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ORIGINAL RESEARCH ARTICLE

Cost-Effectiveness of Recombinant Zoster Vaccine for the Prevention of Herpes Zoster in Hematopoietic Stem Cell Transplant Recipients and Other Immunocompromised Adults in the United States

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Abstract

Introduction Immunocompromised (IC) adults are at increased risk of developing herpes zoster (HZ) and HZ-related complications due to therapy or underlying disease. This study evaluated the cost effectiveness of recombinant zoster vaccine (RZV) versus no vaccine for the prevention of HZ in hematopoietic stem cell transplant (HSCT) recipients and other IC adults aged ≥ 18 years in the United States (US).

Methods A static Markov model simulated cohorts of IC individuals using a 1-year cycle length and 30-year time horizon to estimate the cost effectiveness of RZV. Inputs were sourced from clinical trial results and publicly available sources/literature. Modeled populations included US adult HSCT recipients (base case), patients with human immunodeficiency virus (HIV), patients with breast cancer, patients with Hodgkin's lymphoma, and renal transplant recipients. The model reported societal costs, quality-adjusted life-years (QALYs), and incremental cost-effectiveness ratios (ICERs). Sensitivity and threshold analyses were conducted.

Results In the base case of 19,671 US adult HSCT recipients, RZV resulted in total societal cost savings of US$0.1 million and 109 incremental QALYs versus no vaccine. RZV was a 'dominant strategy' versus no vaccine because vaccination resulted in cost savings with QALY gains. RZV was also cost saving in renal transplant recipients, and cost effective at a willingness-to-pay threshold of US$100,000 per QALY gained in patients with HIV, breast cancer, and Hodgkin's lymphoma, with ICERs of US$33,268, US$67,682, and US$95,972 per QALY gained, respectively, versus no vaccine.

Conclusions Model results show RZV is potentially cost saving for the prevention of HZ in US adult HSCT recipients and US adults with selected immunocompromising conditions, and cost effective for others, supporting the use of RZV to prevent HZ and HZ-related complications in IC adults.

Key Points for Decision Makers

In the base case of US adult hematopoietic stem cell transplant recipients, recombinant zoster vaccine was considered a 'dominant strategy' versus no vaccine because vaccination resulted in cost savings with quality-adjusted life-year (QALY) gains over 30 years.

Analyses of selected immunocompromised adult populations showed that vaccination with recombinant zoster vaccine is likely cost saving (renal transplant recipients) or cost effective (patients with HIV, breast cancer, and Hodgkin's lymphoma) at a hypothetical willingness-to-pay threshold of US$100,000 per QALY gained.

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1 Introduction

Almost one out of every three individuals in the United States (US) will develop herpes zoster (HZ) in their lifetime, accounting for 1 million cases each year nationwide [1]. HZ is caused by a reactivation of the varicella-zoster virus, which persists latently in host neurons following initial infection [1]. While older adults are at an elevated risk of HZ due to natural waning of immune function, the incidence and burden of HZ increases sharply in populations that are immunodeficient or immunosuppressed (hereafter referred to collectively as 'immunocompromised' [IC]) [2–5]. Individuals may be IC due to disease, such as human immunodeficiency virus (HIV) infection, or due to therapy, such as in hematopoietic stem cell transplant (HSCT) recipients. Approximately 2.7% of US adults, or 6.44 million individuals, are estimated to be IC based on a 2013 study [6, 7]. HZ cases in IC populations also result in greater healthcare resource use and costs than HZ cases in immunocompetent populations in the US [4].

In 2017, the Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC) preferentially recommended recombinant zoster vaccine (RZV, Shingrix) for HZ prevention among all immunocompetent adults aged 50 years and older, including those previously vaccinated with zoster vaccine live (ZVL, Zostavax) [8]. In July 2021, the US Food and Drug Administration (FDA) expanded the indication for RZV to include adults aged 18 years and older who are or will be at increased risk for HZ due to immunodeficiency or immunosuppression caused by known disease or therapy; and in October 2021, the ACIP recommendation for RZV was expanded to include adults aged 19 years and older who are or will be at increased risk for HZ [9, 10].

This study evaluated the cost effectiveness of RZV versus no vaccine when used for the prevention of HZ in US adults aged 18 years and older who are IC due to HSCT or other selected IC conditions, with a focus on adults aged 18–49 years.

2 Methods

2.1 Model Overview

Outcomes in this study were estimated using the ZOster eco-Nomic Analysis IC (ZONA IC) Model (not publicly available), an adaptation of the ZONA 50 + Model for populations aged 50 years and older [11, 12]. The model structure and analysis framework for the ZONA IC model is illustrated in Fig. 1. The model estimates the outcomes resulting from different inputs for vaccinating against HZ for selected IC populations who are or will be at increased risk of HZ. This deterministic, static Markov model built in Microsoft Excel (Microsoft Corporation, Redmond, WA, USA) has a 1-year cycle length and follows a hypothetical cohort of adults for 30 years. Given the uncertainty around long-term survival in various IC populations, 30 years was selected as a conservative time horizon to capture all relevant outcomes of HZ and HZ vaccination while balancing the uncertainty of extrapolating beyond 30 years.

