sup>23</sup> Some studies have examined the association between RZV and increased risk of flares.<sup>22,24</sup> For example, a retrospective cohort study using Veterans Affairs Healthcare System data found no association between RZV and increased risk of IBD flare in the 90 days of follow-up among individuals aged  $\geq 50$  years with IBD (odds ratio 1.25 [95% CI, 0.65–2.41]).<sup>25</sup>

We previously published an observational self-controlled case series (SCCS) and retrospective matched cohort study to assess the safety and effectiveness of 2 doses of RZV in Kaiser Permanente Southern California (KPSC) patients aged  $\geq 50$  years with rheumatoid arthritis; there was no increased risk of flare following vaccination and there was evidence that 2 doses of RZV were effective in the prevention of HZ.<sup>26</sup>

We are conducting a retrospective matched cohort observational study to evaluate the real-world effectiveness and an SCCS study to assess safety (flare) of RZV in members of KPSC aged  $\geq 18$  years with IBD (UC and CD) on all types of medication regimens. In this interim analysis, we present the real-world vaccine effectiveness (VE) of 2 doses of RZV and the risk of flares within 30 days following RZV in adults aged  $\geq 50$  years with IBD.

## Materials and methods

### Study setting

KPSC is a large, integrated healthcare system serving over 4.8 million members, whose diverse socio-demographic characteristics reflect those of the Southern California population.<sup>27,28</sup> Membership retention rates are stable, with 93% of members staying with KPSC for longer than a year.<sup>27</sup> Comprehensive health information, including demographics, vaccinations, diagnoses, and pharmacy records, is stored in electronic health records (EHR). As KPSC provides prepaid services, recommended vaccines such as RZV are offered to members at no charge, encouraging them to receive immunizations within the system. Records of vaccinations administered outside of the health plan are incorporated into the EHR, with appropriate documentation. This study was approved by the KPSC Institutional Review Board, which waived the requirement for informed consent due to minimal risk to participants. All authors had access to the study results and reviewed and approved the final manuscript.

### Vaccine effectiveness

#### VE study objectives

The VE objective of this interim analysis was to estimate the VE of 2 doses of RZV in preventing HZ in adults aged  $\geq 50$  years with IBD. We also evaluated the VE of 2 doses of RZV against HZ, stratified by the length of time between the first and second dose. A key objective was to estimate the VE of 2 doses of RZV administered 4 weeks to 6 months apart, consistent with dosing intervals in US prescribing information.<sup>29</sup> Additional objectives included evaluating VE against HZ stratified by age group, condition (UC and CD), and medication used for IBD management (categorized by disease severity and immunosuppressive effect; Supplementary Material), as well as estimating the VE of 2 doses of RZV in preventing postherpetic neuralgia (PHN).

### VE study population

Individuals diagnosed with IBD were identified from the KPSC EHR using an algorithm based on previous literature.<sup>30</sup> IBD was defined as having at least 2 assigned International Classification of Diseases 10th Revision (ICD-10) diagnosis codes (K51.\* for UC and K50.\* for CD) within a 1-year period prior to the index date. The index date was defined as the date of vaccination with the second dose of RZV. The vaccine accrual period spanned from April 2018 to December 2021, with follow-up through December 2022. Due to the indirect impact of the COVID-19 pandemic on healthcare delivery and vaccine-seeking behaviors, individuals with index dates from March to December 2020 were excluded. However, outcomes related to HZ continued to be assessed during this period.

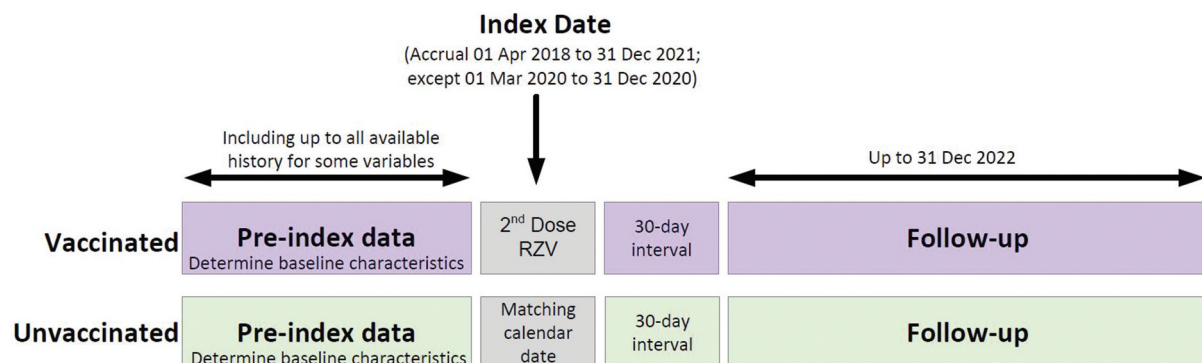
### VE study design: matched cohort

We employed a matched cohort design to achieve the VE objectives (Figure 1). Each vaccinated individual was matched with up to 3 unvaccinated individuals (unvaccinated cohort) based on age, sex, race/ethnicity, condition (UC and CD), and medication category (Supplementary Material Table S1). The index date for the unvaccinated individuals corresponded to the date of vaccination of their vaccinated counterparts.

Both the vaccinated and unvaccinated cohorts were aged  $\geq 50$  years at the index date, had at least 1 year of continuous KPSC membership prior to and until 31 days after the index date, and met the criteria for IBD diagnosis within the year before and including the index date. Individuals diagnosed with HZ from 6 months before to 30 days after the index date, those who received a second RZV dose within 4 weeks of the first dose, those who received another HZ vaccine within 30 days after the index date, or those who died within 30 days after the index date were excluded to ensure HZ cases were incident cases and the vaccination dose interval was consistent with recommendations.

