Making good decisions:
Examining the cost-effectiveness and optimal timing of the herpes zoster vaccine

by

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For

Charli, Mom & Dad

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Abstract

Herpes zoster (shingles) is a disease that approximately 90% of the US population is at risk of developing. This disease causes intense pain which can affect quality of life and has a substantial economic burden. A vaccine is available to prevent the disease, and currently this is the best tool available for combating this disease. However, the vaccine does not have lifelong durability, and it has less efficacy in older people. Therefore, it is important to make good decisions on how and when to administer this vaccine so that we maximize both its benefit and our available resources.

This dissertation uses the techniques of cost-effectiveness analysis, stochastic dynamic optimization, and value of information analysis to focus on decision making about how to best use the vaccine. First, cost-effectiveness was completed to show the value at different ages of vaccination. Stochastic dynamic optimization built upon the cost-effectiveness models to determine the optimal time to administer the vaccine. Finally, value of information analysis examined how the optimal policy may change if perfect information were available on some of the key uncertain parameters.

Results indicate that age 67 is the most cost-effective age to vaccinate men and women. The optimal policy results from the stochastic dynamic program suggest it would be best to start vaccinating men and women at age 66 and to stop at 74 (men) or 77 (women). Results show that there is some value to determining the additional information on key uncertain model parameters. However, the value we can gain is unlikely to be worth the investment in the additional research that would be required.

Overall this dissertation shows that the recommended policies in the US of vaccination at 60 and older could be sub-optimal. Given the results of the models it may be more optimal to change the recommendation to 65 and older so that the benefits of the vaccine are conferred at the best times.

Chapter 1

Introduction

> *"If you play football for a long time like I did, youre gonna learn to deal with a lot of pain...but it is nothing like the pain that shingles causes."*
>
> — Terry Bradshaw*, NFL Hall of Fame Quarterback [1]*

Terry Bradshaw's story is just one of many about the herpes zoster virus, commonly known as shingles. This is a disease that nearly every person in America can develop, and yet is not well understood by the general population [2]. It is estimated that more than 1 million new infections occur each year in the US [3]; assigning herpes zoster (HZ) the highest incidence rate of any neurological disease. In the US, more will people develop HZ annually than Alzheimers, Huntingtons disease, ALS, and brain and nervous system cancers, combined [4–7].

To develop HZ one only needs to have had the chickenpox virus or the chickenpox vaccine. Because nearly every child will get chickenpox or the vaccination, approximately 95% of Americans are at risk for developing HZ [2]. To date, age is the best known risk factor. Categorically, people over age 50 are at the highest risk of infection; this risk continues to increase with age, as does the risk of additional complications. For context, there are more than 90 million people older than age 50 living in the US [8]. It is estimated that one third of adults will develop HZ in their lives and half of adults older than age 85 will experience or have already experienced

HZ [2].

The most common symptoms of HZ are pain and a blistering rash. While a typical disease course for HZ is about one month, the pain associated with HZ can be debilitating, and nearly all patients will experience some pain during the course of the infection [9]. Patients describe the impact of the pain on daily life:

> *"For two weeks I sat up in bed because I couldnt lay down...I didnt want to do anything except sleep and have the pain be over [10]."*

> *"The pain from shingles just made it impossible to even want to move [11]."*

Other descriptions of pain include: "sharp," "stabbing," "piercing needles in the skin," and "burning" [12]. This pain substantially impacts daily functioning, severely reduces quality of life, and can lead to lost productivity. Thus, despite the short disease course [13], HZ carries high health burden.

The main complication associated with HZ is postherpetic neuralgia (PHN) which can present incapacitating pain that can be intense than the pain experienced during the HZ infection. The pain caused by PHN continues after the HZ rash disappears, often lasting several months, or years in rarer cases [12]. The risk of PHN increases with age, a sharp increase occurs after age 60. The pain intensity and duration due to PHN place an additional and severe burden on patients who experience it. Disease incidence, pain intensity, and pain duration allow PHN to have a substantial impact on patients quality of life; making PHN particularly import when discussing HZ, and its treatment and prevention.

While pain presents a major personal burden to patients, the economic burden of this disease is also substantial. The majority of people who develop HZ will seek medical attention and require prescription drugs for the pain and the rash. Including costs for hospital admissions, outpatient visits, emergency department visits, and prescription drugs, the average HZ infection costs about $1000 [14]. The average cost of PHN is estimated at $5000 over a 12 month period [14]. With more than 1 million estimated new HZ infections annually, this equates to well over $1 billion spent on direct medical costs for HZ and PHN alone. Accounting for costs of other

complications such as neurological palsies and skin infections, and lost productivity increase the estimate of the total cost burden. The cost burden is currently unknown.

HZ cannot be cured, and medications have only allowed people to endure the disease. However, a vaccine was approved for use in 2006 by the US Food and Drug Administration (FDA) that can be used to prevent the disease and its complications [15,16] making it an extremely important tool for public health practice, and the best option to date for reducing the burden of disease. The vaccine is approved for any person over age 50, and is currently recommended for any person over age 60 [17]. The HZ vaccine has been shown effective at reducing the burden of disease by lowering the risk of HZ, and perhaps most importantly, "works even better at preventing the really severe cases likeliest to lead to postherpetic neuralgia" [18]. However, the initial efficacy and longevity of the vaccine are both age-dependent [15, 16, 19–22]. Therefore, because people are more at risk of infection and disease complications as they age, and because the vaccine provides different levels of protection based on when it is administered, understanding how the administration of the vaccine affects health outcomes and costs and then making good decisions about when to vaccinate is vital in the attempt to provide the maximum benefit to society by minimizing the burden of HZ and PHN.

Disease prevention is a core tenet of public health [23–26]. However, no disease can be prevented effectively without deciding on a strategy, which requires synthesizing information on the disease, the intervention, and its risks, benefits and costs. Making good decisions on prevention strategies can save resources, which can be used elsewhere and allows us to maximize the resources we have. Given the population at risk, the high cumulative incidence, the impact on quality of life, and the cost, it is evident that HZ is an important disease to both understand and prevent. However, we must also decide how to effectively prevent and reduce the burden of this disease to maximize the use of our resources; this is equally important from the public health perspective [26]. In this dissertation, I will use the decision analytic techniques of cost-effectiveness analysis, stochastic dynamic programming and value of information analysis to provide more understanding of this disease and evaluate strategies for vaccination which can be utilized to make good decisions on how to minimize the

burden of HZ and maximize our resources.

1.1 Disease Etiology and Progression

This section provides a brief overview of the key features of the HZ virus and the disease progression.

Varicella Zoster Virus

Chickenpox is a very common childhood disease [27] caused by the varicella zoster virus (VZV). The disease is transmitted by direct contact or by air through breathing or sneezing [28]. VZV is extremely contagious with between 60 – 100% of exposures leading to infection [28]. Common symptoms of a VZV infection are a pruritic (itchy) vesicular rash, swelling of the cervical lymph nodes, and fever [29]. The rash typically forms on the face, trunk, and scalp; a healthy child can expect to experience between 100 – 300 rash lesions during the infection [30]. Fortunately, most VZV infections will resolve without severe complications.

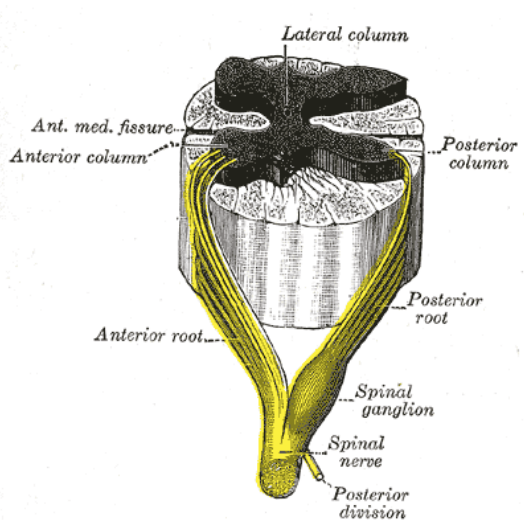

Figure 1.1: Spinal Nerves [31]

A vaccine was licensed for use in 1995 and since then the incidence of chickenpox in the US has reduced by as much as 90% [28]. Given the high chance of infection before the vaccine was introduced and the near universal coverage of the vaccine since 1995, 90-95% of adults in the US still test positive for serologic evidence of the virus [28, 32]; this is due to virus' behavior. Once introduced into the body, VZV virus seeks out and accesses nerve clusters called ganglia. During an infection, the virus can access any ganglion attached to an afferent neuron (a neuron that sends a signal toward the

central nervous system) that is also attached to a VZV rash vesicle on the skin surface. Because the chickenpox rash can develop almost anywhere on the body, the virus theoretically has access to every ganglion on along the neuraxis (brain and spinal cord) [29, 33]. However, the dorsal root ganglion in the spinal cord, shown in Figure 1.1, is the most commonly accessed site by VZV. Once inside a ganglion, the virus enters a latent state. This ability of the virus to establish a latent infection in the host is a defining feature of the herpes virus (Herpesviridae) family, and a necessary condition for the herpes zoster virus [27].

Herpes Zoster Activation

Herpes zoster is initiated by the reactivation of the latent VZV inside a single ganglion [3]. Reactivation of the virus occurs in approximately 25% of all people who carry the latent VZV [34]. It is the seroprevalence of VZV in adults and high chance of re-activation that lead to the high annual incidence of HZ in the US and throughout the world. Unlike other viruses in the Herpesviridae family, the exact triggering mechanism for VZV reactivation is unknown. The predominating theory suggests that, due to age, cell-mediated immunity declines below a level sufficient to keep the virus in its latent state. When this happens the VZV begins to replicate and spread [32, 34, 35]. This helps explain why age is the best known risk factor for an HZ infection.

Herpes Zoster Disease Progression

Once the virus begins to spread, there are three main periods for the HZ infection: 1) Prodromal (pre-rash); 2) Rash; 3) Post-rash. In the prodromal phase, the virus travels from the ganglion back toward the skin surface along the sensory nerves causing necrosis along the way. This is commonly associated with abnormal sensations in the skin such as tickling, tingling, numbness, itchiness, or burning [12,36]. The prodromal period usually lasts between 48-72 hours in the area where the sensory nerves are infected with the virus. This phase terminates when the virus reaches the skin and the rash phase begins [32, 34].

Rash Phase

The start of the rash phase is signaled by the formation of a vesicular rash. The most common places for a rash to form are anywhere between T1 and L2 vertebrae [32] and near the V1 branch of the trigeminal nerve, shown in Figure 1.2. These dermatomes (areas of skin supplied by a single spinal or cranial nerve) typically contain the highest concentration of lesions during a chickenpox infection and are thus the most likely to be affected during an HZ infection. During the rash phase, the initial vesicular lesions will develop into pustules, and then crust over. The HZ rash will resolve and skin will begin to health within two to four weeks after onset. A rash will typically be contained to a single dermatome, unlike the chicken pox rash which affects many dermatomes at once.

Aside from the rash, the main symptom during this phase is pain, and nearly all patients will experience some pain during the course of the infection [9]. The pain experienced by patients in the rash phase has been described as "sharp," "stabbing," and "burning" [12]. This pain substantially impact daily functioning, severely reduce quality of life, and can lead to lost-productivity during the duration of the HZ infection. Thus, despite the short disease course and the minimal chances for mortality and complications [13], HZ carries high health burden.

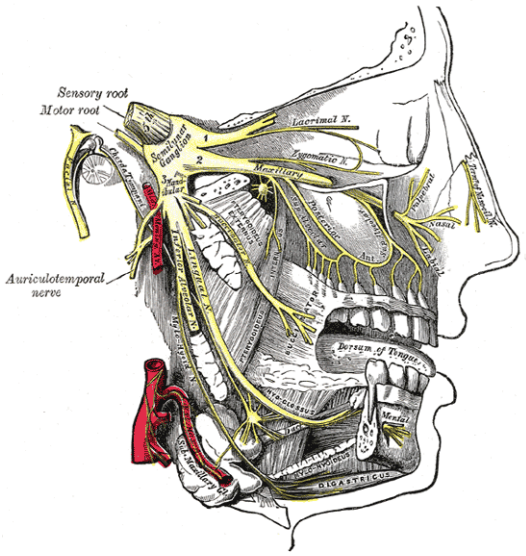

Figure 1.2: Trigeminal Nerve [31]

Post-Rash Phase and PHN

Pain that persists after a certain duration of time in the post-rash phase will often be diagnosed as PHN. Unfortunately, there is no formal medical definition for the length

of time pain must be present to be considered PHN [37] thus consistent diagnosis can be challenging due to ambiguity. The two most commonly used definitions for PHN in the literature are: 1) pain that persists for more than 90 days after the initial infection (PHN3); 2) pain that persists for more than 30 days after the initial infection (PHN1) [38].

Regardless of the definition used, PHN is the most common complication of HZ and is estimated to occur after approximately 10 – 30% of all HZ infections [39, 40]. Similar to HZ, the risk of PHN increases with age; with risk increasing sharply after age 60. There are five distinct types of pain commonly associated with PHN: 1) throbbing pain; 2) stable burning pain; 3) sporadic sharp or shooting pain; 4) allodynia (burning or shooting pain that is caused by simulating the dermatome in a way that normally would not cause pain); 5) hyper-pathia (strong pain reaction by stimulating the dermatome, usually repetitively) [41]. The pain produced by PHN can be more intense than pain experienced during the HZ infection and can last several months, or years in rare cases [42]. Disease incidence, pain intensity, and pain duration allow PHN to have a substantial impact on patients quality of life; making PHN important to consider when deciding on possible HZ prevention strategies.

1.2 Decision Making

Making good decisions is difficult. This is especially true in health care, as it requires balancing and integrating risks, benefits, costs, preferences and other evidence to arrive at a conclusion likely to produce the best outcome [43]. And, unlike many decisions, making poor decisions in health care can result in serious or fatal consequences. A principal challenge to making good decisions is that most decisions are made under conditions of uncertainty [44]. That is, while we know the outcomes of the decision, we have limited information on the chance of achieving that outcome. Decision analytic techniques are available that allow for the aggregation of the available information, the accounting of uncertainty, and the testing of different assumptions. It is these techniques that help provide clarity and additional information to people or agencies that make health care decisions or recommendations [43].

In the US, the Advisory Committee on Immunization Practices (ACIP) is a group of public health experts supporting the Centers for Disease Control and Prevention (CDC) that decide on how to recommend the use of vaccines to prevent and control disease [45]. During the decision process, the ACIP considers the following aspects in its recommendations: disease epidemiology, disease burden, vaccine safety, vaccine efficacy, vaccine effectiveness, vaccine implementation, and economic evaluation [45]. Current recommendations on HZ vaccination from the ACIP have focused on results from decision analysis and economic evaluation technique of cost-effectiveness analysis [17].

1.3 Economic Evaluation

Resources are scarce in health care, therefore decisions on what resources (e.g., treatment, procedures, medications) to provide can and must be made [46–50]. Economic evaluation is a method that examines the costs and consequences of a decision or set of decisions to provide information on the allocation of these resources. This type of evaluation is often best used when questions of efficacy, effectiveness, and availability have been adequately addressed [47]. In the case of HZ vaccination, the questions of efficacy and effectiveness (i.e., can it work?; does it work?) were addressed by the clinical trials for the vaccine [16, 20, 21, 51]. The vaccine is also readily available to the population. Therefore, the economic evaluation conducted by the ACIP for the HZ vaccine examines the costs and consequences of two alternatives (vaccination and no vaccination) to provide information for the recommendations on how the vaccine should be best allocated.

Cost-benefit Analysis

There are two common methods for health economic evaluation, cost-benefit analysis (CBA) and cost-effectiveness analysis (CEA) [52–54]. CBA is the most common form of economic evaluation used outside of the health care sector. Money is one of the broadest value measures and CBA monetizes both costs and outcomes to determine if

benefits outweigh costs [55]. That is, CBA values resources used compared to resources gained or to be gained; if more value is created than lost the treatment or intervention is considered cost-beneficial. The main advantage to CBA is its cross-compatibility with other sectors given the common units of measurement. Because more sectors use CBA than CEA, results from CBAs can be compared together to decide which interventions or projects create the most value and should be prioritized [46, 47].

Cost-effectiveness Analysis

However, monetizing health outcomes is both difficult and controversial. This is a primary reason why CEA is preferred in health care [48, 49, 52]. The goal of CEA is similar nevertheless; costs and outcomes data are aggregated to determine how much money needs to be spent to achieve the desired level of benefit. However, while costs are still measured in monetary units, outcomes are measured in quality adjusted life years (QALYs), which is a metric that accounts for time spent in a certain state of health and the utility of that health state. A QALY will value each health outcome on the same scale [56]. The utility scale used for health states is typically bound between 1 and 0, where 1 is assumed to be equal to perfect health and 0 is assumed to be equal to being dead [46, 47]. These costs and outcomes are combined and compared to a pre-defined threshold of cost-effectiveness. If the result of the CEA produces a value below this threshold, the intervention is considered cost-effective. If the result is over this threshold the intervention is considered not cost-effective.

CEA provides the ability for comparison within the health care sector as the use of the QALY provides a generic outcome measure for health economic evaluation. Thus studies that use CEA can be compared against one another to determine how much benefit can be gained given a certain budget. The ACIP used CEA in the formulation of their most recent recommendation [17]. The knowledge that a vaccine or treatment is cost-effective provides additional information in a decision making process and can help set recommendations for its use.

Limitations of Economic Evaluation

While cost-effectiveness and other forms of economic evaluation are very useful and can provide insights into decision problems, they do have some limitations. Any model is only as good as its inputs and assumptions. If poor quality data is used for the model, or if poor assumptions are made then the outcomes of the model will not likely be informative or worse, misleading [57]. Therefore, in any model, the structure, assumptions, and data must be explicitly presented so that the model can be properly assessed [58]. Additionally, economic evaluation should be seen and used as a tool to inform decision making. However, the results of the model should not be applied mechanically without consideration for other important variables (e.g., epidemiology, equity, safety of the treatment, disease burden, policy implementation, etc.) [48]. That is, while these techniques serve as tools to help influence decision making they are not incontrovertible. The risk with the direct application of conclusions from economic evaluations without considerations of other important factors would likely lead to decisions that would be difficult to alter [48]. Therefore, great care must be taken with the application of the information. Further, results should be updated as new information or data becomes available and decision makers must be flexible in their inclusion of that or any new information into their decision [48].

1.4 Herpes Zoster Cost-effectiveness Literature

To date, there have been 16 CEAs for HZ vaccination; four have been published from the US perspective [59–62], the remaining 12 are from Canada or Europe [63–74]. The US CEAs present conflicting results; brief overviews are presented in Table 1.1. Three of the four studies examined vaccination of people greater than age 60, the other for people between 50 – 59. Three US studies use a $50,000 per QALY threshold to define if the vaccine is considered cost effective [59–61]. In three US CEAs, the incremental cost-effectiveness ratio (ICER) exceeded the cost-effectiveness threshold, thus the vaccine was considered not cost-effective. However, it is important to note that there is no commonly agreed upon cost-effectiveness threshold in the US. Further,

recent studies have shown that a threshold of $50,000 would be too low in the US; research suggests that a US would be between $100,000 and $250,000 [75]. However, results are stark when comparing US CEAs to more non-US CEAs; 11 of the 12 international studies produced an ICER less than $50,000 per QALY [63,65–74], with 4 producing ICERs less than $30,000 per QALY. Most international studies are newer, and majority used newer data and more advanced models.

The results of any cost-effectiveness study are dependent on available data and the assumptions made. A recent systematic review of HZ vaccination CEAs found that, in a majority of studies, duration of vaccine efficacy and vaccination age had the highest impact on vaccine cost-effectiveness [76]. Other categories that received a mark of highest or high impact on the cost-effectiveness results included: PHN costs, PHN length, vaccine costs, discount rates, pain state split (e.g., mild, moderate, severe), HZ incidence, and HZ duration [76]. It is important to understand the assumptions and inputs in any cost-effectiveness study to determine how the final results may be impacted.

Study	Ages	Perspective	Mean ICER	Results	Most Sensitive To	Vaccine Duration	Limitations
Hornberger [59]	≥ 60	Societal	118,764	Most cost-effective for ages 60 – 64	Age, QALY adjustments (HZ, PHN), Vaccine (cost, duration), Time horizon, PHN (duration), Discount rate	30 years	Data on vaccine efficacy beyond three years is lacking
Pellissier [60]	≥ 60	Societal	27,325	Cost-effective for ages 60 – 64, 65 – 69, and 70 – 74	PHN (costs), Complications (costs), Vaccine (duration, efficacy, PHN efficacy, HZ efficacy), QALY adjustments	Life-long	No vaccine waning. No description of time in each state.
Rothberg [61]	≥ 60	Societal	155,361	Most cost-effective for ages 70 – 79	Vaccine (duration, cost, efficacy), PHN (incidence, duration, utility), HZ (incidence, severity), Discount rate	10 years	Assumes no reduction in PHN due to vaccination beyond prevention of HZ
Le [62]	50–59	Societal	351,517	Most cost-effective for age 59	Vaccine (cost, efficacy), PHN (duration)	≈ 10 years	Assumes linear decline in vaccine. Uses costs from previous paper which are from UK study in 1990s

Table 1.1: US CEA studies. ICERs reported in 2015 US Dollars ($).

Assessment of US Cost-effectiveness Analyses

There are notable differences between the US CEAs. Overall, the model constructed by Rothberg et al [61] was sensitive to characteristics of the vaccine, PHN, and HZ. Unfortunately there was limited methodology for how the vaccines efficacy and waning was calculated, and limited information on the time spent in a PHN health state. The authors assume there is no decrease in PHN incidence beyond the decrease attributed to reducing HZ incidence with vaccination. That is, they assume that the vaccine does not impact the severity of the disease for those who still become infected. Brisson et al [77] suggest that just accounting for the additional reduction of PHN can reduce the cost per QALY by as much as 40%. Rothberg et al also assume that an individual either spends less than 12 months with PHN, or several years with PHN. And, there is no account for PHN severity as only one PHN utility score is given. This CEA helps to illustrate the potential importance of PHN and the impact that assumptions about this condition could have on results of the CEA.

Le and Rothberg [62] provide the newest estimate for the cost-effectiveness in the US. They do make use of the new vaccine waning data as well. However, there are some complications with their paper. First, they assume the vaccine wanes using a strictly linear rate. While this assumption may have been more plausible for older studies, current data suggests that the vaccine has a step decline in the efficacy during the first year which would not be captured in the linear model [20, 78]. Second, PHN cost data is from a 1994 study from the UK, which was also used in their previous CEA [61]. The cost of one of the most important parameters (PHN) in many HZ CEA models, in this paper, is 20 years old and from a country where the health care financing structure is very different than in the US. Finally, some epidemiological model inputs (e.g., probability of PHN) are defined by age groups. It was unclear if the authors implemented these probabilities directly into the model as a discontinuity, or they attempted to do some types of fitting for the data. This CEA is the first in the US to examine the impact of the vaccine for people ages 50 – 59. It is an important paper for this reason, but leaves room for improvement on determining the value of vaccination for this group.

Hornberger and Robertus [59] make assumptions about PHN, and vaccine efficacy that may impact the CEA results. First, the authors assume that PHN does not result unless pain has been persistent for 182 days from the start of the rash phase. This definition of PHN may underestimate the proportion of people who actually experience PHN. Prior to developing PHN, people in persistent pain for 6 months are assumed to have the utility value of HZ, which was much higher than PHN. If people develop PHN, there is no severity distinction as there is only one PHN utility value given. Therefore, by using a definition that may underrepresent the incidence of PHN and giving people more utility for longer, this paper may underestimate the QALYs gained by vaccination which can impact the cost-effectiveness results. The authors also admit to having limited data on vaccine efficacy beyond the initial 2005 clinical trial results [59]. The assume an upper limit of 30 years vaccine efficacy based on unreferenced VZV vaccine waning models. This assumption could be problematic as VZV vaccination is a) a different vaccine and b) is typically given during childhood when there is less risk of immunity loss thus longer vaccine duration may be more reasonable. These assumptions are extremely important to this paper as the vaccine was only considered cost-effective if it was assumed to last for the upper limit of 30 years and given to people 70 years old or younger.

Pellissier et al present the best methods of any US CEA for describing how the vaccine efficacy and waning was calculated, however, they do not assume any vaccine waning in the base case analysis [60]. However, the authors only had limited data on the vaccines waning and efficacy at the time of publication. Their model also does not examine the length of time spent with HZ, PHN, or other complications within the model itself. All costs and QALYs in the model were pre-determined and entered into a model where every state is assumed transient. The authors do distinguish between the severity of HZ infections, but not the severity of PHN cases. PHN costs had the highest impact on the results in the probabilistic sensitivity analysis and the second highest impact on results in the one-way sensitivity analysis (vaccine cost was highest). Vaccine efficacy against PHN also had an important impact on the sensitivity analysis. Cost of PHN is likely to vary both by severity [79] and time spent with PHN. Vaccine efficacy will have an important impact on control the costs

of PHN. This paper again shows the ability of vaccine efficacy and PHN to affect the results of the CEA.

1.5 Research Gaps and Opportunities

Based on the assessment of the US CEAs and economic evaluations, it is evident that all make assumptions that impact the results; with efficacy and waning effect of the vaccine, and the characteristics (time, cost, severity) of PHN being two potential crucial drivers of results. With regard to assumptions made about the vaccines effect on HZ and PHN, it is important to note that three of US studies are among the oldest CEAs available [59–61]. The most recent of these three being published by Pellissier et al [60] approximately 18 months after approval of the vaccine by the FDA. Since then, new data on short-term and long-term vaccine efficacy [20, 21, 78] has been published. This data is vital to better establishing both the age-specific initial vaccine efficacy, and also how the vaccine wanes over time. Further, work done by Bilcke et al [19] and van Hoek et al [72] provide methods for using published data to create efficacy and waning estimates for the vaccines protection against HZ and PHN. Incorporating these data and methods into current health economic models will allow for a more accurate prediction of the value of the vaccine and can aid with future recommendations.

In addition to new data on short-term and long-term vaccine efficacy, research has also been published on vaccine efficacy for people ages 50-59 [51]. Currently, there are three non-US CEAs [68, 71, 74] that have included a 50-59 age group. Vaccination of this group was considered cost-effective. While this group was included in the most recent US CEA, the vaccine was not found to be cost-effective for this age group [62]. There have been new publications on the costs and decrements in quality of life from HZ and PHN [14, 80–87]. Further, HZ is unique among vaccine preventable diseases in that much of its total burden is in the form of intangible costs (i.e., pain and suffering) that is borne exclusively by individuals. There is now data available that helps to characterize these intangible costs [88, 89] associated with HZ and PHN. Recent CEAs from Europe [65, 68, 76] have modeled HZ and PHN in ways that better

capture the severity of the condition and can be adapted to account for the impact of time with PHN. Including these additional costs and quality of life data as well adapting the model structure to better account for the impact of HZ and PHN will allow for the creation of a more comprehensive estimate of the cost-effectiveness and the burden of disease. Further, this will be the first US specific evaluation of the HZ vaccine to include both broad age groups (i.e., ACIP recommendations (60 and older) and FDA approval (50 and older)) in the same analysis.

The question of an optimal age for HZ vaccination remains largely unanswered. One CEA study from Belgium explored impact of vaccination at single ages from 60-85; vaccination at age 60 was the most cost-effective [64]. No other study to date has examined the impact of vaccinating at individual years. Further, one complication with some decision models is the ability to only compare one decision at a time (e.g., vaccinate or not at some age). These types of evaluations typically do not account for the decision to defer vaccination or the prior risk of disease. Accounting for these things can help to determine the optimal policy of deciding when people should get vaccinated rather than determining if the vaccine is cost-effective at some age. Finally, no study to date has examined the value of information on model parameters for HZ or the vaccine. Based on the literature, it is evident that certain sets of parameters greatly affect the outcomes of the models. Minimizing the uncertainty of these parameters could help improve recommendations, or help prioritize research about the vaccine.

1.6 Contribution to Literature

This dissertation will add to the existing literature in three ways. First, I will provide a new estimate of the cost-effectiveness for the HZ vaccine from the US perspective. This estimate will incorporate new information on the vaccines waning and efficacy over time. It will also utilize new data on disease costs, and utility lost to better account for the total burden of disease. Finally, it will be the first US study to include a 50-59 age group alongside the 60 and older group. As a result, this research should provide the best estimate of the cost-effectiveness to date. Second, I will examine the

question for the optimal timing of vaccination against HZ. Providing a prediction of the optimal age for the vaccine will be useful in setting policy recommendations and be important to minimizing the burden of disease. I will also investigate the importance of the booster vaccine in making this decision about the optimal age to vaccinate, as having the option for a booster vaccine may change recommendations and further help reduce the burden. Finally, I will provide an estimate of the value of additional information and research for parameters that affect the results and impact possibly policy recommendations. Understanding the value of added research will be important for future research prioritization.

Overview of Chapters

Chapter 2
Cost-effectiveness Analysis of Herpes Zoster Vaccination

The objective of this chapter is to determine the cost-effectiveness of the HZ vaccine at every age between 50 and 100. This chapter will use a cohort state-transition model to estimate the cost-effectiveness.

Chapter 3
Optimal Timing of HZ Vaccination: One vs Two Dose Administration

The objective of this chapter is to determine the optimal age for administering the HZ vaccine to people between ages 50 and 100. This chapter will use a discrete time Markov decision process to determine if people should get vaccinated or defer vaccination at every starting at 50 years old.

Chapter 4
Value of Information Analysis

The objective of this chapter is to determine the value or perfect information on two key vaccine parameters. This chapter uses three different modeling techniques to estimate the value of this information. A comparison of method efficiency is also provided.

Chapter 2

Cost-Effectiveness of Herpes Zoster Vaccination

2.1 Introduction

The objective of this chapter is to determine the cost-effectiveness of the HZ vaccine using a decision analytic model. Only one US CEA has used the most current estimates for vaccine efficacy and waning [62]. In general, studies from the US have also made simplifying assumptions about the impact of PHN which may influence the cost-effectiveness of the vaccine given the ability of PHN to have a severe influence on quality of life. Providing a new estimate of the cost-effectiveness of the HZ vaccine by accounting for the waning and efficacy of the vaccine as well as the impact of PHN will be important for setting future recommendations on vaccination.

The Utility of Simulation Models

Simulation models provide a useful platform to better predict outcomes and costs, and to explore multiple long-term pathways of illness for conditions with uncertain prognoses. To construct a decision analytic model, the best available evidence must be aggregated and synthesized from all available sources (e.g., clinical trials, meta-analyses, cohort studies, etc.) [43]. This chapter will utilize a specific subclass of a

decision analytic simulation called a Markov-like state-transition model to estimate the cost-effectiveness of the HZ vaccine.

State-transition models are commonly used for clinical decision making and decision analytic research when a clinical situation of interest can be deconstructed into conditions or states that describe the health of a patient (e.g., disease free, sick, etc.) and the movement between those different states can be properly characterized. These movements, or transitions (e.g., disease free to sick) are governed by probabilities that occur over explicitly defined time cycles (e.g., the one year probability of transitioning from disease free to sick) [90]. Compared to decision tree models, state-transition models are useful when the timing of an event may change (e.g., incidence increases with age), or if an event may be recurrent [43].

Each state-transition model is constructed by including a set of mutually exclusive and collectively exhaustive health states that define the disease course, and a set of transition probabilities that define movement between states. State-transition models are composed of two or more component models: the natural history model and the intervention model(s). The natural history model simulates the course of the disease assuming no intervention. The intervention model(s) will follow the same disease progression, but the transition probabilities between states will change to reflect the effects of the intervention(s) under consideration [91]. A cohort model was used for this chapter. Cohort models simulate the progression of a medical condition or intervention for a group of people. Because the group is examined as a whole, the model reports the mean effect of the condition or intervention for the specific group or population being studied (e.g., 50 year women who receive a vaccine). Examining the mean effect is a benefit of the cohort model and makes these models easier to interpret, build, and modify. The disadvantage of the cohort model is that the model must abide by the "memoryless" Markovian assumption. This means that the history of previous health states is not accounted for; rather the only health state that affects the transition is the health state the cohort was last in. As a result of this assumption, clinical history (such as time spent in a health state) can be difficult to add to cohort models without including many more model states to account for the variety of different clinical scenarios.

2.2 Methods

Model Structure

To determine the cost-effectiveness of the HZ vaccine a cohort model was constructed to calculate costs and QALYs to formulate incremental cost-effectiveness ratios (ICERs). Model construction and simulation was completed using TreeAge Pro 2016, R1.0. TreeAge is a decision modeling software that provides a graphical user interface for creating basic decision trees, cohort state-transition models, and other types of decision models. To construct the model, established modeling guidelines for general simulation setup, comparison of alternative system configurations, incorporated complexity, and model transparency were followed [58, 90, 92–94].

The model calculated the cost-effectiveness of current zoster vaccine for ages 50 – 100. Figure 2.1 provides an overview of the model. Model health states are defined by ovals and transitions are defined by arcs or lines between health states. Transitions between disease free to HZ, and HZ to PHN are regulated by the vaccine; these transitions are indicated in the Figure 2.1 by yellow circles. The cohort starts in either the natural history model or the intervention model in the disease free health state. The time period between transitions (cycle time) for this model was set to 1 month (30 days). From the initial disease free health state, after each cycle there is a chance of staying disease free or developing HZ. The probability of developing HZ was dependent on age of the cohort and, if vaccinated, the initial efficacy and waning rate of the vaccine; vaccine characteristics are further discussed in **Vaccine Parametrization** and Appendix A.4 on page 185. Once HZ occurs, it was initially characterized as no pain, mild pain, moderate pain, or severe pain. This classification is defined by the Zoster Brief Pain Inventory (ZBPI). The ZBPI is an adapted 11-point Likert scale (0–10) used to quantify four types of pain (worst, least, average, now) [95]. The cut points in the ZBPI scale that characterize these four HZ pain states (no, mild, moderate, severe) are presented in Table 2.1. Further complications can arise due to HZ, however, only those who experience some HZ pain have the chance to experience further complications.

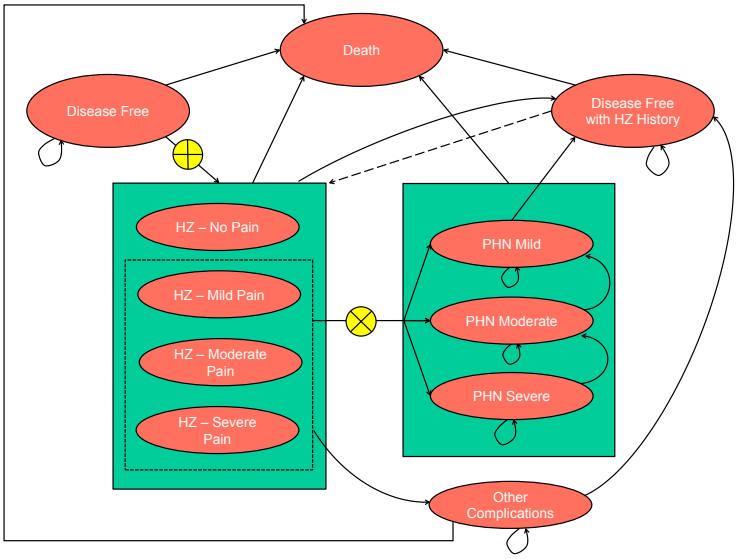

Figure 2.1: State transition model. Yellow circles indicate where the vaccine can have an effect.

