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Determining the optimal strategy for the herpes zoster vaccine in adults

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ABSTRACT

The optimal strategy for the vaccinating against herpes zoster (HZ) vaccine remains unknown. Cost-effectiveness analyses provide insight to the most cost-effective age groups but results vary across studies. The optimal strategy is important given that vaccine efficacy and duration vary depending on vaccination age. Therefore, small changes from the optimal age can affect long-term outcomes and produce sub-optimal results. The objective of this research was to determine the optimal timing policy for HZ vaccination. We simulated cohorts of men and women and use stochastic dynamic programming to evaluate the decision to vaccinate or defer each year from age 50 to 100. If the decision was to defer, the cohort risked developing HZ. If HZ occurred, the cohort was subjected to cost and quality-adjusted life year (QALY) loss for a typical HZ infection (including complications) at that age. If HZ did not occur, the decision was evaluated at the next age. Then, we extend the model to consider the case in which a booster vaccine is available. A set of probabilistic sensitivity analyses were conducted to check model robustness. Results show the optimal policy for women is to vaccinate between ages 66 and 77, and for men between ages 66 and 74, assuming a willingness to pay (WTP) of $100,000 per QALY. It becomes optimal to vaccinate earlier if a booster vaccine is available, and women have a wider range of ages than men. This research is the first to examine exactly when the HZ vaccine should be administered. It is also the first study, to our knowledge, that used stochastic dynamic programming to examine the question of a second dose for any vaccine. This research provides the first simple policy on when to vaccinate and re-vaccinate against HZ.

1. Introduction

It is estimated that one third of adults will develop herpes zoster (HZ – known commonly as shingles) in their lives and half of adults older than age 85 will experience or have already experienced HZ. HZ causes intense pain which can affect quality of life and has a substantial economic burden[1,2]. A vaccine is available to prevent the disease, and currently this is the best tool available for combating HZ.

However, the optimal strategy for the age of administering the herpes zoster (HZ) vaccine remains unknown. In the US, cost-effectiveness analyses (CEAs) using state-transition models (STMs) give some indication of the most cost-effective age group but results vary across studies [3–6]. However, in STMs, only one decision is evaluated in each model iteration [7], and it is difficult to account for future decision options, and outcomes. Therefore, STMs may lead to sub-optimal decisions if there are many decisions required to define a certain treatment strategy.

The optimal strategy is of particular importance given that vaccine efficacy and duration can wane over time depending on the age at vaccination [8–12]. Thus even small changes in the age of administration could affect the long term outcomes and produce sub-optimal results if not administered at the correct time. The key decision tradeoff in this situation is, therefore, vaccination or deferral. People (patients, doctors, etc.) must decide between vaccinating at earlier ages when HZ incidence is lower but the vaccine has a higher initial efficacy and longer duration, or deferring vaccination to a time when HZ incidence is higher but the vaccine, conversely, will have less efficacy and a shorter duration.

Further complicating decisions is the anticipation of a booster vaccine for HZ. Given the waning efficacy in the vaccine and age-dependent risk of HZ the optimal time of a first dose and a booster are interdependent. The Markov decision process (MDP) model allows for the consideration of multiple or sequential decisions

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over time [13]. MDP models come from stochastic, dynamic optimization [14,15] and have recently been applied to optimal allocation of medication or treatment policy problems in health care [16–21]. The MDP method optimizes a dynamic policy over a particular decision objective [16] and can therefore be used to optimize sequential annual decisions to vaccinate.

The objective of this study was to estimate the optimal strategy for vaccination against HZ. First, with a single dose of vaccine, we determined the optimal vaccination strategy. Second, we extend the MDP model to consider the more complex case in which a booster vaccine was available. We discuss the validation of our model and present results, including probabilistic sensitivity analyses.

2. Methods

Answering when should you vaccinate someone who is age Y given that they have not received the vaccine is different than the CEA question of, is it cost-effective to vaccinate someone of age Y at age Y? CEA results may be favorable, but it may be more optimal to defer vaccination. Two separate MDP models: (1) One-dose MDP, (2) Two-dose MDP, were created. Each will be discussed in turn. All models were constructed in R (v.3.2.3). All individuals in the cohorts were assumed to be immunocompetent, to have a history of varicella zoster virus (VZV – known commonly as chickenpox – a necessary condition to be at risk for HZ), to have no history of HZ, and to have no history of HZ vaccination (except in the two-dose MDP).

2.1. State-transition models

STMs were used to estimate the immediate outcomes associated with the states the MDP. STMs projected the lifetime costs and quality-adjusted life years (QALYs) for receiving a vaccine or developing HZ at any age between 50 and 100. The four state STM is shown in Fig. 1. For outcomes associated with vaccination, the STM simulated a cohort as vaccinated and disease free from every age from 50 to 100. In this simulation the individuals in the cohort had the chance to transition to HZ or death at the end of each model period (1 year). HZ was an all-inclusive transient health state that provided a cumulative estimate of the QALYs and costs with a case of HZ, which may include post-herpetic neuralgia (PHN) or ocular complications. For outcomes associated with HZ, the STM simulated a cohort as beginning in the HZ health state from every age from 50 to 100. Similar to the vaccine simulation, this simulation included costs and health outcomes related to PHN or ocular complications. Further information on the STMs and the data used to generate them is available in Table 1 and Appendices A–C.

2.2. One-dose MDP

The STMs provided both lifetime costs and QALYs. MDP rewards are expressed as net monetary benefits (NMB) and Eq. (1) was used to convert those costs and QALYs from the STMs into NMB, under an assumed willingness-to-pay (WTP) of $100,000 per QALY [22]. MDPs were built to solve the optimality Eqs. (2) and (4) using backwards induction [14]. Data used across the STM and MDP models are presented in Table 1.

$$NMB = WTP \times QALY - Cost \quad (1)$$

2.2.1. Structure

In the one-dose MDP a cohort starts at age 49, and an initial decision on vaccination is made when reaching the first decision period at age 50 ($t = 0$). The model has two decisions: (1) Vaccinate (v), (2) Wait (defer vaccination) (w). Decisions are made at annual periods from age 50 ($t = 0$), to age 100 ($t = 50$). In choosing vaccinate, the individuals in the cohort gain immediate rewards for being vaccinated at that age. If the decision was to wait, the individuals in the cohort remain unvaccinated for 1 period (1 year), and face the choice to vaccinate or defer again at the next period. Outcomes generated from the STMs were converted to NMB and applied to the *terminal states* of the MDP model; in which the patient has chosen to be vaccinated or develops the disease and no future decisions are left to be made.

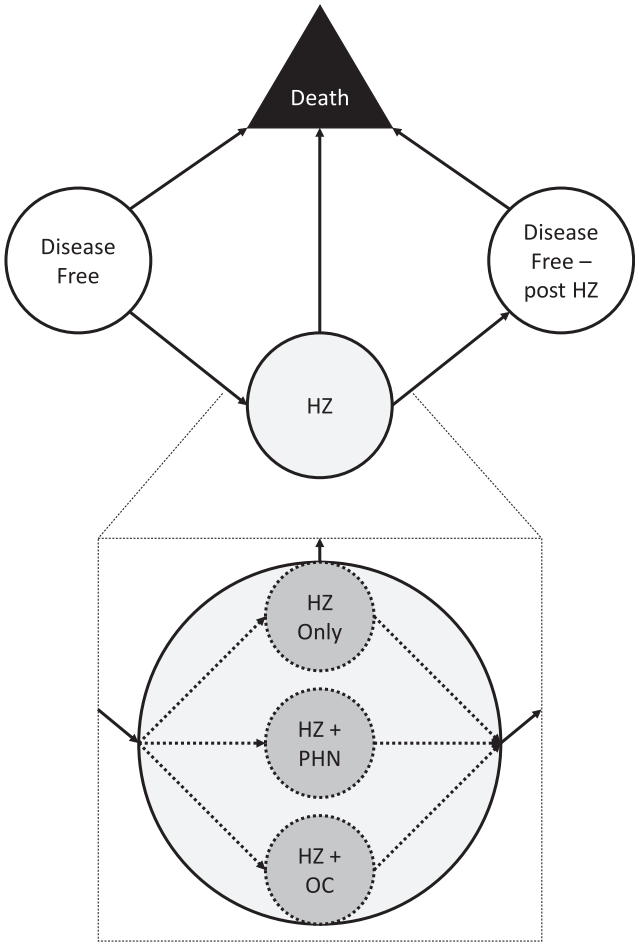

Fig. 1. STM model structure. HZ: Herpes zoster. PHN: Post-herpetic neuralgia. OC: Ocular complications. The diagram shows the overview of the 4-state STM as well as the possible states within the HZ state.