In the ZONA IC Model, outcomes were observed for a selected set of populations of US adults who were IC. There were two strategies: RZV (vaccination of the entire cohort at the simulation start) and no vaccine (vaccination does not occur). After an initial duration where individuals were assumed to have reduced immune function for a discrete number of years (IC status), individuals transitioned to an immunocompetent (healthy) status for the remainder of the

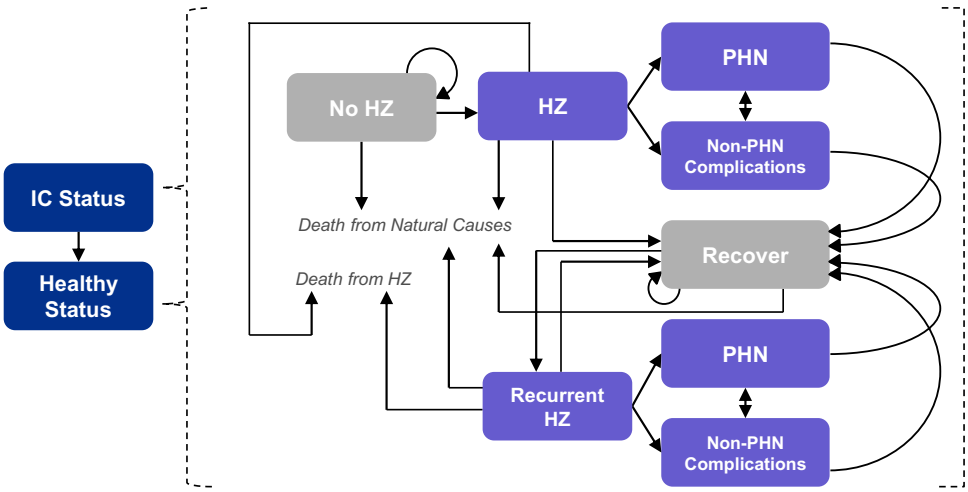

Fig. 1 Structure of the ZONA IC model. Vaccination may or may not occur in the no HZ health status, depending on the modeled strategy. *HZ* herpes zoster, *IC* immunocompromised, *PHN* postherpetic neuralgia, *ZONA* Zoster Economic Analysis.

time horizon. This reflects the temporary nature of some IC conditions and allowed for IC- and immunocompetent-specific model inputs to avoid overestimation of the benefits of RZV. In the healthy status, individuals were assumed to have the same HZ epidemiology, costs, utilities, and all-cause mortality rates as those for the immunocompetent population observed in the ZONA Model, for the respective ages modeled (the ZONA Model is described by Curran et al.) [11]. An annual discount rate of 3% was applied for all costs, life-years, and quality-adjusted life-years (QALYs), aligning with recommendations from the Second Panel on Cost-Effectiveness in Health and Medicine [13]. All cost inputs were inflated to 2019 US dollars (US$) using the medical care component of the US Consumer Price Index for direct medical costs and the general US Consumer Price Index for indirect costs [14, 15].

2.2 Modeled Populations

An autologous HSCT population of 19,671 patients, the estimated number of HSCT procedures conducted in the US in 2017, was modeled in the base case [16]. HSCT recipients are one of the most immunodeficient populations and have a higher incidence of HZ than individuals in the overall IC population; therefore, protecting against HZ would address a critical need [5, 17, 18]. This population is also well-studied and data for RZV efficacy, safety, and differential utility loss in HSCT patients were readily available. Although one study reported a post hoc analysis of trial data to estimate RZV efficacy among adults with hematologic malignancies, RZV efficacy and safety in IC populations have only been formally assessed prospectively in a phase III clinical trial in adult HSCT recipients. Data from this phase III clinical trial were used to estimate RZV efficacy against burden of illness and HZ-related utility loss in HSCT recipients [19–21]. In the model, the population was assumed to be 35 years of age (the approximate midpoint of the assumed base-case cohort age range of 18–49 years), to have received autologous HSCT immediately prior to the start of the model time horizon, and not to have previously received any vaccination against HZ.

Patients in other IC populations were also modeled in Scenario Analyses A–D, specifically: (A) patients with HIV infection; (B) patients with solid tumors, using breast cancer as an example subpopulation; (C) patients with hematological malignancies, using Hodgkin's lymphoma as an example subpopulation; and (D) recipients of a renal transplant.

2.3 Model Inputs and Outputs

All analyses were conducted from the societal perspective with both direct and indirect costs considered. Economic outcomes included vaccination costs, and direct and indirect costs due to HZ resulting from each strategy. Vaccination costs consisted of vaccine acquisition costs, vaccine administration costs, and direct costs of adverse events. Direct costs due to HZ captured medical costs to treat a case of HZ with and without postherpetic neuralgia (PHN), and the costs of other complications due to HZ. Indirect costs consisted of costs arising from working hours lost due to vaccine-related adverse events and HZ (absenteeism), including those hours lost due to PHN, as reported by Eriksson et al. [22]. The outcomes from the two strategies were then compared to calculate differences resulting from RZV versus no vaccine. The key outcome measure for all analyses was the incremental cost-effectiveness ratio (ICER), as measured by the incremental cost per QALY gained. Health outcomes included HZ and PHN cases.