The main complication of HZ is PHN. For this model, PHN is defined as any pain persisting for more than 90 days after the initial infection (PHN3). This is one of the two most commonly used definitions of PHN [37]. One benefit of this model structure is the ability to test changes in PHN status over time conditional upon the initial characterization of PHN. Characterization of PHN states is a feature included in recent cost-effectiveness models from Europe [63, 65, 68, 70], but has not been examined in US models. This structure is shown on the right portion of Figure 2.1. If PHN develops, it is initially characterized as mild, moderate, or severe. This characterization is also defined by the ZBPI; scales are presented in Table 2.1. Current literature suggests that the older an individual is, the more likely he/she will develop PHN and the more severe the episode will be [70]. Once in a PHN health state transitions can occur to move to the next best PHN state at the end of each cycle. The length of time spent in PHN was based on data from the average length of time spent in different PHN states [79]. The assumption for this model is that all people must transition through all better states of PHN before reaching the disease free with HZ history state. Utilizing this ladder-like progression allows for better estimates of

Health States	Description
Disease Free	People start model here, "No HZ"
HZ – No pain	HZ with ZBPI score = 0
HZ – Mild Pain	HZ with ZBPI score = 1 – 3
HZ – Moderate Pain	HZ with ZBPI score = 4 – 6
HZ – Severe Pain	HZ with ZBPI score = 7 – 10
PHN – Mild Pain	PHN with ZBPI score = 1 – 3
PHN – Moderate Pain	PHN with ZBPI score = 4 – 6
PHN – Severe Pain	PHN with ZBPI score = 7 – 10
Ocular Complications	Any complication involving the eye that due to an HZ infection
Neurological Complications	Any complication involving the nervous system due to an HZ infection
Cosmetic Complications	Any outward or visible damage caused by HZ after the rash has disappeared
Disease Free with HZ History	Health state for when people have gone through the course of their infection

Table 2.1: Model states

disutility associated with PHN.

People can also develop non-pain complications. Ocular complications are the most common of the non-pain complications. These complications arise when a case of HZ directly affects the eye. In the majority of cases, symptoms resolve quickly and leave no long-standing issues. In this model we assume that all ocular complications resolve within an average time of 3 months [14] and that no long-standing issues occur. This assumption was made because there were minimal data on the epidemiology (incidence and duration) and disutilities associated with long-standing issues due to zoster-related ocular complications. Other non-pain complications can also occur. These other non-pain complications include: neurologic complications – symptoms include Ramsay Hunt Syndrome (facial paralysis and hearing loss) – and cosmetic complications – symptoms include conditions like scarring, or bacterial superinfection of rash lesions [35, 96]

The probability of developing these other non-pain complications (neurologic and

cosmetic) in the base case analysis was set to 0. This assumption was made because the probability of developing these conditions is low, and there were limited data available on the duration and disutility associated with these health states. Therefore, it was predicted that due to the low probability of occurrence, these states would have a minimal impact on the cost-effectiveness. This assumption tested by including these complications in scenario analysis. From the non-pain complications or the PHN health state, the patient will then transfer to the disease free health state. This model allowed for disease recurrence. No recurrence of PHN or non-pain complications was allowed. The death state could be reached from any health state in the model at any cycle.

Model Inputs & Data

Evidence-based estimates for the parameter inputs were required for the model. Parameters were defined using best available data, and evidence synthesis techniques were used to combine data from published studies. The model required three general categories of specific parameters: transition probabilities, costs, and health outcome values.

- Transition probabilities represent the chance of movement between model states. If data were available, parameters were adjusted for age and gender.
- Costs included direct medical costs, and lost productivity costs. All direct medical costs were adjusted to 2015 dollars using medical care component of the Consumer Price Index (CPI). Lost productivity was applied to all people regardless of employment status.
- Health outcome values reflect the health-related quality of life associated with the included short-term and long-term health states. The inclusion of quality adjustment values for each state of health in the simulation model allowed for the calculation of quality-adjusted life years.

Data were collected from the societal perspective, the most common for decision analysis and recommended by the US Panel on Cost-effectiveness [46]. The societal

perspective accounts for costs and outcomes beyond the health system; this perspective is more inclusive and allows the vaccine to be evaluated on a more comprehensive level. A scenario analysis was included that examines the analysis from the health care perspective.

To collect data, a systematic literature review was conducted for each category of model input required. These reviews assessed the published data relating to the vaccine efficacy, epidemiology, costs, and QALYs associated with HZ and its complications. Search terms for each review were selected based on their use in similar systematic reviews. More information on the systematic literature review is available in Appendix A.6 on page 205. All literature reviews focused on peer-reviewed published literature relating to HZ in the US. Peer-reviewed articles relating to HZ outside the US was considered for disease epidemiology and quality of life (depending on data quality and transferability). All cost data were limited to studies within the US due to transferability issues and differences in health care systems [97]. Data collected from the literature reviews were used to generate transition probabilities, costs, and health outcomes for the model. Inputs were adjusted accordingly to account for demographic factors, including age and gender. Model inputs generated from the systematic reviews are presented in Tables 2.2 – 2.4. Model inputs were also converted from discrete values to distributions to allow for probabilistic sensitivity analyses (PSA) to be conducted; Table 2.5 provides the distributions of the PSA – further discussed in **Sensitivity Analysis**.

Variable	**Base Value**	**Lower Value**	**Upper Value**	**Reference**
All-cause mortality	Age Dependent			[98]
HZ mortality	5.10e-7	4.30e-7	5.60e-7	[99]
HZ recurrence				
Ages 50 – 69	0.0010	0	0.0020	[100]
Ages 70+	0.0027	0	0.0054	[100]
HZ incidence*				
Male – (asymp, xmid, scale)	(13.935, 773.204, 184.470)	(11.148, 773.204, 184.470)	(17.418, 773.204, 184.470)	[101–103]
Female – (asymp, xmid, scale)	(19.227, 824.028, 199.408)	(15.382, 824.028, 199.408)	(24.033, 824.028, 199.408)	[101–103]
Probability of Any Pain | HZ	0.95	0.73	1.00	[15, 84]
Probability of Mild Pain | Any Pain HZ	0.12	0.06	0.43	[15, 84]
Probability of Moderate Pain | Moderate or Severe Pain HZ	0.44	0.20	0.56	[15, 84]
Risk of PHN** – (b_1, b_2)	(1.772e-07, 2.013)	(8.86e-08, 2.013)	(3.544e-07, 2.013)	[42, 79, 104–108]
Probability of Moderate or Severe PHN				
Ages 50 – 59	0.46	0.36	0.56	[79], Assumption
Ages 60 – 69	0.56	0.46	0.66	[79], Assumption
Ages 70 – 79	0.61	0.51	0.71	[79], Assumption
Ages 80 – 85	0.65	0.55	0.75	[79], Assumption
Ages 85+	0.68	0.58	0.78	[79], Assumption

Variable	Base Value	Lower Value	Upper Value	Reference
Probability of Moderate PHN | Moderate or Severe PHN	0.50	0.30	0.80	Assumption
Duration of Mild PHN	6.7	6.1	7.4	[79]
Duration of Moderate PHN	10.0	9.4	10.7	[79]
Duration of Severe PHN	12.5	11.1	14.1	[79]
Probability of Ocular Complications				
Ages 50 – 59	0.03	0.01	0.05	[108], Assumption
Ages 60 – 69	0.04	0.02	0.06	[108], Assumption
Ages 70 – 79	0.05	0.03	0.07	[108], Assumption
Ages 80+	0.07	0.05	0.09	[108], Assumption
Duration of Ocular Complications	3.0	1.0	6.0	[14], Assumption
Probability of Neurological Complications	0	0.02	0.05	[108]
Duration of Neurological Complications	6.0	1.0	12.0	[14]
Probability of Cosmetic Complications	0	0.02	0.05	[108]
Duration of Cosmetic Complications	6.0	1.0	12.0	[14]
Vaccine Efficacy – Initial***	Age Dependent	-0.15	+0.10	[15, 22, 51]
Vaccine Efficacy – Waning****	Age Dependent	0.70	1.30	[15, 22, 51]

Table 2.2: Model inputs – epidemiology. *Logistic function used for HZ incidence: $\frac{asymp}{1+e^{\left(\frac{xmid-age}{scale}\right)}}$. **Power Function used for PHN risk: $b_1 \times age^{b_2}$. ***Absolute change made to initial vaccine efficacy. ****Relative change of made to vaccine waning.

Variable	Base Value	Lower Value	Upper Value	Reference
Costs				
HZ	957	867	1051	[14]
PHN	5831	4055	7936	[14]
Ocular Complications	4163	2986	5543	[14]
Neurological Complications	9872	5520	15253	[14]
Skin Complications	9873	3036	19883	[14]
Vaccine	173.97	150	250	[109–112]
Vaccine – Administration	31.38	30.03	32.73	[110–113]
Vaccine – Severe Adverse Reaction *	0.18	0.11	0.25	[114, 115]
Productivity Lost				
No Pain HZ	5	3	6	[63, 116]
Mild HZ	6	4	8	[63, 116, 117]
Moderate HZ	22	15	30	[63, 116, 117]
Severe HZ	61	39	82	[63, 116, 117]
Mild Pain PHN	4	3	5	[63]
Moderate Pain PHN	30	20	41	[63]
Severe Pain PHN	81	53	110	[63]

Table 2.3: Model inputs – economic. Cost values are presented in 2015 US Dollars ($). Hours of productivity lost are converted into 2015 US dollars ($) by multiplying by the mean hourly wage of $25.20 [118] – Additional detail provided in Appendix. * Detail on cost of severe adverse event cost calculation is available in the Appendix.

Variable	Base Value	Lower Value	Upper Value	Reference
No Pain HZ	0.150	0.100	0.200	Assumption
Mild HZ	0.200	0.133	0.267	[88]
Moderate HZ	0.300	0.200	0.400	[88]
Severe HZ	0.450	0.300	0.600	Assumption
Mild Pain PHN	0.310	0.211	0.433	[88]
Moderate Pain PHN	0.550	0.389	0.731	[88]
Severe Pain PHN	0.770	0.498	0.992	[88]
Ocular Complications	0.240	0.178	0.311	[88]
Cosmetic Complications	0.350	0.200	0.500	Assumption
Neurologic Complications	0.350	0.200	0.500	Assumption
Vaccine – Common Adverse Reaction	0.001	0.0005	0.002	[15, 22]
Vaccine – Severe Adverse Reaction	2.13e-05	6.41e-06	4.57e-05	[115, 119]

Table 2.4: Model inputs – disutilities. Disutilities subtracted from age-dependent baseline QOL [120] – Additional detail provided in Appendix.

Category	**Distribution**
Probability – HZ* – $asymp$	$ln\mathcal{N}(0, 0.099)$
Probability – Any Pain | HZ	$\beta(10.17, 0.82)$
Probability – Mild Pain | Any Pain HZ	$\beta(1.22, 8.95)$
Probability – Moderate Pain | Moderate or Severe Pain HZ	$\beta(13.212, 17.871)$
Probability – PHN* – b_1	$ln\mathcal{N}(0, 0.295)$
Probability – Moderate or Severe PHN**	$\mathcal{N}(0, 0.05)$
Probability – Moderate PHN | Moderate or Severe PHN	$ln\mathcal{N}(-0.693, 0.199)$
Duration – Mild PHN	$ln\mathcal{N}(1.902, 0.05)$
Duration – Moderate PHN	$ln\mathcal{N}(2.30, 0.05)$
Duration – Severe PHN	$ln\mathcal{N}(2.52, 0.07)$
Probability – Ocular Complications**	$\mathcal{N}(0, 0.01)$
Duration – Ocular Complications	$ln\mathcal{N}(1.098, 0.223)$
Vaccine – Initial Efficacy (η)**	$\mathcal{N}(0, 0.035)$
Vaccine – Waning Rate (ζ)*	$\mathcal{N}(1, 0.12)$
Cost – HZ	$\Gamma(414.598, 1/2.308)$
Cost – PHN	$\Gamma(34.691, 1/168.084)$
Cost – Ocular Complications	$\Gamma(40.767, 1/102.114)$
Cost – Vaccine	$\Gamma(23.33, 1/7.5)$
Cost – Vaccine Administration	$\Gamma(2196.6, 70)$
Cost – Vaccine Severe Reactions	$\Gamma(18, 100)$
Hours Productivity Lost – No Pain HZ* †	$\mathcal{N}(1, 0.13)$
Hours Productivity Lost – Mild HZ* †	6/5
Hours Productivity Lost – Moderate HZ* †	22/5
Hours Productivity Lost – Severe HZ* †	61/5
Hours Productivity Lost – Mild PHN* ‡	$\mathcal{N}(1, 0.13)$
Hours Productivity Lost – Moderate PHN* ‡	30/4
Hours Productivity Lost – Severe PHN* ‡	81/4
Disutility – No Pain HZ ††	$\beta(24.75, 140.25)$
Disutility – Mild HZ ††	20/15

Category	Distribution
Disutility – Moderate HZ ††	30/15
Disutility – Severe HZ ††	45/15
Disutility – Mild PHN ‡‡	32/77
Disutility – Moderate PHN ‡‡	55/77
Disutility – Severe PHN ‡‡	$\beta(8.85, 2.65)$
Disutility – Ocular Complications	$\beta(38, 120)$
Disutility – Common Vaccine Complications	$\beta(6, 6000)$
Disutility – Severe Vaccine Complications	$\beta(2.13, 100000)$

Table 2.5: Parameter distributions for probabilistic sensitivity analysis. * – A scaling factor for the parameter was sampled and multiplied by the base value for that parameter. ** – A parameter was sampled and added to base case parameter value. † – 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. ‡ – 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. †† – Disutility for HZ states are correlated with no pain HZ state, all other HZ health states are multiplied by factors listed in the table. ‡‡ – Disutility for PHN states are correlated with severe PHN state, all other PHN health states are multiplied by factors listed in the table.

Vaccine Parameterization

This section describes how the vaccine was parameterized in the model. The protection of the vaccine against HZ (efficacy) was comprised of two parts. First, the initial vaccine efficacy ($\beta_{0j_{HZ}}$). 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 [22]. 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. For this model, I assume that the components (initial efficacy and waning) are combined using the form of a linear

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 2.6: $\beta 0_{j_{HZ}}$ fitted values

equation ($y = mt + b$) 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%. That is, I assume that the vaccine will not ever increase the incidence of HZ. Data on the initial vaccine efficacy and waning came from from clinical trial and observational data [20–22, 51, 78] and were combined using statistical methods similar to those used in other studies [19, 60]. For all analyses, I assume that VE_{ij} changes through the combination of two restricted cubic spline (RCS) models. These models were selected using best fit statistics. The outcomes of the two RCS models are presented in Table 2.6 – 2.7. The general form of the vaccine efficacy equation is shown by Equation 2.1, 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). The base results of this equation are shown in Figure 2.2. More detail on how data were fit and combined is available in Appendix A.4 on page 185.

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

Table 2.7: VE_i fitted values

$$\begin{aligned} VE_{ij_{HZ}} = & \max(0, \beta_{0j_{HZ}} + \eta) \\ & + \beta_1 \zeta i \\ & + \beta_2 \zeta \max(i, 0)^3 \\ & + \beta_3 \zeta \max(i-1, 0)^3 \\ & + \beta_4 \zeta \max(i-2, 0)^3 \\ & + \beta_5 \zeta \max(i-7, 0)^3 \end{aligned} \tag{2.1}$$

There is some data that suggests that the vaccine provides additional protection against PHN beyond the reduction in HZ incidence [22]. 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 [22] I constructed seven possible models for this initial protection benefit against PHN ($\beta_{0j_{PHN}}$) from $t = [0, 1)$. I selected the model presented in Table 2.8 to represent the base case. This selection 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, I made the assumption that 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. I also make the assumption that the additional protection wanes at the same rate as the vaccines protection against PHN; this was accomplished using Equation 2.2. I 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

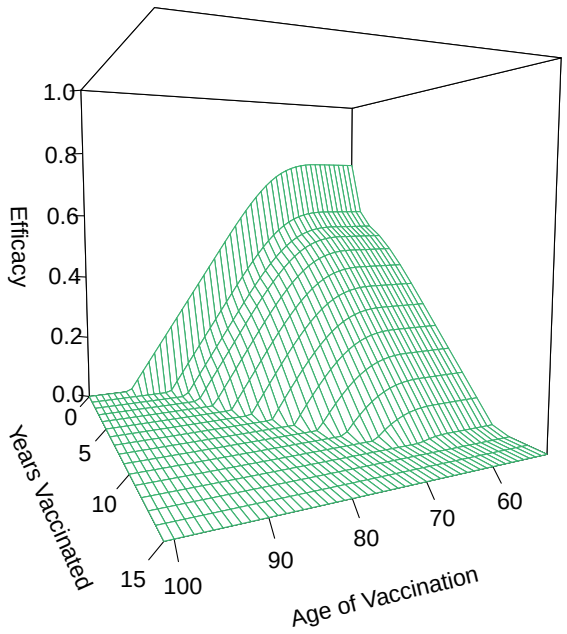

Figure 2.2: Age-specific vaccine waning model against HZ

without the vaccine. The base case additional protection benefit assuming the initial additional protection as shown in Table 2.8 and the waning rate as defined by Equation 2.2 is shown in Figure 2.3.

$$VE_{ij_{PHN}} = \begin{cases} \beta_{0j_{PHN}} \times \frac{VE_{ij_{HZ}}}{\beta_{0j_{HZ}}} & \text{if } \beta_{0j_{HZ}} > 0 \\ 0 & \text{if } \beta_{0j_{HZ}} = 0 \end{cases} \tag{2.2}$$

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									

Table 2.8: $\beta 0_{j_{PHN}}$ fitted values

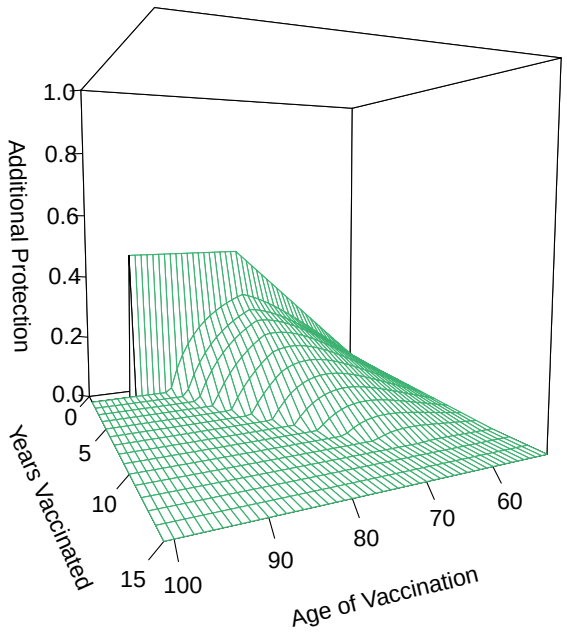

Figure 2.3: Age-specific vaccine waning model of additional protection against PHN

Analysis Plan

Model results were generated using TreeAge software. Results were then exported and imported into R (v.3.2.3) – an open-source data analytic software. Data were cleaned, analyzed, and figures were generated. TreeAge is capable of data analysis and visualization however, there are more options for data analysis and visualization using R and its many packages.

For the analysis, I compared the results of the two mutually exclusive options for this model: vaccination and no vaccination. The costs and effectiveness (measured in QALYs) from each component model were calculated and entered into Equation 2.3 to create incremental cost-effectiveness ratios (ICERs). The ICER provides information on the additional cost per unit of benefit between an option and the next less expensive alternative.

$$ICER = \frac{\Delta\, Costs}{\Delta\, Effectiveness} \tag{2.3}$$

To determine if an intervention is cost-effective, it must be compared to a cost-effectiveness threshold. This threshold represents the maximum willingness to pay (WTP) for a single unit of benefit (one QALY). The base case analysis assumes a WTP of \$100,000 / QALY. However, because there is no standard WTP/QALY in the US [75] I also evaluated model outcomes using against additional WTP values.

The base case analysis examined the cost-effectiveness of the HZ vaccine under the assumption that there is zero probability of neurological and cosmetic complications (i.e., only PHN and ocular complications were allowed to follow an episode of HZ). Cohort model were independently simulated for each age and gender from 50 – 100 using a lifetime time horizon, to determine the cost-effectiveness of the vaccine at that age. For each model, I assumed no prior history or risk of HZ. The probability of death was set to 100% at age 100. Age-dependent probabilities in the model were altered to reflect the age of the cohort being simulated.

I added additional payoff variables to the model to determine intermediate (epidemiological) outcomes. Intermediate outcomes for the model included: number of HZ cases prevented with vaccination; the number of PHN cases prevented with vaccination; and the number of ocular complications prevented with vaccination. For all

intermediate outcomes, a cohort model was simulated to give the lifetime probability of developing HZ, PHN or ocular complications with and without vaccination. I multiplied these final probabilities by 10,000 (i.e., assuming a cohort size of 10,000 men or women) to determine the number of cases of HZ, PHN or ocular complications for a cohort of 10,000 men or women. The difference in the number of cases between the vaccination and no vaccination arms of the model were the number of cases prevented given vaccination.

Sensitivity Analysis

Several sensitivity analyses, a method that examines how responsive outcomes are to changes in parameter inputs and model assumptions, were completed. First, I conducted a one-way sensitivity analysis by varying each of the model parameters independently at the ends of their ranges (shown in Tables 2.2 – 2.4) to examine the effect on outcomes and create a tornado diagram. This identified the model parameters that the cost-effectiveness results were most sensitive to. For any parameters that the model was very sensitive to I conducted additional two-way analyses to determine how interactions between these parameters would change the cost-effectiveness results.

I also performed first order Monte Carlo probabilistic sensitivity analysis with the model to estimate the ICERs given the uncertainty of multiple model parameters simultaneously. To accomplish this, I converted model inputs from discrete values to distributions. For cost inputs, I utilized a gamma (Γ) distribution. For hours of productivity lost, I correlated hours within each overall health state (i.e., HZ or PHN) with one another. No pain HZ and mild PHN were used to correlate all other pain states for HZ and PHN, respectively. This was done so that the possibility of a more severe case of HZ, for example, would not produce fewer hours of productivity loss than a less severe case (additional detail is provided in Table 2.5). For disutilities, I assumed a beta (β) distribution. For disutilities, I also correlated within each overall health state to avoid the situation where a more severe form of disease would have a smaller disutility than a less severe form. For HZ disutilities, all pain states were correlated with mild HZ. For PHN disutilities, all pain states were correlated

with severe PHN; this was done to avoid having a disutility value greater than 1.0. For probabilities that were adjusted by additive means a normal distribution, (mean = 0), was used (e.g., η for initial vaccine efficacy). For probabilities that were adjusted by multiplicative means, a log normal distribution, (mean = 1), was used (e.g., ζ for vaccine waning). The results from the PSA were used to generate cost-effectiveness acceptability curves (CEACs) to determine the probability that the vaccine was cost-effective at different WTPs. All sensitivity analyses were conducted using recommended procedures and guidelines [94].

Scenario Analysis

I also conducted several scenario analyses. I first examined the cost-effectiveness given a non-zero probability of neurologic and cosmetic complications in the base case model. Then I tested the cost-effectiveness of the HZ vaccine using a third order polynomial function to predict $VE_{ij_{HZ}}$; see section A.4 for further detail on this combination. The third-order polynomial model was the second best model behind the RCS model based on best fit statistics. Finally, I tested the remaining six models for the additional protection against PHN. I assumed that all of these models waned at the same rate as the vaccines protection against HZ. I then performed an additional analysis where I held the waning of the vaccines protection against HZ constant and altered the waning of the protection against PHN independently. This was done to gain further insight into the possible effects of protection against PHN.

Model Validation

I performed several validation checks on the model. First, I set all baseline QOL to 1.0, removed the disutilities associated with the health states, and removed the discount rate. I then performed simulations with different age groups and compared the results of the model to the CDC life tables [98]. This procedure provided a check that the cohorts in the model were dying at the expected rate as the removal of QOL and discounting provides an estimation of remaining life-expectancy. Next, I removed the costs and disutilities associated with the vaccine from the base case

Age	Life Expectancy – Model	Life Expectancy – CDC [98]
50	32.75	33.3
60	24.03	24.5
70	16.11	16.4
80	9.41	9.6
90	4.5	4.7
100	0.08*	2.3

Table 2.9: Model validation – life expectancy check – Women. *People at age 100 in the model only live 1 month

model. Under these circumstances the vaccine was predicted to dominate the choice of no vaccination for every age from 50 – 93 and be indifferent between 94 – 100 (the vaccine is assumed to have no benefit after age 93, see Figure 2.2). Finally, to ensure that the vaccine equations were entered into the model correctly, I selected different ages and numbers of years vaccinated and performed the calculations on what the probability of an event should be by hand. I then changed the TreeAge model to reflect the scenarios I was testing and used the evaluator tool to ensure that the probabilities calculated by the model matched the probabilities I had calculated.

2.3 Results

Model Validation

The results from the model validation are presented in Tables 2.9 – 2.11. Table 2.9 shows the comparison of life expectancy in the model to the CDC life table [98]. There are small differences in the life expectancy between the CDC life tables and the results produced by the model. The biggest difference is at age 100, where the CDC life tables predict a life expectancy of 2.3 years and the model estimates life expectancy of 0.08 years (1 month). The main difference between these two estimates is that in the model the probability of death was set to 100% at age 100. Table 2.10 shows the comparison between $VE_{ij_{HZ}}$ as calculated by hand (using data from Tables 2.6 – 2.7 and Equation 2.1) compared to the values calculated by TreeAge.

Scenario	$VE_{ij_{HZ}}$ – Calculated	$VE_{ij_{HZ}}$ – From TreeAge
j: 50, i: 0	0.7814	0.7814
j: 55, i: 10	0.1322	0.1322
j: 60, i: 4	0.4762	0.4762
j: 65, i: 7	0.2769	0.2769
j: 70, i: 2	0.4304	0.4304
j: 75, i: 8	0.0000	0.0000
j: 80, i: 3	0.1245	0.1245
j: 85, i: 5	0.0000	0.0000
j: 90, i: 0	0.0950	0.0950

Table 2.10: Model validation – vaccine efficacy check

All hand calculated values match the values produced by TreeAge indicating that the vaccine efficacy was implemented into the model correctly. Finally, Table 2.11 shows data from an analysis where the costs and disutilities associated with the vaccine were removed. As predicted, the option to vaccinate dominated the do not vaccinate option for every age between 50 – 93 (where the vaccine had some benefit) and the model was indifferent between the options from ages 94 – 100 as the vaccine confers no benefit but also presents no risk or cost to the recipient.

Age	Option	Cost	Effect	Inc Cost	Inc Eff	Inc Analysis
50	Vaccine	349.19	15.94	0	0	
50	No Vaccine	391.41	15.94	42.22	-1.20E-2	(Dominates)
55	Vaccine	352.26	14.35	0	0	
55	No Vaccine	406.09	14.34	53.82	-1.54E-2	(Dominates)
60	Vaccine	344.29	12.66	0	0	
60	No Vaccine	411.39	12.66	67.09	-1.95E-2	(Dominates)
65	Vaccine	330.04	10.92	0	0	
65	No Vaccine	405.54	10.92	75.49	-2.28E-2	(Dominates)
70	Vaccine	315.94	9.15	0	0	
70	No Vaccine	386.36	9.15	70.42	-2.29E-2	(Dominates)
75	Vaccine	299.77	7.40	0	0	

Age	Option	Cost	Effect	Inc Cost	Inc Eff	Inc Analysis
75	No Vaccine	352.92	7.40	53.14	-1.92E-2	(Dominates)
80	Vaccine	275.77	5.72	0	0	
80	No Vaccine	306.28	5.72	30.50	-1.25E-2	(Dominates)
85	Vaccine	239.37	4.17	0	0	
85	No Vaccine	249.56	4.17	10.18	-4.88E-3	(Dominates)
90	Vaccine	187.85	2.88	0	0	
90	No Vaccine	190.23	2.87	2.37	-1.34E-3	(Dominates)
93	Vaccine	154.85	2.22	0	0	
93	No Vaccine	154.88	2.22	3.12E-2	-1.18E-5	(Dominates)
94	Vaccine	142.48	2.00	0	0	
94	No Vaccine	142.48	2.00	0	0	(Indifferent)
99	Vaccine	43.02	0.61	0	0	
99	No Vaccine	43.02	0.61	0	0	(Indifferent)
100	Vaccine	0	5.65E-2	0	0	
100	No Vaccine	0	5.65E-2	0	0	(Indifferent)

Table 2.11: CEA model validation – model check. Costs in 2015 US dollars ($). Effect in QALYs. Inc: Incremental. ICER: Incremental cost-effectiveness ratio. Dominates: Denotes if vaccination strategy dominates no vaccination strategy.

Base Case Analysis

This section highlights the cost-effectiveness results of the base case analysis. The base case model produces a mean incremental cost-effectiveness ratio (ICER) of $137,843 when adjusted for the population and gender balance of the US for age 50-85 [8]. Ages over 85 were removed from this mean to not skew the ICER. The ICER for the current US policy (i.e., 60 and older) is $135,036, adjusting for the population and gender composition of the US for people 60 and older. Figure 2.4 shows the results of the base case analysis. For men and women, vaccination at age 67 produces the lowest ICER with values of $96,278 and $69,961, respectively. For

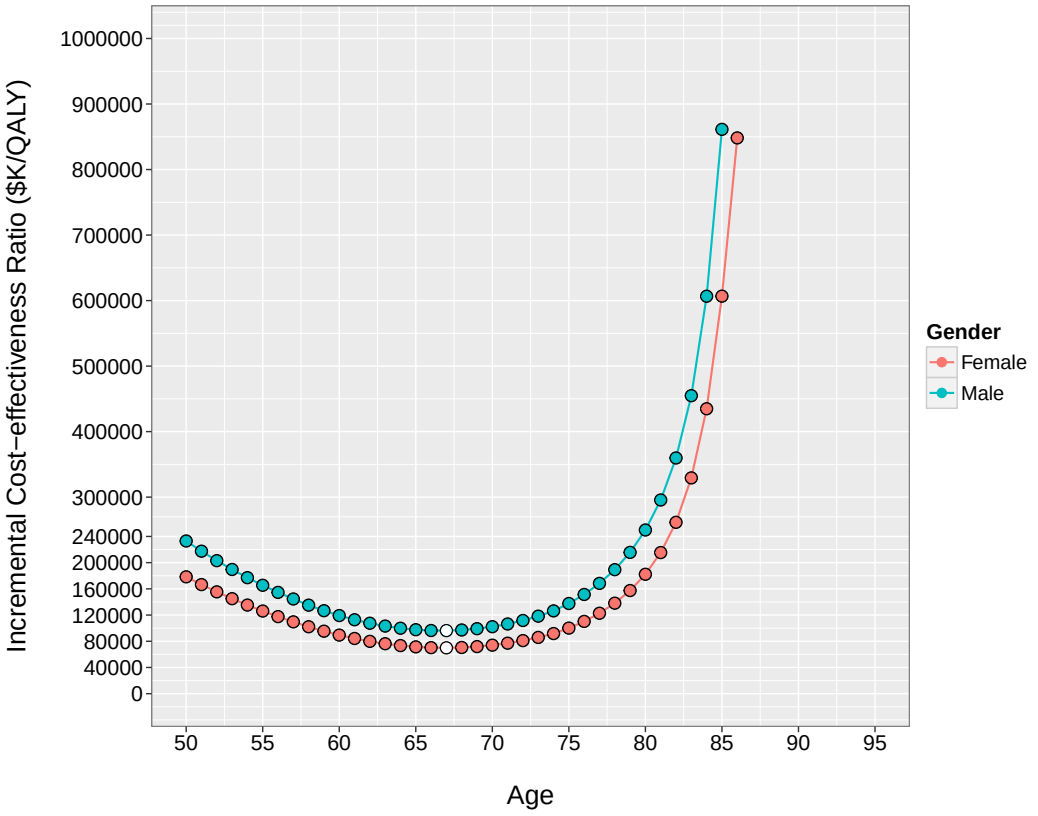

Figure 2.4: ICER by age for men and women. Dots indicate the ICER at age of vaccination. White dot indicates the age with lowest ICER.

women, the vaccine produces an ICER less than $100,000/QALY for ages 59 – 74. For men, the vaccine produces an ICER less than $100,000/QALY for ages 64 – 69. After age 80 for women and men there is a rapid increase in the ICER. The the y-axis on Figure 2.4 only shows values up to $1,000,000. After ages 86 and 85 for women and men, respectively, the ICER reaches values of greater than $1,000,000/QALY, until age 91 when it becomes dominated. The vaccine is more cost-effective for females at every age.

Table 2.12 provides data on intermediate outcomes for the base case analysis for women. The table for men is available in the end of chapter appendix on page 67. Vaccination of 10,000 women at age 50 prevents 180 cases of HZ, 11 cases of PHN, and 5 ocular complications. Using US census projections for the population,

vaccination of every 50 year old would prevent 40,758 cases of HZ in women, 35,475, in men, 76,233 total. Vaccination at ages 64 or 65 prevents the most cases of HZ per 10,000 people (288). Vaccination at ages 69 – 72 prevents the most cases of PHN (49). Using the US population estimates, vaccination of all women at age 67 produces the highest number of PHN cases prevented, 8,489 over their lifetime. This is also the age with the lowest ICER for women. The results of the intermediate outcomes were validated against studies that reported data similarly. Because I parameterized the vaccine in a different way compared to all other cost-effectiveness analyses, I was only able to use data from no vaccination strategies for validation. In total, four studies [59, 62, 67, 69] reported intermediate outcomes data that could be compared. Data generated by this study fell within the reported range from these four studies.

Age	**Δ HZ**	**Δ PHN**	**Δ OC**	**$ – VX**	**Q – VX**	**$ – no VX**	**Q – no VX**
50	180	11	5	554.73	15.949	391.42	15.948
51	189	12	6	556.11	15.636	394.95	15.635
52	197	14	6	557.14	15.320	398.22	15.319
53	206	16	7	557.79	15.001	401.18	15.000
54	215	18	7	558.01	14.678	403.82	14.677
55	224	20	8	557.79	14.351	406.09	14.350
56	233	22	8	557.10	14.020	407.98	14.018
57	242	24	9	555.92	13.685	409.46	13.683
58	252	27	9	554.25	13.346	410.53	13.345
59	261	29	10	552.18	13.005	411.17	13.003
60	269	32	10	549.83	12.662	411.39	12.660
61	276	34	11	547.24	12.317	411.18	12.315
62	282	37	11	544.47	11.971	410.52	11.969
63	286	39	12	541.57	11.623	409.38	11.621
64	288	42	12	538.58	11.274	407.73	11.272
65	288	44	12	535.58	10.923	405.54	10.921
66	285	46	13	532.63	10.570	402.82	10.568
67	280	47	13	529.79	10.218	399.56	10.216

Age	Δ HZ	Δ PHN	Δ OC	$ – VX	Q – VX	$ – no VX	Q – no VX
68	272	48	12	527.03	9.865	395.76	9.863
69	262	49	12	524.28	9.512	391.37	9.510
70	249	49	12	521.47	9.158	386.37	9.157
71	235	49	11	518.55	8.805	380.76	8.803
72	219	49	11	515.49	8.452	374.60	8.450
73	203	48	10	512.25	8.101	367.90	8.099
74	186	47	9	508.78	7.753	360.68	7.751
75	168	45	9	505.31	7.407	352.93	7.405
76	150	42	8	501.44	7.063	344.61	7.061
77	133	40	7	497.11	6.721	335.74	6.720
78	116	37	6	492.30	6.383	326.35	6.382
79	99	33	5	487.02	6.050	316.52	6.049
80	84	30	5	481.30	5.723	306.28	5.722
81	69	26	4	475.10	5.401	295.62	5.400
82	55	23	3	468.35	5.084	284.52	5.084
83	43	19	2	461.08	4.774	273.06	4.773
84	32	15	2	453.33	4.472	261.40	4.472
85	23	12	1	444.91	4.180	249.56	4.179
86	16	9	1	435.39	3.896	237.58	3.896
87	12	7	1	425.12	3.625	225.63	3.625
88	9	6	1	414.63	3.365	213.75	3.365
89	6	5	0	404.04	3.117	201.95	3.117
90	4	3	0	393.39	2.880	190.23	2.880
91	2	2	0	382.66	2.653	178.55	2.653
92	1	1	0	371.76	2.434	166.82	2.434
93	0	0	0	360.38	2.221	154.89	2.221

Table 2.12: Intermediate model outcomes – Women. Δ: The number of cases prevented due to vaccination. OC: Ocular complications. $: Costs, in 2015 US dollars. Q: QALYs. VX: Vaccine option. no VX: No vaccine option.