### VE exposure and outcomes

We identified doses of the RZV vaccine using CVX (vaccine administered) code 187, specifically for zoster vaccine recombinant. HZ outcomes were determined using an algorithm based on ICD-10 diagnosis code B02.\* recorded in any healthcare setting (outpatient, virtual, inpatient, or emergency department [ED]), coupled with a prescription for a non-topical antiviral (acyclovir, valacyclovir, or famciclovir) within 7 days before or after the HZ diagnosis with no non-topical antiviral prescribed between 183 days and 8 days prior to the HZ diagnosis. This algorithm was developed based on previous studies.<sup>31–34</sup> The first instance of HZ diagnosed from 31 days after the index date onwards was considered an incident HZ event. Additionally, all individuals with healthcare encounters 3–6 months post-HZ diagnosis underwent chart review to assess for the presence of PHN, defined as persistent HZ-related pain not attributable to other evident causes.



**Figure 1.** Matched cohort study design for vaccine effectiveness analysis. Vaccinated and unvaccinated individuals were matched on age, sex, race/ethnicity, condition (Crohn's disease, ulcerative colitis), and IBD medication category. Follow-up began 31 days after the index date until occurrence of HZ (outcome), termination of membership, death, receipt of HZ vaccine, or end of study period, whichever came first. IBD, inflammatory bowel disease; HZ, herpes zoster; RZV, recombinant zoster vaccine

Follow-up through the KPSC EHR started from 31 days after the index date until the earliest of HZ occurrence, termination of KPSC membership, death, receipt of an additional HZ vaccine dose, or conclusion of the study period (December 2022). For PHN analysis, follow-up for PHN cases was censored on the date of the PHN event, while follow-up for HZ cases without PHN ended 180 days after the HZ event date.

### **VE statistical analysis**

We described the characteristics of individuals with IBD who met the inclusion criteria. We evaluated the incidence of new HZ and PHN cases, as well as the person-years of follow-up, in both the vaccinated and unvaccinated cohorts to calculate overall incidence rates. Cumulative incidence of HZ was estimated using the Kaplan-Meier method, and differences between vaccinated and unvaccinated groups were assessed using the log-rank test. Cox proportional hazards regression models, stratified by matched sets, were employed to calculate adjusted hazard ratios (HRs) and their 95% confidence intervals (CIs). These models were adjusted for potential confounding factors identified based on scientific relevance and absolute standardized difference (ASD) > 0.1. VE estimates (%) against HZ and PHN, both unadjusted and adjusted, were computed as  $(1 - \text{HR}) \times 100$  when  $\text{HR} \leq 1$ , and  $([1/\text{HR}] - 1) \times 100$  when  $\text{HR} > 1$ . VE analyses against HZ were conducted overall and stratified by age, interval between first and second vaccine doses (4 weeks to 6 months versus > 6 months), condition (UC and CD), and medication category. Due to small sample sizes, the 50–59 and 60–69-year age groups were combined, as were medication categories 1 and 2 for mild or non-immunosuppressive medications, and categories 3, 4, and 5 for immunosuppressive medications associated with a higher HZ risk, consistent with previous studies.<sup>35,36</sup> The power analysis showed that in a cohort study with a 1:3 matching ratio and an average 2.7 years of follow-up, the number of vaccinated subjects needed to detect a VE of 60% with 80% power and a type 1 error rate of 5% ranges between 882 and 706, assuming the incidence of HZ in the unvaccinated population ranges between 12/1,000 and 15/1,000 person-years. All statistical analyses were performed using SAS software version 9.4 or later.

## **Safety**

### **Safety study objectives**

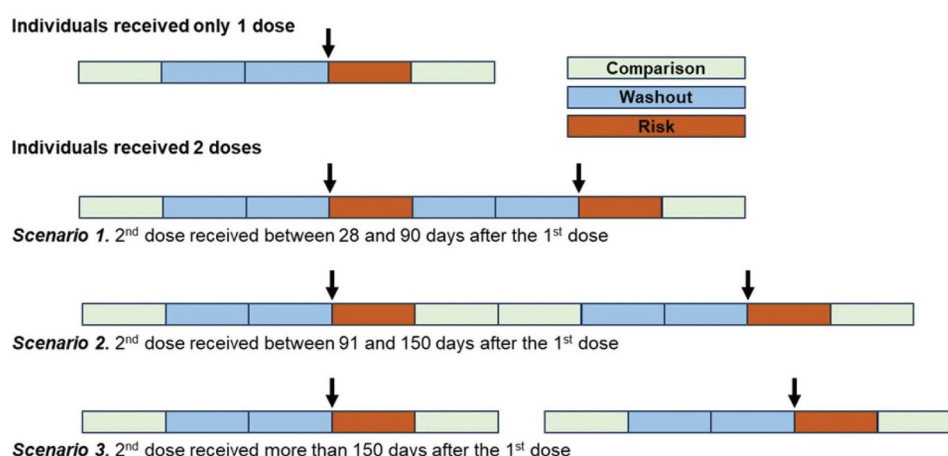
The safety objective was to assess the rate of IBD flares in adults aged  $\geq 50$  years with IBD within 30 days following any RZV vaccination as compared to the rate in self-controlled comparison periods. We also evaluated flare rates stratified by first or second RZV dose, condition (UC and CD), and medication category.

### **Safety study population**

Individuals aged  $\geq 50$  years with IBD were identified as those with at least 2 ICD-10 diagnosis codes for IBD within a 1-year period before the index date, which was defined as the vaccination date with the first dose of RZV. The accrual period for vaccine data spanned from April 2018 to December 2021, excluding individuals with an index date during the COVID-19 pandemic period from March to December 2020 from the study cohort. Individuals who received at least 1 dose of RZV with at least 1 year of continuous KPSC membership prior to and through the index date were included. Individuals who received a second dose of RZV within 4 weeks of the first dose were excluded.