The one-dose MDP is governed by Eq. (2). In this equation $V_t(s_t)$ is the *optimal value function* for the model at time t ($t = 0, \ldots, T$) in state s_t. The action set a at time t includes two actions: $\{v, w\}$, vaccinate and wait, and two states: $\{vx, nvx\}$, vaccinated, and non-vaccinated. $R_t(vx)$ is the immediate rewards gained from vaccinating at time t as determined by the vaccine STM. $R_t(nvx)$ is the immediate QALYs gained for spending one cycle in a disease free state at time t. $R_t(nvx)$ is summed with the discounted lifetime rewards associated with dying, $p(D)$, or transitioning to HZ, $p(HZ)$, in the next cycle ($t + 1$). $V_{t+1}(s_{t+1})$ is the optimal value function at $t + 1$. $V_{t+1}(s_{t+1})$ is initially set by the boundary condition of the model, $V_T(s_T)$, at age 100. At age 100 ($t = 50$), $V_{t+1}(s_{t+1}) = 0$ and the probability of death, $p(D)$, is 100%. Therefore, $V_T(s_T)$ is the optimal value function at the boundary of the model and is the maximum between the immediate rewards for vaccinating and not vaccinating at age 100; shown by Eq. (3). Future outcomes were discounted by 3% ($\lambda = 0.97$).

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Table 1
Model inputs.

Variable	Base	Distribution	Refs.
Epidemiology			
Probability – HZ*			
Men – (L, x_0, k)	(13.93,773.20,184.47)	$L \times ln\mathcal{N}(0, 0.099)$	[24–26]
Women – (L, x_0, k)	(19.23,824.03,199.41)	$L \times ln\mathcal{N}(0, 0.099)$	[24–26]
Probability – HZ – Any pain	0.95	$\beta(10.17, 0.82)$	[35,36]
Probability – HZ – Mild | Any Pain	0.12	$\beta(1.22, 8.95)$	[35,36]
Probability – HZ – Moderate | Moderate or Severe	0.44	$\beta(13.21, 17.87)$	[35,36]
Probability – PHN** – (b_1, b_2)	(1.77e-07,2.01)	$b_1 \times ln\mathcal{N}(0, 0.29)$	[28–34]
Probability – PHN – Moderate or Severe*** (β_1, β_2)	(0.006,0.11)	$P + \mathcal{N}(0, 0.05)$	[30]
Probability – PHN – Moderate | PHN – Moderate or Severe	0.50	$ln\mathcal{N}(-0.69, 0.20)$	Assumption
Duration (months) – PHN – Mild	6.7	$ln\mathcal{N}(1.90, 0.05)$	[30]
Duration (months) – PHN – Moderate	10.0	$ln\mathcal{N}(2.30, 0.05)$	[30]
Duration (months) – PHN – Severe	12.5	$ln\mathcal{N}(2.52, 0.07)$	[30]
Probability – Ocular complications*** (β_1, β_2)	(−0.010,0.0008)	$P + \mathcal{N}(0, 0.01)$	[34]
Duration (months) – Ocular complications	3.0	$ln\mathcal{N}(1.10, 0.22)$	[2]
Vaccine – Initial efficacy (η)	See Appendix A	$\mathcal{N}(0, 0.035)$	[8–12]
Vaccine – Waning efficacy (ζ)	See Appendix A	$\mathcal{N}(1, 0.12)$	[8–12]
Costs			
HZ	957	$\Gamma(414.59, 1/2.31)$	[2]
PHN	5831	$\Gamma(34.69, 1/168.08)$	[2]
Ocular complications	4163	$\Gamma(40.77, 1/102.11)$	[2]
Vaccine	173.97	$\Gamma(23.33, 1/7.5)$	[37–39]
Vaccine – Administration	31.38	$\Gamma(2196.6, 70)$	[37–39]
Vaccine – Severe adverse reaction	0.18	$\Gamma(18, 100)$	[40,41]
Hours productivity lost			
HZ – No pain†	5	$\mathcal{N}(1, 0.13)$	[42,43]
HZ – Mild†	6	$6/5 \times \mathcal{N}(1, 0.13)$	[42–44]
HZ – Moderate†	22	$22/5 \times \mathcal{N}(1, 0.13)$	[42–44]
HZ – Severe†	61	$61/5 \times \mathcal{N}(1, 0.13)$	[42–44]
PHN – Mild‡	4	$\mathcal{N}(1, 0.13)$	[43]
PHN – Moderate‡	30	$30/4 \times \mathcal{N}(1, 0.13)$	[43]
PHN – Severe‡	81	$81/4 \times \mathcal{N}(1, 0.13)$	[43]
Disutilities - Health			
HZ – No pain††	0.150	$\beta(24.75, 140.25)$	Assumption
HZ – Mild††	0.200	$20/15 \times \beta(24.75, 140.25)$	[45]
HZ – Moderate††	0.300	$30/15 \times \beta(24.75, 140.25)$	[45]
HZ – Severe††	0.450	$45/15 \times \beta(24.75, 140.25)$	Assumption
PHN – Mild‡‡	0.310	$31/77 \times \beta(8.85, 2.65)$	[45]
PHN – Moderate‡‡	0.550	$55/77 \times \beta(8.85, 2.65)$	[45]
PHN – Severe‡‡	0.770	$\beta(8.85, 2.65)$	[45]
Ocular complications	0.240	$\beta(38, 120)$	[45]
Vaccine – Common adverse reaction	0.001	$\beta(6, 6000)$	[8,36]
Vaccine – Severe adverse reaction	2.13e−05	$\beta(2.13, 100,000)$	[41,46]

Note, negative intercept in ocular complications – $P > 0$ if age $\geqslant 20$.
‡ Hours of productivity lost for PHN are correlated with mild PHN state, all other PHN health states are multiplied by factors listed in the table.
† Hours of productivity lost for HZ are correlated with no pain HZ state, all other HZ health states are multiplied by factors listed in the table.
* Logistic function used for HZ incidence: $L \Big/ \left[1 + e^{\left(\frac{x_0 - age}{k}\right)}\right]$.
‡‡ Disutility for PHN states are correlated with severe PHN state, all other PHN health states are multiplied by factors listed in the table.
†† Disutility for HZ states are correlated with no pain HZ state, all other HZ health states are multiplied by factors listed in the table.
** Power function used for PHN risk: $b_1 \times age^{b_2}$.
*** Linear equation used for probability of moderate or severe PHN and probability of ocular complications.

$$V_t(s_t) = \max_{a_t \in \{vx, wx\}} \Big\{ R_t(vx), R_t(nvx) + \lambda \big(p(D|s_t, nvx) R_{t+1}(D) + p(HZ|s_t, nvx) R_{t+1}(HZ) + p(DF|s_t, nvx) V_{t+1}(s_{t+1}) \big) \Big\}$$
$$\text{For all } s_t \text{ and } t = 0, \ldots, T-1 \qquad (2)$$

vx: Vaccination state, *nvx*: Waiting state.

$$V_T(s_T) = \max_{a_T \in \{vx, wx\}} \{R_T(vx), R_T(nvx)\} \qquad (3)$$

2.2.2. Probabilistic sensitivity analysis

To examine robustness, we performed second-order Monte Carlo probabilistic sensitivity analysis (PSA) to estimate the optimal strategy given simultaneous uncertainty of multiple model parameters. To accomplish this, we converted model inputs from discrete values to distributions. More detail is available in Appendices A–C. We examined the PSA results to determine which simulated policies recommended vaccination at any age. We also searched the same set of policies by age to determine the probability that an age would be selected into any optimal strategy.

