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Estimated Public Health Impact of the Recombinant Zoster Vaccine

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Abstract

Objective: To investigate the potential public health impact of adult herpes zoster (HZ) vaccination with the adjuvanted recombinant zoster vaccine (RZV) in the United States in the first 15 years after launch.

Methods: We used a publicly available model accounting for national population characteristics and HZ epidemiological data, vaccine characteristics from clinical studies, and anticipated vaccine coverage with RZV after launch in 2018. Two scenarios were modeled: a scenario with RZV implemented with 65% coverage after 15 years and a scenario continuing with zoster vaccine live (ZVL) with coverage increasing 10% over the same period. We estimated the numbers vaccinated, and the clinical outcomes and health care use avoided yearly, from January 1, 2018, to December 31, 2032. We varied RZV coverage and investigated the associated impact on HZ cases, complications, and health care resource use.

Results: With RZV adoption, the numbers of individuals affected by HZ was predicted to progressively decline with an additional 4.6 million cumulative cases avoided if 65% vaccination with RZV was reached within 15 years. In the year 2032, it was predicted that an additional 1.3 million physicians' visits and 14.4 thousand hospitalizations could be avoided, compared with continuing with ZVL alone. These numbers could be reached 2 to 5 years earlier with 15% higher RZV vaccination rates.

Conclusion: Substantial personal and health care burden can be alleviated when vaccination with RZV is adopted. The predicted numbers of HZ cases, complications, physicians' visits, and hospitalizations avoided, compared with continued ZVL vaccination, depends upon the RZV vaccination coverage achieved.

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Herpes zoster (HZ) or shingles results from the reactivation of the varicella zoster virus, which lies dormant in basal root ganglia of individuals who have had varicella, commonly known as chickenpox.[1] Varicella zoster virus—specific T-cell immunity wanes with aging or due to immunosuppressing illnesses or medications, with the result that approximately one-third of the population experiences shingles at some time in their lives.[2,3] The risk of HZ increases substantially with age over 50 years; and as the population ages and people live longer, the burden on individuals and health care providers is projected to increase.[4,5]

Shingles begins with prodromal pain, followed by a unilateral dermatomal rash most commonly affecting the trunk or face. The skin lesions and pain usually resolve within 4 to 6 weeks,[6] but in around 10% to 50% of individuals (depending upon the precise definition and patient age) the pain persists after the rash has resolved, a complication termed postherpetic neuralgia (PHN).[1] PHN is the most common complication of HZ; it can be particularly debilitating, slow to resolve, and difficult to relieve by analgesia.[6] Other complications are rarer such as HZ ophthalmicus (eye complications including keratitis, uveitis/iritis, conjunctivitis, and loss of vision[3,7]); more recently HZ has been associated with an increased vascular risk particularly affecting younger HZ sufferers,[8] with the increased risk of stroke or cardiovascular event diminishing gradually according to age and length of time after the HZ episode.[9]

HZ has a significant burden on quality of life, with 90% of patients reporting pain as

the predominant symptom.[10] In the United States it is estimated that 1 million people suffer an episode of HZ annually, with higher rates of recurrence in older or immunocompromised adults, and as many as 3% of individuals can be hospitalized.[11] Physician, emergency department, and outpatient visits and inpatient hospitals stays all contribute to the health care burden associated with the treatment and management of HZ cases and associated complications.[12] It has been estimated that HZ costs the US health care system $1.3 billion annually,[13,14] with this burden projected to increase with population aging.[15]

HZ can be prevented by vaccination. In the United States, vaccination against HZ was introduced in 2008 for immunocompetent adults aged 60 years and older.[11] At the time there was 1 vaccine available, zoster vaccine live (ZVL). Since then vaccination rates have climbed, surpassing the Healthy People 2020 target of 30% coverage.[16] However, in 2017 a new vaccine, the adjuvanted recombinant zoster vaccine (RZV) was preferentially recommended by the Advisory Committee on Immunization Practices for immunocompetent adults aged 50 years and older, regardless of prior HZ vaccination history.[17] This vaccine has a different clinical profile from that of ZVL. The efficacy of the ZVL vaccine in clinical trials was found to be 38% to 70% dependent upon patient age,[18,19] but this decreased over time with ZVL vaccination conferring little or no protection after 9 years.[20] By contrast, RZV was found to have higher efficacy (>90%), independent of age at vaccination,[21,22] with waning limited and modeled to 1% to 3.6% per year dependent upon age.[13,23] It is estimated that to prevent one case of HZ with ZVL, 32 adults would need to be vaccinated, whereas the number needed to vaccinate to prevent one case with RZV is 10.[13] Both vaccines have been associated with injection-site reactions, with the rates of grade 3 reactions (severe enough to prevent normal activities) at frequencies of 9.4% for RZV and 0.9% for ZVL[17] (although these results might not be directly comparable as discussed by McGirr et al.).[24]