### **Safety study design: self-controlled case series (SCCS)**

A SCCS analysis was conducted to evaluate the risk of IBD flare after RZV vaccination. Each individual served as their own comparator in the analysis. The index date was defined as Day 0. The risk of IBD flare during a pre-defined risk period was compared with self-controlled comparison periods. For those who received only 1 dose of RZV, the risk period for IBD flare assessment was defined as +1 to +30 days following vaccination, with comparison periods set at –90 to –61 days and +31 to +60 days relative to Day 0 (Figure 2). A washout period was established from –60 to –1 days before Day 0. The duration of the 30-day risk period was determined based on the existing literature, the vaccine's mechanism of action,<sup>37</sup> and consultation with external gastroenterology experts. For individuals who received a second dose of RZV, specific risk and comparison periods were defined based on the timing of the second dose (risk and comparison period description, from Supplementary Material; Figure 2).



**Figure 2.** Self-controlled case series design for safety analysis. Each box indicates a 30-day interval, and administration of recombinant zoster vaccine is indicated by arrows. The schematics for individuals that received 2 doses represent the maximum length of time an individual could spend in each period (comparison, washout, or risk). In Scenario 1, the risk window after the first dose could be between 28 and 30 days and the subsequent washout window could be between 0 and 60 days. In Scenario 2, the comparison window between 2 doses could be between 1 and 60 days.

### Safety exposure and outcomes

RZV vaccine doses were identified using CVX code 187, as described in the VE analysis. The safety outcome was limited to clinically significant flares, defined as either new-onset flare or worsening of IBD disease activity (Definition of clinically relevant flare, from Supplementary Material). To ensure accurate identification of disease flares, trained research associates and gastroenterology specialists reviewed the EHR. Events were recorded in the period in which a new episode of flare symptoms occurred.

### Safety statistical analysis

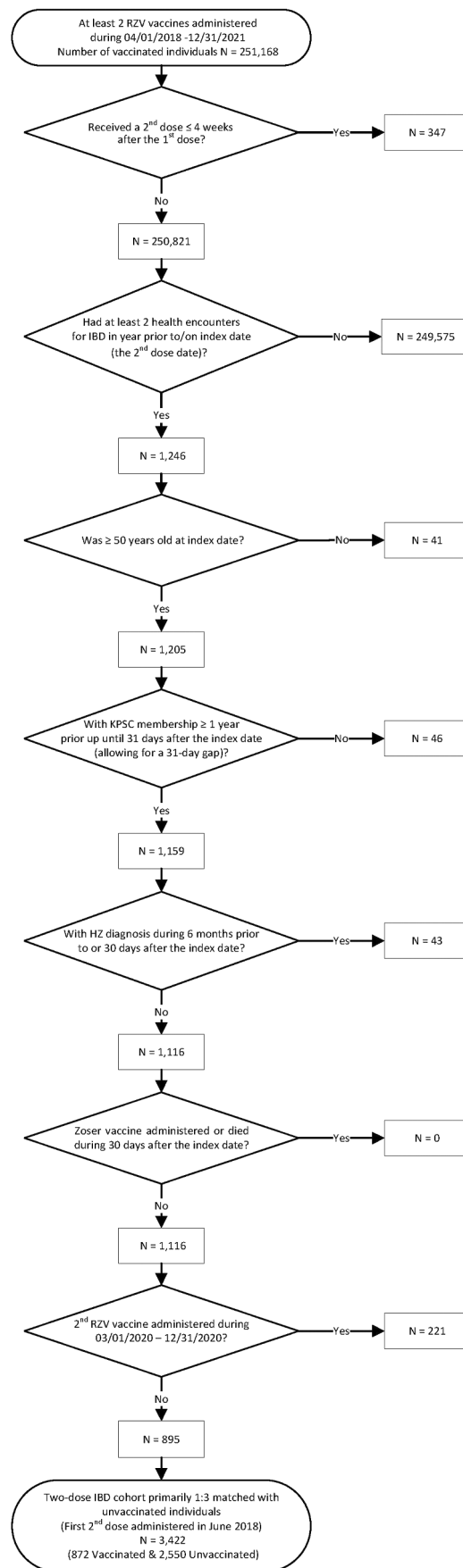
For the safety analyses, we described the characteristics of individuals with IBD who met the inclusion criteria. IRs of IBD flares during risk and comparison periods were calculated by dividing the number of flares by person-time. Relative risks (RRs) and their 95% CI comparing the incidence of flare in the risk period and that in the comparison period were estimated using conditional Poisson regression. This analysis was conducted overall, as well as stratified by first and second vaccine doses, condition (UC and CD), and medication categories 1–2 and 3–5 (combined as described in the VE analyses). The power analysis indicated that at least 34 events in the comparison window were required to achieve 80% power of detecting an increased risk of flare of  $RR = 2$  with a type 1 error of 5%. All statistical analyses were conducted using SAS software version 9.4 or later.

## Results

### Vaccine effectiveness

The VE cohort consisted of 872 2-dose RZV vaccinated and 2,550 matched unvaccinated individuals (Figure 3). Overall, the mean age was 68.4 years (standard deviation [SD] 9.0), 55.4% were female, 74.0% were White, 53.8% had UC (without CD), and 75.5% were managed by Category 1 and 2 medications (Table 1). Compared to unvaccinated individuals, vaccinated individuals had more outpatient visits but fewer ED visits or hospitalizations ( $ASD > 0.1$ ). Vaccinated individuals had a higher frequency of previous zoster vaccine live (ZVL) or varicella vaccinations and longer continuous KPSC membership ( $\geq 11$  years) compared to unvaccinated individuals ( $ASD > 0.1$ ). Other characteristics, including most baseline comorbidities and history of HZ, were well-balanced between the vaccinated and unvaccinated cohorts ( $ASD < 0.1$ ; Table 1).