Sensitivity Analysis

One-way Sensitivity Analysis

A tornado diagram for all model input is shown in Figure 2.5. This indicates the model is most sensitive to the initial efficacy of the vaccine, the waning of the vaccine, the cost of the vaccine, the probability of PHN, the probability of HZ, and the probability of any pain given HZ. Figures 2.6 and 2.7 show the results of the one-way sensitivity analysis of the probability of HZ and PHN for men, respectively. These analyses show that the probability of HZ does not impact the age that produces the lowest ICER. That is, for all probabilities of HZ, age 67 has the lowest ICER. The curves in Figure 2.6 suggest that changing the probability of HZ has the most effect on younger ages. This can be seen on the left where there is more space between the curves than at any other point. Unlike the impact of HZ, changing the probability of PHN does impact the age with the lowest ICER. At the bounds of the lowest probability, the age that produces the lowest ICER for vaccination is 66. At the highest probability of PHN, the age the produces the lowest ICER is 68. Changing the probability of PHN affects both earlier and later ages. With a

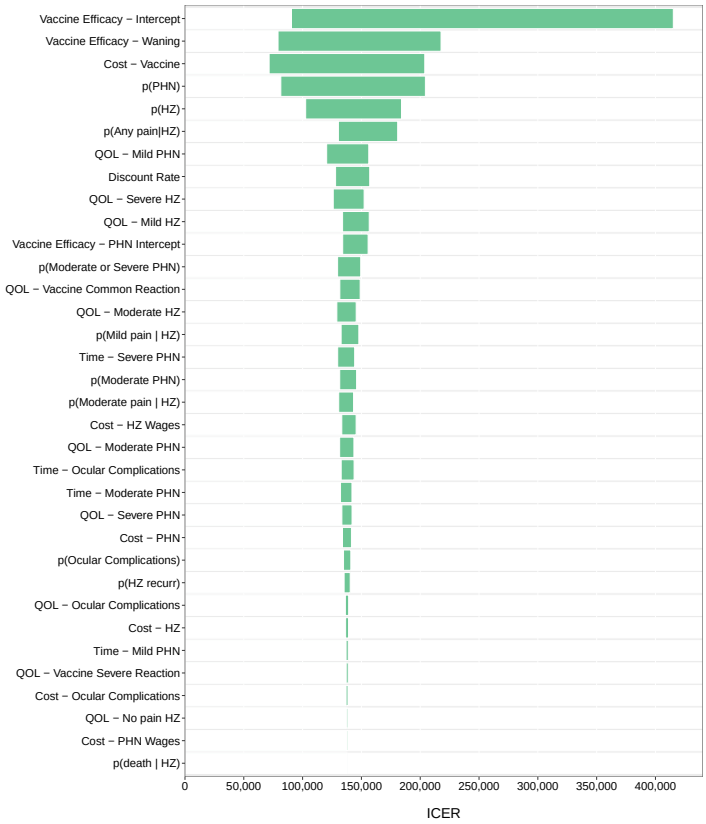

Figure 2.5: Tornado diagram for base case analysis. Ages 50 – 85.

higher probability of PHN the curve is much flatter and produces ICERs less than \$100,000/QALY from ages 56 – 77. With a low probability of PHN, there are no ICERs less than \$100,000/QALY.

Two-way Sensitivity Analysis

Figures 2.8 – 2.10 provide the two-way sensitivity analyses on the three parameters that have the biggest impact on the cost-effectiveness: initial vaccine efficacy, vaccine waning, vaccination cost (including administration fees). All two-way sensitivity analyses in this section are for women age 67. This group was selected because it was the most cost-effective age and gender combination. Further figures for multiple ages are presented in the appendix for this chapter beginning on page 66. Figure 2.8 shows that the base case ICER is less than \$75,000 and under most circumstances the ICER will be less than \$100,000 for age 67. If the waning 'speed' is increased by 20% (i.e., $\zeta = 1.2$) the ICER will be greater than \$100,000 if the initial efficacy remains constant. If the initial efficacy is increased by 10% (i.e., $\eta = 0.10$) and there is no change in the waning, the ICER will be $\leq$ \$50,000.

The interaction between vaccination cost and initial vaccine efficacy is shown in Figure 2.9. Assuming a 10% increase in the initial efficacy of the vaccine the ICER

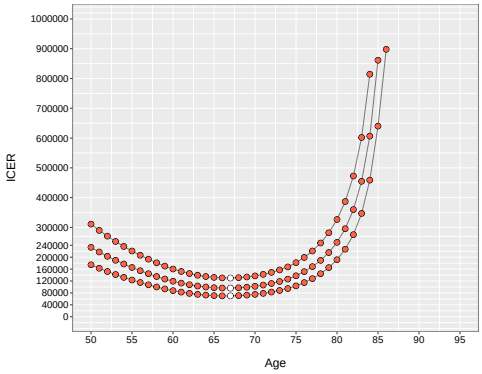

Figure 2.6: Sensitivity analysis of p(HZ) by age – Men. Top line: $asymp = 11.148$. Middle line: $asymp = 13.935$. Bottom line: $asymp = 17.418$

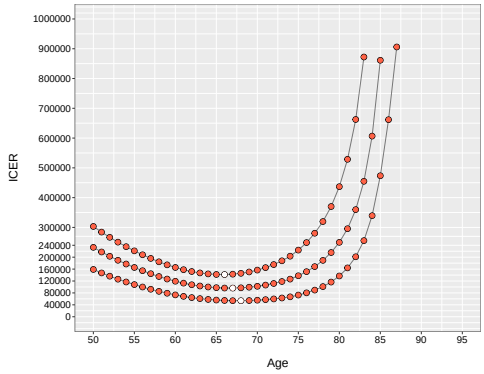

Figure 2.7: Sensitivity analysis of p(PHN) by age – Men. Top line: $b_1 = 8.86e-08$. Middle line: $b_1 = 1.772e-07$. Bottom line: $b_1 = 3.544e-07$

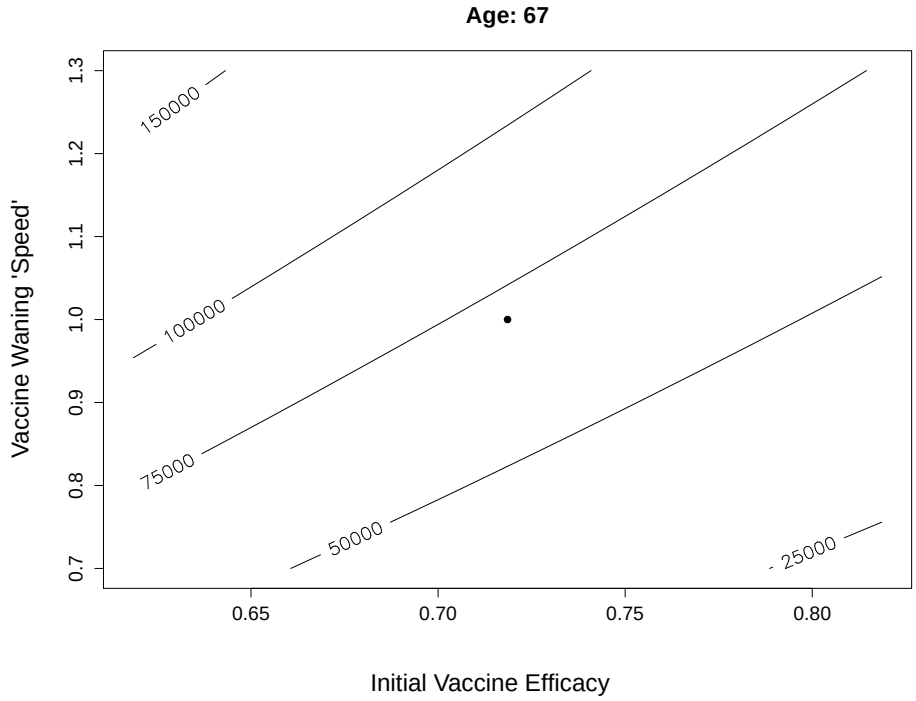

Figure 2.8: Sensitivity analysis of vaccine efficacy vs. vaccine waning – women. Black dot = base case. Contours represent ICER values of vaccination vs. no vaccination.

will be less than $50,000/QALY. Under most circumstances the vaccine produces an ICER less than $100,000. Figure 2.10 shows the interaction between vaccine waning and vaccine cost. A 20% reduction in the waning 'speed' (i.e., $\zeta = 0.80$) and no change in the cost of vaccination will produce an ICER less than $50,000. At the base case vaccination cost, $205 (including administration fees), the ICER would only be greater than $100,000 if the vaccine waned more than 30% faster than predicted. If vaccination costs more than $250, the ICER would also be greater than $100,000.

Figures 2.11 – 2.14 show two-way sensitivity results from some of the other key parameters. Figure 2.11 shows the analysis between the probability of HZ and the probability of PHN (given HZ). This analysis suggests that under most conditions the ICER for the vaccine is less than $100,000. Only if the incidence of HZ drops below 9.5/1000 people and the risk of PHN given HZ drops below 11% is the ICER

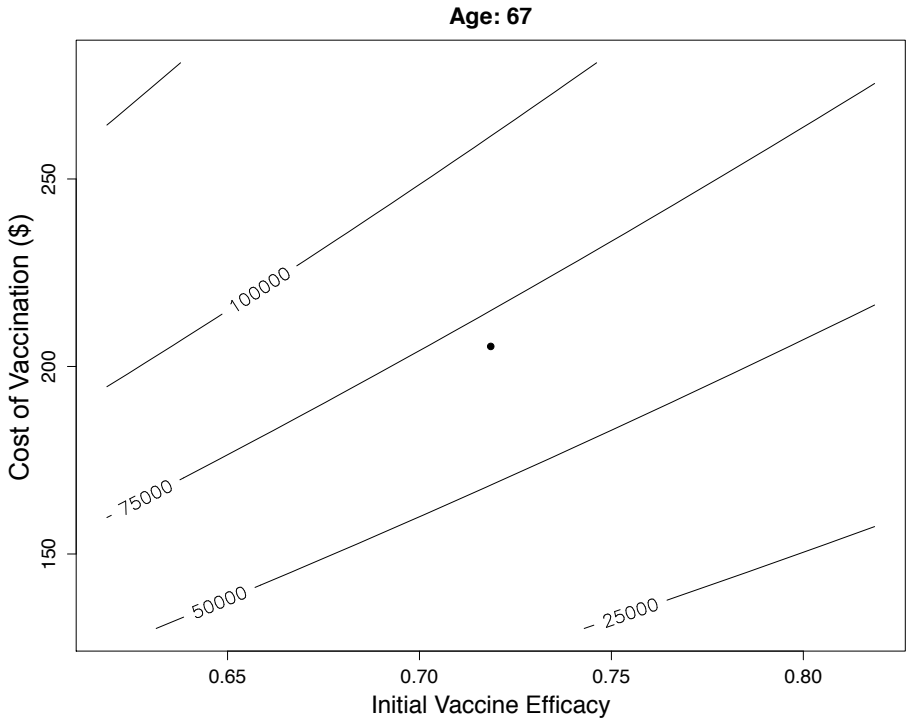

Figure 2.9: Sensitivity analysis of vaccine efficacy vs. vaccination cost – women. Black dot = base case. Contours represent ICER values of vaccination vs. no vaccination.

greater than $100,000. Figure 2.12 shows the interaction between the probability of HZ and the probability of pain (given HZ). In the base case analysis the probability of pain with HZ was 95%. In the majority of circumstances the ICER is below $100,000 unless the probability of pain falls below 70% and the incidence of HZ falls below 9/1000.

Figure 2.13 shows the results of the sensitivity analysis between the probability of HZ and cost of vaccination. If vaccination costs only $175, the ICER can be less that $50,000 if the annual incidence of HZ is greater than 11/1000. At this same probability of infection, vaccination can cost more than $250 and still produce an ICER less than $100,000. Figure 2.14 shows the results of the sensitivity analysis between the probability of PHN given HZ and the cost of vaccination. Under most conditions, the ICER is less than $100,000. If there is a low probability of PHN

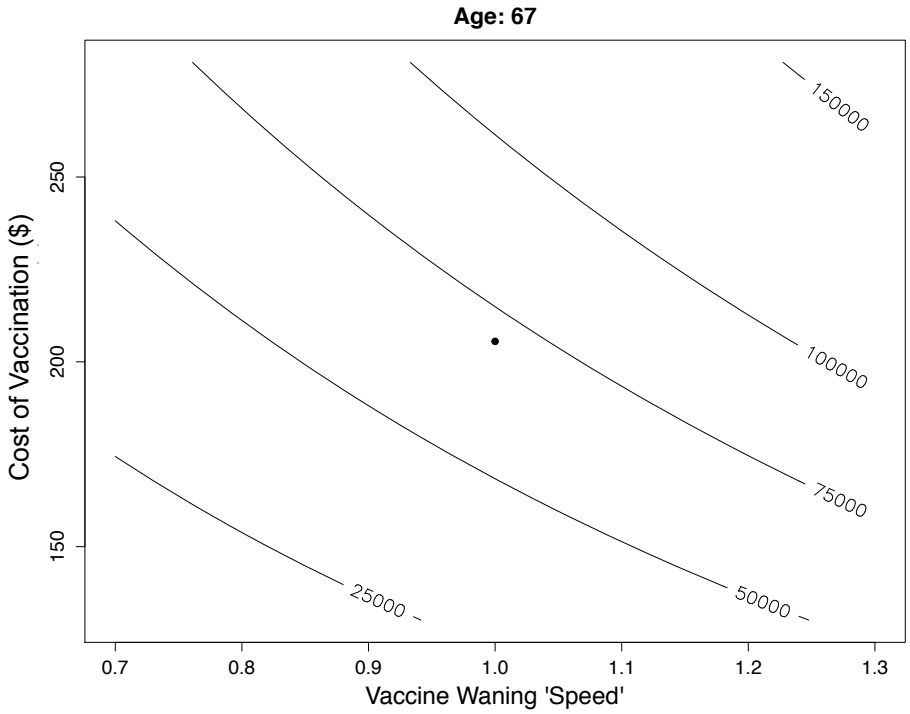

Figure 2.10: Sensitivity analysis of vaccine waning vs. vaccination cost – Women. Black dot = base case. Contours represent ICER values of vaccination vs. no vaccination.

and vaccination is more expensive by approximately $25.00 the ICER greater is than $100,000. With a high chance of PHN and a decrease in vaccination cost to approximately $150, the ICER for vaccination at age 67 can be lower than $25,000. Additional figures for all two-way sensitivity analyses are available in section 2.A.

Probabilistic Sensitivity Analysis

Figures 2.15 – 2.16 provide the results from the probabilistic sensitivity analysis for women and men, respectively. For women, there is at least a 40% probability that the vaccine is cost-effective at a WTP of $100,000 for ages 56 – 76. The vaccine has at least a 60% chance of being cost-effective at a WTP of $100,000 for ages 60 – 73. At the lowest permitted vaccination age (50), the vaccine has a $\geq$ 60% chance of being cost-effective if the WTP is approximately $200,000. Assuming a WTP of $200,000

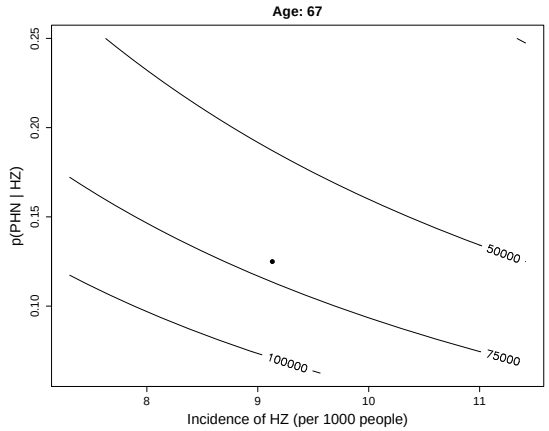

Figure 2.11: p(HZ) vs. p(PHN) – Women. Black dot = base case. Contours represent ICER values of vaccination vs. no vaccination.

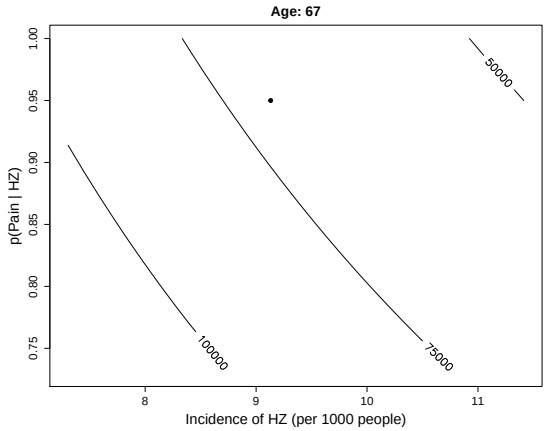

Figure 2.12: p(HZ) vs. p(HZ – any pain) – Women. Black dot = base case. Contours represent ICER values of vaccination vs. no vaccination.

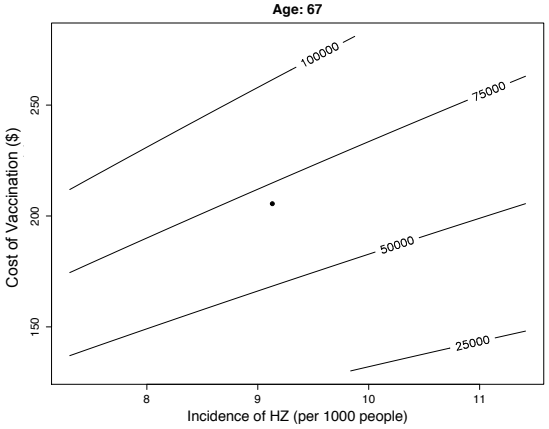

Figure 2.13: p(HZ) vs. vaccination cost – Women. Black dot = base case. Contours represent ICER values of vaccination vs. no vaccination.

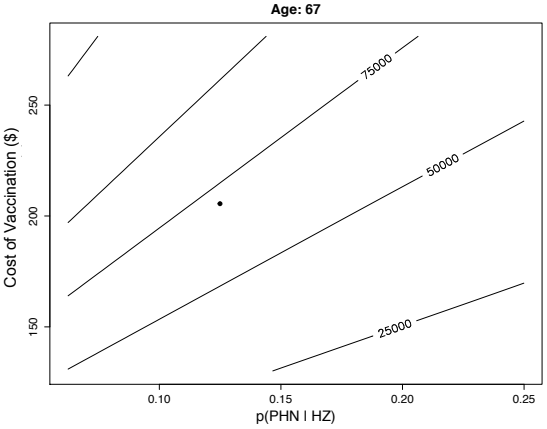

Figure 2.14: p(PHN) vs. vaccination cost – Women. Black dot = base case. Contours represent ICER values of vaccination vs. no vaccination.

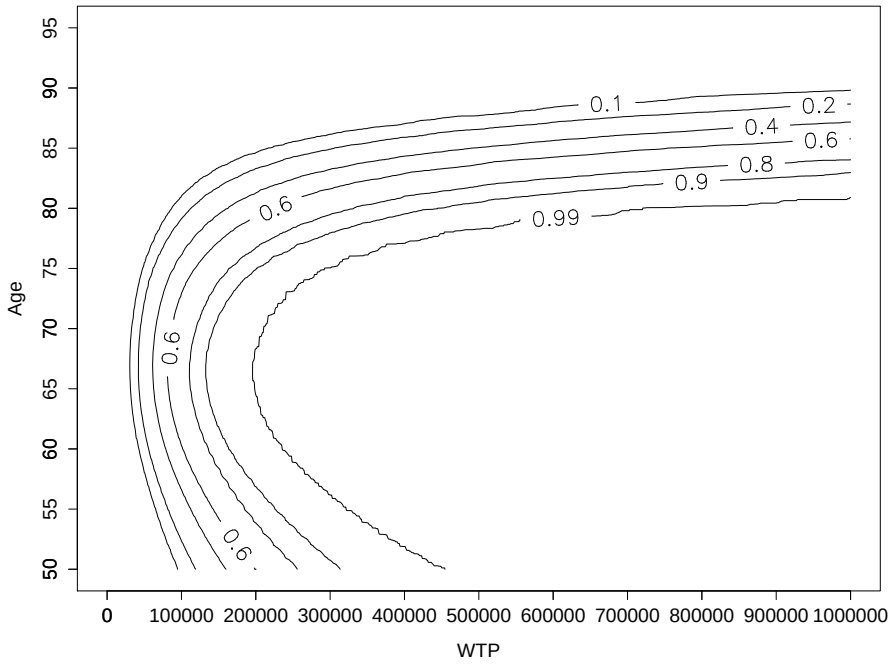

Figure 2.15: Cost-effectiveness acceptability contour – Women. Lines represent probability that vaccination is cost-effective compared to no vaccination.

the vaccine has at least a 90% probability of being cost-effective for ages 56 – 75. Under this WTP, it has a 99% chance of being cost-effective for ages 64 – 69.

For men, the vaccine does not have as high a probability of being cost-effective. For a WTP of $100,000, the vaccine has at least a 40% probability of being cost-effective for ages 60 – 73. Assuming a WTP of $200,000, the vaccine has at least a 20% probability of being cost-effective for age 50 – 81. For ages 57 – 74, this probability increases to 80% with a WTP of $200,000. The WTP needs to be greater than $200,000 for any age to have a 99% chance of being cost-effective. At a WTP of approximately $250,000, the vaccine has a 99% probability of being cost-effective for ages 60 – 71.

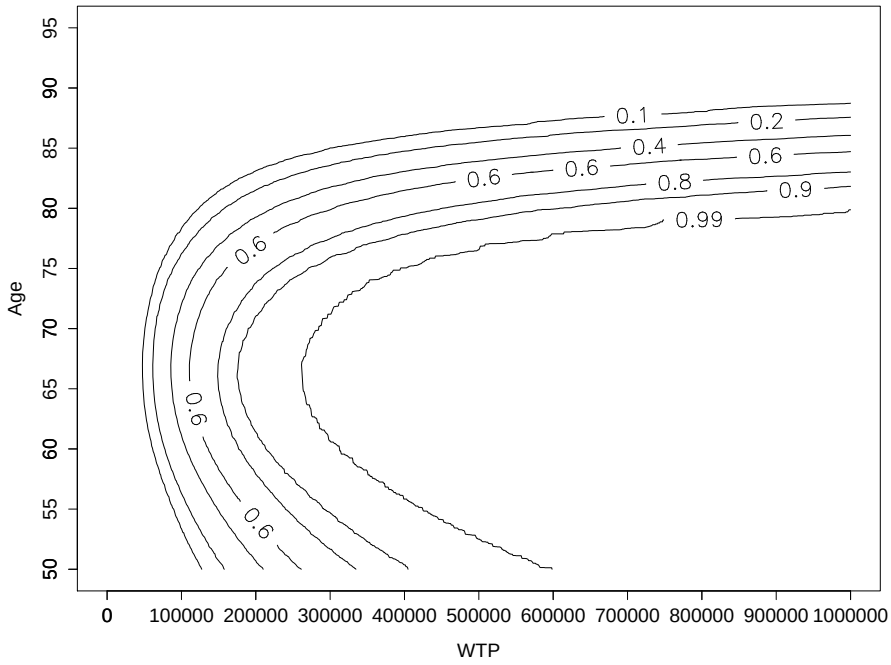

Figure 2.16: Cost-effectiveness acceptability contour contour – Men. Lines represent probability that vaccination is cost-effective compared to no vaccination.

Scenario Analysis

Additional PHN Protection

This section provides the results from the scenario analyses on additional PHN protection. Figures 2.18 and 2.19 show the results from the different options for initial additional protection against PHN; these options are further described on page 205. Figure 2.17 provides a reference guide for the figures in this section. Only figures for women are provided; figures for men are provided in the end of chapter appendix on page 75. Figure 2.18 shows that for every option of initial additional protection against PHN, with the exception of the no additional protection option, the results after age 81 are the same. If there is no additional protection against PHN, the vaccine is less cost-effective at every age with the ICER becoming much greater at

earlier ages. Figure 2.19 provides a zoomed in version of Figure 2.18 between the ages of 60 – 75. The largest difference in range between the ICERs, excluding the no additional protection option is approximately $20,000 at age 70. The minimum ICER for all curves occurs between 65 – 70. The results of this scenario analysis indicate that the choice of the initial additional protection benefit does impact the cost-effectiveness of the vaccine, however, it does not greatly change the age with the lowest ICER.

Figures 2.18 – 2.19 provide insight to the issue of the initial additional protection benefit against PHN. However, the results from these figures also assume that the additional protection benefit wanes at the same rate as the protection against HZ. Figure 2.20 shows the results of a two-way analysis where each of the seven initial additional protection options was tested with altering the waning speed of the additional protection benefit (while holding the waning speed of the HZ vaccine constant (i.e., $\zeta = 1$)). Results show that regardless of how slow or fast the additional protection wanes, the lowest ICERs still fall between 60 – 75 (using $100,000 or less as the reference). The speed of the additional protection does reduce the ICER for older ages. However, the largest differences are achieved for people older than 85 and even assuming a 40% reduction in the waning speed, the ICERs produced are still greater than $250,000.

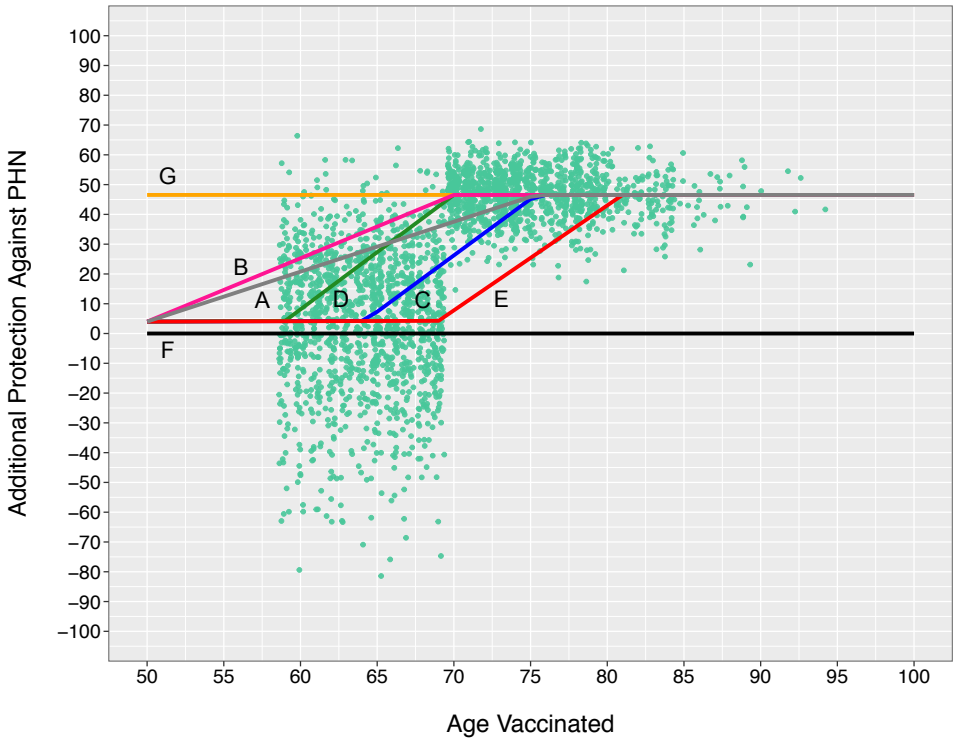

Figure 2.17: Initial additional protection against PHN – reference guide

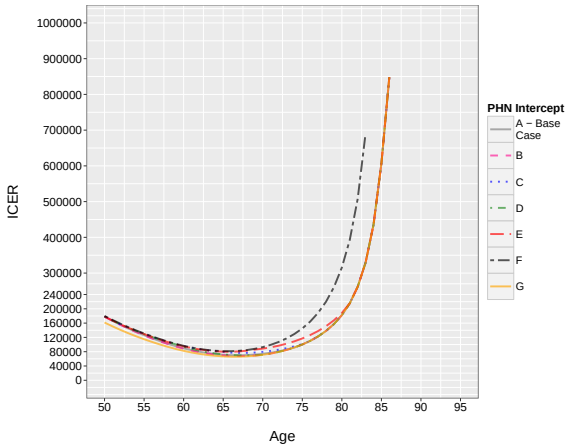

Figure 2.18: Scenario analysis – PHN intercept – Women

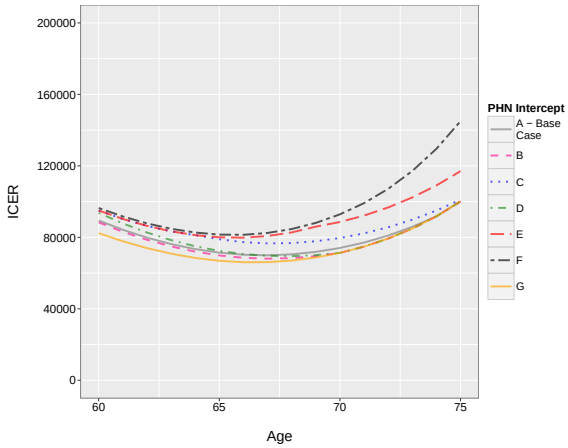

Figure 2.19: Scenario analysis – PHN intercept – Women – zoomed

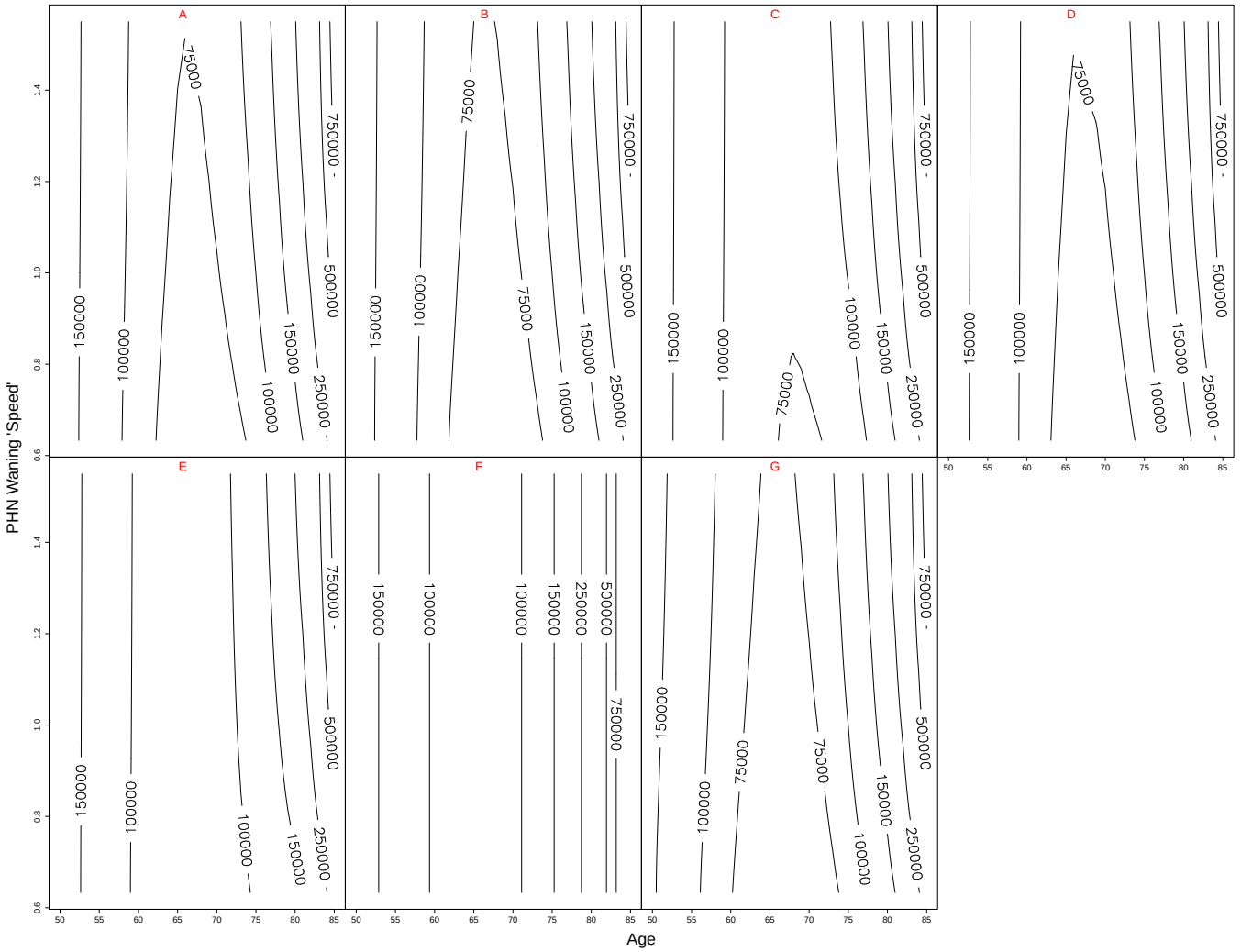

Figure 2.20: Scenario analysis – additional PHN protection efficacy vs waning – Women. Contours represent ICER values of vaccination vs. no vaccination

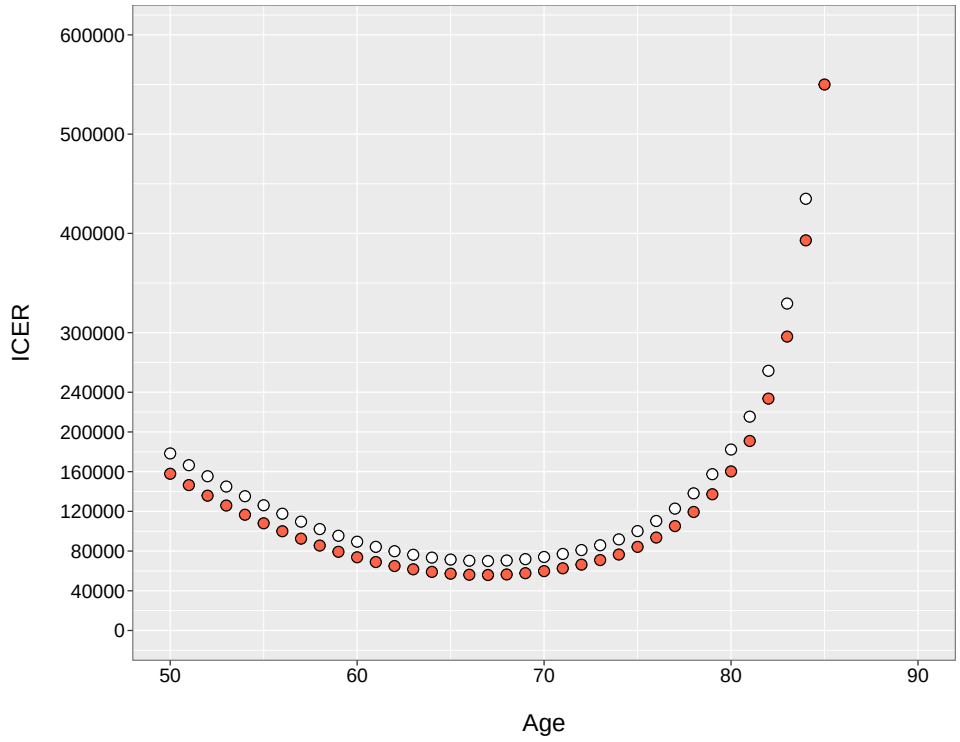

Figure 2.21: Scenario analysis – Other complications – Women. White dots = base case. Red dots = base case including complications.

Other Complications

Including other complications (neurological and cosmetic) into the model improved the cost-effectiveness of the vaccine. Figure 2.21 shows the results for women when other complications were included. Comparing these scenarios, the vaccine is always more cost-effective when the other complications are included. The ICER for women is approximately $20,000 less at age 50, $15,000 less at age 67, and $17,000 less at age 75. Additional figures on the sensitivity of these complications are included in the end of chapter appendix. Figures 2.37 – 2.42 on page 76 show that adjusting the probability of other complications had the biggest impact on the cost-effectiveness. Changing the disutilities associated with these complications has a larger impact of the cost-effectiveness than changing the cost of the complications.