2.3. Two-dose MDP

To examine the two-dose booster problem we made two assumptions. First, we assumed the booster had the same risks and costs as the first dose. Second, the booster vaccine would not have an additive effect with any "remaining" efficacy from the first dose – i.e. the booster dose would, in effect, reset the clock and provide the expected efficacy from age it was given.

2.3.1. Structure

This total model is evaluated as two sub-models; each sub-model has two actions: $\{va, w\}$, vaccinate again and wait, and

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two states: $\{vxa, nvxa\}$, vaccinated again, and not vaccinated again. MDP booster sub-models that examine the booster dose decision were evaluated first and independently. In these booster models, we assume the individuals in the cohort received a first dose at age j. After this initial dose, each subsequent year the decision was made to vaccinate again (va), or wait (w). The second dose models were governed by optimality Eq. (4). The notable differences between Eqs. (2) and (4) are the probability and reward for HZ. In the booster model, $p(HZ|s, w, v_j)$ was adjusted by the age of the initial vaccine j and then adjusted by its waning function noted by conditional dependence v_j. $R_{t+1}(HZ|v_j)$ is calculated from an STM model that simulated the lifetime QALYs and costs for people who developed HZ at some age Y given they had been vaccinated at age j. This is further discussed and the waning function for the vaccine are covered in Appendices A–C. To evaluate the two-dose MDP, 50 independent booster MDPs were run that evaluated all possible combinations of s_t and v_j, each conditional upon the initial age of the first dose j. These MDPs were started at the boundary condition (age 100) and were evaluated backward to j.

$$V_t(s_t|v_j) = \max_{a_t \in \{va,w\}} \Big\{ R_t(vxa), R_t(nvxa) + \lambda \big(p(D|s_t, nvxa) R_{t+1}(D) + p(HZ|s_t, nvxa, v_j) R_{t+1}(HZ|v_j) + p(DF|s_t, nvxa) V_{t+1}(s_{t+1}) \big) \Big\}$$
$$\text{For all } j,\ s_t \text{ and } t = 0, \ldots, T-1 \qquad (4)$$

vx: Vaccination state, nvx: Waiting state.

$$V_T(s_T|v_j) = \max_{a_T \in \{va,w\}} \{R_T(vxa), R_T(nvxa)\} \qquad (5)$$

2.3.2. Probabilistic sensitivity analysis

We also performed second order PSA for the booster model. For this analysis, we utilized the same procedure as for the one-dose model. More detail is available in Appendices A–C. The policies per age of initial vaccination were searched by age to determine the probability a certain age would be selected into the optimal strategy for the second dose.

2.4. Vaccine parameterization

Vaccine efficacy against HZ was comprised of: (1) age-specific vaccine efficacy – defined as time from vaccination through the first year, $t = [0, 1)$; (2) vaccine waning – defined as time of vaccination until the vaccine provided no protection, $t = [0, X]$, where X is some number of years in the future. The component pieces were estimated and combined using published methods [23]. These two components are important as vaccine efficacy has been shown to decline with age and vaccine waning has been shown to increase with age. Fig. 2 provides a 3D overview of the results of the waning by age. More detail on the parameterization is available in Appendices A–C.

2.5. HZ and PHN parameterization

To estimate HZ age-specific incidence, midpoints of age ranges in three selected papers [24–26] were plotted against reported incidence and fit using a logistic function. The logistic function was selected a priori as a recent systematic review [27] suggests that incidence follows a logistic pattern.

To calculate the risk of PHN given HZ, seven papers were used [28–34]. Midpoints of the age ranges were plotted against the corresponding risk of PHN. Different functions were tested with the data; the power function was selected due to goodness-of-fit. Data from ages 18 to 100 were used to create the estimate. There is no distinction made between the risk of PHN for men and women. Fig. 3a and b shows the fit and the confidence interval for HZ incidence and PHN risk.

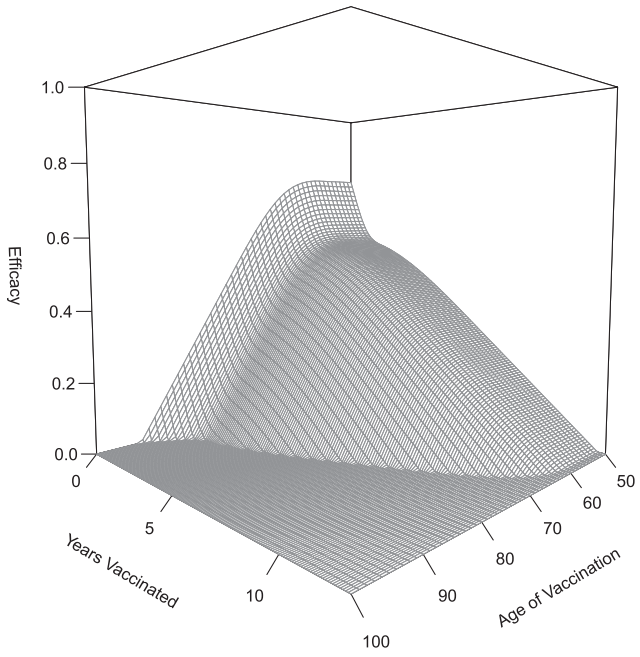

Fig. 2. Age-specific vaccine waning parameterization.

3. Results

3.1. One-dose MDP

Results from the base case analysis for the one-dose model are presented in Fig. 4a and b. The model recommends vaccination between the ages of 66–77 for women, and 66–74 for men who had no prior vaccination. Taking the perspective of a 50-year-old person following the optimal strategy would mean vaccinating no earlier than age 66.

3.1.1. Probabilistic sensitivity analysis

Approximately 9% of PSA simulations show that, for women, the optimal strategy would not include vaccination at any age at a WTP of $100,000. For men, this probability increases to approximately 23%. Results from Fig. 5a are to be interpreted as the probability that vaccination at a given age is included in the optimal strategy. For women, results show that ages 63–85 have some probability of being selected in the optimal strategy. Ages 67–71 have more than an 85% chance of being selected; age 68 has the highest probability of being selected into an optimal strategy. Fig. 5b shows results from the PSA for men. For men, the age range extends from 62 to 84; age 68 also has the highest probability of being selected. As examples, if a woman and man were both unvaccinated at age 68, there is a 90% and 75% chance, respectively, that it would be recommended that they each be vaccinated at that age.

3.2. Two-dose model

The results from the base case analysis for the two-dose model are presented in Fig. 6a and b. These figures define the strategy space for the optimal second stage decisions under all conditions of receiving a first dose, including the possible case that a patient had the initial vaccination at a suboptimal point in time.

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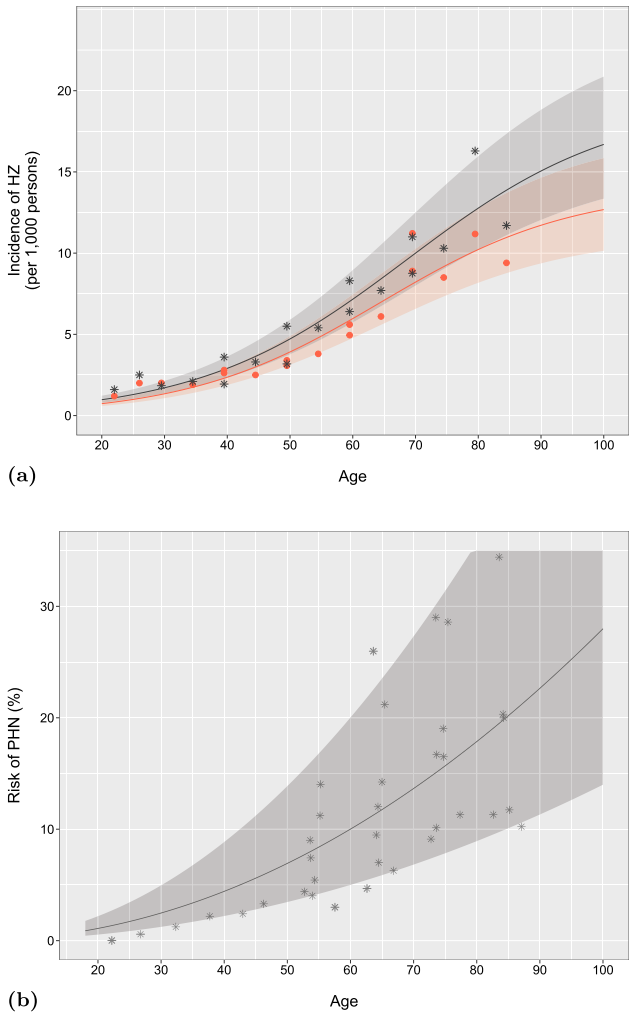

Fig. 3. HZ and PHN parameterization. Panel (a) shows the fitted logistic function for HZ incidence. The grey color is for women, and the red color is for men. The shaded regions represent the confidence intervals. Panel (b) the fitted power function for the risk of PHN given an HZ infection. The risk of PHN was capped at 35%.