Among individuals with IBD who received 2 doses of RZV, there were 9 HZ cases with an HZ incidence of 4.3 (95% CI, 2.3–8.3) per 1,000 person-years compared to 57 HZ cases with an HZ incidence of 12.1 (95%



**Figure 3.** Flow chart of the 2-dose RZV vaccinated and unvaccinated cohort with inflammatory bowel disease for vaccine effectiveness analysis. HZ, herpes zoster; IBD, inflammatory bowel disease; KPSC, Kaiser Permanente Southern California; RZV, recombinant zoster vaccine.

**Table 1.** Baseline characteristics of 2-dose RZV vaccinated and unvaccinated cohorts with inflammatory bowel disease for vaccine effectiveness analysis.

|                                                             | Vaccinated<br>N = 872 | Unvaccinated<br>N = 2,550 | Total<br>N = 3,422 | p-value           | ASD  |
|-------------------------------------------------------------|-----------------------|---------------------------|--------------------|-------------------|------|
| Age at index date, years                                    |                       |                           |                    | 0.23              | 0.04 |
| Mean (SD)                                                   | 68.7 (8.6)            | 68.3 (9.1)                | 68.4 (9.0)         |                   |      |
| Median (Q1, Q3)                                             | 68 (63, 74)           | 68 (62, 74)               | 68 (62, 74)        |                   |      |
| Range                                                       | 50–98                 | 50–99                     | 50–99              |                   |      |
| Age at index date, years, n (%)                             |                       |                           |                    | 1.00              | 0.01 |
| 50–59                                                       | 134 (15.4%)           | 395 (15.5%)               | 529 (15.5%)        |                   |      |
| 60–69                                                       | 341 (39.1%)           | 998 (39.1%)               | 1,339 (39.0%)      |                   |      |
| 70–79                                                       | 302 (34.6%)           | 884 (34.7%)               | 1,186 (34.7%)      |                   |      |
| ≥80                                                         | 95 (10.9%)            | 273 (10.7%)               | 368 (10.8%)        |                   |      |
| Sex, n (%)                                                  |                       |                           |                    | 0.82              | 0.01 |
| Female                                                      | 480 (55.0%)           | 1,415 (55.5%)             | 1,895 (55.4%)      |                   |      |
| Male                                                        | 392 (45.0%)           | 1,135 (44.5%)             | 1,527 (44.6%)      |                   |      |
| Race/Ethnicity, n (%)                                       |                       |                           |                    | 0.71              | 0.06 |
| White                                                       | 636 (72.9%)           | 1,895 (74.3%)             | 2,531 (74.0%)      |                   |      |
| Black                                                       | 48 (5.5%)             | 137 (5.4%)                | 185 (5.4%)         |                   |      |
| Hispanic                                                    | 113 (13.0%)           | 330 (12.9%)               | 443 (12.9%)        |                   |      |
| Asian                                                       | 60 (6.9%)             | 158 (6.2%)                | 218 (6.4%)         |                   |      |
| Other                                                       | 15 (1.7%)             | 30 (1.2%)                 | 45 (1.3%)          |                   |      |
| IBD, n (%) <sup>a</sup>                                     |                       |                           |                    | 0.59 <sup>g</sup> | 0.03 |
| UC                                                          | 466 (53.5%)           | 1,375 (53.9%)             | 1,841 (53.8%)      |                   |      |
| CD <sup>b</sup>                                             | 405 (46.4%)           | 1,174 (46.1%)             | 1,579 (46.1%)      |                   |      |
| UC+CD                                                       | 1 (0.1%)              | 1 (0.0%)                  | 2 (0.1%)           |                   |      |
| Medication category, n (%)                                  |                       |                           |                    | 0.82              | 0.04 |
| Category 1                                                  | 339 (38.9%)           | 1,008 (39.5%)             | 1,347 (39.4%)      |                   |      |
| Category 2                                                  | 313 (35.9%)           | 922 (36.2%)               | 1,235 (36.1%)      |                   |      |
| Category 3                                                  | 154 (17.7%)           | 442 (17.3%)               | 596 (17.4%)        |                   |      |
| Category 4                                                  | 64 (7.3%)             | 176 (6.9%)                | 240 (7.0%)         |                   |      |
| Category 5                                                  | 2 (0.2%)              | 2 (0.1%)                  | 4 (0.1%)           |                   |      |
| Number of outpatient visits <sup>a</sup> , n (%)            |                       |                           |                    | 0.02              | 0.13 |
| 0–4                                                         | 4 (0.5%)              | 42 (1.6%)                 | 46 (1.3%)          |                   |      |
| 5–10                                                        | 128 (14.7%)           | 410 (16.1%)               | 538 (15.7%)        |                   |      |
| ≥11                                                         | 740 (84.8%)           | 2,098 (82.3%)             | 2,838 (83.0%)      |                   |      |
| Number of ED visits <sup>a</sup> , n (%)                    |                       |                           |                    | <0.01             | 0.21 |
| 0                                                           | 622 (71.3%)           | 1,651 (64.8%)             | 2,273 (66.4%)      |                   |      |
| 1                                                           | 156 (17.9%)           | 442 (17.3%)               | 598 (17.5%)        |                   |      |
| ≥2                                                          | 94 (10.8%)            | 457 (17.9%)               | 551 (16.1%)        |                   |      |
| Number of hospitalizations <sup>a</sup> , n (%)             |                       |                           |                    | <0.01             | 0.19 |
| 0                                                           | 770 (88.3%)           | 2,099 (82.3%)             | 2,869 (83.8%)      |                   |      |
| 1                                                           | 77 (8.8%)             | 298 (11.7%)               | 375 (11.0%)        |                   |      |
| ≥2                                                          | 25 (2.9%)             | 153 (6.0%)                | 178 (5.2%)         |                   |      |
| Baseline comorbidities <sup>a</sup> , n (%)                 |                       |                           |                    |                   |      |
| Kidney disease                                              | 155 (17.8%)           | 480 (18.8%)               | 635 (18.6%)        | 0.49              | 0.03 |
| Heart disease                                               | 77 (8.8%)             | 286 (11.2%)               | 363 (10.6%)        | 0.05              | 0.08 |
| Lung disease                                                | 185 (21.2%)           | 607 (23.8%)               | 792 (23.1%)        | 0.12              | 0.06 |
| Liver disease                                               | 74 (8.5%)             | 235 (9.2%)                | 309 (9.0%)         | 0.52              | 0.03 |
| Diabetes                                                    | 178 (20.4%)           | 614 (24.1%)               | 792 (23.1%)        | 0.03              | 0.09 |
| Other autoimmune diseases                                   | 58 (6.7%)             | 214 (8.4%)                | 272 (7.9%)         | 0.10              | 0.07 |
| SARS-CoV-2 infection/COVID-19 diagnosis                     | 21 (2.4%)             | 76 (3.0%)                 | 97 (2.8%)          | 0.38              | 0.04 |
| Immunocompromised status at index date <sup>c</sup> , n (%) |                       |                           |                    | 0.05              | 0.08 |
| Yes                                                         | 252 (28.9%)           | 651 (25.5%)               | 903 (26.4%)        |                   |      |
| No                                                          | 620 (71.1%)           | 1,899 (74.5%)             | 2,519 (73.6%)      |                   |      |
| History of ZVL/varicella vaccination <sup>d</sup> , n (%)   |                       |                           |                    | <0.01             | 0.34 |
| No                                                          | 490 (56.2%)           | 1,754 (68.8%)             | 2,244 (65.5%)      |                   |      |
| Yes, ≤5 years                                               | 51 (5.8%)             | 215 (8.4%)                | 266 (7.8%)         |                   |      |
| Yes, >5 years                                               | 331 (38.0%)           | 581 (22.8%)               | 912 (26.7%)        |                   |      |
| History of HZ <sup>d</sup> , n (%)                          |                       |                           |                    | 0.07              | 0.07 |
| Yes                                                         | 143 (16.4%)           | 355 (13.9%)               | 498 (14.6%)        |                   |      |
| No                                                          | 729 (83.6%)           | 2,195 (86.1%)             | 2,924 (85.4%)      |                   |      |
| Length of continuous membership <sup>d</sup> , years, n (%) |                       |                           |                    | 0.02              | 0.12 |
| 0–5                                                         | 148 (17.0%)           | 526 (20.6%)               | 674 (19.7%)        |                   |      |
| 6–10                                                        | 135 (15.5%)           | 438 (17.2%)               | 573 (16.7%)        |                   |      |
| ≥11                                                         | 589 (67.5%)           | 1,586 (62.2%)             | 2,175 (63.6%)      |                   |      |