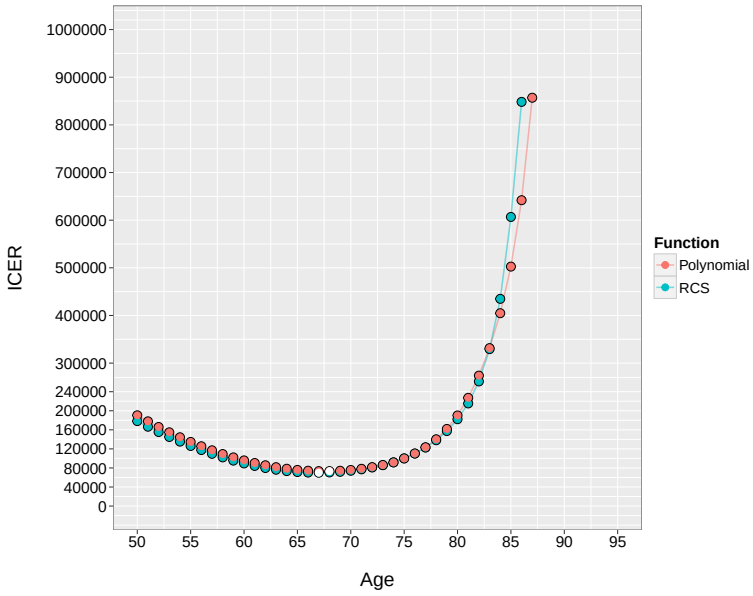

Figure 2.22: Scenario analysis – polynomial waning

Polynomial Vaccine Waning

Figures 2.22 – 2.23 contain the results of the scenario analysis where the polynomial waning function was tested. The base case restricted spline function is also plotted for comparison. Figure 2.22 shows that there is a minimal difference between the two functions at every age. The polynomial function produces the lowest ICER at age 68. Figure 2.23 shows the differences between the ICERs from ages 50 – 80. The zoomed-in figure shows that there is more of a difference between the two function choices on the left side of their respective minimums with the RCS function producing lower ICERs from 50 – 68. After age 68, the ICERs begin to converge and remain close from ages 69 – 80. These plots show that there is a minimal difference in the results depending on the choice of waning function.

No Productivity Loss

Figures 2.24 – 2.25 show the results of the scenario analysis were productivity loss was excluded from the analysis. This scenario represents the health care perspective.

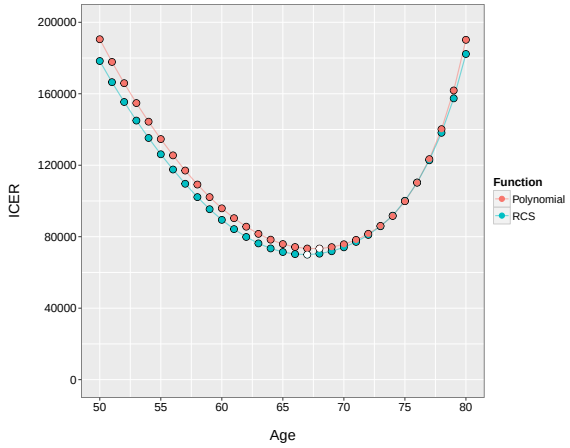

Figure 2.23: Scenario analysis – polynomial waning – zoomed

Without lost productivity being included as a cost the vaccine is less cost-effective at every age as evidenced by comparing the base case values (in red). Age 67 remains the most cost-effective age to vaccinate and the pattern for men and women remain the same with the vaccine being more cost-effective at every age.

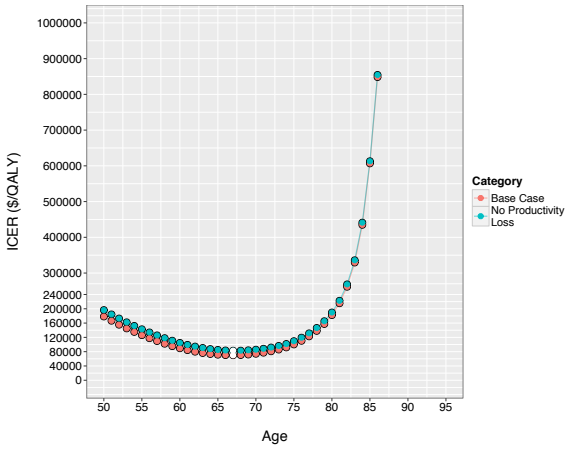

Figure 2.24: Scenario analysis – productivity loss – Women

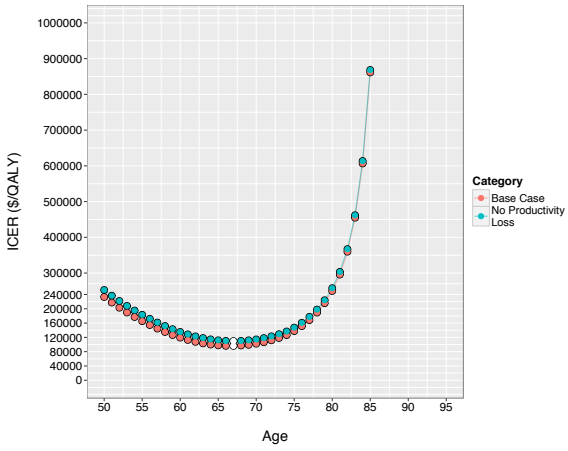

Figure 2.25: Scenario analysis – productivity loss – Men

Community Rated Disutilities

Figures 2.26 – 2.27 provide the results of the scenario analysis where community ratings were used for the disutility values. Table 2.13 shows differences in the values. Using community ratings, disutility values for HZ are much higher and the values for PHN are much lower. This results in the vaccine being more cost-effective at younger ages for both men and women. This result can be see by the difference between the two lines in Figure 2.26 and 2.27. With community ratings the most cost-effective age for vaccination drops to age 65 for both men and women (as indicated by the white dot). After age 70, the two lines in the graph cross which indicates that when using community rating the vaccine is less cost-effective at older ages than in the base case.

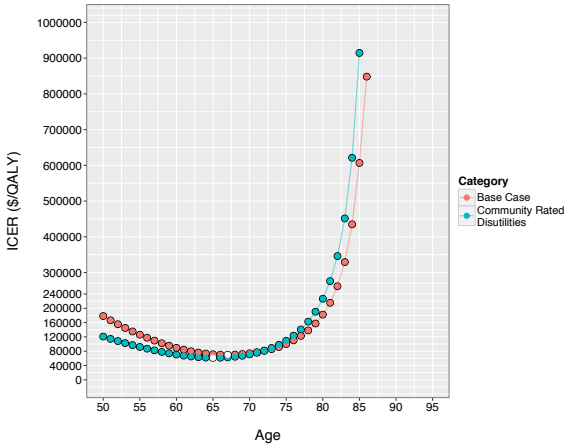

Figure 2.26: Scenario analysis – Community ratings – Women

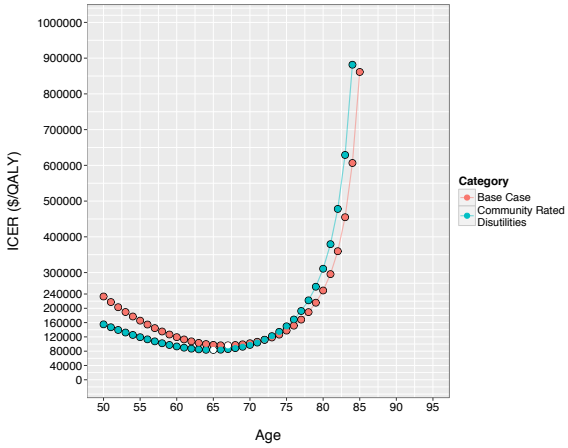

Figure 2.27: Scenario analysis – Community ratings – Men

Variable	Base Case	Community Rating	Reference
HZ – No Pain	0.15	0.30	[88]
HZ – No Pain	0.20	0.50	[88]
HZ – No Pain	0.30	0.70	[88]
HZ – No Pain	0.45	0.90	[88]
PHN – No Pain	0.31	0.18	[88]
PHN – No Pain	0.55	0.18	[88]
PHN – No Pain	0.77	0.22	[88]

Table 2.13: Community disutility ratings

2.4 Discussion

In this chapter, I examine the cost-effectiveness of the current herpes zoster vaccine for every age between 50 and 100 for women and men. The vaccine is always more cost-effective for women than men in the ages where the vaccine is not dominated. This is likely due to women being more susceptible to developing HZ and having a longer life expectancy. For both men and women, age 67 produces the lowest ICER. One-way and two-way sensitivity analysis show that the cost-effectiveness is most sensitive to the initial efficacy of the vaccine, the speed the vaccine wanes, and the cost of the vaccine. Probabilistic sensitivity analysis confirms that vaccinating between the ages of 65 – 70 has the highest chance to be cost-effective assuming a WTP of $100,000.

Vaccine

The vaccine data and its parameterization were two strengths of this research. This was the first US cost-effectiveness analysis to use the new long-term zoster vaccine trial data [20] for an age group over 50 [62]. It was the first study to use new observational data from a large managed-care cohort on the vaccine's waning pattern [78]. Using this data to parameterize the age-specific waning and initial efficacy of the vaccine was accomplished with the aid of zoster vaccine experts at the CDC. For example, their input ensured that the steep decline in efficacy over the first year of vaccination was featured; this decline has not been accounted for in other US studies. Feedback

from the CDC was crucial as it enabled the parameterization of the vaccine to be the best that it could be. However, there is still uncertainty about the vaccine parameters. This was shown in the two-way sensitivity analysis; the initial efficacy and the waning of the vaccine have a large potential impact on the on the results. Given this impact further research may be needed to better predict vaccines efficacy and waning. Techniques like value of information analysis will be important to determine the potential value of this added research.

One limitation of this paper is the effect of the vaccine on pain. There is some evidence that the vaccine reduces the burden of PHN [15] which I have accounted for through the additional protection benefit. But there is also some evidence that those who were vaccinated and develop HZ may develop a less severe case of HZ than unvaccinated individuals [15]. However, these data were not translatable into probabilities for the model. The sensitivity analysis shows that the HZ pain states do have some impact on the ICER. Being able to accurately account for difference in HZ pain states for vaccinated vs non-vaccinated individuals would likely to further reduce the ICERs.

The scenario analysis between the two different waning functions showed minimal differences in the ICERs at every age. The minimum ICER was found at age 67 using the base case restricted cubic spline model and 68 using the third order polynomial model. It is interesting to note that the age that produced the lowest ICER was only different by one year when there was a difference of approximately two years in the durability of the vaccine; this can be seen in Figures A.10 and A.11 on page 200.

PHN and Vaccination

From the beginning of this research, I assumed that the vaccine's additional protection against PHN would be a key driver of the results. However, this was not found. Rather it was the impact of the vaccine against HZ that had the most effect. Seven options for the vaccines initial additional protection and waning (independent of the vaccines waning against HZ) were tested in scenario analysis. The selection of the initial additional protection against PHN (shown in Figures 2.18 and 2.36) was

shown to make some difference to the ICER, however, the base case selection was near the middle of the extremes for the majority of the ages. Further, when the waning of this additional protection was tested independently of waning against HZ (shown in Figure 2.20) I show that the ages where the vaccine is most cost-effective remains between ages 60 – 75. Panel G in Figure 2.20 shows the benefit of assuming a 45% additional protection benefit for all ages; even adding this benefit to the earlier ages (e.g., 50 – 60) and slowing the waning 'speed' against PHN independent of the waning speed against HZ did not greatly change the age range where the vaccine was most cost-effective. Therefore, while being able to correctly determine the additional protection is important for being able to get an exact estimate of the cost effectiveness, the additional protection against PHN did not have as great of an impact on the results as just protection against HZ or the probability of PHN.

Impact of PHN

The impact of the probability of PHN on the ICER was shown in both the one-way and two-way sensitivity analyses. Of all of the non-vaccine epidemiological parameters, this had the greatest impact on the results. One of the strengths of this analysis was the characterization of the PHN states and the use of the ladder-like progression through PHN. This model structure was adapted from recent zoster vaccine models from Europe [63, 65, 68, 70], and provides a better way to characterize the disutility associated with PHN as a whole. The disutility of mild PHN had the largest impact of all PHN related disutilities, most likely because all people with PHN must pass through this state before reaching a disease free health state. It is interesting to note that it was the probability of PHN that had the biggest impact on the results, while all individual components of the PHN had only smaller impacts. Using a concept from "systems thinking" it could be that these model components work together to make their impact greater than the sum of their parts [121]. I see this laddering structure as an important piece to the model. However, for future model simplicity I think it would be reasonable to build a ladder-like PHN sub-model to generate a age-specific PHN disutility values that could then be used for a general PHN health

state.

While the ladder like structure was a strength in its ability to emulate the true disease progression it does have limitations. First, this structure does assume that all people must pass through all better states of PHN before reaching a disease free health state. This assumption was based on available data and while it was the best assumption that could be made given these data, it may not perfectly reflect the underlying disease process. That is, it may be possible for cases of severe or moderate PHN to resolve without the patient experiencing mild PHN. This is an area for future research. In addition, using this structure was a disadvantage from the cost perspective. The best available data were used for costs in this model, however, US specific cost data were not available by PHN state. Papers from Europe [70, 79] have shown that higher costs are associated with worse PHN states. However, due to complications with transferring costs from other countries and health systems where the financing structure may be very different, costs from these papers were not included in the model [97]. The cost of PHN in this model was varied widely in sensitivity analysis and was shown to have little impact on the ICER. Nonetheless, for a more accurate representation of the costs associated with PHN conditions, this is also an area for future research.

Comparisons with other US models

Four previous CEAs have been published for the HZ vaccine in the US [59–62]. Three of these CEAs were published in 2007 or earlier [59–61]; this was near the time when HZ vaccine data were first released as part of the shingles prevention study (SPS). Because the SPS only included people ages 60 and older, the earliest CEAs only includes groups ages 60 and older. When comparing against the other US studies, this research shares the most in common with the 2007 study by Pellissier et al [60]. For characterizing the disease, they also used differing levels of HZ pain using the ZBPI. However, they did not use differing levels of PHN. They also fit vaccine data from the SPS in a similar manner to this paper; using an initial age based efficacy and waning. However, their waning function did not account for the severe drop in

efficacy through the first year, rather it was a linear function. This research shares a common fit pattern of the age specific initial efficacy as both assume a concave shape for similar fitted values. Results from Pellissier et al suggest a minimal change in the ICER between ages 60 – 80. The ICERs produced by my models are the most consistent between ages 60 – 75.

Hornberger and Robertus [59] published a CEA that shows that the only time the vaccine can produce an ICER less than $100,000 is when the vaccine is less than $200, the recipient is less than 70 years old and the vaccine effectiveness lasts more than 30 years. Current information [20, 78] suggests that the vaccine is not likely to last 30 years. Based on my fits of the vaccine data with more current information, at a best case scenario (+0.10% initial efficacy and 30% slower waning at age 50) the vaccine would only last 20 years. The authors also admit to having limited data on vaccine efficacy beyond the initial 2005 clinical trial results [59]. The authors also assume that PHN does not result unless pain has been persistent for 182 days from the start of the rash phase. This definition of PHN may underestimate the proportion of people who actually experience PHN, and allow people to have higher utility for longer periods of time. Thus, Hornberger and Robertus [59] may underestimate the QALYs gained by vaccination which could negatively impact the cost-effectiveness results.

The model constructed by Rothberg et al [61] was sensitive to characteristics of the vaccine, PHN, and HZ. Unfortunately there was limited methodology for how the vaccine's efficacy and waning was calculated. The authors assume there is no decrease in PHN incidence beyond the decrease attributed to reducing HZ incidence with vaccination (i.e., they do not assume an additional protection benefit). Brisson et al [77] suggest that just accounting for the additional reduction of PHN can reduce the cost per QALY by as much as 40%. Rothberg et al also assume that an individual either spends less than 12 months with PHN, or several years with PHN. And, there is no accounting for PHN severity as only one PHN utility score is given. The paper by Le and Rothberg [62] provides the newest estimate for the cost-effectiveness in the US and is an update of the Rothberg et al CEA [61]. Le and Rothberg do make use of newer vaccine waning data. However, they assume that the vaccine wanes using a

strictly linear rate. Second, cost data on PHN is from their previous CEA model [61]. The CEA model by Rothberg et al [61] used cost data from a 1994 cost study from the UK. The cost of PHN is one of the most important parameters in many HZ CEA models. Using cost data that is more than 20 years old and from a country where the health care costs are known to be cheaper than in the US [122, 123] would likely lead to misleading results. Even if these costs had been recent, it is not common practice to transfer costs [97] across health systems due to structure and financing differences.

Other Limitations

One limitation of this paper was the exclusion of cosmetic and neurological complications from the base case analysis. These were included in scenario analysis and their inclusion did lower ICER for every age. However, the results from these scenario analyses are best to not be over-interpreted. There is still only a small body of evidence about these other complications (compared to evidence for complications like PHN). Additional data would be needed, specifically about the disutility and the time spent in this health state before each should be included in the base case analysis. As a result of the possible impact of these parameters, the base case analysis should be seen as a the upper bound for the cost-effectiveness of the HZ vaccine. Another limitation was truncating the model at age 100; this assumption may underestimate the benefit of the vaccine. Despite the probability of death due to HZ being very low, vaccinated individuals would be less likely to experience this event as they would be less likely to experience HZ. Therefore, there is likely to be a bias against the vaccination strategy due to the assumption of a truncated life expectancy as the difference is QALYs would likely be slightly greater than what is reported in this study.

Conclusions

This study was the first in the US to include the 50 – 59 age group alongside the 60+ age group. With the aid of collaborators at the CDC, the vaccine parameterization should be the most realistic representation of how the vaccine behaves. The complex

modeling structure shows the impact on health utility that can be attributed to PHN. Using a threshold of $100,000 this research shows that the vaccine would be cost-effective for women between the ages of 59 – 74 and 64 – 69 for men. There are some policy implications that can be examined from the results. The current recommendation from the ACIP is open-ended (i.e., 60 and above without a stopping age). Results of the CEA as shown by Figure 2.4 and the cost-effectiveness acceptability contours (Figures 2.15 – 2.16) show that the vaccine is not likely to be considered cost-effective using a threshold between $100,000 – $150,000 for people older than age 80. Further using this same threshold it is unlikely to be cost-effective for people younger than 60 (at the very earliest age 55). Therefore, the results of this research indicate that the open-ended recommendation may be recommending vaccination over too wide of a range, and that there may be benefit to reducing that age range.

These results give an indication of the most cost-effective range for vaccination for men and women, but do not address the question of the optimal policy. Each ICER assumes that the cohort does not assume a prior risk of HZ. Because this is a disease that most are at risk for, it will be important to examine the decision to vaccinate or defer when aiding future recommendations. Further, additional work may be needed to determine the true values of vaccines waning and efficacy as both had a substantial impact on the results. However, techniques like value of information should first be used. While this research does provide an update to the cost-effectiveness of the vaccine, further work should be done provide the best possible information to decision makers for developing future recommendations.

2.A Additional Figures and Tables

Age	Δ HZ	Δ PHN	Δ OC	$ – VX	Q – VX	$ – no VX	Q – no VX
50	162	11	5	466.69	15.597	297.60	15.596
51	169	12	5	467.10	15.272	299.84	15.272
52	176	14	6	467.22	14.945	301.85	14.944
53	183	15	6	467.03	14.617	303.63	14.616
54	190	17	6	466.54	14.286	305.15	14.285
55	198	18	7	465.71	13.954	306.41	13.953
56	206	20	7	464.56	13.620	307.39	13.619
57	213	22	8	463.06	13.286	308.09	13.285
58	221	24	8	461.19	12.950	308.48	12.949
59	228	26	9	459.02	12.613	308.53	12.611
60	235	28	9	456.61	12.272	308.19	12.270
61	240	31	10	453.98	11.928	307.45	11.927
62	245	33	10	451.19	11.581	306.29	11.580
63	247	35	10	448.28	11.232	304.68	11.230
64	248	36	11	445.32	10.880	302.64	10.878
65	247	38	11	442.38	10.527	300.17	10.525
66	243	39	11	439.52	10.173	297.28	10.172
67	238	40	11	436.81	9.821	293.99	9.820
68	230	41	11	434.19	9.469	290.28	9.468
69	220	41	10	431.62	9.118	286.13	9.116
70	209	41	10	429.04	8.766	281.52	8.765
71	196	41	9	426.39	8.415	276.45	8.414
72	183	40	9	423.64	8.064	270.93	8.063
73	168	39	8	420.76	7.715	265.02	7.714
74	153	38	8	417.71	7.370	258.73	7.368
75	138	36	7	414.75	7.028	252.11	7.027
76	123	34	6	411.53	6.691	245.16	6.690
77	108	32	6	408.00	6.357	237.84	6.356

Age	Δ HZ	Δ PHN	Δ OC	$ – VX	Q – VX	$ – no VX	Q – no VX
78	94	29	5	404.19	6.028	230.24	6.027
79	80	26	4	400.07	5.705	222.38	5.705
80	68	24	4	395.670	5.389	214.30	5.388
81	56	21	3	391.00	5.081	206.05	5.080
82	44	18	2	386.10	4.781	197.67	4.780
83	34	15	2	380.87	4.489	189.14	4.488
84	26	12	1	375.21	4.202	180.38	4.201
85	18	9	1	369.35	3.930	171.84	3.930
86	13	7	1	362.87	3.671	163.41	3.671
87	10	6	1	355.91	3.424	155.11	3.424
88	7	5	0	348.87	3.189	146.97	3.189
89	5	4	0	341.84	2.966	138.99	2.966
90	3	3	0	334.84	2.754	131.15	2.754
91	2	2	0	327.85	2.552	123.42	2.552
92	1	1	0	320.80	2.357	115.73	2.357
93	0	0	0	313.47	2.168	107.96	2.168

Table 2.14: Intermediate model outcomes – Men. Δ: Number of cases prevented due to vaccination.

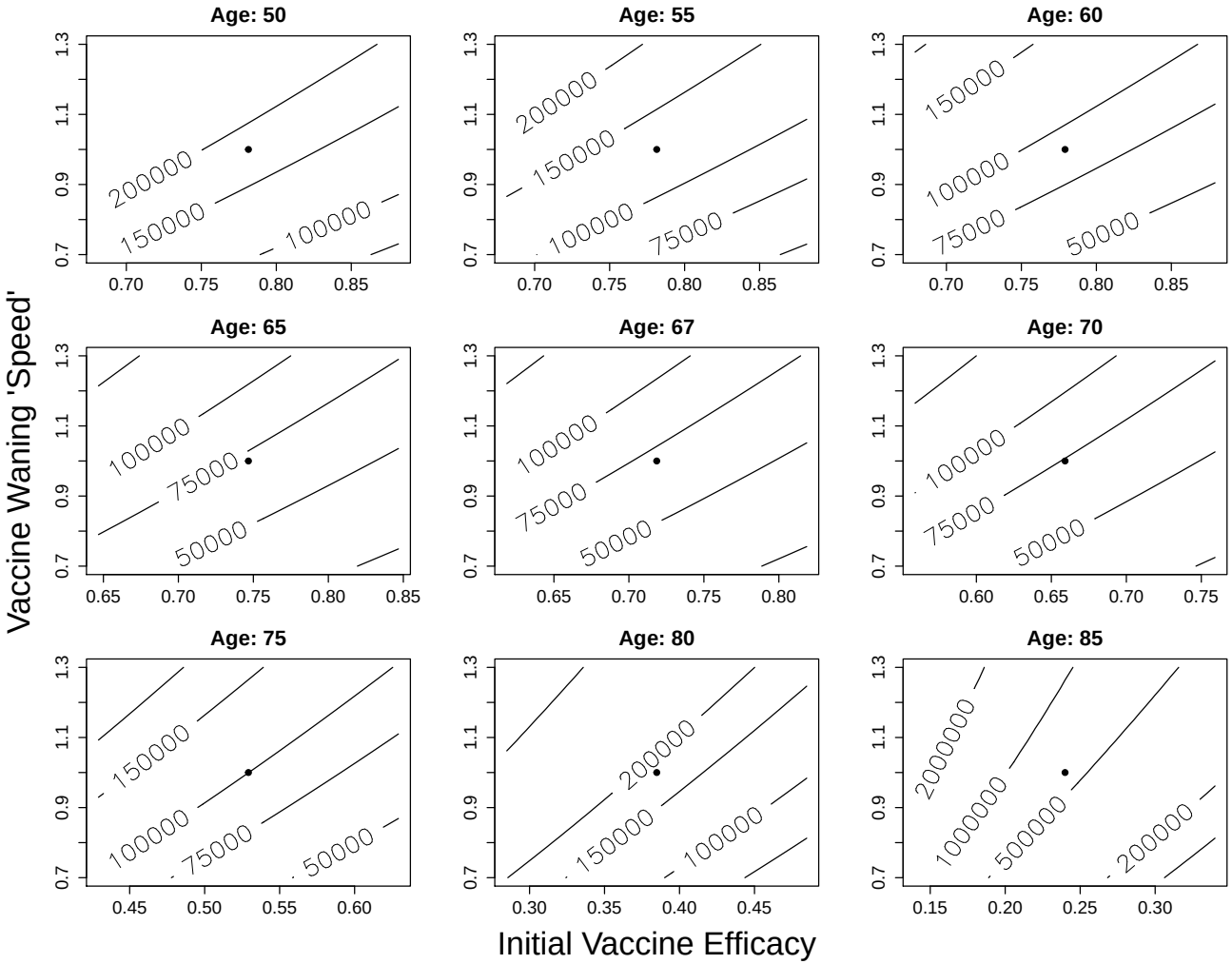

Figure 2.28: Vaccine Efficacy vs. Vaccine Waning Panel – Women. Contours represent ICER values of vaccination vs. no vaccination.

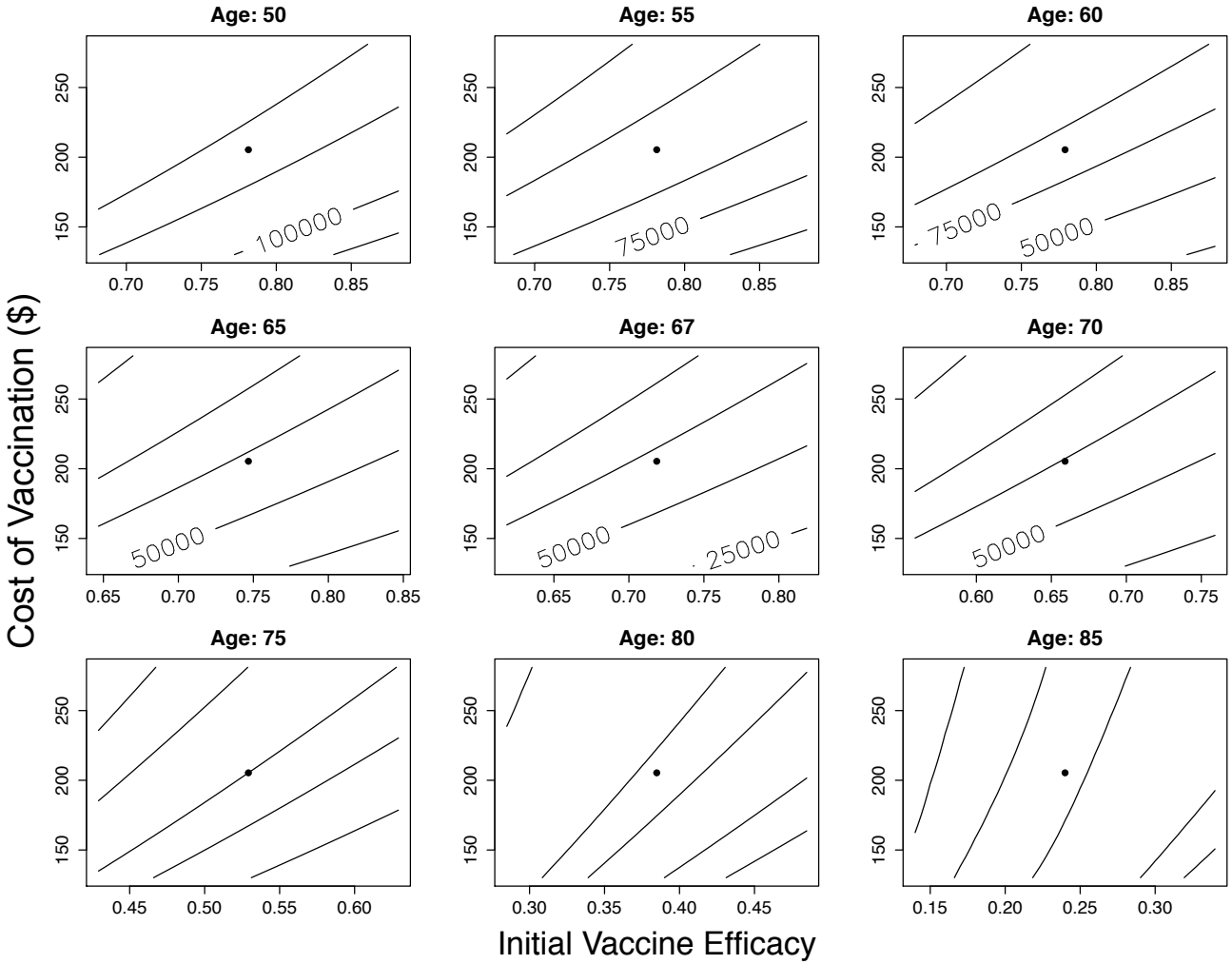

Figure 2.29: Vaccine Efficacy vs. Vaccination Cost Panel – Women. Contours represent ICER values of vaccination vs. no vaccination.

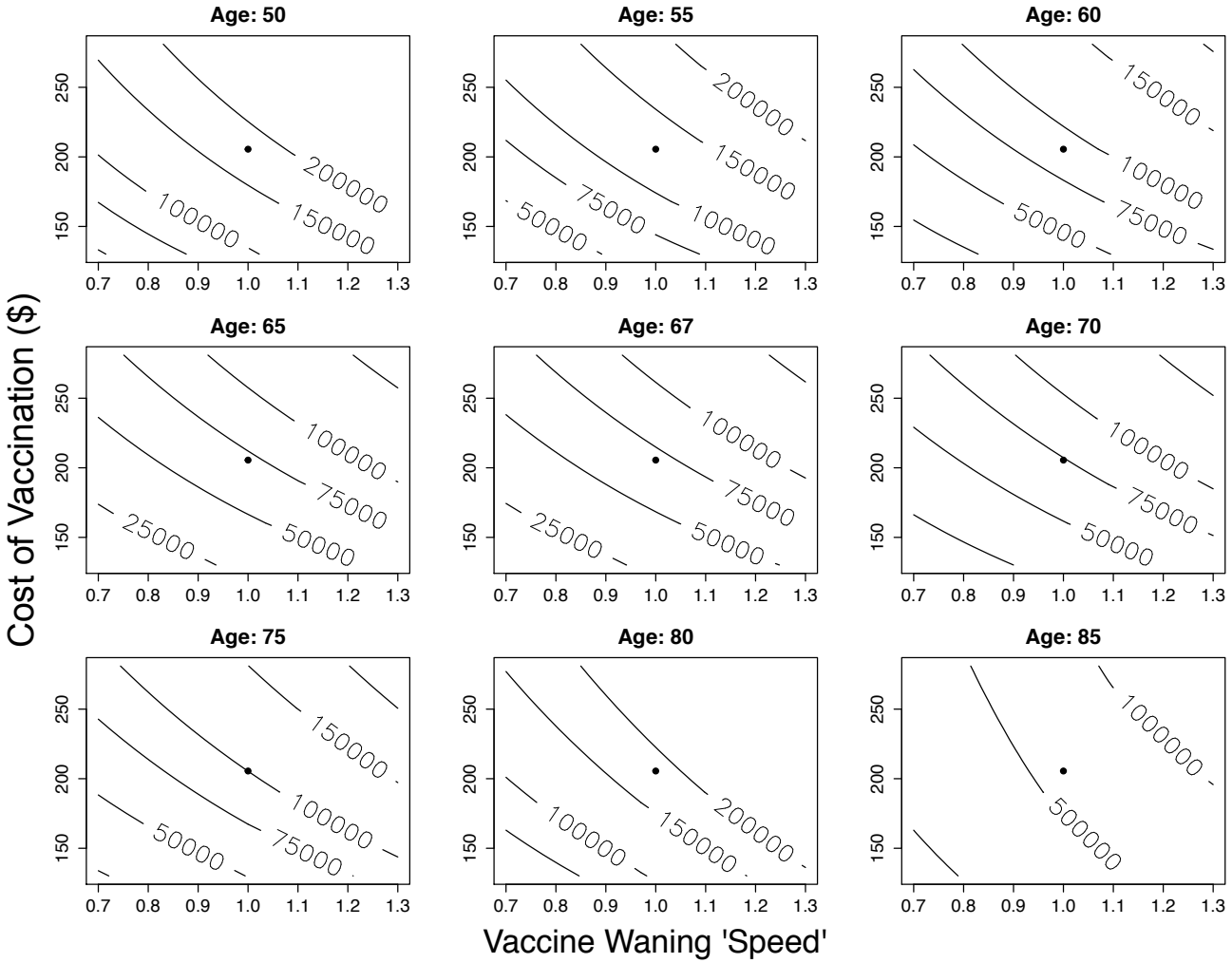

Figure 2.30: Vaccine Waning vs. Vaccination Cost Panel – Women. Contours represent ICER values of vaccination vs. no vaccination.

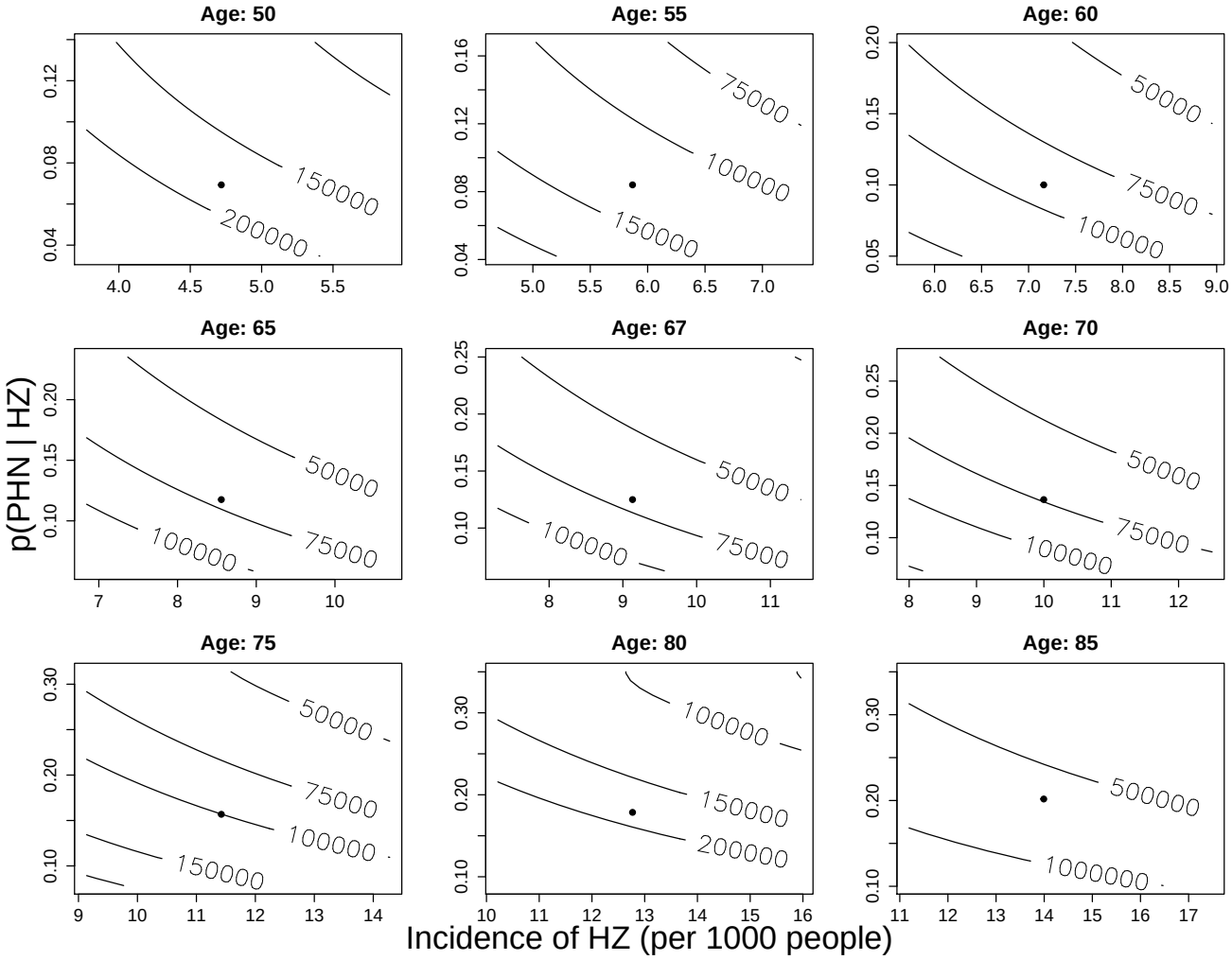

Figure 2.31: p(HZ) vs. p(PHN) Panel – Women. Contours represent ICER values of vaccination vs. no vaccination.