Previous economic evaluations have assessed the value and affordability of vaccination with RZV in the United States.[13,25-28] These analyses, which were conducted to inform HZ vaccination recommendations and RZV reimbursement decisions, modeled the impact of RZV on hypothetical cohorts of older adults or for specific health plan populations that only represented a portion of the US population. Analyses providing public health stakeholders and other policymakers with broad, population-level estimates of the public health impact of potential RZV coverage levels have not been conducted. With the easing of RZV supply constraints,[29,30] and an emphasis on encouraging adult vaccination,[31,32] the potential public impact of HZ vaccination with RZV is of great interest. The objective of this study is to predict the public health impact of implementing HZ vaccination with RZV, when reaching coverage levels comparable with the elderly pneumococcal and influenza vaccines of 65%,[33] over the next 15 years.

METHODS

This analysis is based upon mathematical modeling; therefore, no patients were involved. The model is publicly available and the methodology published.[27] The model accounts for national population characteristics (size and age distribution), epidemiological data (incidence of HZ and complications, and HZ recurrence rate), vaccine characteristics from randomized controlled trials and observational studies (efficacy, waning, second dose compliance for RZV, and adverse event rates), and current and anticipated vaccine coverage in the years after RZV launch.

The model, a dynamic, population-level model with underlying Markov disease framework created in Microsoft Excel (Microsoft, Redmond, Washington), considers the US population eligible for vaccination, namely, immunocompetent adults aged 50+ years. As the population ages, individuals leave the model following the natural mortality rate,[34] and each year a new cohort aged 50 years joins the model, with figures based upon census data.[35] The population can be vaccinated (and if previously vaccinated with ZVL they can be vaccinated with RZV) and the probability of entering one of the health states within the model (HZ, recurrent HZ, PHN, and non-PHN complications) is adjusted accordingly, based on trial data for vaccine efficacy and waning of protection as previously described.[13,36] The structure of the model is