(Continued)

**Table 1.** (Continued).

|                                              | Vaccinated<br>N = 872 | Unvaccinated<br>N = 2,550 | Total<br>N = 3,422 | p-value | ASD |
|----------------------------------------------|-----------------------|---------------------------|--------------------|---------|-----|
| Concomitant vaccination <sup>e</sup> , n (%) |                       |                           |                    | N/A     | N/A |
| Yes                                          | 328 (37.6%)           | N/A                       | N/A                |         |     |
| No                                           | 544 (62.4%)           | N/A                       | N/A                |         |     |
| Time between first and second doses, n (%)   |                       |                           |                    | N/A     | N/A |
| 4 weeks–6 months                             | 695 (79.7%)           | N/A                       | N/A                |         |     |
| >6 months <sup>f</sup>                       | 177 (20.3%)           | N/A                       | N/A                |         |     |

ASD, absolute standardized difference; CD, Crohn's disease; ED, emergency department; HZ, herpes zoster; IBD, inflammatory bowel disease; N/A, not applicable; Q, quartile; RZV, recombinant zoster vaccine; SD, standard deviation; UC, ulcerative colitis; ZVL, zoster vaccine live.

<sup>a</sup>Defined in the 1 year prior to index date.

<sup>b</sup>Four of the vaccinated individuals in the CD category also had UC but could only be matched to other unvaccinated individuals with CD.

<sup>c</sup>HIV/AIDS, leukemia/lymphoma, congenital/other immunodeficiencies, asplenia/hyposplenia, hematopoietic stem cell transplant/solid organ transplant, and receipt of immunosuppressive medications.

<sup>d</sup>Defined based on all available medical records prior to index date.