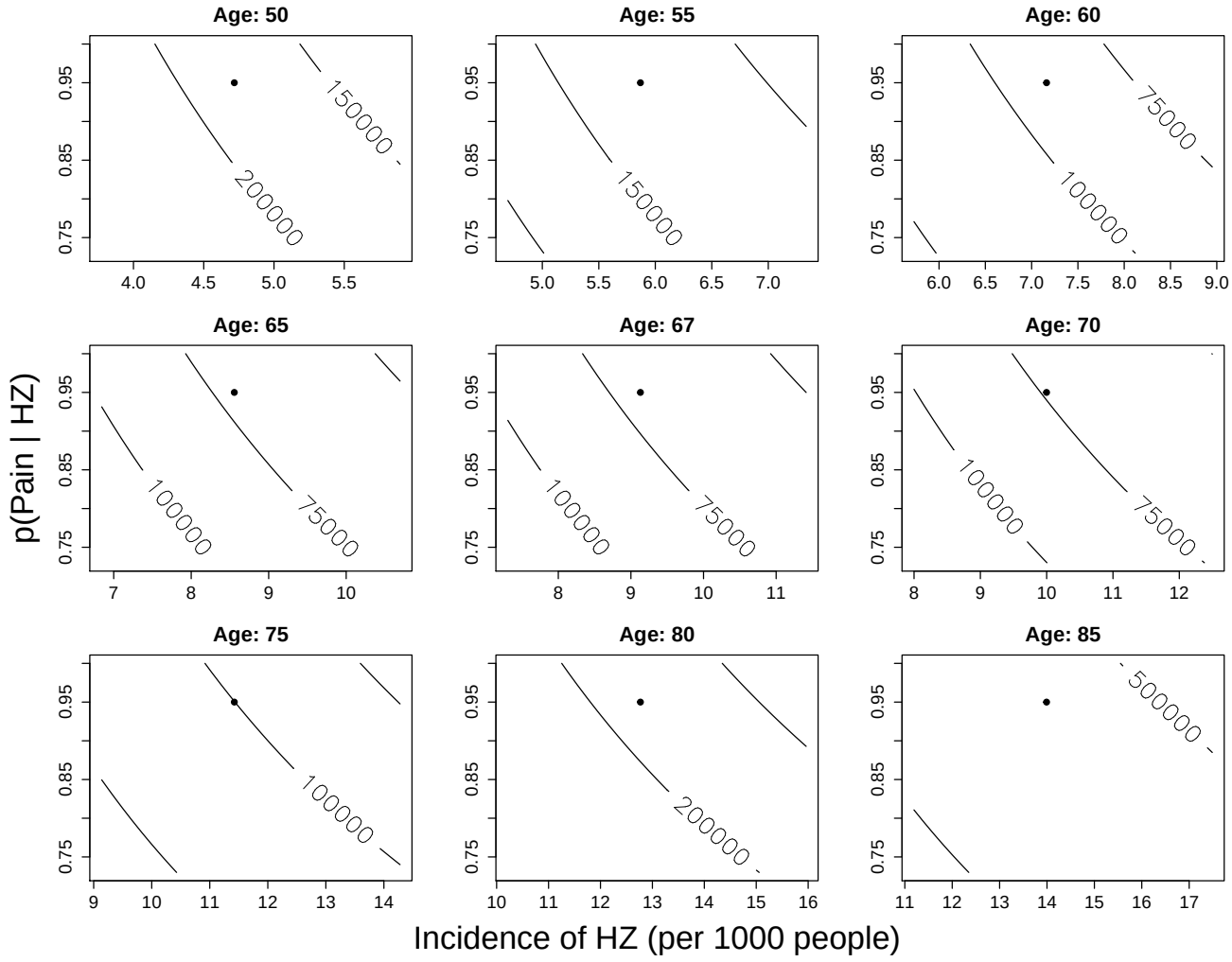

Figure 2.32: p(HZ) vs. p(HZ – Any Pain) Panel – Women. Contours represent ICER values of vaccination vs. no vaccination.

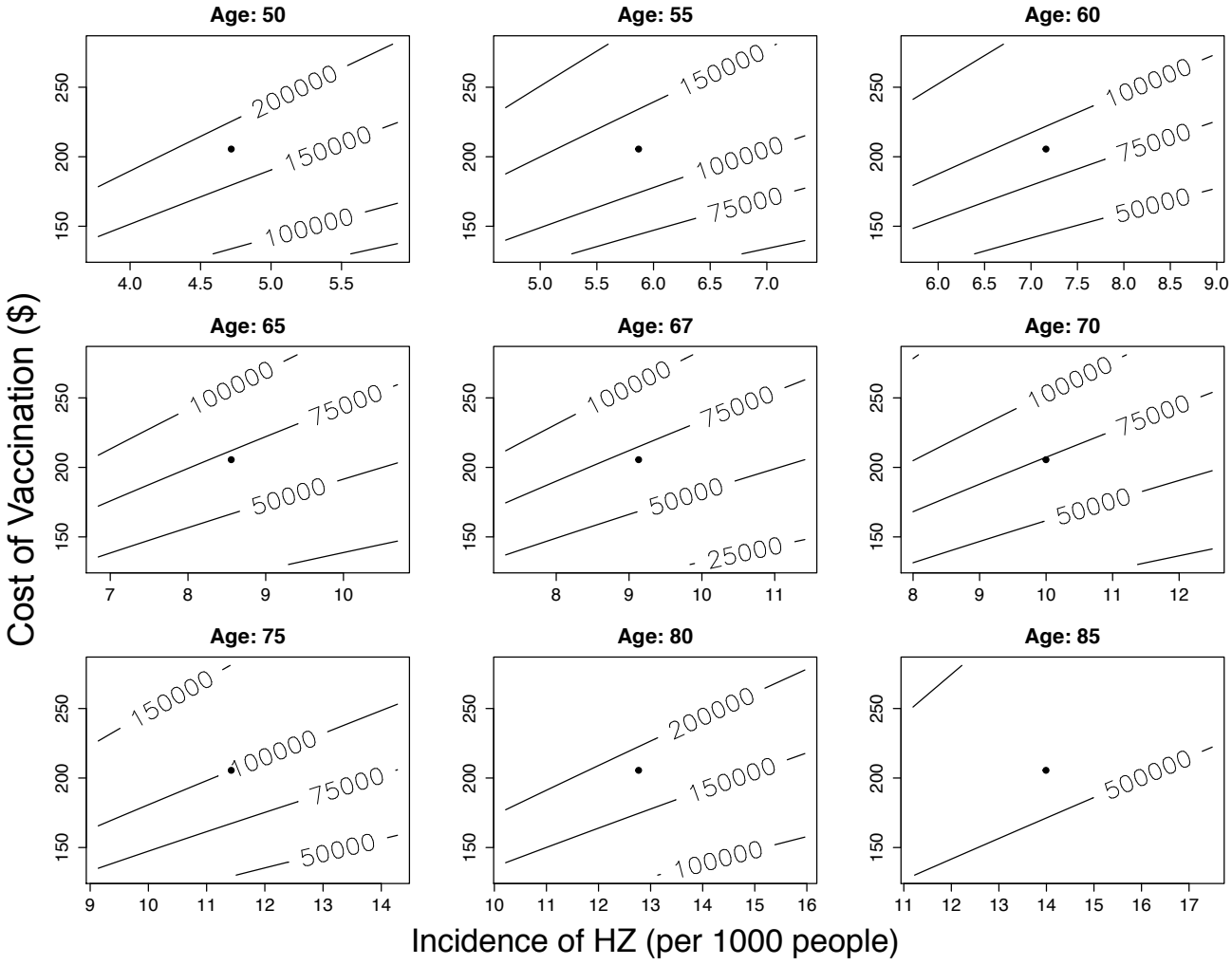

Figure 2.33: p(HZ) vs. Vaccination Cost Panel – Women. Contours represent ICER values of vaccination vs. no vaccination.

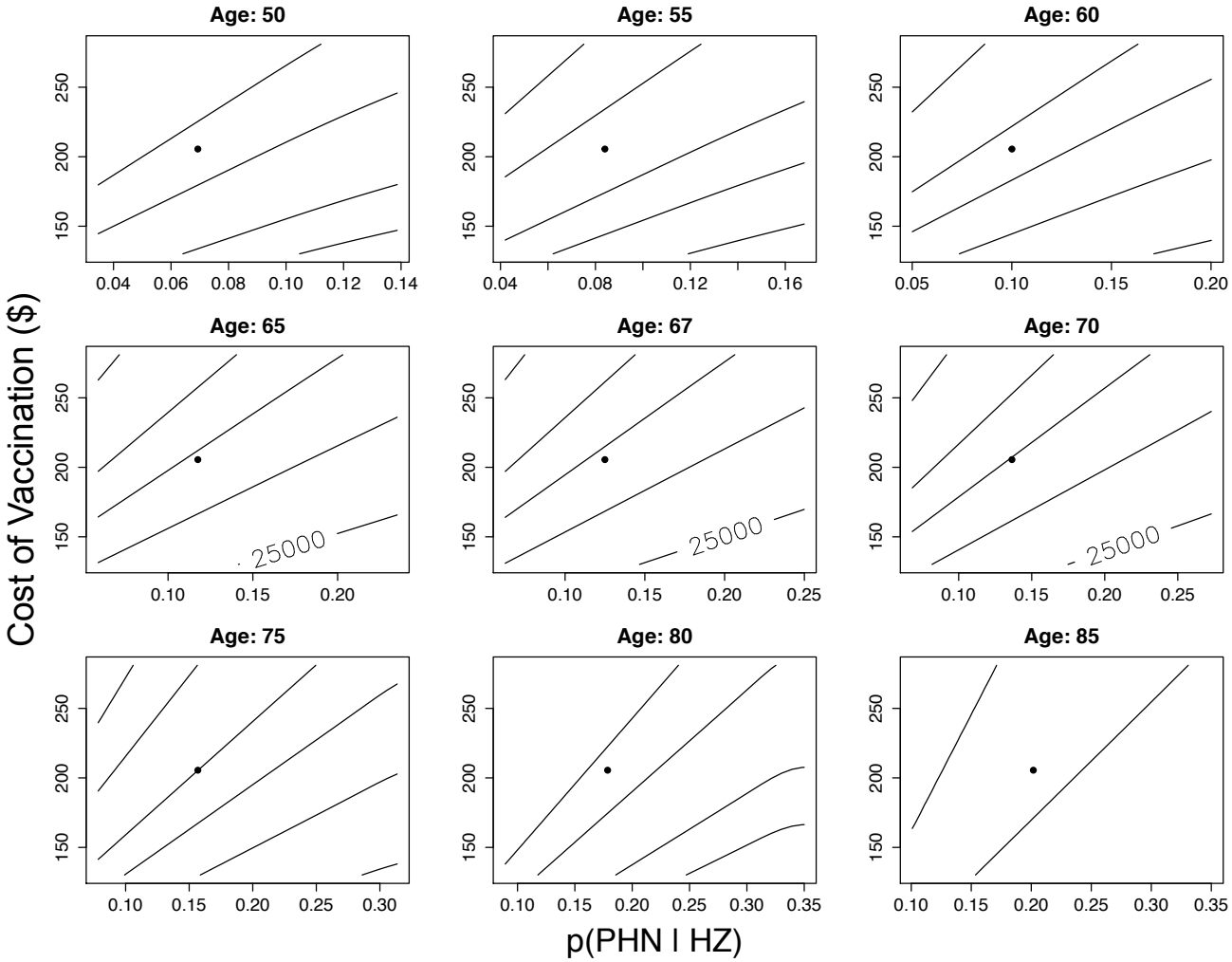

Figure 2.34: p(PHN) vs. Vaccination Cost Panel – Women. Contours represent ICER values of vaccination vs. no vaccination.

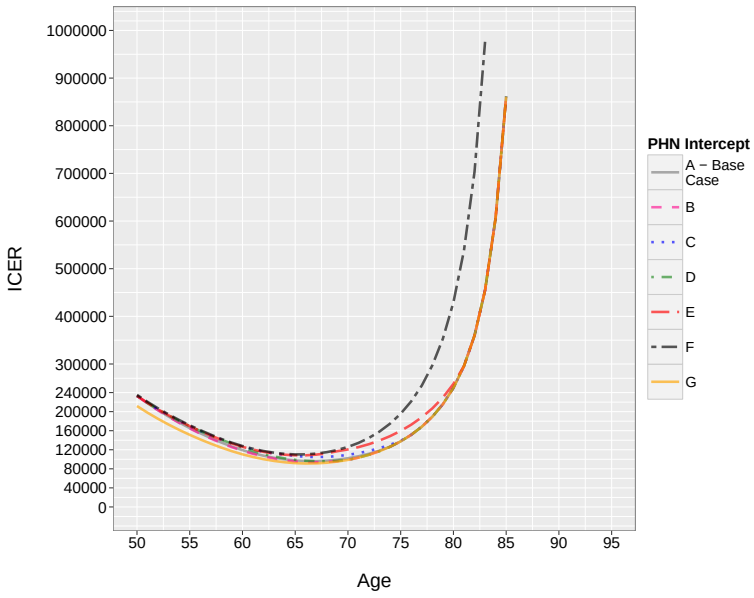

Figure 2.35: Scenario Analysis – PHN Intercept – Men

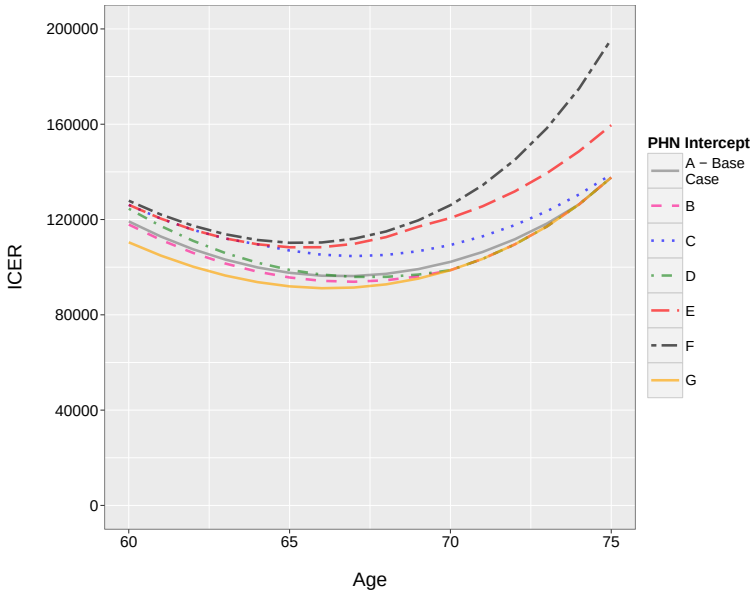

Figure 2.36: Scenario Analysis – PHN Intercept – Men – Zoomed

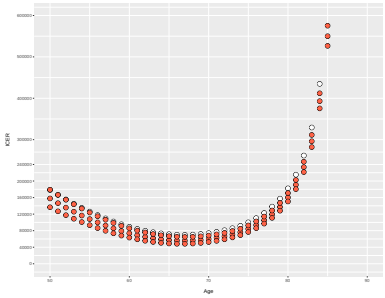

Figure 2.37: Scenario analysis – other complications – Women – probability. White dots - base case analysis. Top red line: $p(comps)$ = lowest, Middle red line: $p(comps)$ = mean. Bottom red line: $p(comps)$ = highest.

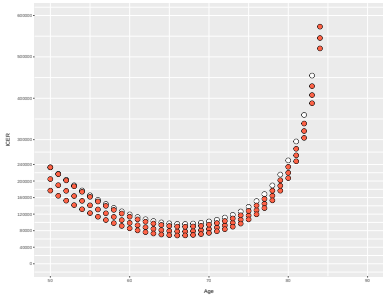

Figure 2.38: Scenario analysis – other complications – Men – probability. White dots - base case analysis. Top red line: $p(comps)$ = lowest, Middle red line: $p(comps)$ = mean. Bottom red line: $p(comps)$ = highest.

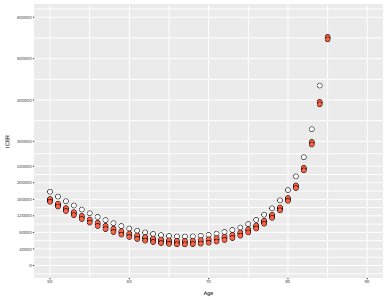

Figure 2.39: Scenario analysis – other complications – Women – costs. White dots - base case analysis. Top red line: cost = lowest, Middle red line: cost = mean. Bottom red line: cost = highest.

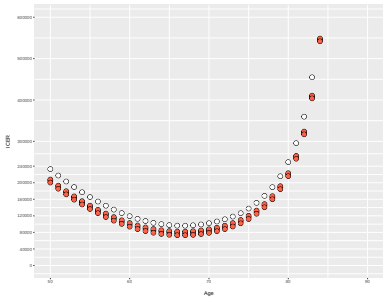

Figure 2.40: Scenario analysis – other complications – Men – costs. White dots - base case analysis. Top red line: cost = lowest, Middle red line: cost = mean. Bottom red line: cost = highest.

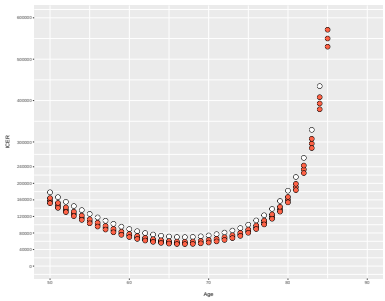

Figure 2.41: Scenario analysis – other complications – Women – QOL. White dots - base case analysis. Top red line: lost QOL = lowest, Middle red line: lost QOL = mean. Bottom red line: lost QOL = highest.

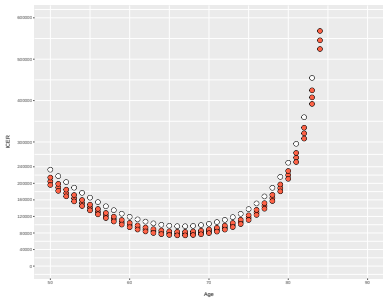

Figure 2.42: Scenario analysis – other complications – Men – QOL. White dots - base case analysis. Top red line: lost QOL = lowest, Middle red line: lost QOL = mean. Bottom red line: lost QOL = highest.

Chapter 3

Markov Decision Processes: One & Two Dose Administration

3.1 Introduction

The question of an optimal policy for the age of administering the herpes zoster vaccine remains largely unanswered. Cost-effectiveness analyses have given some indication of the most cost-effective age group (e.g., people ages 65 – 70) but results vary across studies [59–61]. The optimal policy is of particular importance given that vaccine efficacy and duration can change greatly depending on the age at vaccination. Thus even marginal 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 objective of this chapter is to estimate the optimal timing of the vaccination against HZ by answering the following two questions:

1. Conditional upon only one dose being available, at what ages is it optimal to receive the HZ vaccine?

2. Conditional upon an individual having received the initial vaccine at any previous age X, where X falls in the range of $[50, 99]$, is it ever optimal for that individual to receive a second dose of the vaccine?

Utility and Background on Markov Decision Processes

This chapter will build on the results from Chapter 2 and utilize a different type of decision analytic simulation model. In a state-transition model, only one decision can be evaluated in each model iteration [124]. State-transition models can provide information on a current decision but it is difficult to account for future decision options, and outcomes. And, while these models are common, they can be less valuable if there are many decisions required for a certain treatment, or if the same decision needs to be evaluated at different time points. Therefore, using state-transition models in those situations may lead to sub-optimal performance [125].

The Markov decision process (MDP) model, however, is a class of decision model that allows for the consideration of multiple or sequential decisions over time. MDP models are over 60 years old and come from the field of stochastic, dynamic optimization [126, 127]. They have only recently been applied to optimal allocation of medication or treatment policy problems in health care [128–133]. The MDP method optimizes a dynamic policy over a particular decision objective. For example, the method could determine the age of vaccination that maximizes the quality of life gained or minimizes the costs incurred [128]. Thus, the MDP model could be used to determine the optimal vaccination age that could help to minimize the burden of disease.

Five sets of information are required for every MDP [125]:

1. Decision epochs
2. System states
3. Available actions
4. Rewards dependent on state and action taken
5. Probabilities dependent on state and action taken

Decision epochs are time points in the model when a decision on an action is made. The time between epochs is called a period and these periods are analogous to cycles

in state-transition models [124]. System states are the set of mutually exclusive and collectively exhaustive states that define the outcomes in the model. Similar to a state-transition model, transition probabilities are used to defined the movement between the possible states of the model. Actions are the decisions that are made at each decision epoch. Rewards (monetary or other) are assigned for the actions taken at some epoch. When an action is selected the decision maker receives the award and the "system evolves to a possibly different state at the next decision epoch" [125].

3.2 Methods

Two separate MDP models: 1) One Dose MDP; 2) Two Dose MDP, were created to answer the the questions for this chapter. Each model and its methods will be discussed in turn.

One Dose Model

Structure

An overview of the one dose MDP model is shown in Figure 3.1. In this model a cohort is assumed to start at age 49, and an initial decision on vaccination is made when reaching the first decision epoch at age 50 ($t = 0$). The MDP model has two states: 1) Vaccinate (v); 2) Wait (defer vaccination) (w). Decisions are made at annual decision epochs from age 50 ($t = 0$), to age 100 ($t = 50$). In choosing vaccinate, the cohort gains immediate rewards for being vaccinated at that age. If the decision is to wait, the cohort remains unvaccinated for 1 period (1 year), and faces the choice to vaccinate or defer again at the next decision epoch. Data for the MDP model comes from cohort state-transiton models similar to the models used in the cost-effectiveness analysis in Chapter 2.

The cohort state-transition models (STMs) were constructed in R (v.3.2.3) to give the lifetime costs and QALYs for a cohort who either receives the vaccine or develops HZ at any age between 50 and 100. These costs and QALYs are the immediate rewards that are associated with the states and actions of the MDP. Figure 3.1 is

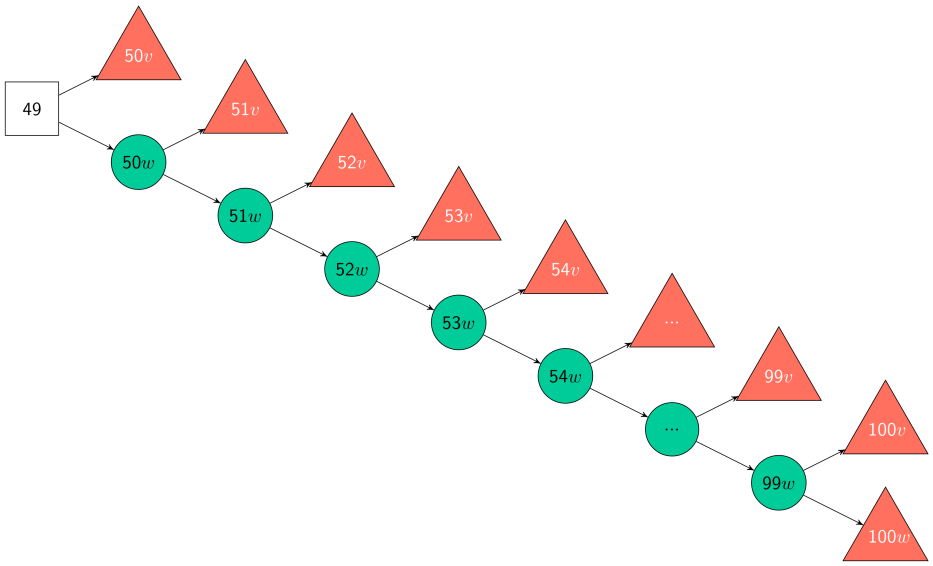

Figure 3.1: One dose MDP model

further deconstructed in Figure 3.2; this figure shows where the STM outputs are implemented within the MDP. Any red triangle in Figures 3.1 and 3.2 implies a terminal state; it is in these states where STM outputs are assigned. If one chooses to vaccinate (v), then immediate rewards are collected. These rewards are the lifetime costs and QALYs associated with vaccinating at that age. The vaccination STM, shown in the top half of Figure 3.2, has four states: 1) disease free, 2) herpes zoster, 3) disease free 2, 4) death. In this model, the cohort starts as disease free and has the chance to transition to HZ or death at the end of each model cycle. Cycle time for all STMs was set to 1 year to match the period length of the MDP. HZ is an all-inclusive health state that provides a cumulative estimate of the QALYs and costs with a case of HZ, which may include PHN or ocular complications. A further description of this STM is available in Appendix B.1 on page 208.

If the decision is wait (w), then the cohort is assumed to stay disease free for the current model period, and has the chance of transition into HZ, death, or back to disease free at the start of the next period (shown in the bottom half of Figure 3.2). The lifetime costs and QALYs associated from developing HZ in the next period were

derived from a HZ STM where a cohort starts in a HZ health state rather than a disease free health state. Similar to the vaccine STM, this HZ health state provides a cumulative estimate of the HZ, which can include PHN or ocular complications. The reward for death in all models is assumed to be 0.

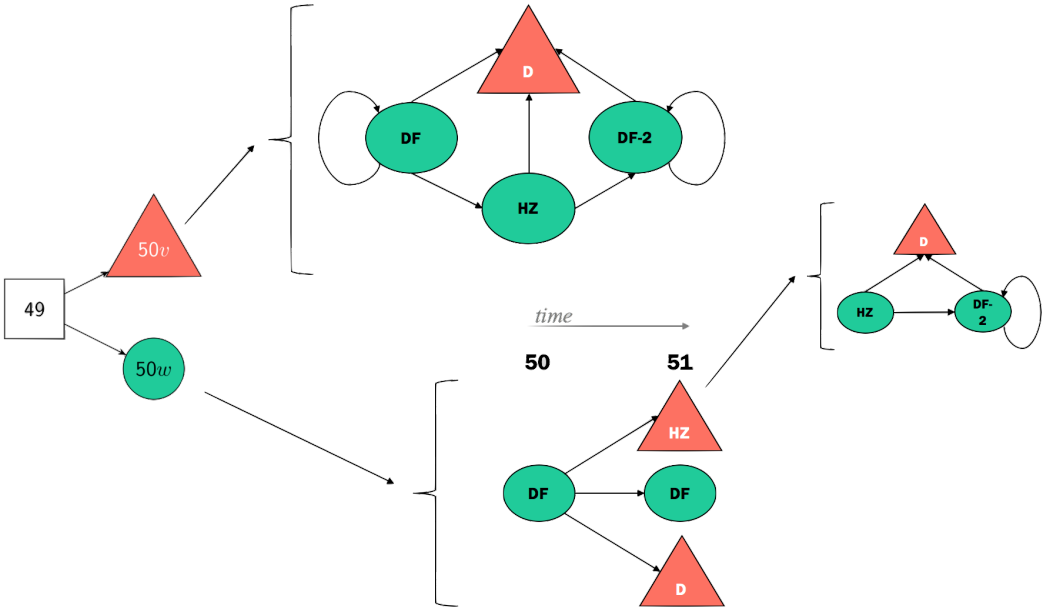

Figure 3.2: One dose MDP model breakdown. DF: Disease Free; HZ: Herpes Zoster, DF-2: Disease Free 2; D: Death.

The one dose MDP model is governed by the optimal value function, shown by Equation 3.1. In this equation $V_t(s_t)$ is the optimal value function for the model at time t ($t = 1, ..., T$) in state s. The action set a at time t includes only two actions that correspond to the states in the model: $\{v, w\}$. $R_t(v)$ is the immediate rewards gained from vaccinating at time t as determined by the vaccine STM. $R_t(w)$ is the immediate QALY reward gained for spending one cycle in a disease free state at time t. $R_t(w)$ 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 Equation 3.2. The optimal value function at the boundary is substituted for $V_{t+1}(s_{t+1})$ at age 99 ($t = 49$) and once this condition is set, the model runs recursively from age 99 to age 50, updating $V_{t+1}(s_{t+1})$ each year. Discounting in the model (shown by λ) was set to 3% (0.97)). Further information on the STMs and the data used to generate them is available in the appendix on page 208.

$$V_t(s_t) = \max_{a_t \in \{v,w\}} \Bigg\{ R_t(v), R_t(w) + \lambda \Big(p(D|s_t, w) R_{t+1}(D) + p(HZ|s_t, w) R_{t+1}(HZ) + p(DF|s_t, w) V_{t+1}(s_{t+1}) \Big) \Bigg\} \tag{3.1}$$

$$\text{For all } s_t \text{ and } t = 1, ..., T-1$$

$$V_T(s_T) = \max_{a_T \in \{v,w\}} \{R_T(v), R_T(w)\} \tag{3.2}$$

Analysis Plan

The MDP was built using R (v.3.2.3). First, the STMs outputs were loaded into the R environment. The MDP was constructed by programming Equation 3.1 using the base language. Care was taken to ensure that there was continuity between the structures of the MDP and the STM (i.e., that transitions were occurring at the same time and that rewards were being assigned in the same way). To run the model recursively, a loop was created that started the MDP at the boundary condition and worked backwards through each age from 100 to 50 selecting the optimal decision at each decision epoch. This method is known as backwards induction [125].

Table 3.1 provides the data used to generate the base case results of the one dose MDP model. The data in this table is representative of women only; data for men

is given in at the end of the chapter appendix on page 115. Transition probabilities for this model were taken from the data used for the cost-effectiveness analysis in Chapter 2. The probability of death comes from the CDC life tables [98]; the model assumes no death from zoster cases. The probability of developing HZ was determined by using the logistic equation and its parameters presented in Table 2.2 on page 27. The rewards for vaccination and HZ ($R_t(v), R_t(HZ)$), in Table 3.1 are expressed as net monetary benefits (NMB). The STMs provided both lifetime costs and QALYs and Equation 3.3 was used to convert those values into NMB, under an assumed willingness-to-pay (WTP) of \$100,000. The immediate reward for waiting ($R_t(w)$) was the baseline QOL for the cohort multiplied by the WTP [120].

$$NMB = WTP \times QALY - Cost \tag{3.3}$$

Age	$R_t(v)$	$R_t(w)$	$R_t(HZ)$	$p(HZ)$	$p(D)$	$p(DF)$
50	1,608,177	82,900	1,571,554	0.005	0.003	0.992
51	1,577,634	82,600	1,540,585	0.005	0.004	0.992
52	1,546,759	82,300	1,509,260	0.005	0.004	0.991
53	1,515,540	82,000	1,477,528	0.005	0.004	0.991
54	1,483,918	81,700	1,445,387	0.006	0.004	0.990
55	1,451,892	81,400	1,412,821	0.006	0.005	0.990
56	1,419,445	81,100	1,379,851	0.006	0.005	0.989
57	1,386,599	80,800	1,346,547	0.006	0.005	0.988
58	1,353,414	80,500	1,312,944	0.007	0.006	0.988
59	1,319,944	80,200	1,279,128	0.007	0.006	0.987
60	1,286,263	79,900	1,245,139	0.007	0.007	0.986
61	1,252,415	79,600	1,210,993	0.007	0.008	0.985
62	1,218,411	79,300	1,176,683	0.008	0.008	0.984
63	1,184,248	79,000	1,142,186	0.008	0.009	0.983
64	1,149,893	78,700	1,107,483	0.008	0.010	0.982
65	1,115,344	78,400	1,072,663	0.009	0.011	0.981
66	1,080,679	78,100	1,037,793	0.009	0.012	0.979

Age	$R_t(v)$	$R_t(w)$	$R_t(HZ)$	$p(HZ)$	$p(D)$	$p(DF)$
67	$1,045,967$	$77,800$	$1,002,892$	0.009	0.013	0.978
68	$1,011,226$	$77,500$	$967,927$	0.009	0.014	0.976
69	$976,425$	$77,200$	$932,899$	0.010	0.015	0.975
70	$941,563$	$76,900$	$897,834$	0.010	0.017	0.973
71	$906,659$	$76,600$	$862,836$	0.010	0.018	0.971
72	$871,834$	$76,300$	$828,008$	0.011	0.020	0.969
73	$837,181$	$76,000$	$793,421$	0.011	0.022	0.967
74	$802,774$	$75,700$	$759,051$	0.011	0.025	0.964
75	$768,585$	$75,400$	$724,866$	0.011	0.027	0.962
76	$734,587$	$75,100$	$690,934$	0.012	0.030	0.959
77	$700,836$	$74,800$	$657,307$	0.012	0.033	0.955
78	$667,405$	$74,500$	$624,153$	0.012	0.036	0.951
79	$634,449$	$74,200$	$591,550$	0.013	0.040	0.947
80	$602,051$	$73,900$	$559,470$	0.013	0.045	0.942
81	$570,178$	$73,600$	$527,872$	0.013	0.050	0.937
82	$538,795$	$73,300$	$496,903$	0.013	0.055	0.932
83	$508,036$	$73,000$	$466,827$	0.014	0.062	0.925
84	$478,184$	$72,700$	$437,626$	0.014	0.069	0.917
85	$449,214$	$72,400$	$409,361$	0.014	0.077	0.909
86	$421,188$	$72,100$	$382,276$	0.014	0.087	0.899
87	$394,347$	$71,800$	$356,389$	0.014	0.098	0.888
88	$368,715$	$71,500$	$331,691$	0.015	0.109	0.876
89	$344,269$	$71,200$	$308,123$	0.015	0.122	0.863
90	$320,964$	$70,900$	$285,616$	0.015	0.136	0.849
91	$298,725$	$70,600$	$264,044$	0.015	0.151	0.833
92	$277,425$	$70,300$	$243,207$	0.015	0.168	0.817
93	$256,864$	$70,000$	$222,802$	0.016	0.185	0.799
94	$236,748$	$69,700$	$202,369$	0.016	0.204	0.781
95	$216,615$	$69,400$	$181,200$	0.016	0.223	0.761
96	$195,752$	$69,100$	$158,133$	0.016	0.244	0.740

Age	$R_t(v)$	$R_t(w)$	$R_t(HZ)$	$p(HZ)$	$p(D)$	$p(DF)$
97	173,021	68,800	131,305	0.016	0.265	0.719
98	146,563	68,500	97,570	0.016	0.287	0.697
99	113,255	68,200	51,479	0.017	0.309	0.675
100	67,686	67,900	0	0	1	0

Table 3.1: One vaccine MDP input parameters – Women. WTP = $100,000.

Optimal Value Curve

To examine the impact of WTP on the optimal policy, an optimal value curve analysis was conducted [134]. As WTP changes the optimal policy will also change; the optimal value curve is used to show changes in expected costs and expected QALYs as WTP changes. To generate this curve the following procedure was used:

1. Load raw cost and QALY data from the STMs needed for the MDP
2. Set WTP to 0
3. Use WTP to convert raw costs and QALYs to NMB for immediate MDP rewards
4. Run MDP
5. Save optimal policy
6. Increase WTP
7. If maximum WTP reached then stop; otherwise return to Step 3

This loop was completed for each WTP from $0 to $2,000,000 by $2,000 increments, and each MDP provided an optimal policy for its corresponding WTP. Next another procedural loop was conducted to determine only the costs and QALYs associated with each optimal policy for each WTP. Each iteration of following loop produced one set of costs and QALYs (a cost,QALY set) associated with the optimal policy at a particular WTP.