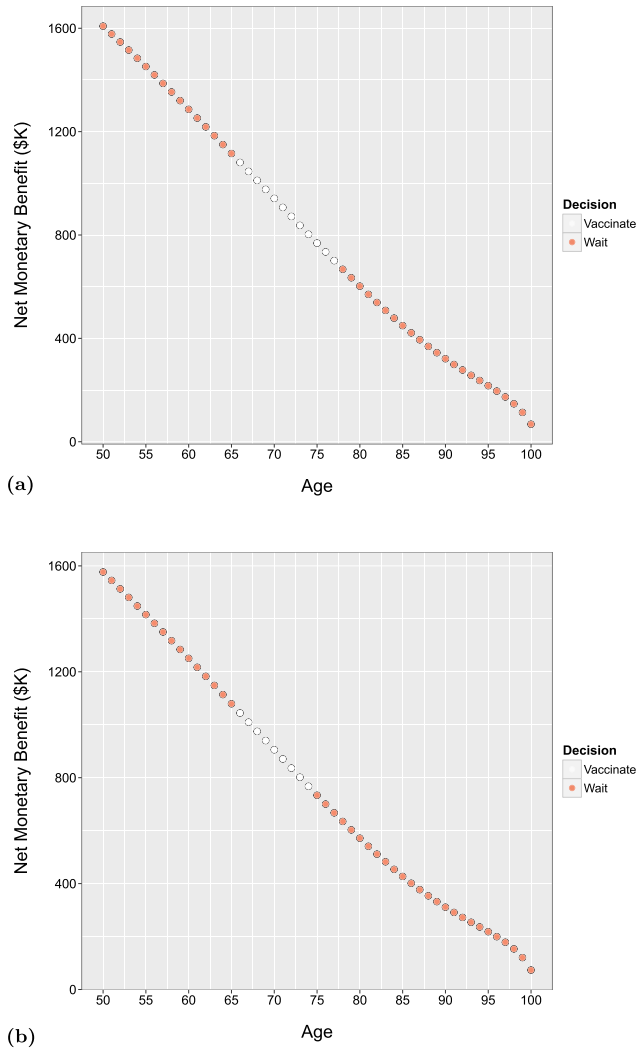

Fig. 4. Optimal strategy: vaccination decisions by age – one-dose MDP – WTP: $100,000. Panel (a) shows results for women, panel (b) shows results for men.

If a woman received her first dose at age 66 (the first age the vaccine was considered optimal in the one-dose model), the optimal strategy would recommend a second dose between the ages of 75–77. The optimal strategy includes a second dose for any women who received their first dose between the ages of 50 and 67.

If a man received his first dose at age 66, the optimal strategy would not recommend second dose at any point. For men, the optimal strategy includes a second dose for those who received their first dose between the ages of 50 and 63.

3.2.1. Probabilistic sensitivity analyses

Fig. 7a and b shows a heat map of a second dose at a given age being included in the optimal strategy conditional upon the age of the first dose. For women, ages 67–73 have the highest probability of being recommended for an optimal strategy for the second dose with a probability of between 80% and 89%. The range of ages for the second dose for women extends from 64 to 84, depending on the age of the initial dose. Ages 81–84 never have more than a 19% chance of being selected. For men, similar to the one-dose PSA, there is less chance for the second dose to be optimal at any age. Ages 67–70 have the greatest chance of being selected into an optimal strategy with a probability of between 70% and 79%. The range of ages for a second dose for men extends from 64 to 83. Ages 81–83, regardless of the age of the initial vaccine have less than a 10% chance of being selected.

4. Discussion

This research provides a first look at an optimal strategy for HZ vaccination based on age, sex, and prior vaccination history. As it is difficult to use STMs to optimize multiple decisions or sequential decisions over time, MDP models were used to decide when to vaccinate or defer vaccination. This research is also the first to examine the opportunity of receiving a second dose of the HZ vaccine given the original dose may have been given at any time previously.

In the base case analysis, results suggest that age 66 is the first age recommended for vaccination assuming a single dose. For women, there are more ages where vaccination is recommended compared to men (66–77) and (66–74) respectively. The PSA showed that there are more scenarios where the vaccine would not be optimal for men compared to women. Some possible explanations for the differences are life expectancy and disease incidence. Women have a longer life expectancy than men [47]. Women also have an increased risk of disease compared to men [48]. Thus, more women are likely to be alive and those who are alive are more likely to get the disease than their male counterparts.

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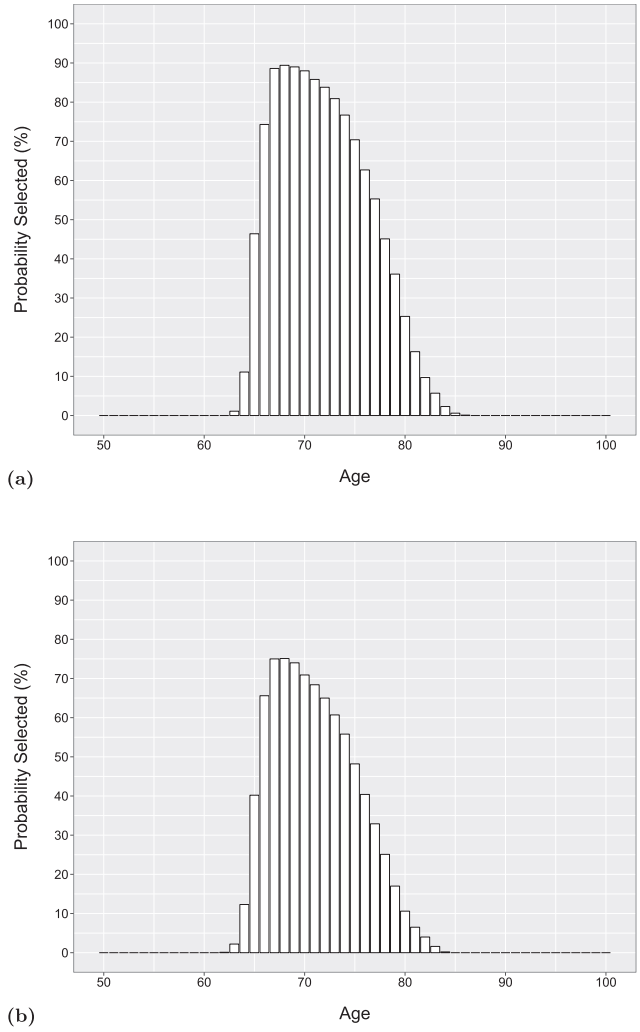

Fig. 5. Probabilistic sensitivity analysis – one-dose model – WTP: $100,000. Panel (a) shows results for women. Panel (b) shows results for men.