Model input values were identified through a targeted literature review focused on publications from 2005 to 2020 (Table 1, electronic supplementary material [ESM] Tables A1–A7). Some model inputs had values that varied by age. As a cohort aged annually, the inputs corresponding to the cohort's age were applied. Some model input values also depended on whether they were being applied to individuals with IC or a healthy status. The duration of the IC status before individuals transitioned to a healthy status differed between the populations modeled in different scenarios. The base-case analysis assumed HSCT patients were IC for 5 years, based on an epidemiological study of HZ among autologous HSCT recipients [23]. The IC status duration and associated rationale for the other selected IC populations are detailed in Table 1. The input values applied to individuals aged 50 years and older with a healthy status have been previously described; the input values applied to individuals aged 18–49 years with a healthy status are presented in ESM Table A4 [11].

For the scenario analyses, we conducted simple linear regression analyses that linked HZ incidence with RZV efficacy, using the results from the placebo arm of a phase III clinical trial and efficacy and waning estimates from immunocompetent and IC cohorts in the same phase III trial and other RZV clinical trials [19, 20, 24, 25]. For each selected IC population, the regression analyses estimated potential differences in RZV efficacy and waning as a function of HZ risk while IC. Further details about the values, sources, derivations, and standard errors for all inputs used in the analyses can be found in the electronic supplementary Appendix.

Deterministic sensitivity and threshold analyses were conducted to estimate the sensitivity of ICERs to each of the models' input values. A probabilistic sensitivity analysis was conducted to explore uncertainty around the model's outcomes, given the uncertainty around the model's inputs, including 5000 Monte Carlo simulations.

Table 1 ZONA IC Model settings varied in scenario analyses, considering RZV versus no vaccine for United States adults with different immunocompromised conditions

Input	Input value				
	Base-case analysis (HSCT population)[a]	HIV population (Scenario A)[b]	Breast cancer population (Scenario B)[c]	Hodgkin's lymphoma population (Scenario C)[d]	Renal transplant population (Scenario D)[e]
Population size	19,671	1,018,846	279,100	8480	22,106
Population starting age (years)	35	35	45	25	40
IC status duration (years)	5	30	2	2	30
Annual incidence of initial and recurrent HZ (per person-year)	0.0600	0.0093	0.0171	0.0336	0.0244
Annual probability all-cause mortality	0.0994	0.0347	0.0217	0.0284	Ages 18–49 years: 0.0030 Ages 50–59 years: 0.0090 Ages 60+ years: 0.0470
Initial RZV efficacy against HZ[f]					
One dose	58.0%[g]	78.9%[h]	77.2%[h]	69.8%[h]	75.6%[h]
Two doses	72.5%	98.6%	96.5%	87.2%	94.5%
Initial RZV efficacy against PHN[f]					
One dose	75.9%[h]	78.0%[h]	77.8%[h]	77.4%[h]	77.6%[h]
Two doses	94.8%	97.5%	97.2%	96.7%	97.0%
Annual waning of RZV efficacy[f]					
One dose	18.2%[i]	4.6%[i]	8.2%[i]	12.2%[i]	10.2%[i]
Two doses	9.1%	2.3%	4.1%	6.1%	5.1%

HIV human immunodeficiency virus, *HSCT* hematopoietic stem cell transplant, *HZ* herpes zoster, *IC* immunocompromised, *PHN* postherpetic neuralgia, *RZV* recombinant zoster vaccine, *US* United States, *ZONA* Zoster Economic Analysis

[a]The population size was the total number of HSCTs performed on individuals aged 21 years and older in 2017 in the US, as reported by the Center for International Blood and Marrow Transplant Research [16]

[b]The population size was the estimated number of individuals aged 20 years and older living with diagnosed HIV in 2018 in the US, as reported by the Centers for Disease Control and Prevention [28]. The starting age of the population was approximately the mean age of individuals living with HIV in an epidemiological study of HZ in individuals with HIV [38]. The IC status duration and annual incidence of HZ were from the same study, which reported the annual incidence of HZ among HIV patients at an urban HIV clinic between 2002 and 2009, calculated from data from The Johns Hopkins University AIDS database. The annual probability of all-cause death was derived from the study by Siddiqi et al. [39] which reported a 28.86-year estimated average life expectancy in 2011 after diagnosis of HIV

[c]The population size was the total number of individuals of all ages projected to be diagnosed with breast cancer in 2020, as reported by Siegel et al. [27]. The population reflects a younger breast cancer population; National Cancer Institute data [39], which reported that 19.7% of breast cancer diagnoses occurred in patients between the ages of 45 and 54 years, were used. The IC status duration and annual incidence of HZ were from the study by Habel et al. [18], who reported the annual incidence of HZ among adults with solid tumor malignancies and by level of immunosuppression. The annual probability of all-cause death was set to the 5-year survival probability for patients with breast cancer reported by Noone et al. [41]

[d]The population size was the total number of individuals of all ages projected to be diagnosed with Hodgkin's lymphoma in 2020, as reported by Siegel et al. [27]. The starting age of the population reflects the age at which adults are most frequently diagnosed, i.e. 20–34 years per National Cancer Institute data [40]. The IC status duration and annual incidence of HZ were estimated from the findings reported by Habel et al. [18], who reported the annual incidence of HZ among adults with hematologic malignancies and by level of immunosuppression. The annual probability of all-cause death was set to the 5-year survival probability for patients with Hodgkin's lymphoma reported by Noone et al. [41].