1. Load MDP structure with raw costs and QALYs as rewards for actions (not NMB)

2. Load WTP
3. Load optimal policy associated with WTP
4. Run MDP where decisions are fixed based on loaded optimal policy
5. Record costs associated with optimal policy
6. Run MDP where decisions are fixed based on loaded optimal policy
7. Record QALYs associated with optimal policy
8. Save costs, QALYs, WTP, and optimal policy (one cost,QALY set)
9. Update WTP
10. Return to Step 3

This second loop was completed for all WTPs run in the first loop. This provided a set of cost and QALY data that could be plotted. The data collected from these loops provide information that can be used to visualize the changes in costs and QALYs gained as WTP changes.

Sensitivity Analysis

I conducted two sets of sensitivity analyses, a method that examines how responsive outcomes are to changes in parameter inputs and model assumptions, were completed. First, I conducted a one-way sensitivity analysis by varying each of the model parameters independently at the ends of their ranges to examine the effect on outcomes. This identified the model parameters that the results were most sensitive to. Inputs for the one-way sensitivity analysis are presented in Table 3.2.

I also performed second order Monte Carlo probabilistic sensitivity analysis (PSA) to estimate the optimal policy given uncertainty of multiple model parameters simultaneously. To accomplish this, I converted model inputs from discrete values to distributions. For cost inputs, I utilized a gamma (Γ) distribution. For disutilities, I assumed a beta (β) distribution. I then performed Monte Carlo simulations on the STMs and used those results to perform independent MDP simulations to determine the optimal policy. I used seeding to ensure the same variables were being used in

Variable	Base	Lower	Upper	STM	MDP
Vaccine – Initial Efficacy	0.00	-0.10	0.10	×	
Vaccine – Waning Rate	1.00	0.70	1.30	×	
$p(HZ)$ – $asymp$ – Women	19.277	15.382	24.033	×	×
$p(HZ)$ – $asymp$ – Men	13.935	11.148	17.418	×	×
$p(PHN\|HZ)$ – b_1	1.772E-7	8.86E-8	3.544E-7	×	
$p(OC\|HZ)$	0.00	-0.02	0.02	×	
Cost – HZ (without complications)	1934	1559	2287	×	
Cost – HZ with PHN	†			×	
Cost – HZ with OC	4163	2896	5543	×	
Cost – Vaccine	205.53	180.14	282.98	×	
Disutility – HZ (without complication)	0.03	0.019	0.0415	×	
Disutility – HZ with PHN	†			×	
Disutility – HZ with OC	0.09	0.065	0.129	×	
Disutility – Vaccine Complications	8.397E-5	4.16E-5	1.68E-4	×	

Table 3.2: Inputs for one-way sensitivity analysis. OC: ocular complications. † – Age dependent variables, tables with all data available on page 214. × in the table indicates what model (STM or MDP) the variable is contained within.

each STM and MDP in the same iterations (e.g., STM and MDP PSA iteration one share the same probability of HZ – prior to adjustment for vaccination). More detail is available in the Appendix on page 212.

The results of the PSA were used to generate two pieces of information. First results of the PSA were used to estimate the probability that vaccination was optimal at any age. To accomplish this, individual MDP models were run for each Monte Carlo iteration performed (e.g., 1000 Monte Carlo runs = 1000 MDP models). Once all 1000 MDPs were run, an R code was developed that searched all 1000 policies and determined which policies recommended vaccination at any age. The total number of policies where vaccination was recommended was divided by the total number of Monte Carlo iterations to determine this probability. Second, the same 1000 policies produced by the MDPs were searched by age to determine the chance that a certain

age would be selected into the optimal policy (from 0 - 100%). The total number of times an age was selected into an optimal policy was divided by the total number of Monte Carlo iterations (1000).

Variable	**Distribution**
Vaccine – Initial Efficacy*	$\mathcal{N}(0, 0.035)$
Vaccine – Waning Rate**	$\mathcal{N}(1, 0.12)$
Probability – HZ** – $asymp$	$ln\mathcal{N}(0, 0.099)$
Probability – PHN** – b_1	$ln\mathcal{N}(0, 0.295)$
Probability – Ocular Complications*	$\mathcal{N}(0, 0.01)$
Cost – HZ	$\Gamma(106.14, 1/18.02)$
Cost – PHN	†
Cost – Ocular Complications	$\Gamma(41.96, 1/99.20)$
Cost – Vaccine	$\Gamma(23.33, 1/7.5)$
Cost – Vaccine Administration	$\Gamma(2196.6, 70)$
Cost – Vaccine Severe Reactions	$\Gamma(18, 100)$
Disutility – HZ	$\beta(24.39, 804.59)$
Disutility – PHN	†
Disutility – Ocular Complications	$\beta(16.4, 254.81)$
Disutility – Common Vaccine Complications	$\beta(6, 6000) \times (30/365)$
Disutility – Severe Vaccine Complications	$\beta(2.13, 100000) \times (30/365)$

Table 3.3: Parameter distributions for PSA. * – A parameter was sampled and added to base case parameter value. ** – A scaling factor for the parameter was sampled and multiplied by the base value for that parameter. † – Age dependent distributions, table of distributions available on page 218

Two Dose Model

There is currently no booster vaccine available for HZ. However, one study has investigated the immunogenicity of a second dose of the HZ vaccine [135]. Given that the vaccine is available for purchase and a first dose could have been given at a

sub-optimal time in the past, it is important to consider if and when a person should get a second dose. To answer this question I make the following assumptions for the base case analysis. First, the second dose of the vaccine is not a booster vaccine. Rather it is the administration of the original vaccine a second time. Therefore, it is assumed to have the same risks and costs as the first dose. Second, I assume that the second dose does not provide any additional benefit from remaining efficacy from the first vaccine. For example, if a person is originally vaccinated at age 50, his/her first dose is projected to last 12 years. If he/she was vaccinated with a second dose at age 57, there would be no added benefit from the extra five years of efficacy remaining with the first dose. I relax this assumption in scenario analysis.

Structure

An overview of the two dose model is shown in Figure 3.3. This model is evaluated in two pieces, each piece has two states: 1) Vaccinate/Vaccinate Again (v or va); 2) Wait (w). The model that covers the second dose decision was the first to be evaluated, this is shown by the vertical arms in Figure 3.3 that begin with jv, where j is an age from [50, 99]. Each of these arms is a MDP sub-model (second dose model) that is evaluated independently. In these two dose models, it is assumed that the cohort receives in first dose at age j. After this initial dose, each subsequent year the choice must be made to either vaccinate again va, or wait. These second dose models are governed by optimal value function in Equation 3.4. The notable differences between Equations 3.1 and 3.4 are the the probability and reward for HZ. In the second dose model, $p(HZ|s, w, v_j)$ is adjusted by the age when the initial vaccine j was given and then adjusted by its waning function, shown by v_j. $R_{t+1}(HZ|v_j)$ is calculated from an R 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 in Appendix B.1. To evaluate the two dose MDP, 50 independent 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. Each of these MDPs started at the boundary condition where age = 100, and worked recursively to the age of the

first dose j.

$$V_t(s_t|v_j) = \max_{a_t \in \{va,w\}} \Bigg\{ R_t(va), R_t(w) + \lambda \Big(p(D|s_t, w) R_{t+1}(D) + p(HZ|s_t, w, v_j) R_{t+1}(HZ|v_j) + p(DF|s_t, w) V_{t+1}(s_{t+1}) \Big) \Bigg\} \tag{3.4}$$

For all j, s_t and $t = 1, ..., T-1$

$$V_T(s_T|v_j) = \max_{a_T \in \{va,w\}} \{R_T(va), R_T(w)\} \tag{3.5}$$

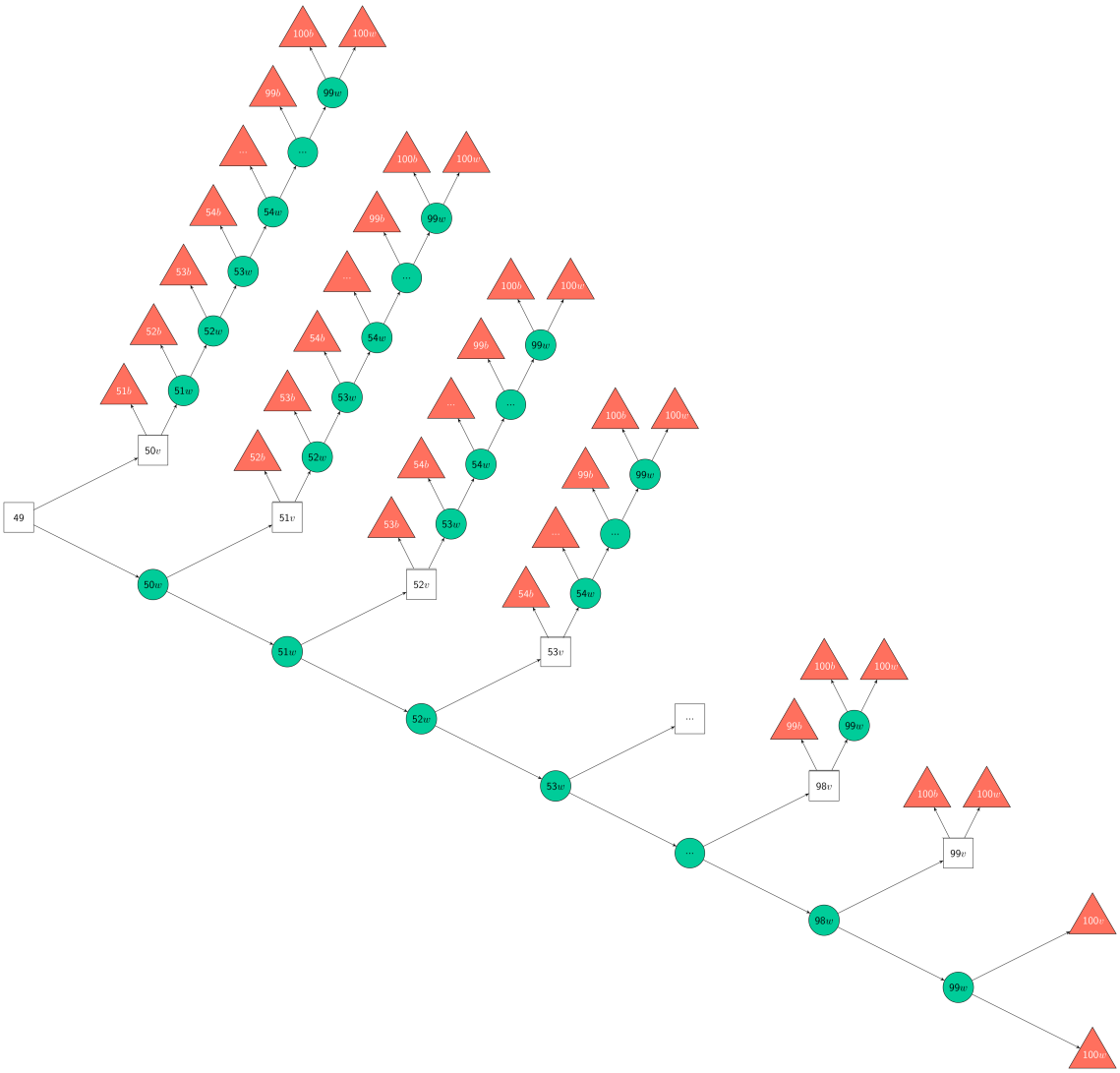

Figure 3.3: Two dose MDP model. White boxes indicate the age of initial vaccination. Vertical arms from the white boxes are the second dose MDP models.

Evaluation of the two dose models provided an update for the initial estimates of the lifetime QALYs and costs; shown in Figure 3.4 by blue squares. Using these new estimates of the lifetime QALYs and costs conditional upon a second vaccination being available at some time in the future, Equation 3.1 was used to evaluate the model shown in Figure 3.4. This provided an estimate of the optimal policy of evaluating two doses versus one dose.

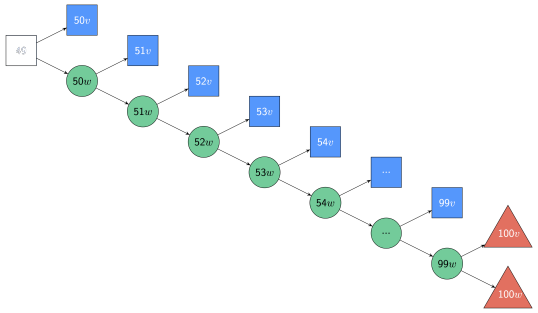

Figure 3.4: Two dose MDP model – second step

Sensitivity Analysis

Sensitivity analysis was also performed in the two dose models. First, parameters of interest from the one dose model were adjusted to the ends of their ranges to examine the impact on the results. This helped identify if there were any parameters that also greatly impacted the two dose model. I then performed first order Monte Carlo PSA with the model to estimate the optimal policy given the uncertainty of multiple model parameters simultaneously. For this analysis, I utilized the same procedure as for the one dose model. In brief, I ran PSA on the STM models used as inputs for the two dose MDP. I then adjusted shared parameters in the MDP by the same values and ran a separate MDP for each set of PSA results from the STMs. More detail is available in the Appendix on page 212.

The results of the PSA were used to generate two pieces of information. The 1000 policies per age of initial vaccination were searched by age to determine the chance that a certain age would be selected into the optimal policy for the second dose (from 0 - 100%). The total number of times an age was selected into an optimal policy was divided by the total number of Monte Carlo iterations (1000). I performed this analysis of PSA data for the model structures in Figure 3.3 and 3.4. This analysis for

Figure 3.3 provided the probability that an age for the second dose would be selected into an optimal policy conditional upon the age when the first dose was received. The analysis using the structure in 3.4 provided the probability for the initial age of vaccination to be selected into a policy where two doses would be optimal compared to one.

Scenario Analysis

One benefit of modeling studies is the ability to test scenarios that may be too difficult to test with clinical trials or observational studies. For the two dose model, I ran two scenario analyses to examine research questions that have not been well researched using other methods. First, as previously discussed, there is no indication that a second dose of vaccine provides additional benefits [135]. To examine the difference that a possible boost in efficacy could create I tested two scenarios. In these scenarios the initial efficacy of the second dose was increased by a fixed amount. In the first case, I assume that the initial efficacy was increased by two percentage points above its expected value at some age (e.g., $VE_{ij} + 0.02$). In the second analysis, I increased the initial efficacy by five percentage points above its expected value (e.g., $VE_{ij} + 0.05$).

For the other scenario analysis, I examined the policy regarding a new HZ vaccine. A new vaccine in development and early data suggests that it will have a much higher initial efficacy than the current vaccine [136]. No data are currently available on the waning of this vaccine. Given the new vaccine may be a large improvement over the current vaccine, I sought to determine at what age a person should receive this new vaccine, given that he/she may have had the current vaccine at some previous age. To do this, I made the following assumptions. First, the vaccine has an initial efficacy of 97% across all age groups [136]. Second, the new vaccine will wane at the same rate as the current vaccine. Third, the new vaccine does not provide any additional protection against PHN. Forth, as no price has been set, I assume that the new vaccine will cost the same at the current vaccine. Finally, I assume the new vaccine as the same safety profile as the current vaccine (i.e., the same QALY loss).

Vaccine Parameterization – All Models

In all (non-scenario) analyses the initial efficacy and waning of the vaccines protection against HZ and PHN were assumed to to be the same as for the cost-effectiveness model in Chapter 2. The protection of the vaccine was comprised of two parts. First, the initial efficacy of the vaccine ($\beta_{0_{jHZ}}$). 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 and t is measured in years. Second, the waning of the vaccine. Vaccine waning was assumed to occur from the time of the vaccination through the time when the vaccine provided no further protection benefit, ($t = [0, X]$), where X is some number of years in the future. These component pieces were combined using the form of a linear equation ($y = mt + b$) to create the age specific efficacy and waning of the vaccine (VE_{ij}). That is, the initial efficacy was assumed to be the intercept (b), the waning was assumed to be the slope (m), t was the number of years vaccinated ($t = [0, X]$), and y was the protection of the vaccine against HZ. These components are not strictly linear, rather they were fit using restricted cubic spline functions (RCS) and then combined using this equation form. The minimum value for vaccine efficacy was 0%; that is, the vaccine could not have a negative effect. Data on the initial vaccine efficacies and waning over time came from from clinical trial and observational data [20–22, 51, 78] and were combined using statistical methods [19]. More detail on how this data was fit and combined is available in Appendix A.4 on page 185. Equation 3.6 shows the equation used to model vaccine efficacy and waning, where i is the number of years vaccinated and j is the age of vaccination.

$$\begin{aligned} VE_{ij_{HZ}} = \beta_{0_{jHZ}} &+ \beta_1 i \\ &+ \beta_2 \max(i, 0)^3 \\ &+ \beta_3 \max(i - 1, 0)^3 \\ &+ \beta_4 \max(i - 2, 0)^3 \\ &+ \beta_5 \max(i - 7, 0)^3 \end{aligned} \tag{3.6}$$

This model also assumed the same base case initial protection against PHN as the cost-effectiveness analysis. There is some evidence that the vaccine provides additional

protection against PHN beyond the reduction in HZ incidence [22]. This data was 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. However, available data only covers the initial additional protection against PHN ($\beta_{0j_{PHN}}$) from $t = [0, 1)$ and there is unfortunately no data on how this additional protection benefit wanes with time. Therefore, the assumption was made that the additional protection benefit against PHN lasts only as long as the protection against HZ incidence. I also assume that the the additional protection wanes at the same rate as the vaccines protection against HZ; this was accomplished using Equation 3.7. I 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 a same likelihood of acquiring PHN given a HZ infection as someone without the vaccine.

$$VE_{ij_{PHN}} = \begin{cases} \beta_{0j_{PHN}} \times \frac{VE_{ij_{HZ}}}{\beta_{0j_{HZ}}} & \text{if } \beta_{0j_{HZ}} > 0 \\ 0 & \text{if } \beta_{0j_{HZ}} = 0 \end{cases} \tag{3.7}$$

Model Validation

Validation of the models was done in two steps. The STMs were first validated to ensure they were producing the correct data. Next the MDP was validated to ensure it was using the data correctly. To validate the STMs I first set all baseline QOL to 1.0, removed the disutilities associated with the health states, and removed the discount rate. I then performed simulations with different age groups and compared the results of the model to the CDC life tables [98]. This procedure provided a check that the cohorts in the model were dying at or close to the expected rate as the removal of QOL and discounting provides an estimation of remaining life-expectancy. Next, I ran a cost-effectiveness simulation between the arms of the STM models to further test the results. To do this, I removed the costs and disutilities associated with the vaccine from the base case model. I also changed the starting state of the HZ STM to ensure that every person started as disease free. Under these circumstances the vaccine was

predicted to dominate the choice of no vaccination for every age from 50 – 93 and be indifferent between 94 – 100 (the vaccine is assumed to have no benefit after age 93, as shown in Figure 2.2.) Finally, to ensure that the vaccine equations were entered into the model correctly, I selected different ages and numbers of years vaccinated and manually performed the calculations on what the probability of an HZ or PHN should be. I then changed the VX STM in R to reflect these scenarios, to ensure that the probabilities calculated by the model matched the probabilities I had calculated. Data from STMs was then implemented into the MDP structure. To validate the MDP model, I first removed the cost and disutility associated with vaccination. I then changed the initial efficacy function from the restricted cubic spline model to a linear model that predicted 100% efficacy at age 50 and 0% efficacy at age 100 (thus, 2% absolute decrements per year). Under this scenario, there was was no cost or QALY penalty associated with getting vaccinated, and the vaccination (in terms of efficacy) would be less optimal (in terms of initial efficacy and durability) each year. Therefore, it was predicted that the model should always select the vaccinate option as vaccination will always have benefit (expect at age 100), it will be free of cost and QALY penalties, and each earlier age would confer more benefit than the next later age (i.e., there would be no reason to delay vaccination). I also utilized print statements within the code to ensure that the equations were running correctly and using the correct probabilities. Finally, to verify the results, I built a MDP model using Microsoft excel and data from Table 3.1 to calculate the policy manually; I then compared those results to the MDP simulation built in R.

3.3 Results

Model Validation

The results from the model validation are presented in Tables 3.4 – 3.6. Table 3.4 shows the comparison of life expectancy in the model (calculated by setting the background health utility to 1.0 for all ages and removing the discount rate). There is a difference in the life expectancy between the CDC life tables and the life expectancy

Age	Life Expectancy – Model	Life Expectancy – CDC [98]
55	28.80	28.80
65	20.42	20.30
75	13.06	12.90
85	7.17	6.90
95	3.31	3.30
100	1*	2.3

Table 3.4: Model validation – life expectancy check – Women. *People at age 100 in the model are set to only live 1 year

produced by the model. The biggest difference is at age 100, where the CDC life tables predict a life expectancy of 2.3 years and the model estimates life expectancy of 1 year. The main difference between these two estimates is that in the STM the probability of death was set to 100% at age 100. Table 3.5 shows the comparison between $VE_{ij_{HZ}}$ as calculated by hand compared to the values calculated within the R STMs. For consistency, I used the same scenarios as the cost-effectiveness model in Chapter 2. All hand calculated values match the values produced by R indicating that the vaccine efficacy was implemented into the model correctly. Finally, Table 3.6 shows data from an analysis where the costs and disutilities associated with the vaccine were removed. As predicted, the option to vaccinate dominated the do not vaccinate option for every age between 50 – 93 (where the vaccine had some benefit) as demonstrated by the negative ICERs (due to less cost with more effect). When the model was indifferent between the options from ages 94 – 100 as the vaccine confers no benefit but also presents no risk or cost to the recipient. Figure 3.5 shows the results of the MDP validation. Here, as predicted, the model selected vaccination as the optimal choice at every age. This indicated the the code for the model was making the correct choices based on the input data it received.

One Dose Model

The results from the base case analysis for women are presented in Figure 3.6. Assuming a WTP of $100,000, the model recommends vaccination between the ages of

Scenario	$VE_{ij_{HZ}}$ **– Calculated**	$VE_{ij_{HZ}}$ **– From R**
j: 50, i: 0	0.7814	0.7814
j: 55, i: 10	0.1322	0.1322
j: 60, i: 4	0.4762	0.4762
j: 65, i: 7	0.2769	0.2769
j: 70, i: 2	0.4304	0.4304
j: 75, i: 8	0.0000	0.0000
j: 80, i: 3	0.1245	0.1245
j: 85, i: 5	0.0000	0.0000
j: 90, i: 0	0.0950	0.0950

Table 3.5: Model validation – vaccine efficacy check

Age	VX Q	VX C	NV Q	NV C	I.C	I.Q	I.Analysis
50	16.09	340.22	16.09	384.75	-44.53	0.001	(Dominates)
55	14.52	344.82	14.52	401.65	-56.83	0.001	(Dominates)
60	12.87	338.88	12.87	409.80	-70.91	0.002	(Dominates)
65	11.16	327.20	11.16	407.46	-80.26	0.002	(Dominates)
70	9.42	316.64	9.42	392.55	-75.91	0.002	(Dominates)
75	7.69	305.20	7.69	363.90	-58.69	0.002	(Dominates)
80	6.03	286.51	6.02	322.00	-35.49	0.001	(Dominates)
85	4.50	256.47	4.50	269.74	-13.27	0.0005	(Dominates)
90	3.21	210.00	3.21	214.18	-4.18	0.0001	(Dominates)
94	2.37	167.84	2.37	167.84	0	0	(Indifferent)
100	0.68	0	0.68	0	0	0	(Indifferent)

Table 3.6: CEA validation results. VX: Vaccine arm, NV: No Vaccine arm, C: costs, Q: QALYs, I.C: Incremental costs, I.Q: Incremental QALYs, I.Analysis: Incremental analysis, denotes if vaccination strategy dominates no vaccination strategy.

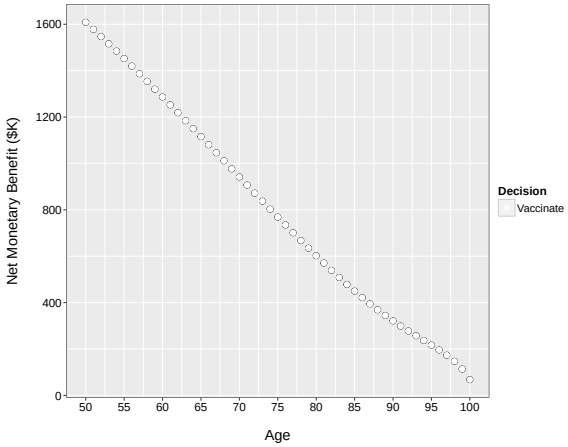

Figure 3.5: Optimal policy – validation

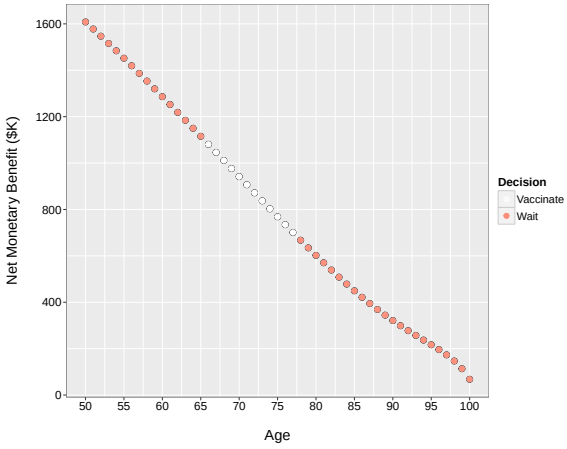

Figure 3.6: Optimal policy – one dose model – Women

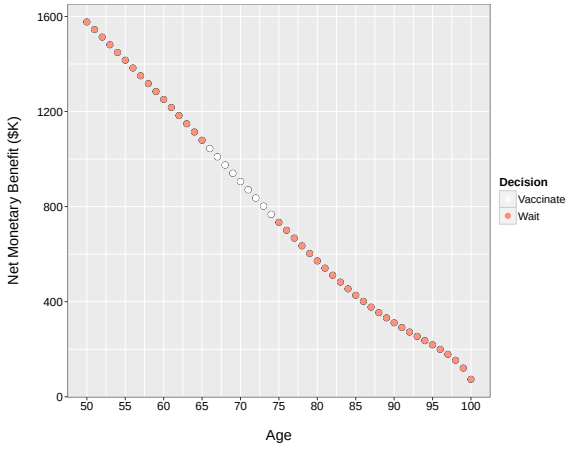

Figure 3.7: Optimal policy – one dose model – Men

66 – 77. Taking the perspective of a 50 year old woman (the age at the first decision epoch), following the optimal policy would mean vaccinating at age 66 and would produce a net monetary benefit of approximately $1.6 million. The results of the optimal policy for men are presented in Figure 3.7. Assuming a WTP of $100,000, the model recommends vaccination between the ages of 66 – 74.

Figure 3.8 presents the results from the optimal value curve for women. This analysis takes the perspective of a 50 year old woman. Assuming a WTP of $0, it

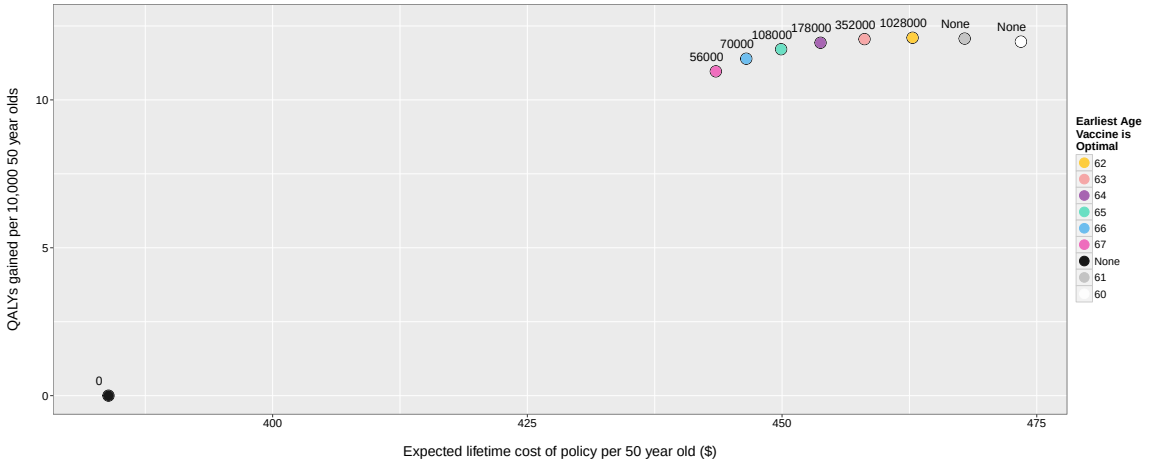

Figure 3.8: Optimal value curve – Women. WTP / QALY is written above curve points.

would never be optimal to vaccinate any women and the expected lifetime discounted costs of that policy would be approximately $375 per person; no additional QALYs would be gained. As the WTP increases to $56,000 age 67 would be the first age where vaccination is recommended. Following this policy would lead to an increase of approximately 10 QALYS for 10,000 50 year olds and an expected lifetime cost of $440 per person. As the WTP increases, the optimal policy changes to recommend vaccination at earlier ages as shown by Figure 3.8. This pattern plateaus at age 62 under a WTP of $1,028,000. The figure shows that vaccination at earlier ages (e.g., 60 or 61) produces higher costs and lower QALYs, thus these policies are dominated. Using the base parameter values, for women, age 62 is the youngest age where vaccination would ever be recommended. The optimal value curve for men is shown in Figure 3.17 in the end of chapter appendix on page 116. This curve shows a similar pattern to the optimal curve for women. For men, the WTP is higher for initiating vaccination at newer ages. The lowest WTP is $72,000 for vaccination at age 67. The other main difference is that age 61 is the lowest age recommended for vaccinating men at a WTP of $1,470,000.

Sensitivity Analysis

Figure 3.9 shows the results from the one-way sensitivity analysis for women. Overall, the model was robust to changes in most parameters. At a WTP of $100,000 the earliest age where vaccination would be recommended is 64; this assumes that the vaccine is waning at the slowest possible rate (30% slower). Based on deviation from the base case (either direction), vaccine efficacy, vaccine waning, vaccine cost, disutility of PHN, and $p(PHN|HZ)$ had the most effect on the policy. For women, the latest initial age for vaccination is 67, this occurs if the vaccine is expensive, the initial efficacy of the vaccine is lower (-10%), or the vaccine is waning at the fastest possible rate (30% faster). Figure 3.18 on page 117 shows the results of the one-way sensitivity analysis for men. The model for men is most sensitive to, based on deviation from the base case (either direction), vaccine efficacy, vaccine waning, vaccine cost, disutility of PHN, $p(PHN|HZ)$, and $p(HZ)$. At the fastest waning rate, the lowest initial efficacy, the highest vaccine cost, and the lowest probability of PHN given HZ, the optimal policy does not recommend vaccinating men at any age.

The results from the probabilistic sensitivity analysis are shown in Figures 3.10 – 3.11. Figure 3.10 shows the probability (for men and women) of vaccination being recommended at any age. For men, the PSA shows that in approximately 23% of simulations, the optimal policy would not include vaccination at any age at a WTP of $100,000. For women, this probability drops to approximately 9%.

Results from Figure 3.11 are to be interpreted as the probability from 0 – 100% of any one age being selected into the optimal policy for women. Figure 3.11 shows the results assuming WTP was fixed at $100,000. At this WTP the model suggests that ages 63 – 85 have some probability of being selected into the model. Ages 67 – 71 have more than an 85% chance of being selected; age 68 has the highest probability of any ages of being selected into an optimal policy. Figures for men can be found in the appendix at the end of the chapter appendix on page 118. For men, the age range extends from 62 – 84; age 68 also has the highest probability of being selected. However, none of the ages in the range has over an 75% chance of being selected.

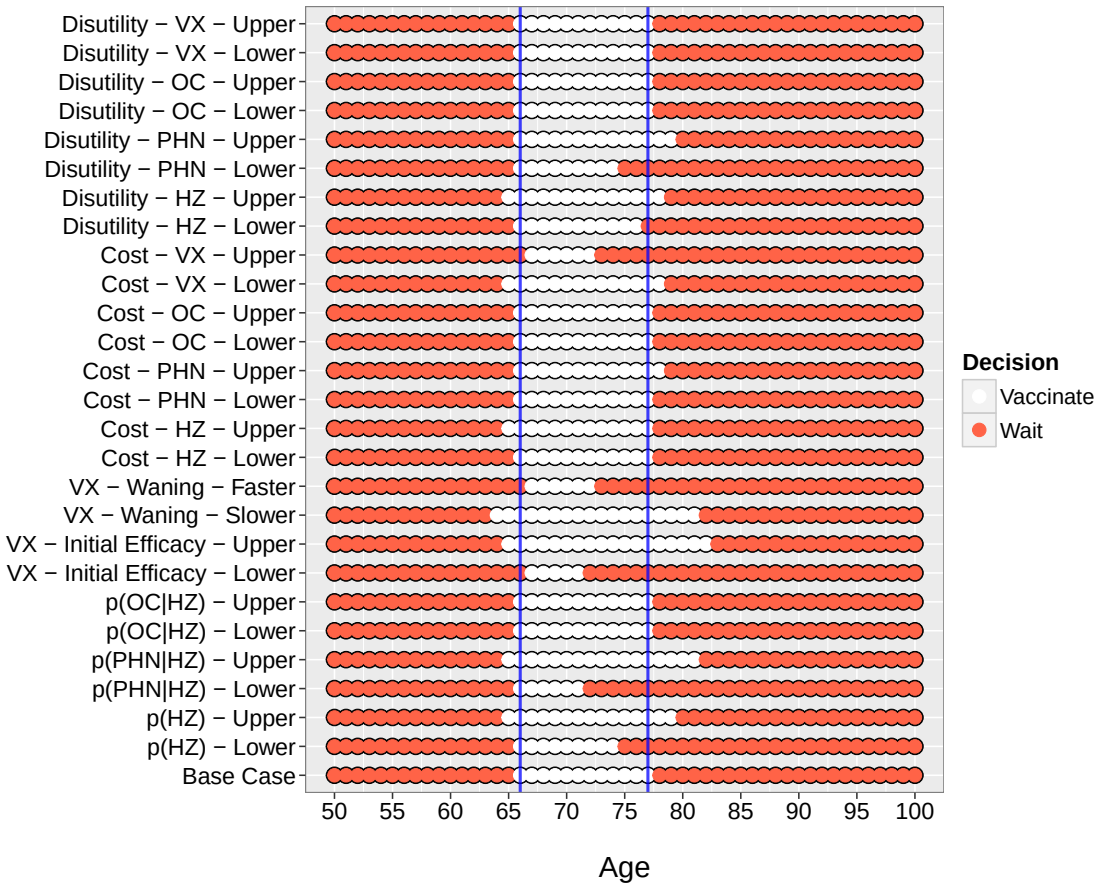

Figure 3.9: One-way sensitivity analysis results – Women. Blue line indicates the base case age range. WTP = $100,000/QALY

Two Dose Model

The results from the base case analysis for the two dose model are presented in Figure 3.12. This figure provides the results for women only; the figure for men can be found at the end of chapter appendix on page 119. For women, results show that receiving a second dose is optimal if an individual was initially vaccinated between the ages of 50 – 67. Using base case parameter estimates it is never optimal to administer the booster vaccine until the original vaccine has been exhausted completely. For men, receiving the second dose would only be optimal if the individual was originally vaccinated between the ages of 50 – 63.