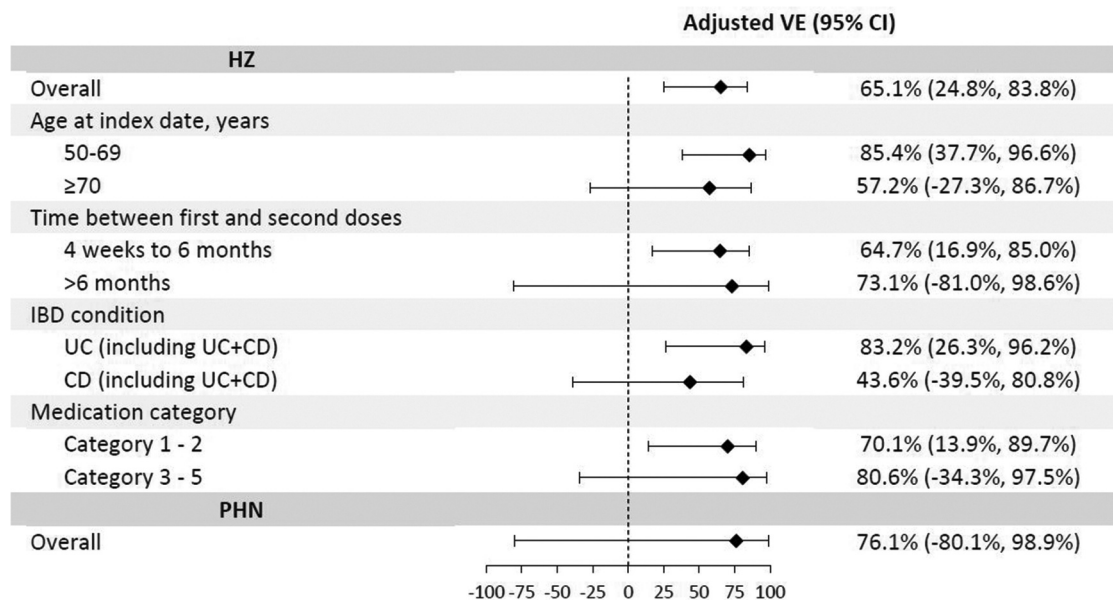
<sup>e</sup>Individuals with concomitant vaccines on the same day as RZV received: influenza vaccine (48%), COVID-19 vaccine (2%), pneumococcal vaccine (25%), tetanus-diphtheria-acellular pertussis vaccine (26%), and other (17%); 69% received concomitant vaccines with the 1<sup>st</sup> dose and 43% with the 2<sup>nd</sup> dose.

<sup>f</sup>Among individuals who received the 2<sup>nd</sup> dose >6 months after the 1<sup>st</sup> dose, the range of time between 2 doses was from 185 days to 2.9 years with median of 11.0 months.

<sup>g</sup>Fisher's exact *p*-value.

CI, 9.3–15.7) per 1,000 person-years in the unvaccinated group (Table S2). The cumulative incidence of HZ was significantly higher in the unvaccinated individuals than in the vaccinated individuals ( $p = .0031$ ) (Figure S1). The overall adjusted VE of 2 doses of RZV against HZ was 65.1% (95% CI, 24.8–83.8) in analyses adjusted for immunocompromised status, history of HZ, number of outpatient visits, number of ED visits, number of hospitalizations, history of ZVL/varicella vaccination, and length of continuous membership (Figure 4, Table S2).

Variations of the adjusted VE point estimates existed in subgroup analyses by age, time between first and second doses (i.e., second dose was administered 4 weeks to 6 months or >6 months following the first dose), condition (UC and CD), and medication category used to manage IBD (Figure 4, Table S2). However, the CIs were wide due to the small number of HZ cases in the vaccinated group. Those who received



**Figure 4.** Vaccine effectiveness of 2 doses of RZV in preventing herpes zoster and postherpetic neuralgia among individuals with inflammatory bowel disease (N = 3,422). CD, Crohn's disease; CI, confidence interval; HZ, herpes zoster; IBD, inflammatory bowel disease; PHN, postherpetic neuralgia; RZV, recombinant zoster vaccine; UC, ulcerative colitis; VE, vaccine effectiveness. Note: Table S2 contains detailed data related to this figure.

their second dose 4 weeks to 6 months after the first dose as consistent with label had similar adjusted VE to the overall group (64.7% [95% CI, 16.9–85.0]). For analysis of PHN, in the vaccinated cohort, the PHN incidence was 1.0 (95% CI, 0.2–3.8) per 1,000 person-years compared to 1.5 (95% CI, 0.7–3.1) in the unvaccinated group (Table S3). The adjusted VE against PHN was 76.1% (95% CI, –80.1–98.9; Figure 4).

## Safety

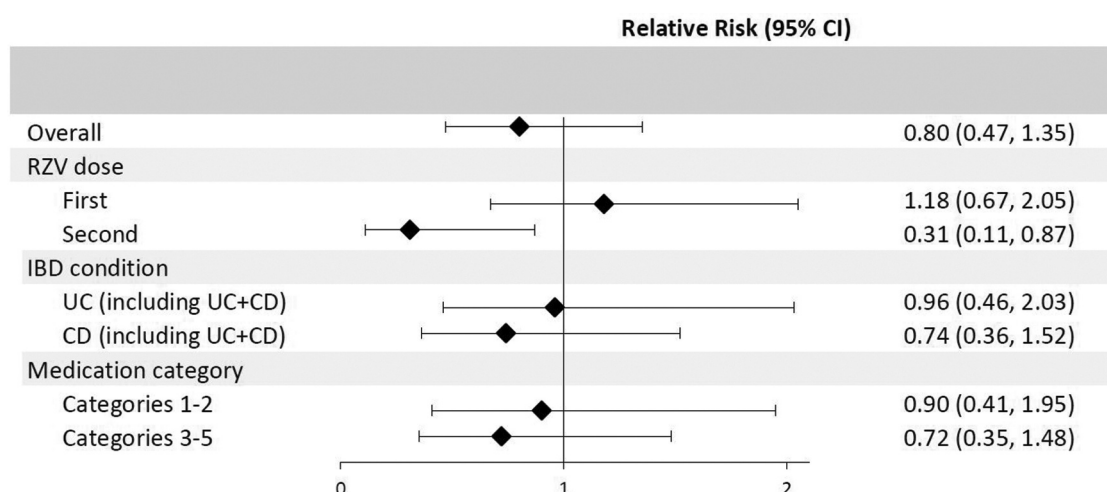
In the safety cohort defined in Figure S2, RZV recipients with IBD (N = 1,199) had a mean age of 68.2 years (SD 9.1), 53.8% were female, 69.6% were White, 55.7% had UC (without CD), and 72.8% were managed by Category 1 and 2 medications (Table 2). Most individuals in this cohort (77.6%) received 2 RZV doses, and 34.8% received concomitant vaccines (Table 2). There were 23 IBD flare cases with an incidence of 131.80 (95% CI, 87.59–198.34) per 1,000 person-years in the risk window, compared to 37 IBD flare cases with an incidence of 155.29 (95% CI, 112.52–214.33) per 1,000 person-years in the comparison window (Table S4). The RR of flare in those who received at least 1 dose of RZV was 0.80 (95% CI, 0.47–1.35; Figure 5; Table S4). The RR of IBD flare was not significantly elevated whether the individual was receiving the first (1.18; 95% CI, 0.67–2.05) or second (0.31; 95% CI, 0.11–0.87) dose of RZV, whether the individual had UC or CD (UC:

**Table 2.** Baseline characteristics of RZV recipients with inflammatory bowel disease for safety analysis.

| Demographic characteristics                  | Vaccinated<br>N = 1,199 |
|----------------------------------------------|-------------------------|
| Age at index date, years                     |                         |
| Mean (SD)                                    | 68.2 (9.1)              |
| Median (Q1, Q3)                              | 68 (62, 74)             |
| Range                                        | 50–97                   |
| Age at index date, years, n (%)              |                         |
| 50–59                                        | 219 (18.3%)             |
| 60–69                                        | 456 (38.0%)             |
| 70–79                                        | 393 (32.8%)             |
| ≥80                                          | 131 (10.9%)             |
| Sex, n (%)                                   |                         |
| Female                                       | 645 (53.8%)             |
| Male                                         | 554 (46.2%)             |
| Race/Ethnicity, n (%)                        |                         |
| White                                        | 836 (69.6%)             |
| Black                                        | 87 (7.3%)               |
| Hispanic                                     | 165 (13.8%)             |
| Asian                                        | 90 (7.5%)               |
| Other                                        | 21 (1.8%)               |
| IBD condition, n (%)                         |                         |
| UC                                           | 668 (55.7%)             |
| CD                                           | 527 (44.0%)             |
| UC+CD                                        | 4 (0.3%)                |
| Medication category, n (%)                   |                         |
| Category 1                                   | 449 (37.5%)             |
| Category 2                                   | 423 (35.3%)             |
| Category 3                                   | 226 (18.8%)             |
| Category 4                                   | 85 (7.1%)               |
| Category 5                                   | 16 (1.3%)               |
| Number of RZV doses, n (%)                   |                         |
| One dose                                     | 269 (22.4%)             |
| Two doses                                    | 930 (77.6%)             |
| Concomitant vaccination <sup>a</sup> , n (%) |                         |
| Yes                                          | 417 (34.8%)             |
| No                                           | 782 (65.2%)             |

CD, Crohn's disease; IBD, inflammatory bowel disease; Q, quartile; RZV, recombinant zoster vaccine; SD, standard deviation; UC, ulcerative colitis.

<sup>a</sup>Individuals with concomitant vaccines on the same day as RZV received: influenza vaccine (47%), COVID-19 vaccine (2%), pneumococcal vaccine (26%), tetanus-diphtheria-acellular pertussis vaccine (24%), and other (17%); 79% received concomitant vaccines with the 1<sup>st</sup> dose and 28% with the 2<sup>nd</sup> dose.



**Figure 5.** Relative risk of flares after RZV among individuals with inflammatory bowel disease (N = 1,199). CD, Crohn's disease; CI, confidence interval; IBD, inflammatory bowel disease; RZV, recombinant zoster vaccine; UC, ulcerative colitis. Note: Table S4 contains detailed data related to this figure.

0.96, 95% CI, 0.46–2.03; CD: 0.74, 95% CI, 0.36–1.52), and whether their IBD was managed by category 1–2 (0.90; 95% CI, 0.41–1.95) or category 3–5 (0.72; 95% CI, 0.35–1.48) medications.

## Discussion

In this study, we provide real-world data on the effectiveness and safety of RZV in individuals with IBD who are aged  $\geq 50$  years. Overall, receipt of 2 doses of RZV was associated with a two-thirds reduced risk of HZ (VE = 65.1%, 95% CI, 24.8%–83.8%). The effectiveness appeared to be higher in the younger age group (aged 50–69 years) and in those with UC compared to those with CD; however, the VE estimates had wide confidence intervals, limiting our ability to draw definitive conclusions. In the final analysis, more subjects and longer follow-up time will be included to increase the power of the analyses. We did not observe an increase in the risk of IBD flares in the 30 days following RZV vaccination compared to the comparison periods (RR = 0.80 [95% CI, 0.47–1.35]), supporting the safety profile of RZV in patients with IBD.

Our results on RZV effectiveness in individuals with IBD are comparable to findings from previous studies. A retrospective analysis using a US claims database between 2018 and 2021 reported an overall VE of 73.4% for 2-dose RZV against HZ among individuals aged  $\geq 50$  years with IBD (63.5% for UC and 85.7% for CD),<sup>38</sup> while our study estimated VEs of 83.2% for UC and 43.6% for CD. The discrepancy could be due to random variation and deserves further investigation from a larger sample size. In a study conducted among Medicare Part D community-dwelling beneficiaries aged  $\geq 65$  years, the 2-dose RZV VE among individuals with autoimmune diseases including UC was 68.0% (95% CI, 62.3–72.8).<sup>39</sup> In another US study using data on patients with IBD from the National Veterans Affairs Healthcare System, the crude HZ incidence rate in recipients of 2 doses of RZV was lower compared with unvaccinated individuals aged  $\geq 50$  years (0.00 and 3.93 per 1,000 person-years, respectively, in individuals aged 50–60 years and 1.80 and 4.57 per 1,000 person-years, respectively, in individuals aged  $> 60$  years).<sup>22</sup> In a more recent cohort study using the TriNetX database including adults with IBD aged  $\geq 50$  years, individuals vaccinated with RZV had a lower risk of HZ (adjusted odds ratio 0.44, 95% CI, 0.32–0.62) compared to unvaccinated matched adults with IBD.<sup>36</sup>