[e]The population size was the total number of kidney transplants performed in 2020 in the US among individuals aged 18 years and older. [26] The starting age of the population was assumed, based on Organ Procurement and Transplantation Network data [24], which showed that approximately 57% of the more than 50 transplants studied were in adults aged 35–49 years. The IC status duration was based on the assumption of lifetime maintenance use of immunosuppressants for renal transplant recipients, per clinical expert opinion. The annual incidence of HZ was obtained from the study by Pergam et al. [42], set to the annual incidence rate of HZ among 500 patients who received kidney transplants between 1995 and 2007. The annual probability of all-cause death was set to annual death rates for recipients of deceased donor kidney transplants reported by Kaballo et al. [43].

[f]The initial efficacy of RZV and annual waning of RZV in each population was estimated from regression equations based on the association between placebo HZ incidence and RZV efficacy and waning in immunocompetent and IC populations from RZV clinical trials [19, 21, 24, 25]; the placebo HZ incidences used to estimate efficacy and waning from the regression equations for the IC conditions were derived from the study by Blank et al. [38] (HIV), Pergam et al. [42] (renal transplant), and Habel et al. [18] (Hodgkin's lymphoma and breast cancer)

[g]We assumed a 20% relative reduction from two-dose efficacy, due to a lack of data for one-dose RZV (i.e., high second-dose compliance) in the clinical trials. We assumed a ± 20% relative change from the base-case value for the uncertainty range

[h]We assumed a 100% relative increase from two-dose waning of efficacy, due to a lack of data for one-dose RZV (i.e., high second-dose compliance) in the clinical trials. Assumed ± 50% relative change from the base-case value for the uncertainty range

[i]The value shown was applied until the population returned to healthy status or until the population reached an age at which all-cause mortality was greater than the annual probability of death shown

Scenario analyses A–D modeled patients with HIV, patients with solid tumors (using breast cancer as an example subpopulation), patients with hematological malignancies (using Hodgkin's lymphoma as an example subpopulation), and recipients of a renal transplant, respectively. Their starting ages varied but were all between 18 and 49 years, aligning with the research and health policy question. Cohort sizes were determined as either the estimated yearly incidence of a condition in the US (breast cancer, 279,100; Hodgkin's lymphoma, 8480; renal transplant, 22,106) or its prevalence (HIV; 1,018,846) [16, 26–28]. Epidemiology, duration of IC status, and the efficacy and waning of RZV applied in the scenario analyses were varied.

Scenario Analysis E was conducted to vary the following three parameters: starting age, IC duration, and HZ incidence. For starting age 35 years, IC status duration (1–30 years) and annual HZ incidence (10–80 per 1000 person-years) were simultaneously varied. Additionally, for the population cohorts with starting ages of 25, 35, and 45 years, each combination of IC status duration (15 or 30 years) and annual HZ incidence (6–10 per 1000 person-years) was also explored. Age-specific annual probabilities of all-cause mortality were assumed to be twice the probability of immunocompetent individuals, to reflect IC populations having an underlying risk for death that is greater than the general US population but less than the HSCT population modeled in the base-case analysis. All other ZONA IC Model input values applied in Scenario E were consistent with the values applied in the base-case analysis for US HSCT adults aged 35 years.

3 Results

3.1 Base Case: Hematopoietic Stem Cell Transplant (HSCT) Recipients

A plain language summary of the results of this study is presented in ESM Fig. A1. For the base-case cohort of 19,671 HSCT recipients, RZV resulted in 2297 and 422 fewer HZ and PHN cases, respectively, versus no vaccine. When the cohort was vaccinated with RZV, discounted direct costs and indirect costs due to HZ (US$9.4 million and US$2.0 million, respectively) were lower than with no vaccine, while the associated vaccination costs were US$10.0 million. This amounted to a total discounted societal cost of US$21.4 million (Table 2). Thus, total discounted societal cost savings of US$0.1 million were observed for RZV versus no vaccine over a time horizon of 30 years. RZV also resulted in a gain of 109 discounted QALYs versus no vaccine. RZV was therefore a dominant strategy relative to no vaccine (i.e., more QALYs gained with a lower total cost).

3.2 Sensitivity and Threshold Analyses

The results of the deterministic sensitivity analysis are presented in Fig. 2. The ICER for the HSCT population was most sensitive to the following inputs based on their defined uncertainty ranges: direct medical costs per HZ case, annual incidence of initial HZ (i.e., first occurrence of HZ), IC status duration, annual waning of RZV efficacy, and initial efficacy of RZV against HZ. The maximum ICER (US$49,215 per QALY gained) was observed when the IC status duration was assumed to be 2 years. Only the results for the top 20 inputs are presented in Fig. 2. The majority (82%, most of which are not shown) of input variations did not increase or decrease the ICER by more than US$5000 per QALY gained.

The probabilistic sensitivity analysis showed RZV in the HSCT population had a 44.5% probability of being a cost-saving strategy versus no vaccine (Fig. 3). At a hypothetical willingness-to-pay threshold of US$100,000 per QALY gained, vaccinating with RZV would be considered cost effective in 97.1% of simulations.

Threshold analyses assessed how much change in key parameters would render RZV no longer cost effective in the HSCT population (i.e., result in an ICER higher than US$100,000 per QALY gained). RZV would not be cost effective if the annual incidence of initial and recurrent HZ per person-year was ≤ 0.024, or 60% lower than the base-case value; the IC status duration was 1 year or less (−80%); or the initial RZV efficacy was $\leq 36.3\%$ for HZ or $\leq 47.4\%$ for PHN (− 50%) (Fig. A2).