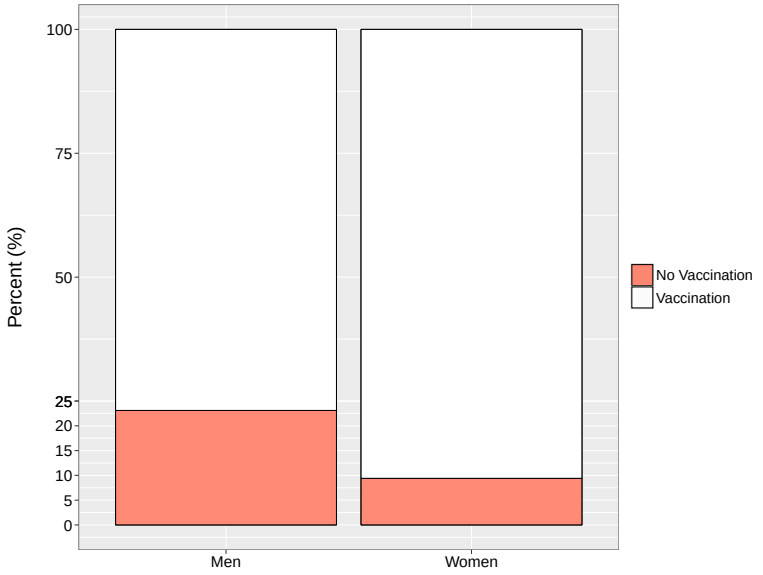

Figure 3.10: Probabilistic sensitivity analysis – Men v Women

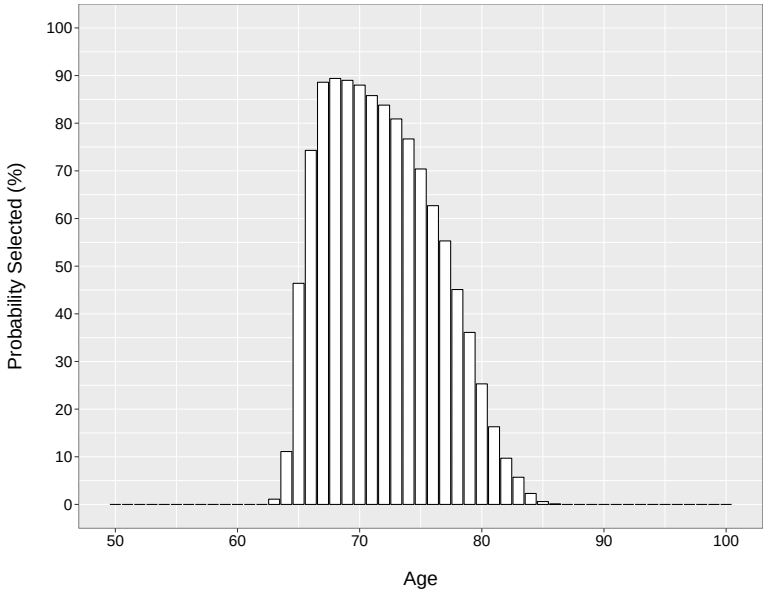

Figure 3.11: Probabilistic sensitivity analysis – Women – WTP: $100,000

Figure 3.13 shows the policy for women when considering if it is ever optimal to have a two dose policy compared to a one dose policy. Results suggest that it would be optimal for women between the ages of 62 – 67 to receive two doses of the HZ vaccine. If the first dose was administered between 62 – 67, then, using Figure 3.12 it would be optimal to receive the second dose at between the ages 72 – 76 (depending on the age of the first dose). Figure 3.21 on page 120 shows the policy for men when considering if it would ever be optimal to receive two doses of the vaccine. Results suggest that, under base case assumptions, it would never be optimal to recommend a two dose policy for men.

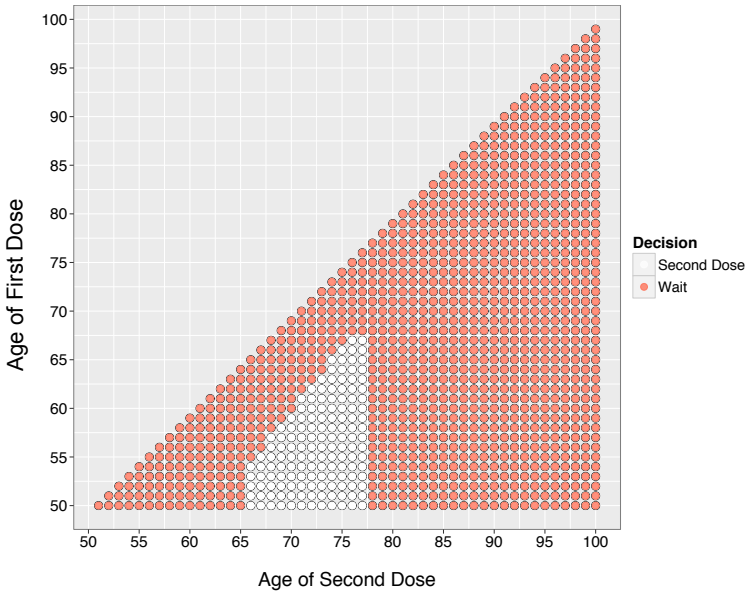

Figure 3.12: Optimal policy – two dose model – Women

Sensitivity Analyses

Results from the one-way sensitivity analysis are presented in the end of chapter appendix on pages 121 – 123. The one-way sensitivity analysis shows that the second dose is also responsive to some of the key parameters in the one-way sensitivity analysis from the one dose model. The response of the second dose follows the same pattern as the one dose model. If the vaccine if more efficacious, wanes slower, or

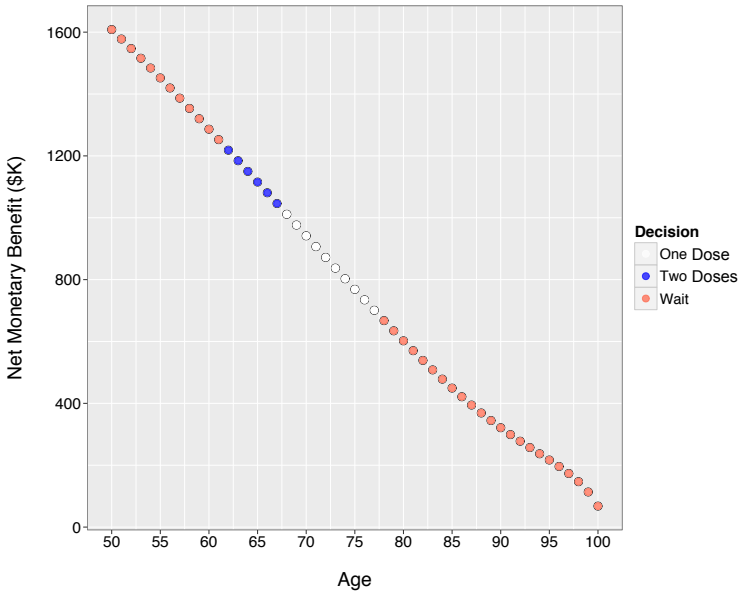

Figure 3.13: Optimal policy – two dose model, second step – Women

the probability of PHN is higher, the second dose is recommended over a wider range. If evaluated using the model structure from Figure 3.4, it becomes optimal to recommend the two dose compared to one dose policy over a wider age range. Conversely, if the vaccine has worst parameters (i.e., faster waning or lower efficacy) or the probability of PHN is lower, then the policy space for a second dose is reduced, and a two dose policy is never optimal compared to a one dose policy.

Figure 3.14 shows a heat map of the probability of an age of the second dose being selected into the optimal policy conditional upon the initial age of the first dose. This figure is specific to women only. Based on Figure 3.14, ages 67 – 73 have the highest probability of being recommended for an optimal policy for the second dose with a probability of between 80 – 89%. The range of ages for the second dose for women extends from 64 – 84, depending on the age of the initial dose. Ages 81 – 84 never have more than a 19% chance of being selected into an optimal policy. Figure 3.34 on page 124 shows the PSA results for men. Similar to the one dose PSA, there is less chance for the second dose to be optimal at any age. For men, ages 67 – 70 have the greatest chance of being selected into an optimal policy with a probability

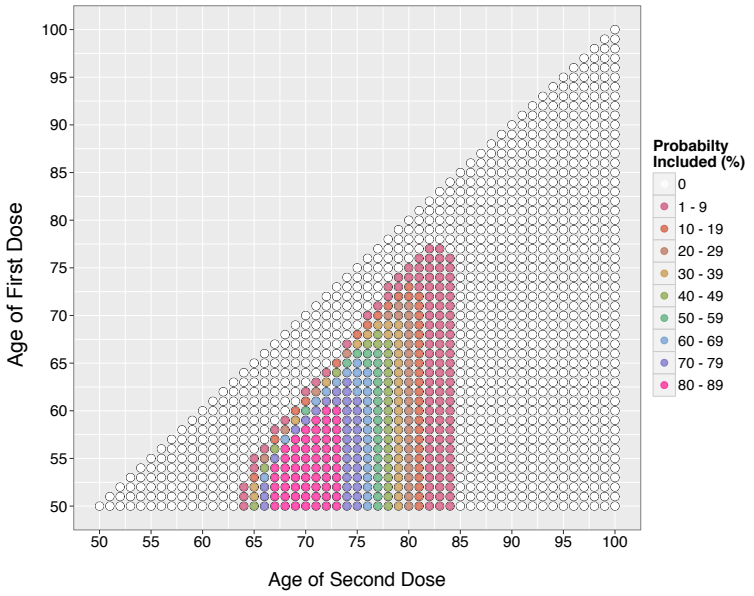

Figure 3.14: Probabilistic sensitivity analysis – two dose model – Women

of between 70 – 79%. The range of ages for a second dose for men extends from 64 – 83. Ages 81 – 83, regardless of the age of the initial vaccine have less than a 10% chance of being selected into an optimal policy.

Figure 3.15 shows the probability, for women, of a single age being selected into an optimal two dose policy. The ages on this plot are when the first dose would be given. Therefore, for women, ages 54 – 70 all have some probability of being selected into a policy where it would be optimal to vaccinate with two doses. Age 62 has the highest probability of any of the ages to be selected into a policy, with approximately a 55% chance. Ages 61 – 65 all have over a 40% chance of being selected into an optimal policy. The same figure for men is presented on page 124. For men, ages 55 – 69 have some chance of being selected into an optimal two dose policy. Age 62 has the highest chance at approximately 32%. Ages 61 – 64 have a 25% or greater chance for being selected into a policy that would recommend two doses versus one.

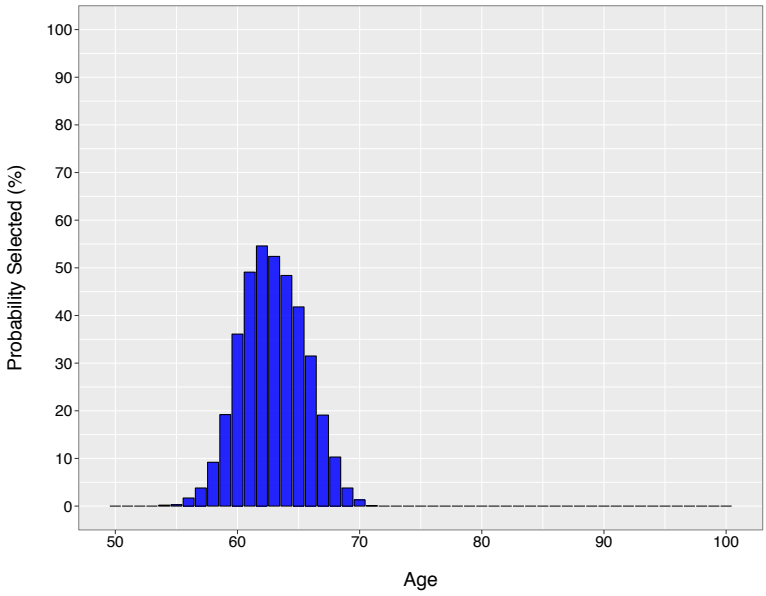

Figure 3.15: Probabilistic sensitivity analysis – two dose model, second step – Women

Scenario Analyses

The results for the scenario analysis assuming a higher initial efficacy for the second dose are available in Figures 3.36 – 3.39 on page 125. Compared to the base case figures, the scenario analysis shows that if you assume a two percentage point increase in initial efficacy for the second dose, the second dose is recommended at more ages compared to the base case analysis. Increasing the initial efficacy by five percentage points above base case further increases the policy space. When examining the optimality of a two dose vs. one dose policy, increasing the initial efficacy results in the two dose policy being optimal over a wider age range. Figure 3.16 shows the results of the scenario analysis of determining the age that the new vaccine should be given as a second dose conditional upon the current vaccine being given at some previous age as a first dose. The earliest recommended age for a second dose with the new vaccine is 69; this is four years after the earliest recommended age of the second dose when using the current vaccine. For any women who were vaccinated at age 80 or older with the current vaccine, it would be optimal to vaccinate with the

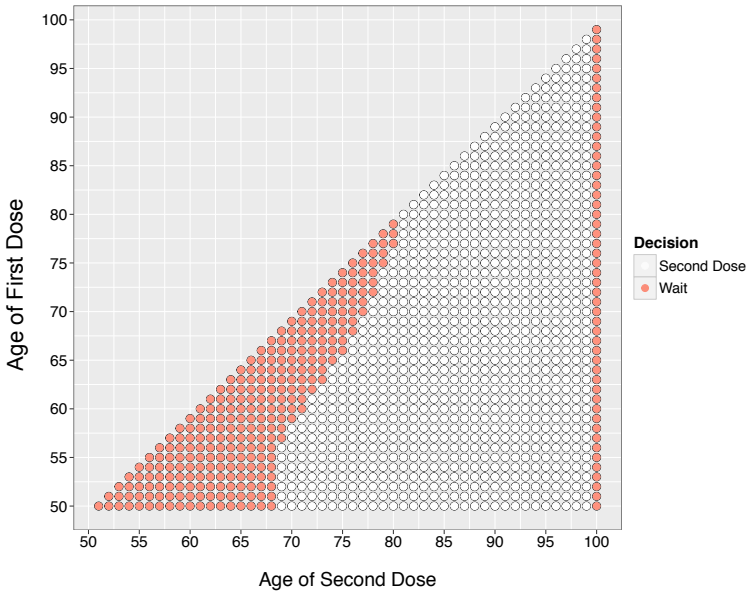

Figure 3.16: Scenario analysis – two dose model, new vaccine – Women

new dose the following year. The policy space for receiving a second dose with the new vaccine is much larger than the policy space for receiving a second dose of the current vaccine.

3.4 Discussion

This research determined the optimal policy for the HZ vaccine for women and men. As it is difficult to use state-transition models to account for multiple decisions or sequential decisions over time, a MDP model was utilized to decide when to vaccinate women and men. The model made decisions at annual decision epochs for a cohort starting at age 49. This research also examined the opportunity of receiving a second dose of the herpes zoster vaccine given that the original dose may have been given at some time in the past.

In the base case analysis, results suggest that age 66 is the first age recommended for vaccination. For women, there are more ages where vaccination is recommended compared to men, (66 – 77) and (66 – 74) respectively. Some possible explanations

for the differences are life expectancy and disease incidence. Women have a longer life expectancy than men [98]. Therefore, recommending vaccination at later ages for women could be because more women are likely to be alive in those later years. Women also have an increased risk of disease compared to men (see Figure A.1 on page 178). Thus, more women are likely to be alive and those who are alive are more likely to get the disease than their male counterparts.

When examining the one-way sensitivity analysis there are no scenarios when the vaccine is not recommended at some age for women. Conversely, there are four situations in the one-way sensitivity analysis where no vaccination is the optimal policy for men (fastest waning speed, lowest initial efficacy, lowest probability of PHN, highest vaccine cost). The probabilistic sensitivity analysis also shows that there are more scenarios where the vaccine would not be optimal for men compared to women (see Figure 3.10). From the one dose model it is evident that the vaccine is more likely to be beneficial under more circumstances for women than for men. This finding is consistent with the results of the cost-effectiveness analysis in Chapter 2.

Two Dose Model

The results from the two dose model match the same trend presented by 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 the initial dose at some time in the past. The results for women show that it would be optimal to receive the second dose over a wider range of ages compared to men. When the data from this question was used to determine if there were policies where it was optimal to ever receive two doses compared to one; there were ages where it was optimal for women to receive two doses (62 – 67). However, under the base case assumptions, it was only ever optimal for men to receive one dose even when a second dose was available.

The PSA for the two dose models provides some further insight into the two dose recommendation for men versus women. In comparing the two heat maps for the determining the probability of an age for a second dose being recommended given vaccination at some first age (Figures 3.14 and 3.34), women are much more likely to

have a second dose recommended over more ages. For example, if the initial dose of the HZ vaccine was given at age 50, for women ages 67 – 73 have a 80 – 89% chance of being selected as part of an optimal policy for the second dose. For men, ages 67 – 70 were the most likely to be selected with a probability of 70 – 79%. Similar to the one dose model, the PSA suggests that that second dose is more likely to be recommended, and more likely to be recommended over a wider age range for women than men. When examining the PSA for the two dose policy compared to the one dose policy, the results show that the two dose policy would be optimal for women approximately 50% of the time. For men it would only be optimal 30% of the time (See Figures 3.15 and 3.35). Because women are more likely to live longer than men [98], 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 makes sense 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.

The results of this research also highlight the importance of modeling studies. There has only been one clinical study that has examined the impact of receiving a second dose [135]. Levin et al examined the impact of the second dose 10 years after receiving the first dose. Their study did include the comparison of patients who were receiving an initial dose, however the metric of efficacy was cellular response to the vaccine. While cellular responses have been shown to be able to predict efficacy in the zoster vaccine [137], clinical trial or long-term observational data on the protective effect of a second dose is not available. Levin et al [135] did not show a significant difference in the cellular response between those who were receiving the second dose 10 years after the initial dose and those who were receiving the vaccine for the first time. Their study was also restrictive to a sample of people age 70 and older. In this research, we show that assuming the second dose of the vaccine confers no additional protection (as the results presented by Levin et al [135] suggest) that the second dose could still be optimal to receive for women. Further, this research examines the results assuming the option to get a second dose at any time after the first dose. In their paper, Levin et al [135] call for further research to be done on the multiple dose question to determine the benefits of the 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 additional benefit there is still a 50% chance for women and a 30% for men that receiving two doses of the vaccine would be optimal. If further studies found that the second dose produced more benefit, the range of ages for the second dose would likely increase, as shown by the scenario analysis.

Limitations

This study does have limitations. The MDP and its state-transition models were run in annual epochs and cycles. This was in part done for simplicity but also to reflect what could be actual policies. The cost-effectiveness in Chapter 2 was run in monthly cycles and shorter cycles should give a better estimate of the durability of the vaccine. That is, if the vaccine were to last seven years and one month in a model that uses monthly cycles, it would last a full eight years in a model that uses annual cycles. Therefore, the waning models used in this research may slightly overestimate the benefit of the vaccine. However, any additional benefit gained by the choice of annual cycles should never be greater than 11 months. Further, this additional benefit should be minimal (estimated at less than 2%). The choice of annual cycles does more accurately reflect the policy space for the vaccine. If the MDP were run in monthly epochs, the model could have suggested that it would be optimal to vaccinate at 65 years and 8 months (for example). While this may more optimal than vaccinating at 66 years of age, it would be unlikely to reflect an actual policy. The STMs also uses a collapsed health state for HZ; all potential complications occur within this HZ health state. The results from the CEA in Chapter 2 used a more complicated model, but results show that the model was robust to small changes in within the PHN state. For simplicity, the structure was collapsed for this paper. While this may have impacted the results, sensitivity analysis showed that the MDP was only slightly impacted by the changes in costs and utilities of PHN. Similar to the the CEA, the probability of PHN had one of the biggest impacts on the results. Therefore, while the collapsed health state may not provide as accurate of results, it did provide a

similar pattern of results and make model construction much simpler, which aided in ability to perform PSA on both the one and two dose models. The uncertainty in the parameters is also a limitation of this research. However, the PSA and the sensitivity analyses help to address these concerns and show what parameters the model is most sensitive and robust to. The PSA is of particular importance as it helps to narrow show the likely range of the optimal policy for both men and women.

Policy Implications

The results from this model have important policy implications. In the CEA presented in Chapter 2, I found that the vaccine is unlikely to be cost-effective (at a WTP of $100,000) for people below age 60 and greater than age 80. In this analysis, the MDP model narrows that range while simultaneously accounting for the risk of deferring vaccination. The MDP shows (based on Figures 3.6 – 3.7) that the optimal range is 66 – 77 for women and 66 – 74 for men. This analysis agrees with the CEA that the vaccine is likely to provide more benefit to women, however it also shows that delaying the start of vaccination until the mid-to-late 60s is more optimal even if the vaccine is considered cost-effective for women in their early 60s (as shown by the CEA). The Monte Carlo simulations for the MDP further support the decision to wait until the mid-to-late 60s to vaccinate. This is evidenced by age 65 being included in less than 50% of all optimal policies for women, with ages 64 and 63 being included in less than 15% of all optimal policies; results for men share a similar pattern. 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 a sub-optimal time. Finally, while the new vaccine has not come to market yet, the two-dose MDP shows that it will likely be optimal for women and men to receive this new vaccine as a second dose even if the current vaccine has already been given.

The MDP is important as it provides policy-makers with an optimal policy (i.e.,

a clear start and stop age). It is important to note that STMs could be setup to determine the most optimal age of vaccination by comparing all possible vaccination ages against one another for a cohort starting at age 50 (i.e., 50 different options). However to determine the optimal policy (not just the optimal age) using STMs would require 2^{50} different simulations (in theory) as there are 50 decision epochs in this model, each with two actions. When expanding the problem to include a second dose it becomes apparent that an STM is likely not a reasonable solution. Therefore, the MDP and the CEA should be seen as complements to one another. The CEA can 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.

Conclusions

This paper shows that the vaccine is likely to be optimal over a wider range for women than men, similar to the cost-effectiveness analysis of Chapter 2. Based on a search of the literature, this is the first paper, to my knowledge, that uses a MDP structure to evaluate the question of multiple vaccine doses. Further, this paper adds a probabilistic sensitivity analysis for both the one and two dose questions, accomplished in part due a simple model structure. This is uncommon due to complications with probabilistic sensitivity analysis with MDPs [138]. Results indicate that there is likely to be a stopping time for both men and women. Current ACIP recommendations are open-ended (i.e., there is no stopping age); this research is potentially valuable for future recommendations given that it shows a narrower range where the vaccine is most likely to be optimal. Finally, similar to the cost-effectiveness, the vaccine parameters (efficacy and waning) had the biggest impact on the optimal policy. Future research on these parameters may be necessary to make the best recommendations possible.

3.A Additional Figures and Tables

Age	$R_t(v)$	$R_t(w)$	$R_t(HZ)$	$p(HZ)$	$p(D)$	$p(DF)$
50	1,576,803	85,900	1,538,623	0.004	0.005	0.991
51	1,545,038	85,700	1,506,499	0.004	0.006	0.990
52	1,513,013	85,400	1,474,199	0.004	0.006	0.990
53	1,480,824	85,200	1,441,664	0.004	0.007	0.989
54	1,448,404	84,900	1,409,012	0.005	0.007	0.988
55	1,415,870	84,700	1,376,180	0.005	0.008	0.987
56	1,383,160	84,400	1,343,281	0.005	0.008	0.986
57	1,350,387	84,200	1,310,184	0.005	0.009	0.986
58	1,317,412	83,900	1,276,912	0.006	0.010	0.985
59	1,284,274	83,700	1,243,292	0.006	0.010	0.984
60	1,250,792	83,400	1,209,395	0.006	0.011	0.983
61	1,217,037	83,200	1,175,120	0.006	0.012	0.982
62	1,182,907	82,900	1,140,599	0.006	0.013	0.981
63	1,148,534	82,700	1,105,793	0.007	0.013	0.980
64	1,113,872	82,400	1,070,890	0.007	0.015	0.979
65	1,079,123	82,200	1,035,905	0.007	0.016	0.977
66	1,044,295	81,900	1,001,037	0.007	0.017	0.975
67	1,009,586	81,700	966,165	0.008	0.019	0.974
68	974,876	81,400	931,337	0.008	0.020	0.972
69	940,212	81,200	896,451	0.008	0.022	0.970
70	905,492	80,900	861,623	0.008	0.024	0.968
71	870,827	80,700	826,770	0.008	0.026	0.966
72	836,146	80,400	792,150	0.009	0.028	0.963
73	801,703	80,200	757,759	0.009	0.031	0.960
74	767,492	79,900	723,835	0.009	0.034	0.957
75	733,749	79,700	690,233	0.009	0.037	0.954
76	700,333	79,400	656,992	0.009	0.041	0.950
77	667,272	79,200	624,234	0.010	0.045	0.946

Age	$R_t(v)$	$R_t(w)$	$R_t(HZ)$	$p(HZ)$	$p(D)$	$p(DF)$
78	634, 708	78, 900	592, 095	0.010	0.049	0.941
79	602, 766	78, 700	560, 559	0.010	0.054	0.936
80	571, 431	78, 400	529, 821	0.010	0.060	0.930
81	540, 898	78, 200	499, 867	0.010	0.067	0.923
82	511, 154	77, 900	470, 697	0.011	0.073	0.916
83	482, 188	77, 700	442, 038	0.011	0.081	0.909
84	453, 747	77, 400	414, 942	0.011	0.091	0.898
85	426, 874	77, 200	389, 027	0.011	0.101	0.888
86	401, 189	76, 900	364, 402	0.011	0.112	0.876
87	376, 796	76, 700	340, 946	0.011	0.125	0.864
88	353, 583	76, 400	318, 744	0.011	0.138	0.851
89	331, 618	76, 200	297, 609	0.012	0.152	0.836
90	310, 733	75, 900	277, 566	0.012	0.167	0.821
91	290, 942	75, 700	258, 366	0.012	0.183	0.805
92	271, 998	75, 400	239, 912	0.012	0.201	0.787
93	253, 805	75, 200	221, 774	0.012	0.219	0.769
94	235, 937	74, 900	203, 583	0.012	0.237	0.750
95	218, 025	74, 700	184, 469	0.012	0.257	0.731
96	199, 193	74, 400	163, 282	0.012	0.277	0.711
97	178, 314	74, 200	137, 819	0.012	0.298	0.690
98	153, 187	73, 900	104, 577	0.013	0.318	0.669
99	120, 325	73, 700	56, 979	0.013	0.339	0.648
100	73, 186	73, 400	0	0	1	0

Table 3.7: One vaccine MDP input parameters – Men. WTP = \$100,000.

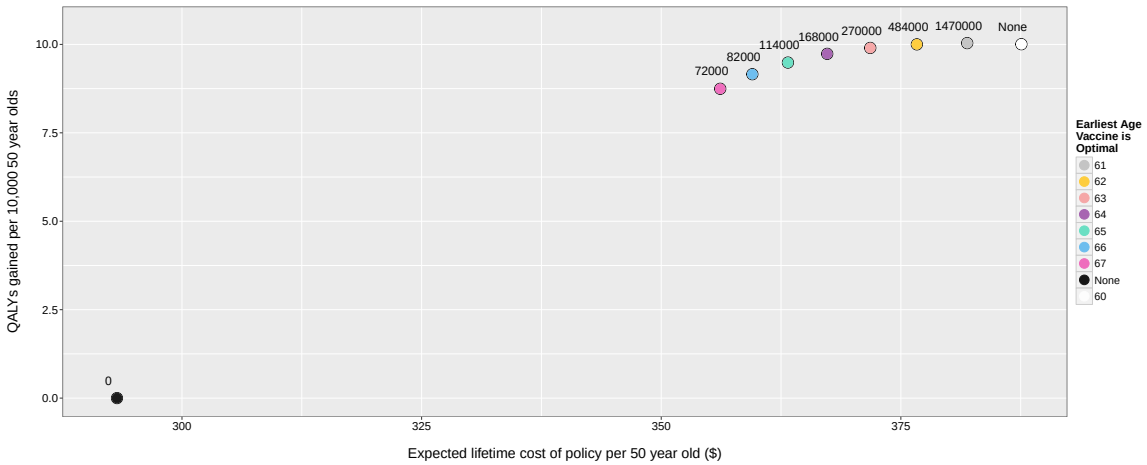

Figure 3.17: Optimal value curve – Men

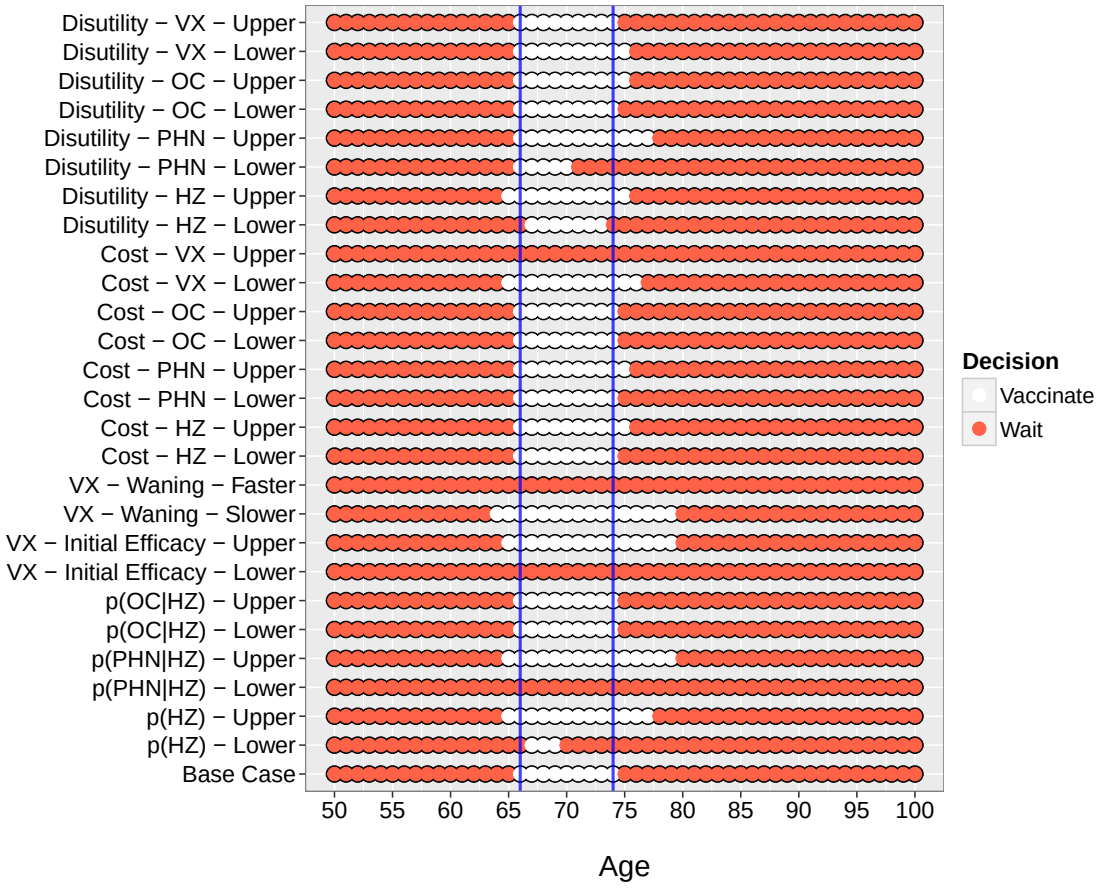

Figure 3.18: One-way sensitivity analysis – Men

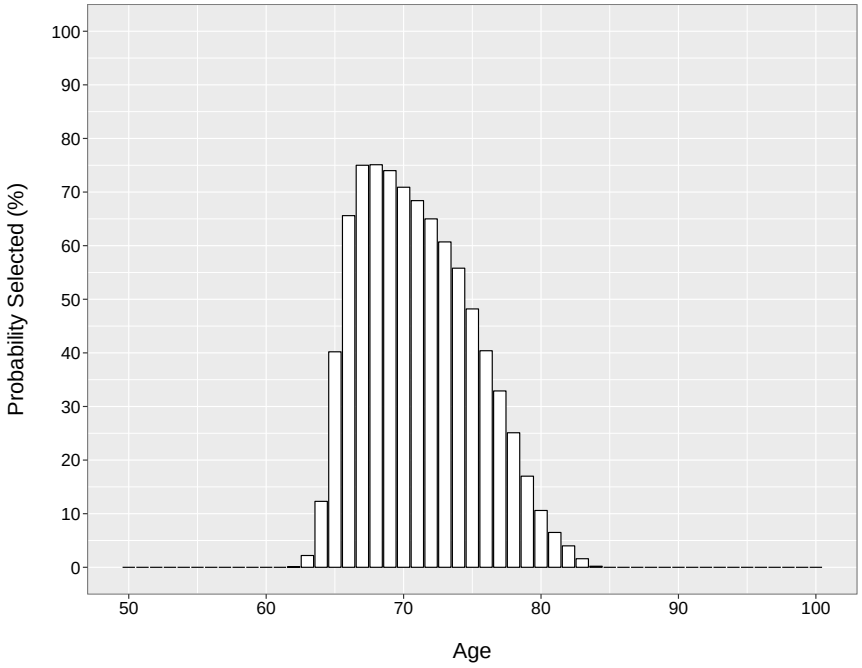

Figure 3.19: Probabilisitic sensitivity analysis – Men

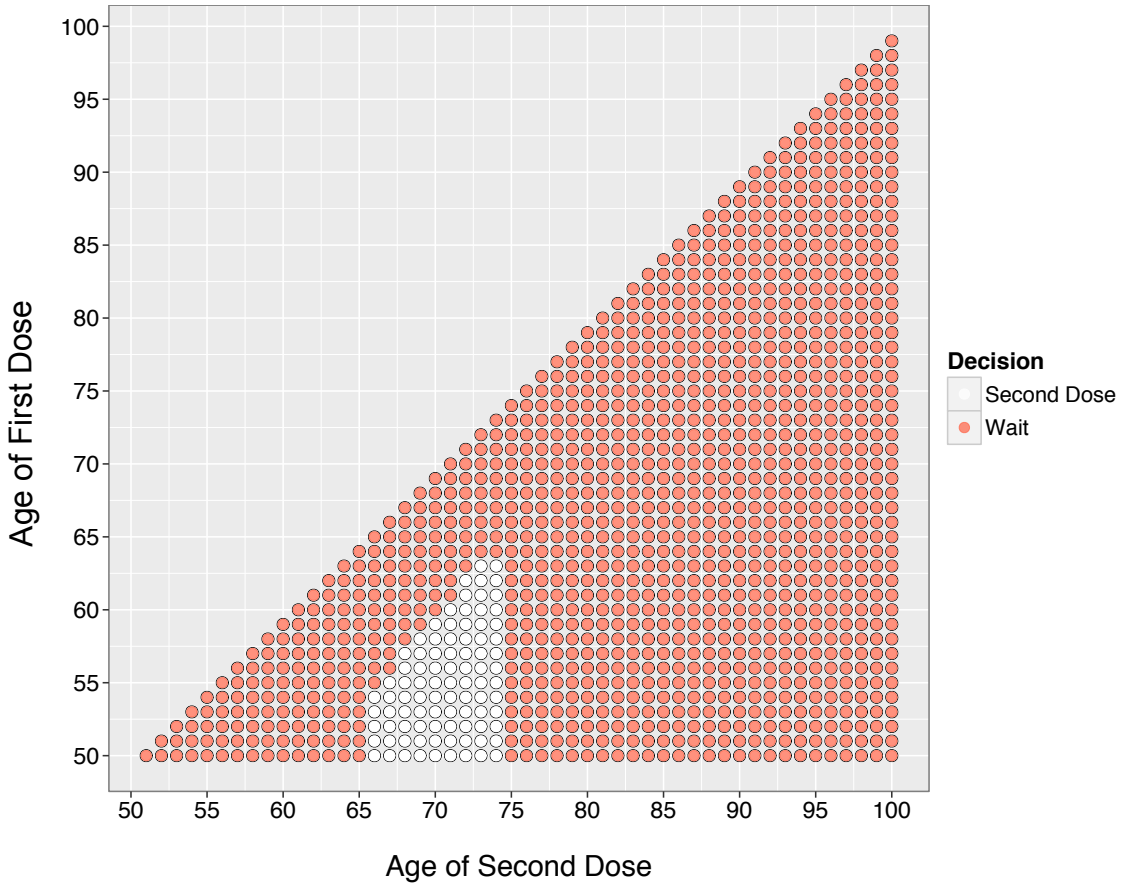

Figure 3.20: Optimal policy – two dose model – Men

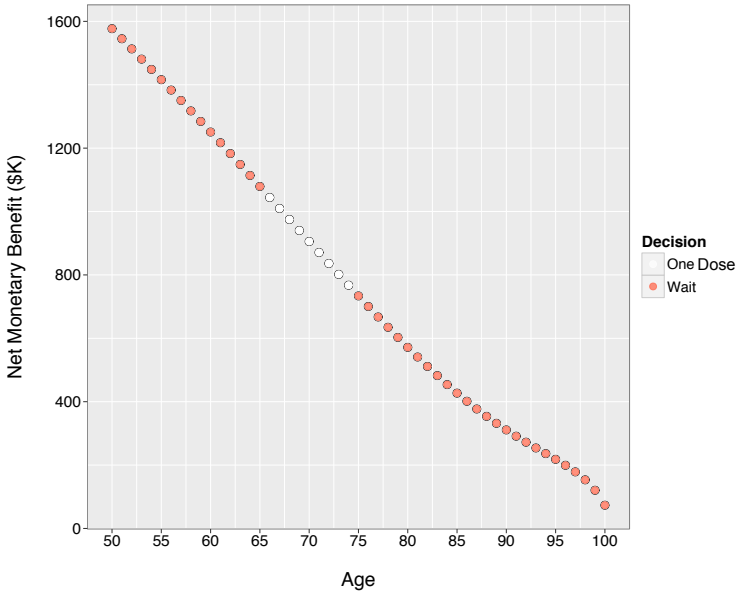

Figure 3.21: Optimal policy – two dose model, second step – Men

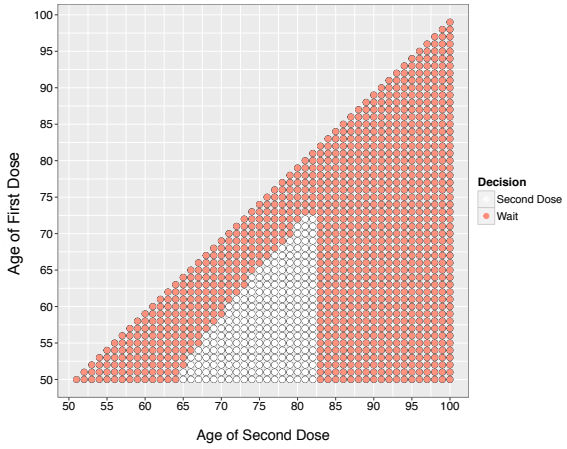

Figure 3.22: Sensitivity analysis – two dose model – initial efficacy, higher, women