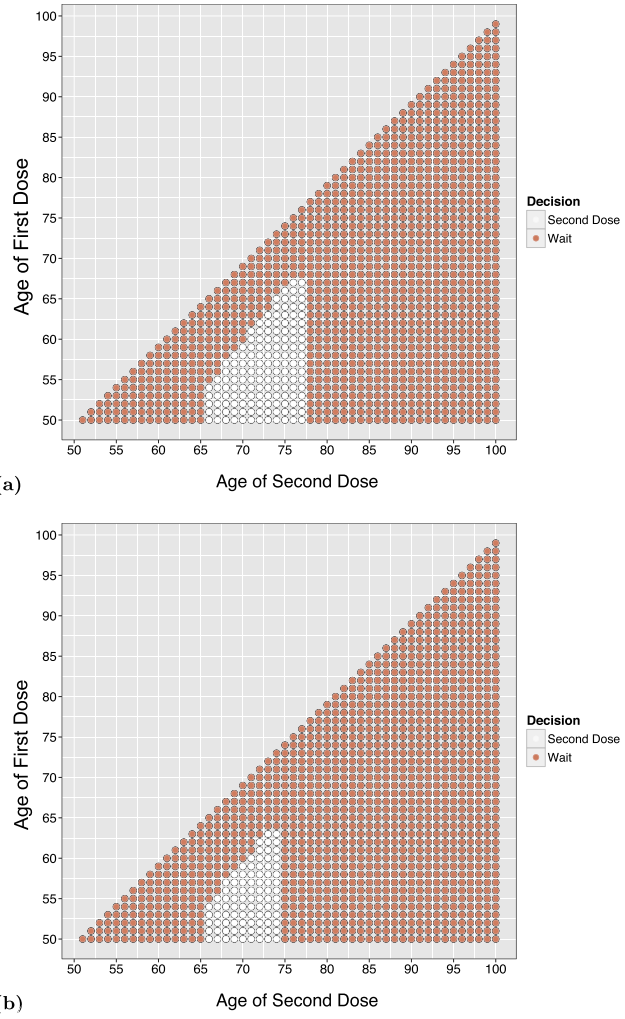

Fig. 6. Optimal strategy – two-dose model – WTP: $100,000. Panel (a) shows results for women. Panel (b) shows results for men.

Results from the two-dose model match the same trend presented for the one-dose model. In the base case analysis the objective was to determine if and when a person should receive a second dose conditional upon having received a first dose at any time previously. Results for women show that it would be optimal to receive the second dose over a wider age range than men. The two-dose PSA provides further confirmation of this two-dose recommendation for women. Comparing the two heat maps (Fig. 7a and b), the PSA suggests that a second dose is more likely to be recommended, and over a wider age range for women than men. Because women are more likely to live longer than men [47], they are more at risk for the disease, and are more likely to develop complications (due to increased life expectancy and increased probability of complications with age), it follows that it would be more likely to recommend a second dose for women so that they are covered during the periods when they are most at risk.

4.1. Other studies

The results of this study extend the work of others. There has been one clinical study that examined the impact of receiving a second dose [49]. This study examined the impact of the second dose 10 years after receiving the first dose. The study included comparison patients who were receiving an initial dose, however the metric of efficacy was cellular response. While cellular response has been shown to be able to predict efficacy in the zoster vaccine [50], clinical trial or long-term observational data on the protective effect of a second dose are not available. Levin et al. [49] showed no significant difference in cellular response between receiving a second dose 10 years after receiving the initial dose. Their study was also restricted to people age 70 and older. In our study, we assumed the booster would not have an additive effect with any "remaining" efficacy from the first dose (as suggested by [49]), and found a booster dose could still be optimal to receive for women. Further, we examine the option to get a second dose any time after the first dose. In their paper, the authors[49] call for further research to be done on the multiple dose question to determine the benefits of receiving the second dose. If the objective of future studies is to determine the potential benefit of the second dose, we have shown, using a modeling study, that even if the second dose confers no additive benefit from the first dose there is still a chance that receiving two doses of the vaccine would be optimal.

4.2. Policy implications

The results from this model have important policy implications. Mainly, the MDP is important as it provides policy-makers with a clear range of ages at which HZ vaccination would be optimal, thus narrowing the range of the current policy while simultaneously

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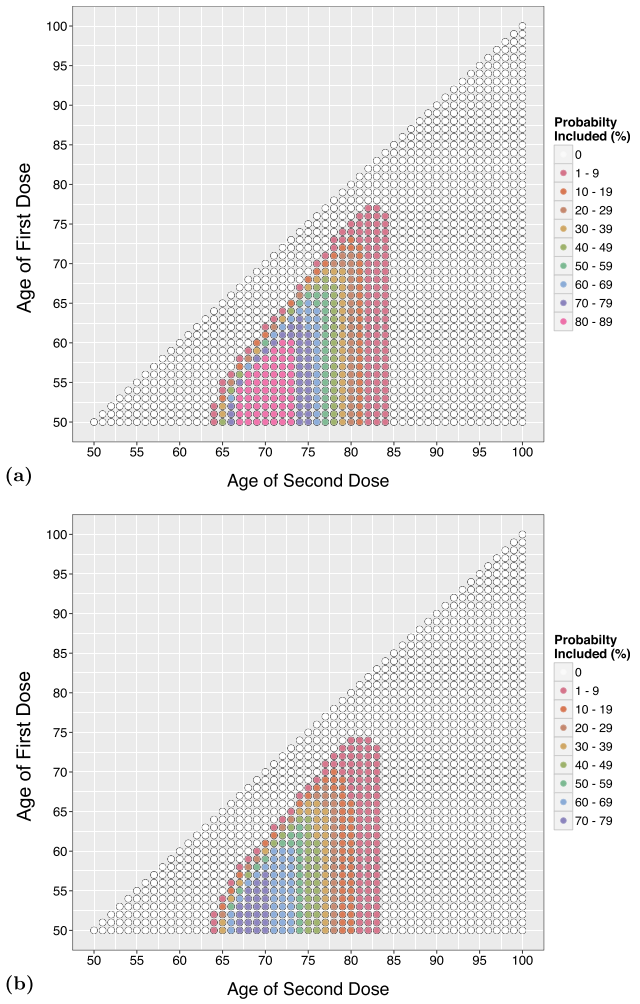

Fig. 7. Probabilistic sensitivity analysis – two-dose model – WTP: $100,000. Panel (a) shows results for women. Panel (b) shows results for men.

accounting for the risk of deferring vaccination. This analysis also agrees with CEAs that the vaccine is likely to provide more benefit to women. Given the results of this analysis, putting a cap on the recommendations at (or near) age 80 moving the starting age to (or near) 66 would provide a more optimal vaccination policy than the current policy. It is also evident that a second dose of the current vaccine may be valuable to consider for women, especially for those women who may have received their first dose at an earlier age (50–60).

4.3. Limitations

The models were all defined to have annual periods. The choice of annual periods accurately reflects the policy space for the vaccine, however shorter periods could give a more precise estimate of vaccine durability. The STM uses a collapsed health state for HZ; all complications occur within this HZ health state. This simple structure allowed us to perform PSA on both the one-dose and two-dose models. The uncertainty in the parameters is another potential limitation. However, the PSA helped to examine the impact of parameter uncertainty and show the robustness of the results.

It would be possible to use STMs to determine the most optimal age of vaccination by comparing all possible vaccination ages against one another for a cohort starting at age 50 - the first age the vaccine is approved for use [10]. However to determine the optimal strategy (i.e., when to start and stop) using STMs would require 2^{50} different simulations (in theory) as there are a minimum of 50 periods in this model (i.e., ages 50–100), each with two actions. When expanding the problem to include a booster it becomes apparent that solving an STM by completely solving all possible combinations of actions would be intractable.

4.4. Conclusions

This is the first paper, to our knowledge, that uses an MDP model to evaluate the question of multiple vaccine doses. Therefore, the MDP and the STM should be seen as complements to one another. The STM, commonly used in CEA, could be used provide insight as to the possible range for a policy and the MDP can provide a means to optimize that range in an efficient manner. Further, this paper adds a probabilistic sensitivity analysis for both the one and two-dose questions. This is an innovative application due to complications with probabilistic sensitivity analysis with MDPs that could be applied to other vaccines [51]. Results indicate that there is likely to be an upper limit to the optimal age of vaccination for both men and women. Current ACIP recommendations are open-ended (i.e., there is no stopping age); therefore our findings are potentially valuable for future recommendations given that it shows a narrower range where the vaccine is most likely to be optimal.