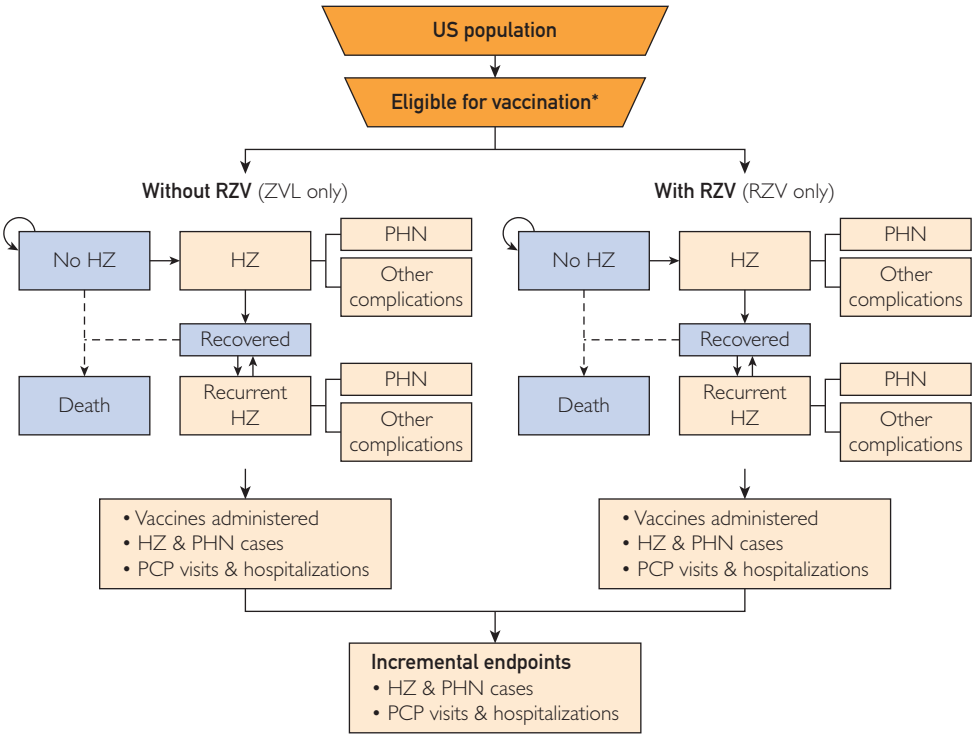

FIGURE 1. Population funnel and cohort-level transitions used in the model. An asterisk (*) indicates immunocompetent adults aged 50 years and older. "HZ" and "recurrent HZ" are modeled as events occurring during years spent in the "No HZ" and "recovered" health states, respectively. "PHN" and "non—PHN complications" are modeled as proportions of overall HZ (or recurrent HZ) cases. All-cause mortality can occur from either the "No HZ" or the "recovered" health states. HZ-related mortality is not included in the model. HZ, herpes zoster; PCP, primary care physician; PHN, postherpetic neuralgia; RZV, adjuvanted recombinant zoster vaccine; ZVL, zoster vaccine live.

shown in Figure 1. This model framework, which has been used to estimate the budget impact of RZV vaccination for US health plans,[27] is more suitable for calculating the population-level public health impact of HZ vaccination than cohort-level models used in previous cost-effectiveness analyses.

The model compares a "without RZV" scenario, which is intended to represent a world in which RZV is not available and vaccination with ZVL continues, and a "with RZV" scenario over a time horizon of 15 years. In the "without RZV" scenario, current vaccination rates with ZVL,[33] dependent upon age, were assumed to increase by 10% over the 15-year time horizon in alignment with HZ vaccination rate trends before RZV introduction.[33] For RZV, the vaccination rate begins at 0% and is assumed to linearly increase to 65% over the corresponding 15 years, which is the coverage achieved for pneumococcal and influenza vaccines in a similar age-group.[33] As RZV is a 2-dose vaccine, the second dose compliance was modeled as 76%, consistent with Centers for Disease Control and Prevention (CDC) estimates.[37] As described previously,[27] model inputs were retrieved based on the best available and most recent nationally representative estimates. These nationally representative values were aligned with the current study's objective of estimating the population-level public health impact for the United States.

Model outcomes include the number of individuals vaccinated and the number of cases of HZ, PHN, primary care physician (PCP)

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visits, and hospitalizations avoided when comparing the RZV and ZVL vaccination scenarios. The difference between the two scenarios is presented as the potential incremental benefit of adopting RZV. Target coverage levels for RZV were varied from 30% to 80% in additional scenarios to assess the public health impact of reaching alternative levels of RZV vaccination coverage.

RESULTS

Table 1 shows the modeled number of vaccinees per year for ZVL and RZV over the 15-year time horizon. The predicted cumulative number of RZV vaccine recipients, assuming vaccination coverage reaches 65%, is approximately 94 million (M) over the first 15 years after RZV adoption. The number vaccinated per year varies dependent upon the target RZV vaccination coverage and the number of individuals entering the model each year.

The cumulative number of HZ and PHN cases avoided is shown in Figure 2, comparing increasing RZV coverage to 65% of the eligible US population over 15 years with a 10% increase in ZVL coverage over the corresponding period. The curve shape shows that the cumulative number of cases avoided increases at a higher rate over time, increasing to an estimated 4.6 M HZ cases and 368,000 HZ cases with PHN cases avoided over 15 years.

In Figure 3, the corresponding cumulative numbers of PCP visits and hospitalizations avoided are presented, also increasing at a higher rate over time. Assuming the target of 65% coverage is reached in 15 years, in 2032 approximately an additional 1.3 M PCP visits and 14,400 hospitalizations are estimated to be avoided, when comparing the RZV vaccination scenario with ZVL. During the 15-year period, this approximates to a cumulative avoidance of 10.7 M PCP visits and 111,000 hospitalizations beyond what could be expected from a 10% ZVL vaccine coverage increase over the same period.