3.2.1 Scenario Analyses: Other Immunocompromised Populations

For the population of 1,018,846 individuals with HIV (Scenario A), RZV resulted in 118,583 and 15,026 fewer HZ and PHN cases, versus no vaccine. RZV also resulted in a total societal cost increase of US$112.2 million and 3373 incremental QALYs gained relative to no vaccine. This translated to an ICER of US$33,268 per QALY gained. Vaccination with RZV of 279,100 patients with breast cancer (Scenario B) resulted in 38,069 and 3184 fewer HZ and PHN cases, versus no vaccine. RZV also resulted in a total societal cost increase of US$34.2 million and 506 incremental QALYs gained, compared with no vaccine, translating to an ICER of US$67,682 per QALY

Table 2 Cost and QALY outcomes for RZV versus no vaccine for US adults IC due to HSCT (base case) and other conditions (Scenarios A–D)

Base case[a]			
	RZV	No vaccine	Incremental (RZV vs. no vaccine)
Total societal cost (US$)[a]	21,355,313	21,461,730	−106,417
Direct costs due to HZ (US$)	9,360,330	18,956,241	9,595,9110
Indirect costs due to HZ (US$)	2,016,822	2,505,489	488,666
Vaccination costs (US$)	9,978,160	NA	NA
QALYs	213,289	213,180	109
ICER (US$ per QALY gained)	NA	NA	Cost saving

Scenario analyses[b]								
	Scenario A: HIV population		Scenario B: Breast cancer population		Scenario C: Hodgkin's lymphoma population		Scenario D: Renal transplant population	
	RZV	No vaccine	RZV	No vaccine	RZV	No vaccine	RZV	No vaccine
Total societal cost (US$, millions)	663.4	551.2	196.7	162.4	5.5	3.8	37.3	43.0
Direct costs due to HZ (US$, millions)	140.0	526.2	33.2	103.7	0.8	3.0	24.9	41.1
Indirect costs due to HZ (US$, millions)	6.6	24.9	21.9	58.8	0.4	0.7	1.2	1.9
Vaccination costs (US$, millions)	516.8	0	141.6	0	4.3	0	11.2	0
Total societal cost difference [RZV vs. no vaccine] (US$, millions)	112.2		34.2		1.7		−5.8	
Incremental QALYs gained (RZV vs. no vaccine)	3373		506		18		156	
ICER (US$ per QALY gained)	33,268		67,682		95,972		Cost saving	

HIV human immunodeficiency virus, *HSCT* hematopoietic stem cell transplant, *HZ* herpes zoster, *IC* immunocompromised, *ICER* incremental cost-effectiveness ratio, *NA* not applicable, *QALY* quality-adjusted life year, *RZV* recombinant zoster vaccine, *US* United States

[a]All outcomes are discounted. Population size: 19,671

[b]HIV scenario population size: 1,018,846; breast cancer scenario population size: 279,100; Hodgkin's lymphoma scenario population size: 8480; renal transplant scenario population size: 22,106. See electronic supplementary Table A8 for more detail

gained. For the population of 8480 patients with Hodgkin's lymphoma (Scenario C), RZV resulted in 849 and 94 fewer HZ and PHN cases, respectively, versus no vaccine. RZV also resulted in a total societal cost increase of US$1.7 million and 18 incremental QALYs gained, compared with no vaccine. This translated to an ICER of US$95,972 per QALY gained. When the population of 22,106 renal transplant recipients was vaccinated with RZV (Scenario D), there were 4453 and 603 fewer HZ and PHN cases, respectively. Additionally, the total societal costs decreased by US$5.8 million, there were 156 incremental QALYs gained, and RZV was found to be cost saving versus no vaccine.

In Scenario E, when the IC status duration and the annual HZ incidence during IC status were simultaneously varied, the majority of ICERs were cost saving (Table 3). ICERs were highest with the shortest IC durations and lowest annual HZ incidence.

4 Discussion

Results for the base-case analysis in HSCT recipients and adults with other selected IC conditions suggest RZV is likely cost effective for the prevention of HZ in US IC adults aged 18 years and older in selected IC populations, and may be cost saving for some IC populations. RZV is also effective in reducing HZ and PHN cases in selected IC populations. These results were robust to a wide range of uncertainties in key parameters that influenced the health outcomes and the overall costs of the vaccine program.

To our knowledge, our study is only the second to comprehensively evaluate the cost effectiveness of an HZ vaccine in IC cohorts. The CDC has developed a similar model, the results of which informed the 2021 ACIP recommendation for RZV in adults aged 19 years and older who are or will be at increased risk for HZ because of immunodeficiency or immunosuppression caused by known disease or therapy [10]. Results from the CDC model showed vaccination with RZV was cost saving for