Conflict of interest

This research was funded by a PhRMA Foundation Pre-Doctoral Fellowship - recipient: MJH. MJH is a current employee of Aquarius Population Health, a commercial research consultancy which has received funding from commercial and academic organizations for work outside of the submitted work in the last 5 years.

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Appendix A. Vaccine parameterization

The protection of the vaccine against HZ (efficacy) was comprised of two parts. First, the initial vaccine efficacy ($\beta_{0_{jHZ}}$). This was defined as the efficacy from the time of the vaccination through the first year ($t = [0, 1)$); j is the age of vaccination, t is measured in years. This initial efficacy changes by age [8]. Second, the waning of the vaccine (VE_i). Vaccine waning was assumed to occur from the time of the vaccination through the time when the vaccine provided no further protection, ($t = [0, X]$), where X is a some random number of years in the future. We assume that the components (initial efficacy and waning) are combined using the form of a linear equation to create the age-specific efficacy and waning of the vaccine (VE_{ij}). That is, the initial protection was assumed to be the intercept (b), the waning was assumed to be the slope (m), t was the number of years vaccinated from $[0, X]$, and y was the protection of the vaccine against HZ. *Note*, this does not assume that the components (initial efficacy and waning) are strictly linear; rather these components were estimated separately and then combined using this equation form. The minimum value for vaccine efficacy was 0%; we assume that the vaccine will not ever increase the incidence of HZ. Data on the initial vaccine efficacy and waning came from clinical trial and observational data

Table 2
$\beta 0_{j_{HZ}}$ fitted values. Rows are the age decade, columns are the age year. For example, [3,2] = 0.635 for age 71.

Age	0	1	2	3	4	5	6	7	8	9
5	0.781	0.781	0.781	0.781	0.781	0.781	0.781	0.781	0.781	0.780
6	0.779	0.776	0.771	0.765	0.757	0.746	0.733	0.718	0.701	0.681
7	0.659	0.635	0.610	0.584	0.557	0.529	0.501	0.472	0.442	0.414
8	0.384	0.355	0.327	0.298	0.269	0.240	0.211	0.182	0.153	0.124
9	0.095	0.066	0.037	0.008	0	0	0	0	0	0
10	0									

Table 3
VE_i fitted values.

β_1	β_2	β_3	β_4	β_5
−0.20834831	0.031716085	−0.065752089	0.034499987	−0.000463984

[8–12] and were combined using statistical methods similar to those used in other studies [4,23]. For all analyses, we fit VE_{ij} as the combination of two restricted cubic spline (RCS) models. Our final models were selected using best fit statistics. The outcomes of the two RCS models are presented in Tables 2 and 3. The general form of the vaccine efficacy equation is shown by Eq. (6), where i is the number of years vaccinated from $[0, X]$, j is the age of vaccination from $[50, 100]$, η is the adjustor for the initial efficacy in sensitivity analysis (base value = 0), and ζ is the adjustor for waning efficacy in sensitivity analysis (base value = 1).

$$\begin{aligned} VE_{ij_{HZ}} = \max(0, \beta_{0j_{HZ}} + \eta) \\ +\beta_1\zeta i \\ +\beta_2\zeta \max(i,0)^3 \\ +\beta_3\zeta \max(i-1,0)^3 \\ +\beta_4\zeta \max(i-2,0)^3 \\ +\beta_5\zeta \max(i-7,0)^3 \end{aligned} \quad (6)$$

There is some data that suggests that the vaccine provides additional protection against PHN beyond the reduction in HZ incidence [8]. Data were used to provide an estimate of the initial additional protection benefit of the vaccine against PHN, where additional protection is defined as any reduction beyond what can be attributed to a reduction in HZ incidence. Using a synthetic data set created from available data [8] we constructed a model for the initial protection benefit against PHN ($\beta_{0j_{PHN}}$) from $t = [0, 1)$. This construction was based on understanding of the disease, the vaccine, and discussions with zoster vaccine experts at the US Centers for Disease Control and Prevention (CDC). There is unfortunately no data on how the additional protection benefit wanes with time. Therefore, we assume the additional protection benefit against PHN lasts only as long as the protection against HZ incidence. That is, if the vaccine is assumed to provide X years of protection against HZ, then the individual is assumed to also receive the same number of years of extra protection against PHN. We also assume that the additional protection wanes at the same rate as the vaccines protection against PHN; this was accomplished using Eq. (7). We finally assume that the vaccine provides a minimum of 0% extra protection against PHN. At 0% additional protection, an individual who was vaccinated would have the same likelihood of acquiring PHN given HZ as someone without the vaccine. The base case additional protection benefit assuming the initial additional protection is shown in Table 4.

$$VE_{ij_{PHN}} = \begin{cases} \beta_{0j_{PHN}} \times \frac{VE_{ij_{HZ}}}{\beta_{0j_{HZ}}} & \text{if } \beta_{0j_{HZ}} > 0 \\ 0 & \text{if } \beta_{0j_{HZ}} = 0 \end{cases} \quad (7)$$

Appendix B. State-transition models for MDP

B.1. STMs for one dose MDP

Data for the one dose MDP was generated from the STM; shown in Fig. 1. This model was used to generate the lifetime costs and QALYs for people who were either vaccinated, or who developed a case of zoster without vaccination. Those who were vaccinated started the model in the disease free health state. After each cycle, the cohort had the chance to develop HZ, die, or remain disease free. The cycle-time for the model was set to one year with a 3% (0.97) discount rate for costs and QALYs. At age 100, the probability of death was set to 100%. If HZ occurs, the cohort spends one cycle with disease. Within that cycle, there is the opportunity to develop further complications (HZ with PHN, or HZ with ocular complications), however, these complications occur within the cycle only (as shown by Fig. 1). The costs and QALYs for the intra-HZ states were determined by sub-models that will be presented in the following sections. This model structure assumption was based on HZ without complications typically lasting for one month and the majority of complications resolving within one year. At the end of the HZ cycle, the cohort can transfer to disease free with a history of HZ or to death should death occur. The lifetime costs and QALYs for HZ without vaccination was determined by using the same STM but starting the cohort in the HZ state at some age. All data for this STM and its sub-models comes from data presented in Table 1 in the main paper.

B.1.1. HZ sub-model

To determine the costs and disutility due to a case of HZ a decision tree model was constructed. Model states are shown in Fig. A.1. In this model it is assumed that every person starts with HZ, which is differentiated by pain states. Results from the model produced the average costs and disutility due to uncomplicated HZ. The time horizon for this model was 1 month.

Table 4
$\beta 0_{j_{PHN}}$ fitted values. Rows are the age decade, columns are the age year. For example, [2,2] = 0.234 for age 61.

Age	0	1	2	3	4	5	6	7	8	9
5	0.040	0.57	0.075	0.093	0.110	0.128	0.146	0.164	0.182	0.199
6	0.217	0.234	0.252	0.270	0.288	0.305	0.323	0.341	0.359	0.376
7	0.394	0.412	0.429	0.447	0.465	0.465	0.465	0.465	0.465	0.465
8	0.465	0.465	0.465	0.465	0.465	0.465	0.465	0.465	0.465	0.465
9	0.465	0.465	0.465	0.465	0.465	0.465	0.465	0.465	0.465	0.465
10	0.465									

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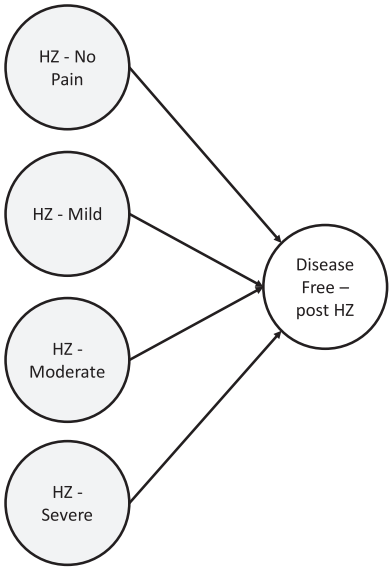

Fig. A.1. HZ sub-model structure.