To investigate the impact of achieving alternative coverage levels on the potential public health impact of RZV vaccination, in Table 2 (and Supplemental Figure, available at http://www.mayoclinicproceedings.org) the incremental numbers of PCP visits and hospitalizations avoided are presented varying RZV

TABLE 1. Number of Individuals Vaccinated Each Year (Thousands)[a,b]

	Year													
	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	Total
RZV vaccine coverage rate after 15 years (%)																
80	5547	8983	8870	8732	8601	8477	8338	8212	8048	7898	7759	7618	7491	7313	7152	119,038
70	4687	7700	7607	7492	7384	7282	7167	7062	6927	6802	6686	6569	6463	6315	6181	102,325
65	**4258**	**7059**	**6975**	**6873**	**6776**	**6684**	**6581**	**6487**	**6366**	**6254**	**6150**	**6045**	**5950**	**5817**	**5696**	**93,969**
60	3828	6417	6344	6253	6168	6086	5996	5912	5805	5706	5614	5520	5436	5318	5210	85,613
50	2969	5134	5081	5014	4951	4891	4824	4763	4683	4610	4541	4472	4409	4320	4239	68,901
40	2110	3852	3818	3775	3734	3695	3653	3613	3562	3513	3468	3423	3382	3323	3268	52,189
30	1251	2569	2554	2536	2517	2500	2481	2464	2440	2417	2396	2374	2354	2325	2297	35,477
ZVL vaccine																
2018 coverage rate +10% over 15 years	859	1283	1263	1239	1217	1195	1171	1150	1122	1096	1073	1049	1027	998	971	16,712

[a]RZV, (adjuvanted) recombinant zoster vaccine; ZVL, zoster vaccine live.
[b]Boldface indicates the base case.

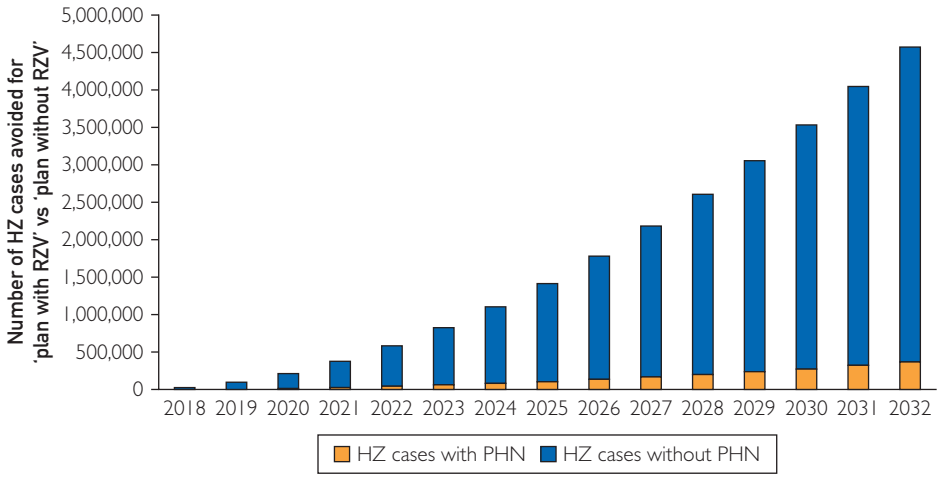

FIGURE 2. The cumulative incremental number of cases avoided when adjuvanted recombinant zoster vaccine (RZV) vaccination is increased to 65% of the eligible population over 15 years. Zoster vaccine live (ZVL) vaccine coverage increased by 10% over the same period. HZ, herpes zoster; PHN, postherpetic neuralgia.

vaccination coverage from a target of 30% to 80% over 15 years. It can be seen with the highest target vaccination rate of 80% for RZV that, after 4 years, the incremental number of PCP visits avoided in 1 year has exceeded that which can be achieved with a target 30% coverage in the 15th year (more than 511,000 vs 436,000, respectively). With