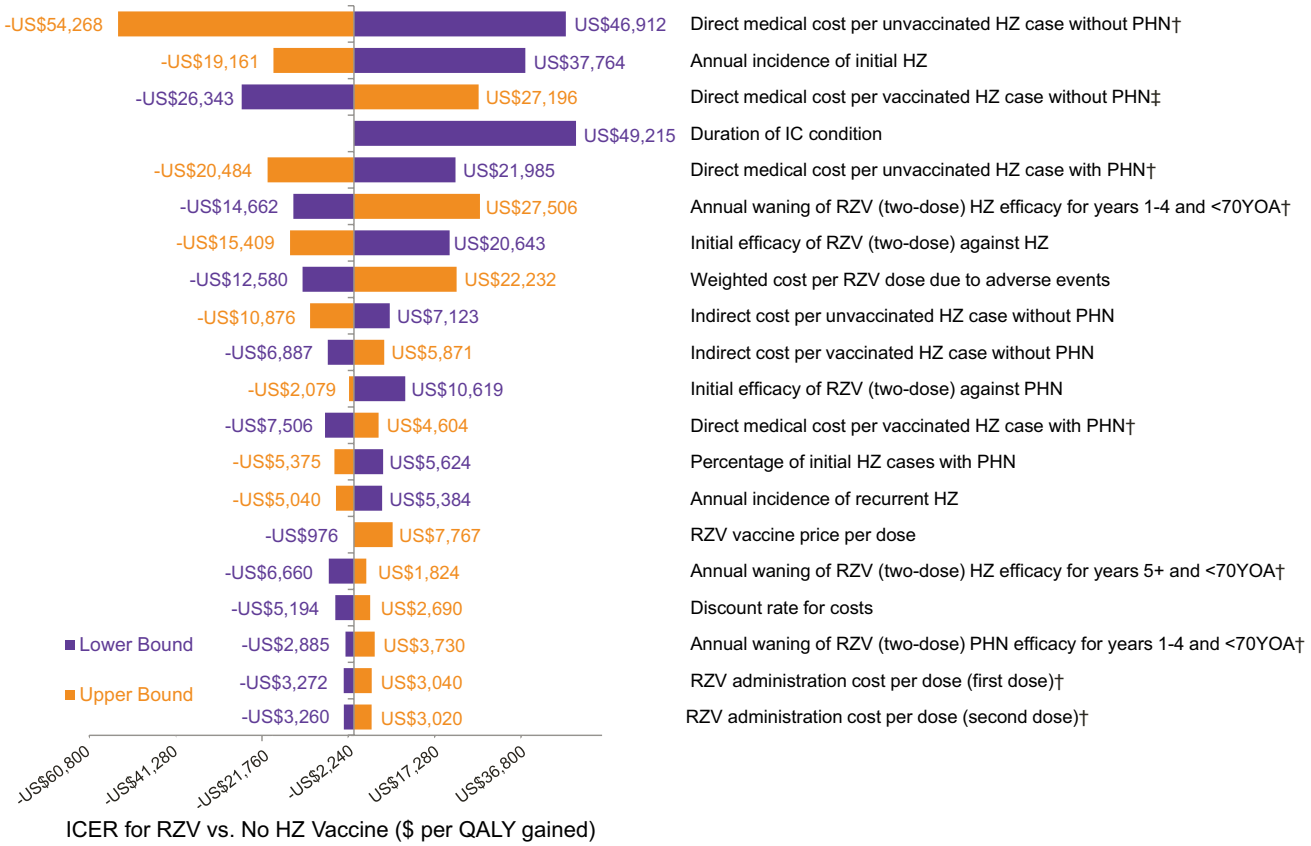

Fig. 2 Deterministic sensitivity analysis results for the cost effectiveness of RZV versus no vaccine strategy for US HSCT adults aged 35 years. †Individual variation of an input that is also varied in this deterministic sensitivity analysis grouped with other potentially correlated inputs. *HSCT* hematopoietic stem cell transplant, *HZ* herpes zoster, *ICER* incremental cost-effectiveness ratio, *PHN* postherpetic neuralgia, *QALY* quality-adjusted life-year, *RZV* recombinant zoster vaccine, *US* United States, *YOA* years of age

the base case of adult HSCT recipients aged 18–49 years, aligning with results of the present analysis [29].

Previous analyses found RZV was a cost-effective intervention for immunocompetent adults aged 50 years and older in the US [11, 30–32]. Estimates of RZV's efficacy and durability in the prevention of HZ and associated complications were lower in an HSCT clinical trial study than in trials with immunocompetent adults, as would be expected due to the HSCT cohort's IC status, which results in a decreased responsiveness to vaccination [19, 33]. However, our analysis demonstrated that the increased risk, utility impact, and cost impact of HZ cases in HSCT and the other modeled IC cohorts were high, making the cost-effectiveness estimates for RZV versus no vaccine in IC cohorts similar to those for older adults.

In our base case of US adult HSCT recipients, RZV resulted in total societal cost savings of US$0.1 million and 109 incremental QALYs versus no vaccine, and RZV was also cost saving in scenario analysis of recipients of a renal transplant. At a hypothetical willingness-to-pay threshold of US$100,000 per QALY gained, a common threshold reported in US cost-effectiveness analyses [34], RZV was cost effective in the scenario analyses of patients with HIV, breast cancer, and Hodgkin's lymphoma, with ICERs of US$33,268, US$67,682, and US$95,972 per QALY gained, respectively, versus no vaccine. Our findings were comparable with ICERs reported by studies focusing on immunocompetent adults, which ranged from approximately US$10,000 to US$91,000 per QALY gained [11, 30–32]. The probabilistic sensitivity analysis results emphasize the robustness of the base-case results, and the conclusions drawn from them. Overall, this study provides valuable cost-effectiveness information that can be considered by policy makers, alongside other criteria deemed relevant for decision making (e.g., feasibility of implementation and impact on health equity).