B.1.2. PHN sub-model

The costs and disutility due PHN were calculated using a Markov-like model; shown in Fig. A.2. We assumed the cohort starts with PHN, initially characterized as mild, moderate, or severe. The likelihood of starting in any of these three states is age dependent (as PHN severity increases with age) [30]. The data for these states are given in Table 1. The model contained a laddering structure where a person must move through all better states of PHN before reaching the disease free state. At each cycle, a person collected some disutility due to their PHN. There was no background QOL in this model. This model produces the average disutility and cost due of a case of PHN. Cycle time was set to 1 month.

B.1.3. Ocular complications sub-model

The costs and disutility due ocular complications were calculated using a Markov-like model; shown in Fig. A.3. In this model every person began with an ocular complication, and had a chance of moving to disease free after each model cycle. Unlike PHN, there is no stratification for severity. While this is unlikely, there is limited data on the epidemiology, costs, and disutility for differing

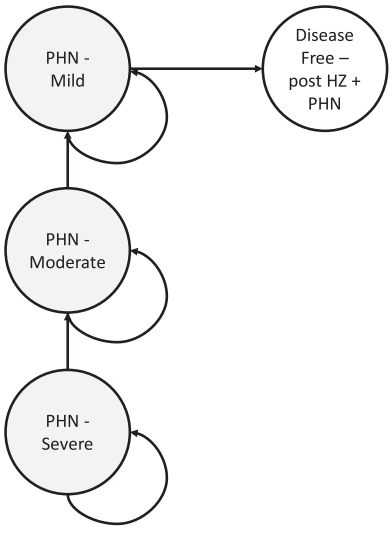

Fig. A.2. PHN sub-model structure.

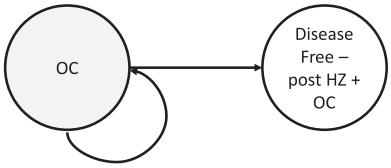

Fig. A.3. Ocular complications model structure.

levels of severity with ocular complications. At each cycle, the cohort collects some disutility due to their complication. There was no background QOL in this model. There is no background QOL in this model. This model produces the average disutility and cost due of an ocular complication. Cycle time was set to 1 month.

B.2. STM for booster model

Data for the two dose MDP was generated by creating a one additional STM. The model follows the same structure as the model presented in Fig. 1. This model was used to generate the lifetime costs and QALYs for people who received a vaccine at some age *j* and developed HZ at some age *Y*. Determining when HZ occurs given the age of vaccination is important as the probability of developing PHN increases with age as does the probability of more severe PHN [28–34]. The probability of developing PHN given HZ was adjusted by the age when the vaccine was originally received *j* and the number of years the person had been vaccinated *i*. HZ was still a transient state so the initial transition occurred within the cycle.

Appendix C. Probabilistic sensitivity analysis

A probabilistic sensitivity analysis was conducted for the one and two dose MDP models. To conduct this analysis, the distributions were created from discrete inputs. Using R, the STM submodel PSA output data was analyzed to define distributions for the costs and QALY inputs for the STM. Best practice recommendations were followed when determining the distributions. Once all parameters had been converted to distributions a second order Monte Carlo PSA was run for each STM (1000 iterations). To ensure continuity between the STMs, a priori seeded distributions were used. To do this, distributions for the PSA analysis were created in a separate R file; the distributions were drawn, saved, and loaded into each of the R files for the STMs. Each saved distribution contained 1000 values. We coded the PSA STMs to load variables into the model by position. Therefore, PSA STM 1 would load one set of parameter values from position 1 of the distributions loaded into the file. This allowed all STMs use one set of distributions across all models; this also guaranteed that values that needed to be consistent across all models would be.

For the one dose model PSA was conducted for each age between 50 and 100 independently. Variables in the analysis were saved to check the continuity between the models. Each age between 50 and 100 had 1000 data points, therefore there was an opportunity to run 1000 different one dose MDP iterations, each with a complete set of input data. Data was structured so that each MDP iteration sampled the complete set of outcome data for ages 50–100, from each PSA sample (e.g., MDP iteration 1 used data from PSA iteration 1 for ages 50–100). Each of the 1000 MDP iterations produced an optimal strategy over the time horizon. Each strategy was converted into a binary formatted vector (1 = vaccinate, 0 = wait), where each location in the vector corresponded to an age (e.g., vector location 1 = age 50). The sum across each vector location was taken and divided by the total number of iterations to produce the probability that a particular age would be part of the

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optimal policy given a certain WTP. The two-dose PSA followed the exact same procedure, we just also included the use of the two-dose STM that predicted the lifetime costs and QALYs for an individual who was vaccinated at age *j* and developed HZ at some age *Y*. Distributions used for the PSA analysis are shown in Table 1.