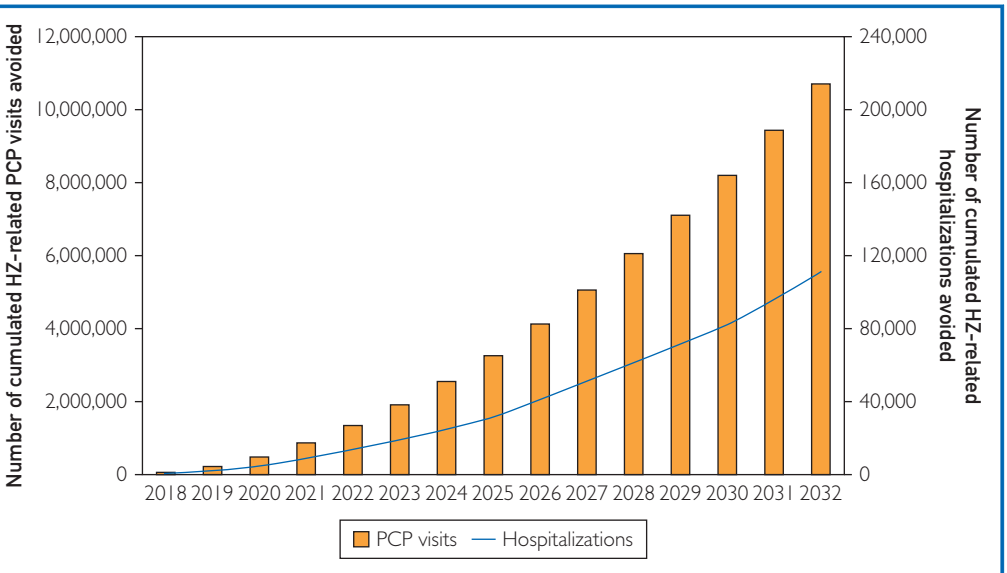

FIGURE 3. The cumulative incremental number of primary care physician (PCP) visits and hospitalizations avoided when adjuvanted recombinant zoster vaccine vaccination coverage is increased to 65% of the eligible population over 15 years. Zoster vaccine live vaccine coverage increased by 10% over the same period. HZ, herpes zoster.

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the base case 65% target vaccination rate for RZV, after 5 years the incremental number of annual PCP visits avoided surpasses that achieved in the 15th year with a vaccination rate of 30% (476,000 vs 436,000, respectively). Looking at the incremental annual hospitalizations avoided, the highest reduction achieved with a 50% target coverage (9860) is achieved 5 years earlier with a target of 65% RZV coverage.

DISCUSSION

Previous economic analyses have shown that RZV is a good value for the money and have estimated the impact of RZV adoption on short-term health care payer budgets. To our knowledge, this study is the first to assess the longer-term potential public health impact of RZV in the United States. Results showed that significant numbers of HZ and PHN cases can be avoided with RZV vaccination, together with the associated PCP visits and hospitalizations, representing a substantial reduction in human suffering and health care burden. The vaccination coverage rate with the RZV vaccine is estimated to have a considerable impact upon the overall public health, with higher vaccination rates accelerating the attainment of vaccination benefits.

Current adult vaccination rates in the United States are suboptimal, with HZ vaccination coverage around 30%, significantly lower than the 65% coverage rate achieved with pneumococcal and influenza vaccination of older adults.[33] Recommendations in favor of HZ vaccination by public health bodies, such as the CDC, have been shown to significantly increase interest in HZ vaccination, according to Google search data[38]; however, the CDC recommendation has failed to translate into sustained higher HZ vaccination rates. Several investigators have suggested an explanation, citing out-of-pocket costs as an obvious financial barrier (compared with pneumococcal and influenza vaccines) and recommending that in order to increase HZ vaccination, copayments should be eliminated or, at least, reduced.[39,40]

One attempt to increase adult vaccination rates has involved the public and private sectors developing adult immunization performance measures (including zoster vaccination) and adding these to the 2019

TABLE 2. Incremental Number of PCP Visits and Hospitalizations Avoided Varying Target RZV Coverage From 30% to 80% Over 15 Years[a,b,c]