While the base-case analysis included HSCT recipients as a well-studied, highly IC population that has a higher incidence of HZ than individuals in the overall IC population, the scenario analyses investigated RZV cost effectiveness in other IC conditions to address the heterogeneity of IC patients in real-world settings. Model input values

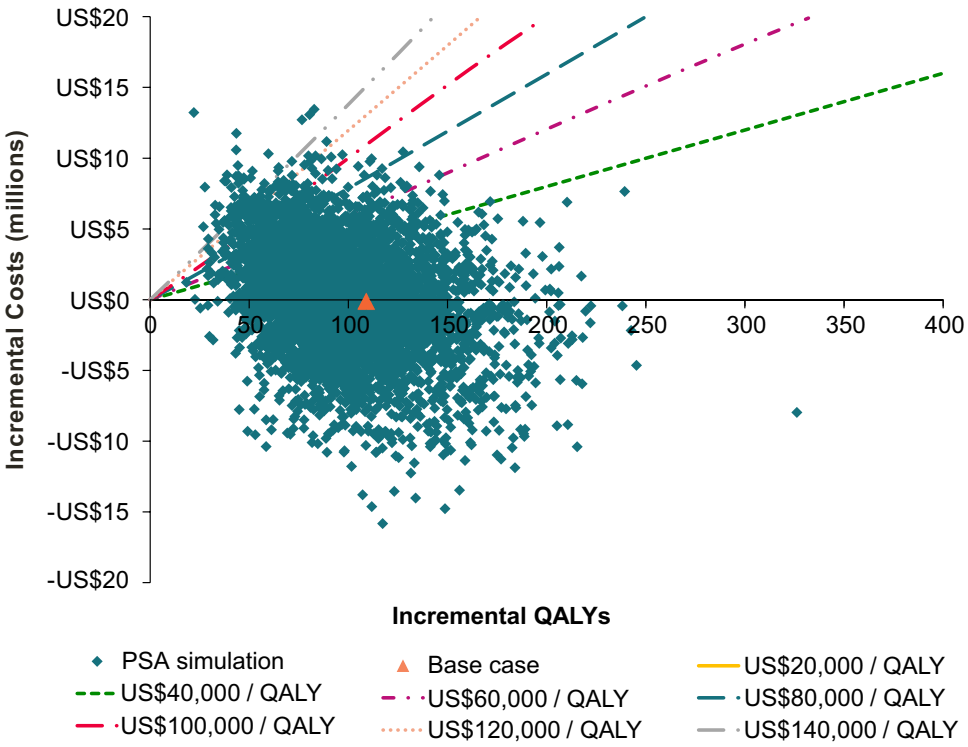

Fig. 3 Incremental costs versus incremental QALYs from 5000 probabilistic sensitivity analysis simulations of RZV versus no vaccine for US HSCT adults aged 35 years. *HSCT* hematopoietic stem cell transplant, *PSA* probabilistic sensitivity analysis, *QALYs* quality-adjusted life-year, *RZV* recombinant zoster vaccine, *US* United States

Table 3 Scenario E: ICERs for RZV versus no vaccine for US IC adults, across ranges of values for starting age, IC status duration, and annual herpes zoster incidence

IC status duration (years)	Annual incidence of HZ (per 1000 person-years)[a], based on a starting age of 35 years				
	10	20	40	60	80
1	US$548,377	US$312,732	US$146,083	US$82,966	US$51,646
2	US$300,961	US$133,185	US$33,046	Cost saving	Cost saving
3	US$199,578	US$70,612	Cost saving	Cost saving	Cost saving
4	US$143,150	US$38,106	Cost saving	Cost saving	Cost saving
5	US$104,716	US$17,323	Cost saving	Cost saving	Cost saving
30	Cost saving	Cost saving	Cost saving	Cost saving	Cost saving

		Annual incidence of HZ (per 1000 person-years)[a]				
		6	7	8	9	10
Starting age (years)	25					
IC status duration (years)	15	US$66,285	US$47,555	US$33,256	US$21,985	US$12,878
	30	US$18,192	US$8549	US$480	Cost saving	Cost saving
Starting age	35					
IC status duration	15	US$31,638	US$21,137	US$12,565	US$5,455	Cost saving
	30	US$12,694	US$7989	US$1211	Cost saving	Cost saving
Starting age	45					
IC status duration	15	US$12,828	US$13,225	US$7028	US$1569	Cost saving
	30	US$3533	US$6251	US$3327	US$304	Cost saving

All ZONA IC Model input values other than those varied in this scenario were consistent with the base-case analysis for US HSCT adults (starting age 35 years)

HSCT hematopoietic stem cell transplantation, *HZ* herpes zoster, *IC* immunocompromised, *ICER* incremental cost-effectiveness ratio, *RZV* recombinant zoster vaccine, *US* United States, *ZONA* Zoster Economic Analysis