References

[1] Dworkin Robert H, Portenoy Russell K. Pain and its persistence in herpes zoster. Pain 1996;67(2):241–51.
[2] Yawn Barbara P, Itzler Robbin F, Wollan Peter C, Pellissier James M, Sy Lina S, Saddier Patricia. Health care utilization and cost burden of herpes zoster in a community population. Mayo clinic proceedings, vol. 84. Elsevier; 2009. p. 787–94.
[3] Hornberger John, Robertus Katherine. Cost-effectiveness of a vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. Ann Internal Med 2006;145(5):317–25.
[4] Pellissier James M, Brisson Marc, Levin Myron J. Evaluation of the cost-effectiveness in the united states of a vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. Vaccine 2007;25(49):8326–37.
[5] Rothberg Michael B, Virapongse Anunta, Smith Kenneth J. Cost-effectiveness of a vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. Clinical Infect Dis 2007;44(10):1280–8.
[6] Le Phuc, Rothberg Michael B. Cost-effectiveness of herpes zoster vaccine for persons aged 50 years. Ann Internal Med 2015;163(7):489–97.
[7] Alagoz Oguzhan, Hsu Heather, Schaefer Andrew J, Roberts Mark S. Markov decision processes: a tool for sequential decision making under uncertainty. Med Dec Mak 2010;30(4):474–83.
[8] P. Rohan, Zoster Vaccine Live (oka/merck) Zostavax, Report. Food and Drug Administration; 2005.
[9] Schmader KE, Oxman MN, Levin MJ, Johnson G, Zhang JH, Betts R, et al. Persistence of the efficacy of zoster vaccine in the shingles prevention study and the short-term persistence substudy. Clin Infect Dis 2012;cis638.
[10] Schmader Kenneth E, Levin Myron J, Gnann John W, McNeil Shelly A, Vesikari Timo, Betts Robert F, et al. and tolerability of herpes zoster vaccine in persons aged 50–59 years. Clin Infect Dis 2012;54(7):922–8.
[11] Morrison Vicki A, Johnson Gary R, Schmader Kenneth E, Levin Myron J, Zhang Jane H, Looney David J, et al. Long-term persistence of zoster vaccine efficacy. Clin Infect Dis 2015;60(6):900–9.
[12] Tseng HF, Luo Y, Hales Craig M, Harpaz Rafael, Sy Lina S, Bialek Stephanie R, et al. Declining herpes zoster vaccine effectiveness in adults 60 years and older. ID Week 2015; 2015.
[13] Puterman ML. Markov decision processes: discrete stochastic dynamic programming, Wiley series in probability and statistics. Wiley-Interscience; 2005 <https://books.google.com/books?id=Y-gmAQAAIAAJ>, ISBN 9780471727828.
[14] Bellman Richard. A markovian decision process, Technical report. DTIC Document; 1957.
[15] Howard RA. Dynamic programming and markov processes, technology press research monographs. MIT Press; 1960. ISBN 9780262080095 <https://books.google.com/books?id=hMH5jwEACAAJ>.
[16] Schaefer Andrew J, Bailey Matthew D, Shechter Steven M, Roberts Mark S. Modeling medical treatment using markov decision processes. In: Operations research and health care. Springer; 2004. p. 593–612.
[17] Ayer Turgay, Alagoz Oguzhan, Stout Natasha K. Or forum-a POMDP approach to personalize mammography screening decisions. Oper Res 2012;60 (5):1019–34.
[18] Shechter Steven M, Bailey Matthew D, Schaefer Andrew J, Roberts Mark S. The optimal time to initiate HIV therapy under ordered health states. Oper Res 2008;56(1):20–33.
[19] Alagoz Oguzhan, Maillart Lisa M, Schaefer Andrew J, Roberts Mark S. The optimal timing of living-donor liver transplantation. Manage Sci 2004;50 (10):1420–30.
[20] Nunes Luiz Guilherme Nadal, Carvalho Solon Venâncio de, Rodrigues Rita de Cássia Meneses. Markov decision process applied to the control of hospital elective admissions. Artif Intell Med 2009;47(2):159–71.
[21] Magni Paolo, Quaglini Silvana, Marchetti Monia, Barosi Giovanni. Deciding when to intervene: a markov decision process approach. Int J Med Inf 2000;60 (3):237–53.
[22] Neumann Peter J, Cohen Joshua T, Weinstein Milton C. Updating cost-effectiveness—the curious resilience of the $50,000-per-qaly threshold. New Engl J Med 2014;371(9):796–7.
[23] Bilcke Joke, Ogunjimi Benson, Hulstaert Frank, Van Damme Pierre, Hens Niel, Beutels Philippe. Estimating the age-specific duration of herpes zoster vaccine protection: a matter of model choice? Vaccine 2012;30(17):2795–800.
[24] Donahue James G, Choo Peter W, Manson JoAnn E, Platt Richard. The incidence of herpes zoster. Arch Internal Med 1995;155(15):1605–9.
[25] Insinga Ralph P, Itzler Robbin F, Pellissier James M, Saddier Patricia, Nikas Alexander A. The incidence of herpes zoster in a united states administrative database. J Gen Internal Med 2005;20(8):748–53.
[26] Leung Jessica, Harpaz Rafael, Molinari Noelle-Angelique, Jumaan Aisha, Zhou Fangjun. Herpes zoster incidence among insured persons in the united states, 1993–2006: evaluation of impact of varicella vaccination. Clin Infect Dis 2011;52(3):332–40.
[27] Kawai Kosuke, Gebremeskel Berhanu G, Acosta Camilo J. Systematic review of incidence and complications of herpes zoster: towards a global perspective. BMJ Open 2014;4(6):e004833.
[28] Cebrián-Cuenca Ana M, Díez-Domingo Javier, San-Martín-Rodríguez María, Puig-Barberá Joan, Navarro-Pérez Jorge, et al. Epidemiology and cost of herpes zoster and postherpetic neuralgia among patients treated in primary care centres in the Valencian community of Spain. BMC Infect Dis 2011;11(1):302.
[29] Gialloreti Leonardo E, Merito Monica, Pezzotti Patrizio, Naldi Luigi, Gatti Antonio, Beillat Maud, et al. Epidemiology and economic burden of herpes zoster and post-herpetic neuralgia in Italy: a retrospective, population-based study. BMC Infect Dis 2010;10(1):230.
[30] Gauthier A, Breuer J, Carrington D, Martin M, Remy V. Epidemiology and cost of herpes zoster and post-herpetic neuralgia in the United Kingdom. Epidemiol Infect 2009;137(01):38–47.
[31] Helgason Sigurdur, Petursson Gunnar, Gudmundsson Sigurdur, Sigurdsson Johann A, et al. Prevalence of postherpetic neuralgia after a first episode of herpes zoster: prospective study with long term follow up. BMJ 2000;321 (7264):794.
[32] Hope-Simpson RE. Postherpetic neuralgia. Brit J Gen Pract 1975;25 (157):571–5.
[33] Stein Alicia N, Britt Helena, Harrison Christopher, Lynne Conway E, Cunningham Anthony, Raina MacIntyre C. Herpes zoster burden of illness and health care resource utilisation in the australian population aged 50 years and older. Vaccine 2009;27(4):520–9.
[34] Yawn Barbara P, Saddier Patricia, Wollan Peter C, St Sauver Jennifer L, Kurland Marge J, Sy Lina S. A population-based study of the incidence and complication rates of herpes zoster before zoster vaccine introduction. Mayo clinic proceedings, vol. 82. Elsevier; 2007. p. 1341–9.
[35] Drolet Mélanie, Brisson Marc, Levin Myron J, Schmader Kenneth E, Oxman Michael N, Johnson Robert W, et al. A prospective study of the herpes zoster severity of illness. Clin J Pain 2010;26(8):656–66.
[36] Oxman MN, Levin MJq, Johnson GR, Schmader KE, Straus SE, Gelb LD, et al. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. New Engl J Med 2005;352(22):2271–84.
[37] Hedden Megan A, Kuehl Peggy G, Liu Yifei. Economic analysis of a herpes zoster vaccination program in 19 affiliated supermarket pharmacies. J Am Pharm Assoc: JAPhA 2014;54(4):390–6.
[38] Wood Heidi M, McDonough Randal P, Doucette William R. Retrospective financial analysis of a herpes zoster vaccination program from an independent community pharmacy perspective. J Am Pharm Assoc: JAPhA 2008;49 (1):12–7.
[39] Doucette William R, McDonough Randal P, Mormann Megan M, Vaschevici Renata, Urmie Julie M, Patterson Brandon J. Three-year financial analysis of pharmacy services at an independent community pharmacy. J Am Pharm Assoc 2012;52(2):181–7.
[40] Dunn Jeffrey D, Sclar David A. Anaphylaxis: a payor's perspective on epinephrine autoinjectors. Am J Med 2014;127(1):S45–50.
[41] Tseng HF, Liu A, Sy L, Marcy SM, Fireman B, Weintraub E, et al. Safety of zoster vaccine in adults from a large managed-care cohort: a vaccine safety datalink study. J Internal Med 2012;271(5):510–20.
[42] Drolet Mélanie, Levin Myron J, Schmader Kenneth E, Johnson Robert, Oxman Michael N, Patrick David, et al. Employment related productivity loss associated with herpes zoster and postherpetic neuralgia: a 6-month prospective study. Vaccine 2012;30(12):2047–50.
[43] Annemans L, Bresse X, Gobbo C, Papageorgiou M. Health economic evaluation of a vaccine for the prevention of herpes zoster (shingles) and post-herpetic neuralgia in adults in belgium. J Med Econ 2010;13(3):537–51.
[44] Singhal Puneet K, Makin Charles, Pellissier James, Sy Lina, White Ron, Saddier Patricia. Work and productivity loss related to herpes zoster. J Med Econ 2011;14(5):639–45.
[45] Lieu Tracy A, Ortega-Sanchez Ismael, Thomas Ray G, Rusinak Donna, Katherine Yih W, Choo Peter W, et al. Community and patient values for preventing herpes zoster. Pharmacoeconomics 2008;26(3):235–49.
[46] Neuner Joan M, Hamel Mary Beth, Phillips Russell S, Bona Kira, Aronson Mark D. Diagnosis and management of adults with pharyngitis: a cost-effectiveness analysis. Ann Internal Med 2003;139(2):113–22.
[47] Arias Elizabeth. United States life tables, 2010; 2010.
[48] Schmader Kenneth E, Dworkin Robert H. Natural history and treatment of herpes zoster. J Pain 2008;9(1):3–9.
[49] Levin Myron J, Schmader Kenneth E, Pang Lei, Williams-Diaz Angela, Zerbe Gary, Canniff Jennifer, et al. Cellular and humoral responses to a second dose of herpes zoster vaccine administered 10 years after the first dose among older adults. J Infect Dis 2016;213(1):14–22.
[50] Gilbert Peter B, Gabriel Erin E, Miao Xiaopeng, Li Xiaoming, Su Shu-Chih, Parrino Janie, et al. Fold rise in antibody titers by measured by glycoprotein-based enzyme-linked immunosorbent assay is an excellent correlate of protection for a herpes zoster vaccine, demonstrated via the vaccine efficacy curve. J Infect Dis 2014;jiu279.
[51] Zhang Y, Haipeng W, Denton BT, Wilson JR, Lobo JM. Conducting probabilistic sensitivity analysis for decision models based on markov chains; 2015. https://pdfs.semanticscholar.org/2d0e/915673707c30f2be8365adf4974492e6fdad.pdf.

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