Vaccine coverage (RZV), %	Visits avoided	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	Cumulative
80	Hosp	988	2129	3160	5461	6533	7463	8138	8,705	12,766	13,196	13,502	13,699	13,842	19,401	19,031	148,013
80	PCP	89,478	219,644	344,202	511,167	631,088	742,256	839,975	929,647	1,133,841	1,217,653	1,291,656	1,353,008	1,408,341	1,600,272	1,625,129	13,937,357
70	Hosp	801	1740	2593	4474	5379	6168	6755	7,253	10,578	10,984	11,285	11,507	11,679	16,203	15,973	123,374
70	PCP	73,323	182,106	286,571	426,141	527,794	622,344	706,002	783,000	955,676	1,029,087	1,094,195	1,148,607	1,197,724	1,363,164	1,387,347	11,783,083
65	Hosp	707	1546	2310	3980	4802	5521	6064	6,527	9483	9879	10,177	10,412	10,597	14,605	14,444	111,054
65	PCP	65,246	163,337	257,756	383,629	476,147	562,388	639,015	709,677	866,594	934,804	995,464	1,046,406	1,092,416	1,244,610	1,268,457	10,705,946
60	Hosp	613	1351	2026	3487	4225	4874	5373	5,802	8389	8773	9069	9316	9516	13,006	12,915	98,734
60	PCP	57,169	144,568	228,941	341,116	424,500	502,433	572,028	636,353	777,511	840,521	896,733	944,205	987,108	1,126,056	1,149,566	9,628,809
50	Hosp	425	962	1459	2500	3070	3579	3991	4,350	6201	6561	6852	7125	7352	9809	9857	74,094
50	PCP	41,014	107,030	171,310	256,091	321,205	382,521	438,055	489,707	599,346	651,955	699,272	739,804	776,491	888,948	911,785	7,474,535
40	Hosp	237	573	893	1513	1916	2285	2609	2,898	4012	4350	4636	4933	5189	6611	6800	49,455
40	PCP	24,860	69,492	113,680	171,066	217,911	262,609	304,081	343,060	421,181	463,389	501,811	535,402	565,874	651,840	674,004	5,320,261
30	Hosp	49	184	326	526	762	990	1227	1,446	1824	2138	2419	2742	3026	3414	3742	24,815
30	PCP	8705	31,954	56,050	86,041	114,616	142,698	170,108	196,413	243,015	274,823	304,349	331,001	355,258	414,732	436,223	3,165,986

[a]Hosp, hospital; PCP, primary care physician; RZV, adjuvanted recombinant zoster vaccine.
[b]ZVL zoster vaccine live vaccine coverage increased by 10% over the same period.
[c]Boldface indicates the base case.

Healthcare Effectiveness Data and Information Set, a widely used set of performance measures reportable by private US health plans.[41] Additional initiatives have involved professional associations recommending to members to vaccinate and providing guidance for various patient groups. Among these are the American College of Rheumatologists[42] and the National Psoriasis Foundation.[43]

However, even with recommendations and targets in place, it is clear that the strongest influencers for vaccination are the patients' physicians. The key reason for a patient being vaccinated is them having received a recommendation from a health care provider.[44] Therefore, PCPs must know the vaccination policy, agree with the policy, recommend vaccination, and then ideally have the office systems to facilitate vaccination, such as standing orders and immunization reminder systems.[45] Additionally, pharmacies can play a part by improving patient awareness and education[45] and by providing vaccination outside office hours, thereby increasing access and convenience for patients.[46] In summary, coordination of efforts across all health care professionals regardless of role is essential to create an environment for ensuring access to and use of vaccines.[47]

Study Limitations

The limitations of the model and data used for this analysis, including the generalizability of vaccine efficacy from clinical trial populations to a real-world setting, have been discussed previously. Target coverage levels considered for RZV in this study were projections based on coverage levels observed for other older adult vaccines and may not reflect real-world uptake of RZV vaccination. The vaccine efficacy and safety estimates were obtained from clinical trial data and may differ from real-world settings. Early real-world effectiveness data for RZV are beginning to emerge,[48,49] and future modeling exercises incorporating robust estimates for effectiveness and coverage will allow for better validation of the outcomes projected in this study.

The analysis has several strengths: the modeling approach has been published previously; the input parameters are based on the best available national data; the model is publicly available and has a user-friendly interface, and the inputs, calculations, and assumptions are transparent.

CONCLUSION

This modeling analysis predicts the public health impact of HZ vaccination, with a focus on RZV adoption post launch. Results show that the potential public health impact of vaccinating with RZV is dependent on the vaccine coverage achieved, with higher vaccination rates providing larger and earlier reductions in the number of HZ cases and the associated health care burden. A concerted effort across all health care providers is required to improve HZ vaccination rates to maximize the public health impact possible through RZV vaccination.

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SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **CDC** = Centers for Disease Control and Prevention; **HZ** = herpes zoster; **PCP** = primary care physician; **PHN** = postherpetic neuralgia; **RZV** = adjuvanted recombinant zoster vaccine; **ZVL** = zoster vaccine live

Potential Competing Interests: D.v.O. and D.C. are employees of the GSK group of companies and hold shares

in the GSK group of companies. B.J.P., P.O.B., and J.J.S. were employees of the GSK group of companies at the time the study was conducted. W.L.H. and J.C. are employees of RTI Health Solutions, which received funding via a contractual agreement with the GSK group of companies to perform the work contributing to this research. Y.Z. was an employee of RTI Health Solutions at the time the study was conducted.

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