We did not observe an increased risk of flares within 30 days following RZV vaccination. These observations are consistent with previous studies in individuals with IBD reporting on the risk of flares associated with RZV. A retrospective cohort study reported that the 90-day cumulative incidence of IBD flare was not significantly different between the RZV vaccinated and unvaccinated groups (1.2% among vaccinated versus 1.0% among unvaccinated,  $p = 0.503$ ); the odds ratio for IBD flare associated

with RZV vaccination was 1.25 (95% CI, 0.65–2.41).<sup>25</sup> Another study using data from MarketScan enrollees aged 50–64 years and Medicare beneficiaries aged  $\geq 65$  years with immune-mediated inflammatory diseases also found no significant increase in the risk of IBD flares following 1 or 2 doses of RZV vaccination.<sup>24</sup> In that study using an SCCS design, 7% and 9% developed flares in the control window, compared to 7%–8% and 9% in the risk window following dose 1 or dose 2 among MarketScan and Medicare enrollees, respectively. Unlike previous studies, our study reviewed the medical records of all subjects to determine if they had a flare; thereby providing a highly accurate and complete identification of IBD flares.

Our study had several notable strengths. First, as a large, integrated health care system, details of all episodes of patient care collected as part of daily clinical practice were available to researchers in near real-time. KPSC's comprehensive EHR enabled accurate capture of exposure, outcomes, and covariates. The high retention rate and stability of KPSC membership allowed for rapid accrual of a large, representative sample size to evaluate the implications of vaccination. Second, because our study did not restrict inclusion by type of IBD medication regimen, our study results may be generalizable to individuals with IBD on a variety of medication regimens. Third, chart reviews were performed by trained research associates and IBD specialists to examine the onset of worsening symptoms and medication changes to identify IBD flares. This allowed for accurate and specific definition of IBD flares that would not be achievable using diagnosis codes only. Finally, we used the SCCS design to compare the risk of flares in different time periods for the same person. The SCCS design inherently controls for fixed individual-level confounders,<sup>40,41</sup> and controls for time-varying covariates such as age and seasonality by using comparison periods before and after the risk period.

Our study also had some limitations. First, misclassification of exposure or outcomes was possible. However, given the accuracy and comprehensiveness of our EHR data, misclassification was expected to be minimal. Mild HZ or PHN outcomes not requiring clinical evaluation may have been missed, but this potential misclassification was expected to be non-differential across the exposure groups. Second, although we adjusted for potential confounding by using a matched cohort design and multivariable modeling, residual confounding might still exist. Further, due to the small number of HZ and PHN outcomes, especially in subgroup analyses, some covariates needed to be dropped from the models for convergence purposes. Additionally, differences in health care utilization between vaccinated and unvaccinated individuals were possible but were not expected to be substantial because the study population consisted of individuals with  $\geq 2$  healthcare encounters with an associated diagnosis code for IBD in the year prior to the index date. Also, because our study was conducted in a large, US integrated health care system, the generalizability of our study findings may be of limited use for uninsured populations with IBD, or those who receive care in other types of health systems or outside the US. Lastly, the COVID-19 pandemic may have had an impact on vaccine uptake as well as other health care-seeking behaviors. Therefore, we did not accrue vaccinations from March through December 2020.

Our study provides real-world evidence that the 2-dose RZV vaccination schedule is effective in preventing HZ in adults aged  $\geq 50$  years with IBD who are at increased risk of HZ and associated complications. We did not observe an increase in the risk of IBD flares in the 30 days following vaccination with RZV. Our study contributes to the growing body of evidence regarding RZV vaccination benefits for individuals with IBD to reduce the burden of HZ in this population. Longer follow-up time in the final analysis will reveal the durability of protection in this patient population.

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Dr. Hung Fu Tseng had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis and agreed by all authors.

## Author contributions

CRedit: **Hung Fu Tseng**: Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Writing – original draft; **Lina S. Sy**: Conceptualization, Methodology, Supervision, Writing – review & editing; **Emily Rayens**: Conceptualization, Writing – review & editing; **Bradley K. Ackerson**: Conceptualization, Investigation, Methodology, Validation, Writing – review & editing; **Jennifer H. Ku**: Conceptualization, Methodology, Writing – review & editing; **Jun Wu**: Conceptualization, Data curation, Formal analysis, Investigation, Software, Validation, Writing – review & editing; **Yi Luo**: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Supervision, Validation, Writing – review & editing; **Yanjun Cheng**: Conceptualization, Data curation, Formal analysis, Investigation, Software, Validation, Writing – review & editing; **Avanish R. Patel**: Conceptualization, Investigation, Methodology, Validation, Writing – review & editing; **Zendi Solano**: Conceptualization, Investigation, Methodology, Project administration, Supervision, Validation, Writing – review & editing; **Justine De Jesus**: Investigation, Project administration, Validation, Writing – review & editing; **Britta Amundsen**: Investigation, Project administration, Validation, Writing – review & editing; **Ana Florea**: Conceptualization, Methodology, Writing – review & editing; **Elizabeth Chmielewski-Yee**: Conceptualization, Methodology, Project administration, Writing – review & editing; **Driss Oraichi**: Writing – review & editing; **Harry Seifert**: Conceptualization, Methodology, Writing – review & editing; **Huifeng Yun**: Conceptualization, Methodology, Writing – review & editing; **Lei Qian**: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Supervision, Validation, Writing – review & editing.

## Disclosure statement

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## Data availability statement

The datasets generated and/or analyzed during the current study are not publicly available due to privacy concerns.

## Meeting presentation

The corresponding abstract was submitted and accepted for presentation at IDWeek 2024 (Oct 16–19).

## Trademark statement

Shingrix is a trademark licensed to or owned by GSK.

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