[a]RZV efficacy and waning values were estimated based on the annual HZ incidence value considered. For more detail, please see the 'Data Sources' subsection in the manuscript, and electronic supplementary Figs. A3 and A4

were based on clinical trial results and data from a targeted literature review that was conducted to ascertain realistic input values. Our analysis made simplifying assumptions that the IC status duration was a discrete number of years, and that the cohort maintained a healthy status for the remainder of the time horizon. The IC duration and resulting HZ risk are likely more dynamic in real-world IC cohorts. However, in some simulations (e.g., HIV) the cohort remained IC for the full time horizon, aligning with the disease pathology. Notably, analyses showed that RZV cost effectiveness was more favorable when HZ incidence and vaccine efficacy were high, IC duration was long, and vaccine efficacy waning and IC condition-specific mortality were low. When individuals are highly immunosuppressed, generally HZ incidence, disease burden, HZ costs, and natural mortality will be high, while starting vaccine efficacy will be lower and vaccine efficacy waning will be higher (as compared with those who are less immunosuppressed).

Our base-case analysis assumed HSCT patients were IC for 5 years based on an epidemiological study of HZ among autologous HSCT recipients [23]. We assumed that the period observed in that study covered the relevant period of elevated HZ risk for HSCT patients. We considered briefer durations of IC status in the deterministic sensitivity and threshold analyses, but those analyses applied the 5-year annual incidence estimate from that epidemiological study. Had we assumed a 2-year IC status duration in the base-case analysis, we also would have applied higher annual HZ incidence during IC status, closer to 80–90 cases per 1000 person-years, as multiple studies have observed in the first 2 years following HSCT [19, 23, 35].

Although our base-case analysis starting age was 35 years, the available vaccine efficacy and HZ incidence data were taken from trials with older populations [19, 23]. In the phase III clinical trial, the vaccine efficacy among individuals aged 18–49 years was 72%, compared with 67% in those aged ≥ 50 years; the overall efficacy was 68% [19]. To address potential bias, we conservatively used the overall vaccine efficacy estimate in the model, as opposed to the 72% efficacy observed for ages 18–49 years where better results for RZV would have been observed. The annual HZ incidence estimated from Sahoo et al. was applied because it had the longest follow-up (median 39.7 months) among the studies considered, and provided a 5-year annual incidence estimate following HSCT [17, 19, 23, 35, 36]. Although the 35-year-old starting age for the HSCT population was selected to focus analyses on adults aged 18–49 years, and it is not reflective of the mean age of the HSCT population in the studies considered (median age 55.5 years in the study by Sahoo et al.), the age-related relationship for HZ incidence in this population was not statistically significant, with an incidence rate ratio of 1.08 (0.91–1.27) for ages 50–59 years versus 18–49 years [17, 23].

Limited data were available to estimate RZV effectiveness and durability in IC cohorts other than HSCT, therefore regression analyses were conducted using data from RZV clinical trials in immunocompetent and IC cohorts to estimate these values [19, 20, 24, 25]. The regression calculated the relationship between HZ incidence and RZV efficacy (i.e., higher incidence, lower efficacy, and vice versa). A key limitation of this approach is that it assumes that differences in RZV efficacy across populations are entirely explained by differences in HZ incidence; other immunological factors and age may also be relevant.

Different all-cause mortality rates were used for the healthy (immunocompetent) and IC cohorts. Due to the lack of data, we conservatively applied HZ case-fatality estimates for an immunocompetent population to both the healthy and IC status [37]. Although death is uncommon in HZ infections, immunosuppression is recognized as a risk factor. Our estimate of HZ-related mortality is therefore likely an underestimate.

5 Conclusions

The results of this study show RZV may be cost saving for the prevention of HZ in US adults aged 18 years and older with selected IC conditions and cost effective for others. Furthermore, these results support the use of RZV to prevent HZ and its associated complications in IC adults. Our findings may inform clinicians and policy makers in decision making around the efficacy and value of RZV in IC adults, where the absence of a vaccine indicated for prevention of HZ has resulted in high unmet medical need. The present analysis assessed the cost effectiveness of RZV in selected IC populations. Further research is necessary to better understand the impact of RZV across the highly heterogeneous IC population.

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Declarations

Conflict of interest Ahmed Salem, Elizabeth M. La, Desmond Curran, and Sara Poston are employees of the GSK group of companies and

report holding shares in the GSK group of companies. Justin Carrico and Katherine A. Hicks report payments to RTI Heath Solutions from the GSK group of companies for the conduct of this study. Brandon J. Patterson reports holding shares in the GSK group of companies and is a former employee of the GSK group of companies. Stéphane Lorenc and Christopher F. Carpenter declare to have received consulting fees from the GSK group of companies. All authors declare no other financial and non-financial relationships and activities.

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Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Code availability (software application or custom code) The Microsoft Excel-based model used in this study is proprietary property of GSK and cannot be shared.

Authors' contributions Substantial contributions to study conception and design: AS, EML, DC, BJP, JC, SL, KAH, SP, CFC. Substantial contributions to analysis and interpretation of the data: AS, EML, DC, BJP, JC, SL, KAH, SP, CFC. Drafting the article or revising it critically for important intellectual content: AS, EML, DC, BJP, JC, SL, KAH, SP, CFC. Final approval of the version of the article to be published: AS, EML, DC, BJP, JC, SL, KAH, SP, CFC.

Data sharing statement The Microsoft Excel-based model used in this study is proprietary property of GSK and cannot be shared. All data generated or analyzed during this study are included in this published article or as supplementary information files.

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