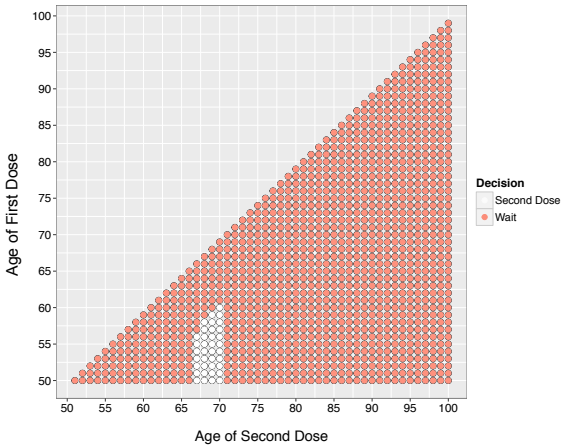

Figure 3.23: Sensitivity analysis – two dose model – initial efficacy, lower, women

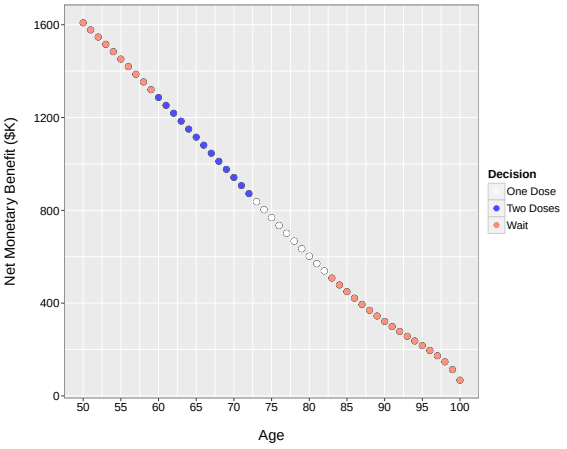

Figure 3.24: Sensitivity analysis – two dose model, second step – initial efficacy, higher, women

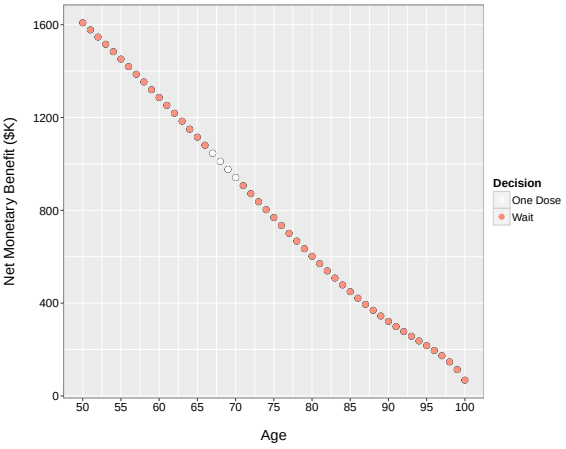

Figure 3.25: Sensitivity analysis – two dose model, second step – initial efficacy, lower, women

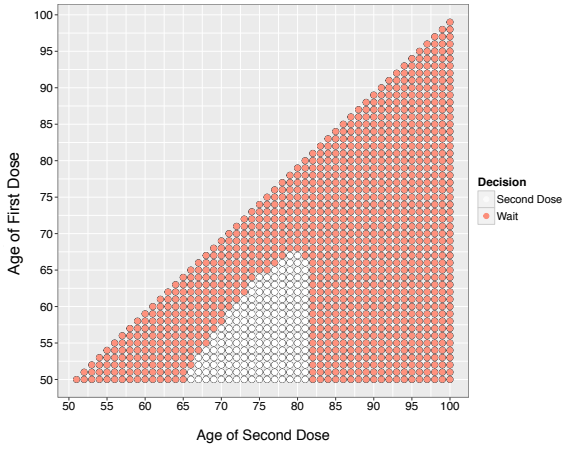

Figure 3.26: Sensitivity analysis – two dose model – waning speed, slower, women

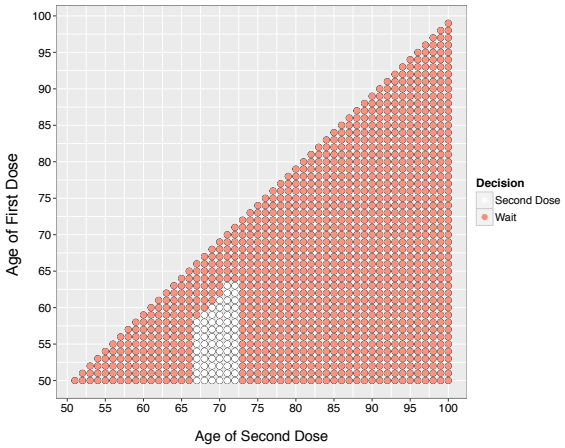

Figure 3.27: Sensitivity analysis – two dose model – waning speed, faster, women

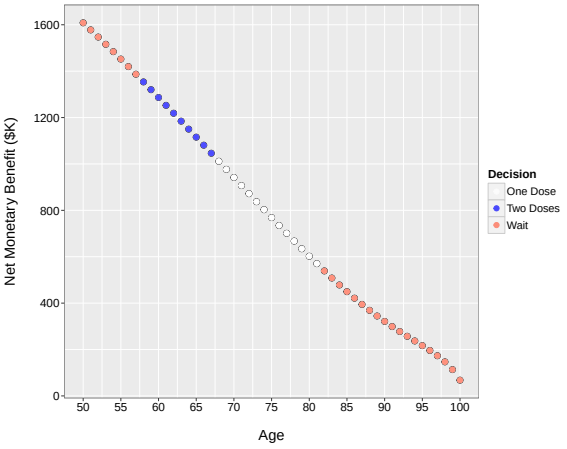

Figure 3.28: Sensitivity analysis – two dose model, second step – waning speed, slower, women

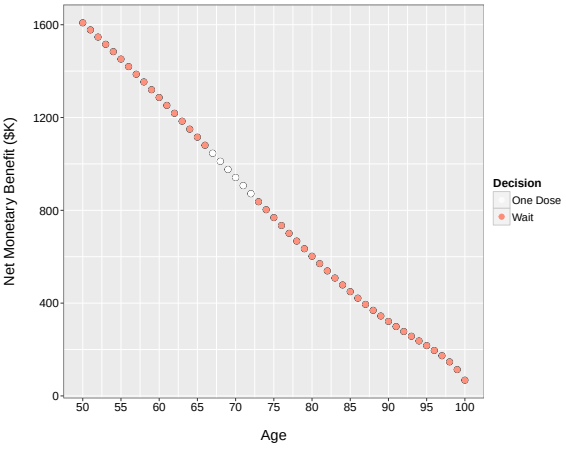

Figure 3.29: Sensitivity analysis – two dose model, second step – waning speed, faster, women

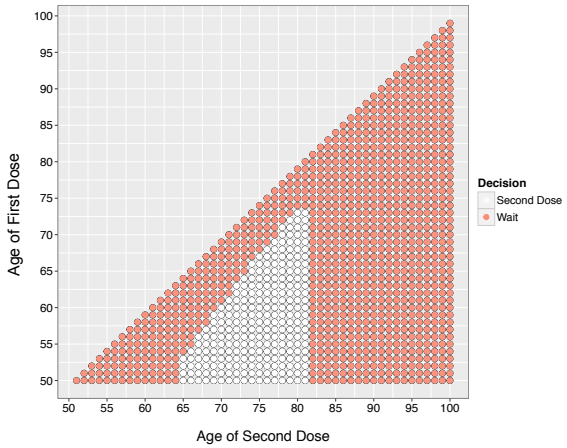

Figure 3.30: Sensitivity analysis – two dose model – p(PHN|HZ), upper, women

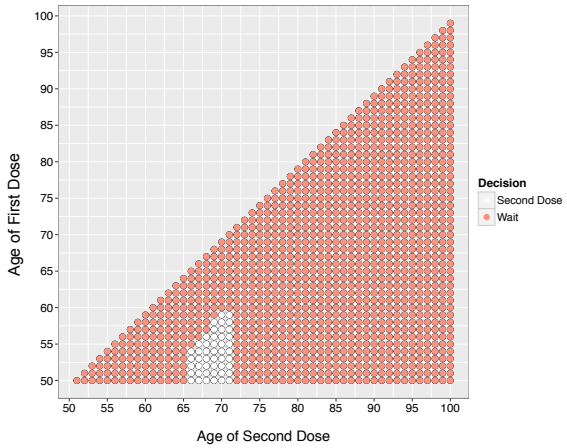

Figure 3.31: Sensitivity analysis – two dose model – p(PHN|HZ), lower, women

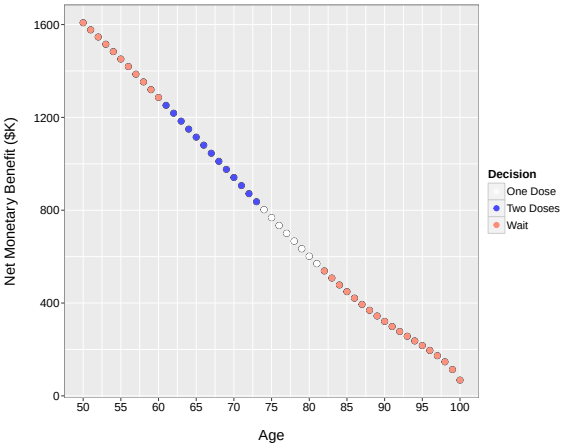

Figure 3.32: Sensitivity analysis – two dose model, second step – p(PHN|HZ), upper, women

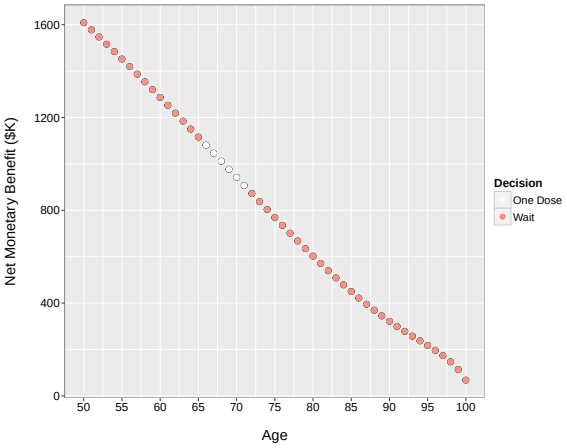

Figure 3.33: Sensitivity analysis – two dose model, second step – p(PHN|HZ), lower, women

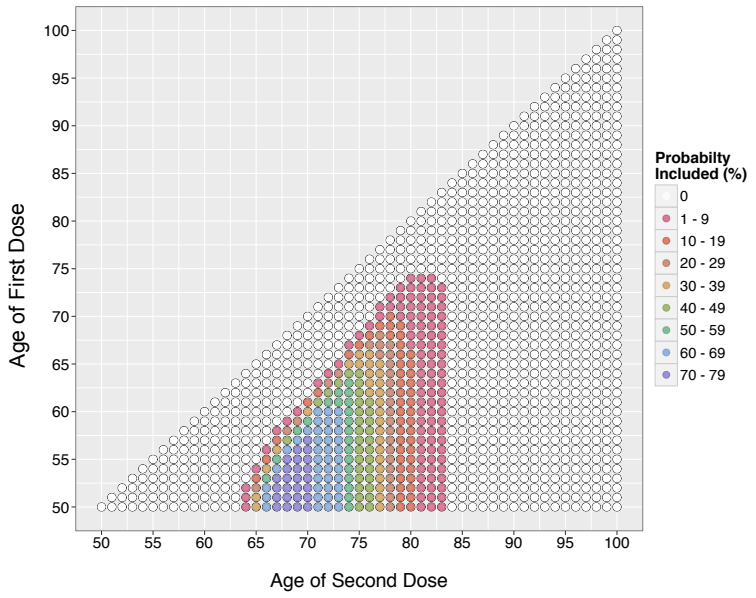

Figure 3.34: Probabilisitic sensitivity analysis – two dose model – Men

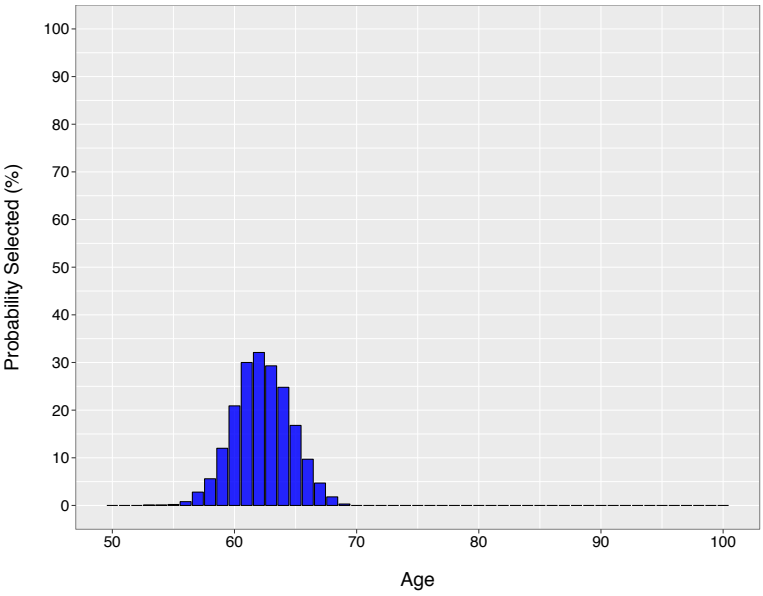

Figure 3.35: Probabilisitic sensitivity analysis – two dose model, second step – Men

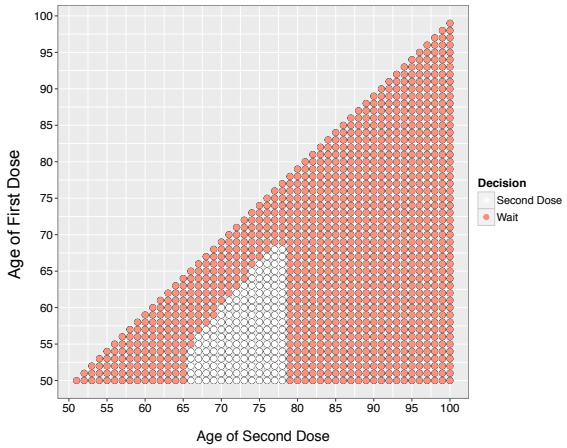

Figure 3.36: Scenario analysis – two dose model – + 2 percentage points

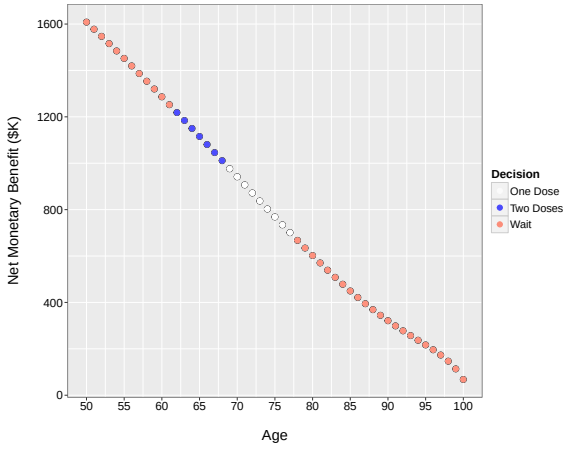

Figure 3.37: Scenario analysis – two dose model, second step – + 2 percentage points

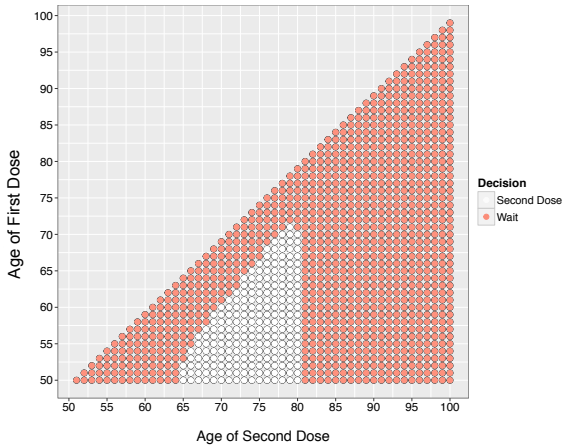

Figure 3.38: Scenario analysis – two dose model – + 5 percentage points

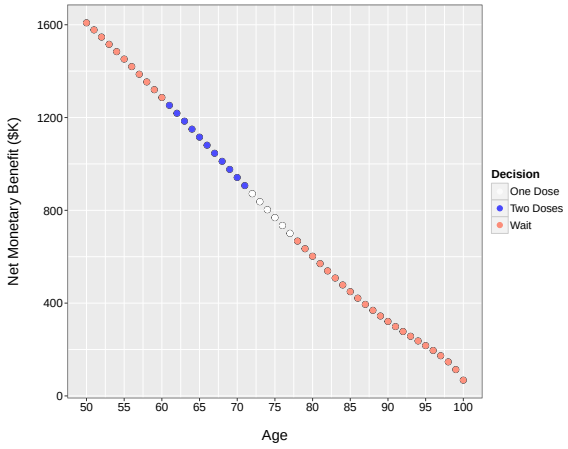

Figure 3.39: Scenario analysis – two dose model, second step – + 5 percentage points

Chapter 4

Value of Information Analysis: Vaccine Waning & Efficacy

4.1 Introduction

The objective of this chapter is to determine the value of information on the initial efficacy and waning characteristics of the herpes zoster vaccine. As shown by the previous two chapters, the waning speed of the vaccine and its initial efficacy can substantially impact the cost-effectiveness and the optimal policy. For example, in men, having a lower vaccine efficacy or a vaccine that wanes more quickly produces a policy that does not recommend vaccination at any age assuming all other parameters are held at base case values. Because these parameters can have this impact on vaccine recommendations it may be valuable to gather additional information to determine how recommendations may change. However, before any additional research is undertaken, it is important to estimate the value of the information that could be gained.

Background and Utility of Value of Information Analysis

The underlying objective of health economic evaluation is to make decisions that maximize the health gains from available resources [46–50, 55]. To make the most of

the available resources in health care, good decisions must be made, and to make good decisions two questions which must be answered [139]. First, should a technology (e.g., treatment, medication, device) be recommended? Second, is there further evidence needed to support the decision? Answering the first question is often accomplished with the aid of modeling exercises such as using a state-transition model to predict the cost-effectiveness (similar to Chapter 2, more common), or using an MDP to determine the optimal policy (similar to Chapter 3, less common). If there is sufficient evidence that a technology should be recommended, for example showing a high probability of cost-effectiveness, that provides valuable information to decision makers. However, decisions based on current information are dependent on the quality of that information [139]. Further, due to uncertainty, there is always a chance that a "wrong" decision will be made based on the current information. Therefore, if there is uncertainty in the model or model parameters, that uncertainty could impact the recommendation and additional research may be needed. Should this occur, the technology could either be recommended with a request for additional research, or not recommended until the additional research is completed. The HZ vaccine fits into the first of these two categories as it has been widely adopted around the world but further work may be needed to improve recommendations. This has been a general objective of this dissertation thus far. However, because resources are scarce, the potential value that could be gained should be quantified so as to not waste resources in the pursuit of information that may be little value to decision makers. This is the objective of value of information (VOI) analysis; to assess the potential value of additional research to help set priorities and ensure that resources are efficiently allocated. VOI analysis comes from foundations in Bayesian and statistical decision theory. These techniques have and have been applied successfully to health care in recent years for a number of different technologies [140–143] and have been used in setting research priorities [139].

4.2 Methods

To complete a value of information analysis three steps must be completed. First, a decision model must be constructed. Decision models were created for Chapter 2 and 3 as part of this dissertation. Second, the decision model must be subjected to a probabilistic analysis. This was also accomplished in Chapters 2 and 3 in doing probabilistic sensitivity analysis (PSA). Finally, a sampling algorithm must be applied to the probabilistic form of the model to determine the value of the unknown information.

Expected Value of Partially Perfect Information

It is most common to determine the expected value of perfect information (EVPI) first. EVPI selects the optimal decision under the assumption of perfect information on all model parameters. To perform an EVPI analysis, Equation 4.1 is needed. The EVPI is the difference in expected payoff assuming perfect information compared to the payoff under current information (uncertainty). In Equation 4.1, θ is the set of all unknown parameters in the model. Given these unknowns, the optimal decision that can be made is the age of vaccination j that produces the highest average net monetary benefit (NMB) (where $j \in \{\otimes, 50, ..., J\}$; where $\otimes$ designates never vaccinate). This is shown on the right side of Equation 4.1 by $\max_j E_\theta NMB(j, \theta)$.

$$EVPI = E_\theta[\max_j NMB(j, \theta)] - \max_j E_\theta[NMB(j, \theta)] \tag{4.1}$$

With perfect information, θ would be known; as a result the future outcomes of the model would be certain and the age of vaccination j that produces the maximum net benefit could be selected each time with each new set of θ parameters. This selection would be given by $\max_j NMB(j, \theta)$ [139]. However, as θ is unknown the values of simulations under perfect information must be averaged over all values of θ. This is shown on the left side of Equation 4.1 by $E_\theta \max_j NMB(j, \theta)$.

However, I am interested in the value of perfect information on two specific parameters in the model: 1) the initial efficacy of the vaccine, 2) the waning speed

of the vaccine. Therefore, this analysis will focus on the expected value of partially perfect information (EVPPI) to determine the value of those parameters rather than the EVPI which evaluates the value of perfect information for every parameter in the model. EVPPI analysis uses Equation 4.2.

$$EVPPI_{\varphi} = E_{\varphi}\Big[\max_{j} E_{\psi|\varphi}[NMB(j,\varphi,\psi)]\Big] - \max_{j} E_{\theta}[NMB(j,\theta)] \tag{4.2}$$

Equation 4.2 shares one maximization term with Equation 4.1: $\max_j E_\theta NMB(j,\theta)$. This again shows that the optimal age of vaccination, j, given all the unknown parameters, θ, is the expectation of all simulated outcomes of θ. In Equation 4.2, the two parameters of interest (initial efficacy and waning speed) are represented by φ. Assuming perfect information about these parameters, it would be possible to make a decision about the optimal age of vaccination j by averaging over all remaining unknown variables in the model (ψ, where $\psi \subsetneq \theta$). This is shown by: $\max_j E_{\psi|\varphi}[NMB(j,\varphi,\psi)]$ in Equation 4.2. However, similar to EVPI, the values of φ are not known and therefore must be averaged over their simulated values of φ (where $\varphi \subsetneq \theta$, $\varphi \cup \psi = \theta$ and $\varphi \perp\!\!\!\perp \psi$). The EVPPI analysis will always be positive or 0, but never negative. In the case of vaccination, if the optimal age j under perfect information is the same as the optimal age without information (i.e., under current information), then the value of information is zero as the decision does not change. If, under perfect information, j is different than the recommendation under current information, the NMB under perfect information will be greater than the NMB under current information, thus the EVPPI will always be ≥ 0.

Three separate EVPPI analyses were conducted. Each of these analyses used a different probabilistic modeling approach to estimate the EVPPI. The method used for each analysis will be discussed in turn below. In brief, EVPPI analysis was conducted using the MDP model structure from Chapter 3. EVPPI analysis was then completed using a forward simulation state-transition model. Finally, EVPPI analysis was completed using a non-parametric regression technique for efficient computation.

Of note, in a standard EVPPI analysis, it would be important to consider the EVPPI for every age group that could be affected by the results (e.g., people age: 50,

51, ..., 100). However, for the following analyses, I assume the perspective of a people age 64. This decision was made given the projected lifetime over which the information would be valuable. There is currently a new vaccine in development. Early trial data suggests that the new vaccine will be more efficacious than the current vaccine [136]. Because of this increase in efficacy I assume the new vaccine will be more highly utilized than the current vaccine when it is released to market. However, the new vaccine is not likely to be available to the public for 24 – 48 months. Therefore, I assume the lifetime of the information generated by this analysis of the current vaccine is approximately 3 years (36 months). Given the projections of the MDP in Chapter 3 (with 66 being the optimal age of vaccination in the base case analysis), assuming the perspective of a cohort at age 64 would allow for the information to be valuable for the next 2 – 4 years. Therefore, the decision to vaccinate can be optimized from ages 64 – 68 when it is most likely optimal to vaccinate people. If, for example, the analysis took the perspective of a 50 year old and it was optimal to vaccinate between 64 – 68, the information would have to be valuable for the next 14 – 18 years, which is unlikely given the circumstances.

MDP Structure Analysis

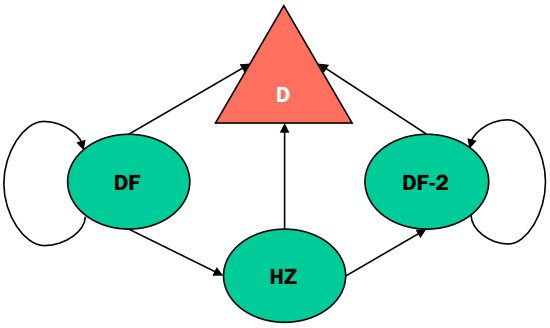

Figure 4.1: State-transition model. DF: Disease-free. HZ: Herpes zoster. DF-2: Disease free 2. D: Death.

The first EVPPI analysis was conducted using the MDP model structure from the one dose analysis in Chapter 3. Probabilistic state-transition models (STMs)

were needed to generate the data for the MDP structure. The STMs shared the same structure as the STMs used to inform the MDP analysis in Chapter 3. These models were created using R (v.3.2.3), and are shown by Figure 4.1. In the vaccination STM the cohort starts in the disease free state and each cycle has the chance to transition to the HZ state or the death state. If a transition to HZ occurs, the cohort will stay in HZ for one cycle and then either transition to disease free 2 or death, if death occurs. HZ is an all-inclusive health state that provides a cumulative estimate of the QALYs and costs with a case of HZ, which may include PHN or ocular complications. If disease free 2 is reached, the cohort will remain in this state until death occurs. The vaccination model calculates the lifetime costs and QALYs for someone who has been vaccinated at some age. The HZ natural history model starts a cohort in the HZ state at some age. Like the vaccination model, HZ is a transient state and the cohort will only spend one cycle with HZ. This model calculates the lifetime costs and QALYs for for developing HZ at some age. The probability of HZ related death was set to 0 for this analysis, and the probability of death was set to 100% at age 100. The cycle time for these state-transition models was set to 1 year. The model takes the lifetime perspective and assumes a 3% discounting per year (0.97).

Once the STMs were constructed, a sampling algorithm was implemented to generate the data needed. This sampling algorithm uses two nested levels of Monte Carlo sampling over the plausible ranges for both the parameters of interest and the remaining uncertain parameters. First, values for the initial vaccine efficacy and waning speed (φ) were drawn from their respective distributions and fixed. This was the outer loop of the sampling algorithm. Once outer values were fixed, one set of the remaining unknown variables (ψ) were drawn from there respective distributions and one probabilistic model was run; this was the inner loop of the sampling algorithm. A total of 1000 inner loops were run for each outer loop; 1000 outer loops were run creating a 1000×1000 sampling simulation.

Because the MDP structure requires data for all ages of vaccination tested, the two-level Monte Carlo simulation was required for every age from 64 (the start age of the analysis) to 100. This lead to a total of $1000 \times 1000 \times 37 \times 2$ simulations to generate the data needed for men and women. Because the HZ STM has no vaccination

component a first order Monte Carlo simulation was run to generate the data needed to estimate the lifetime costs and QALYs for those who developed HZ at some age (i.e., 1000×37×2 HZ PSA simulations). Seeding of the distributions was used to ensure continuity across all STMs.

Once all data was generated from the STMs it was implemented into the MDP structure – which was an adaptation of the model built in Chapter 3 for the one dose optimization problem. A WTP of $100,000 was used to convert all STM data to NMB for use in the MDP structure. The goal of this structure was to determine which of the possible ages of vaccination produced the highest net monetary benefit using the same backwards induction method as in Chapter 3. Models were run that fixed vaccination between the ages of 64 – 72; a no vaccination policy was also included. Note that this is MDP structure is not a true MDP as the decision is being fixed at different ages rather than the model selecting the best ages to vaccinate. The structure of the model is the same, but the decision process is fixed. The models were run using parallel processing.

After all MDP structures had been simulated, all data were averaged by age of vaccination j over all inner and outer loops to determine the optimal age of vaccination under current information j_c. Then, results for each outer loop were averaged by age of vaccination j over all inner loops. This provided the optimal age of vaccination j_p under the perfect information provided by each outer loop. The NMBs for each outer loop iteration o were evaluated by comparing j_p to j_c.

Forward Simulation Analysis

The second EVPPI analysis used forward simulation STMs to determine which age of vaccination j would produce the highest NMB. The forward simulation models were built as an adaptation of the vaccination STM presented in Figure 4.1. In the forward simulation models, a cohort started in the disease free state and had the chance to transition to the HZ state or the death state at every cycle. HZ was a one cycle transient health state, from which the cohort would either transition to disease free 2 or death, if death occurred. If disease free 2 was reached, the cohort

would remain in the disease free 2 state until death occurs. The probability of disease related death was set to 0 for this analysis, and the probability of death was set to 100% at age 100. The cycle time for this state-transition model was set to 1 year. The model takes the lifetime perspective and assumes a 3% discounting per year.

In these forward simulation models, the cohort started at age 64 and was vaccinated at age j. When vaccinated, the transition probability from disease free to HZ is reduced by the age when the vaccine was received and was adjusted by the waning function for subsequent cycles. This model fixes the time when the vaccine was given to evaluate multiple vaccination possibilities. Vaccination was fixed from ages 64 – 72, and independent forward simulations were run for each fixed age of vaccination. A never vaccinate option was also included. The forward simulation models provided the lifetime costs and QALYs for a cohort of 64 year olds who were either never vaccinated ($j = \otimes$) vaccinated at some point in the future ($j \geq 64$). Once the model structure had been set up, the same methods from the EVPPI analysis using the MDP structure were used to apply the two-level Monte Carlo simulation to the forward simulation models. One 1000×1000 simulation was run for each age of vaccination between 64 and 72. Simulations were run for men and women leading to a total of 1000×1000×9×2 simulations. Once all simulations were complete, the lifetime costs and QALYs associated with each age of vaccination were converted to NMB using the following formula: $NMB_{(joi)} = \lambda QALY_{(joi)} - Cost_{(joi)}$, where λ is the WTP, j is the age of vaccination, o is the outer loop iteration, and i is the inner loop iteration. All NMBs were averaged by j over all iterations of o and i to determine the optimal age of vaccination under current information j_c. The NMBs were then averaged by j over all values of i to determine the optimal age of vaccination the given perfection information in the outer loop j_p. Once finished, j_p was compared to j_c for each outer loop iteration to determine the EVPPI for each outer loop, $EVPPI_o$. All values of $EVPPI_o$ were averaged to determine $EVPPI_\varphi$. This procedure was done for varying WTP values from \$0 to \$1,000,000 to determine how the EVPPI changes with WTP.

Strong's Regression Analysis

One of the main issues with the two-level Monte Carlo simulation required for EVPPI is computational burden. For example, using the two-level method for this analysis requires 1000×1000×9×2 simulations using forward simulation. When the MDP was used to evaluate the same set of decisions from age 64, it would required 1000×1000×37×2 simulations to simulate the required data, plus an additional 1000×1000×9×2 simulations in the MDP to determine the same information. Using parallel processing or high performance computing (HPC) can significantly decrease computation time, however, this also assumes that the modeler has access to those technologies, and knowledge of how to best utilize them. As a result of these limitations, newer and more efficient EVPPI methods have emerged [144–148]. Strong et al have developed methods using non-parametric regression techniques to provide an efficient method to estimate the EVPPI [145–147]. This section will discuss these methods and their application to this problem.

Strong's method works by using generalized additive model (GAM) regression. Regression analysis is a useful statistical technique for estimating relationships between variables. Linear regression is perhaps the most commonly used method, however, many relationships do not follow a linear form [149]. GAM regression is a flexible method that can be used for estimating non-linear relationships. This method alters the typical regression equation by replacing coefficients with functions. These functions are then predicted based on the data available. A benefit of GAM models is that no prior assumption is required about the distributional form of the function, which is what makes these models flexible and 'non-parametric'. Functions are predicted using an algorithm that smooths the relationship between the data [149].

In order to utilize this method, steps need to be taken to alter the EVPPI equation (Equation 4.2). First, as shown in Equation 4.3, the right maximization term is changed using the the Law of Total Expectation and the independence between φ and ψ.

$$EVPPI_{\varphi} = E_{\varphi}\Big[\max_{j} E_{\psi|\varphi}[NMB(j,\varphi,\psi)]\Big] - \max_{j} E_{\varphi}\Big[E_{\psi|\varphi}[NMB(j,\varphi,\psi)]\Big] \quad (4.3)$$

Once this change has been made, the inner expectation, $E_{\psi|\varphi}[NMB(j,\varphi,\psi)]$, can be manipulated. This expectation will be reframed as a regression problem. This is done in three steps. First, results from a probabilistic sensitivity analysis (PSA) of N samples, indexed by $n = 1, ..., N$, are needed. Given these N PSA samples, it is possible to express the net monetary benefit for the age of vaccination j using PSA sample n as a conditional expectation plus an error term; shown by Equation 4.4 [147].

$$NMB(j,\theta^{(n)}) = E_{\psi|\varphi^{(n)}}[NMB(j,\varphi^{(n)},\psi)] + \epsilon^{(n)} \tag{4.4}$$

Once the inner expectation is reframed, it can be seen that Equation 4.4 changes for each value of $\varphi^{(n)}$. This implies that NMB can be written as some unknown function $f(j,\varphi)$. This is then used to determine the net monetary benefit for each of the N PSA simulations. This is shown by Equation 4.5 [147].

$$NMB(j,\theta^{(n)}) = f(j,\varphi^{(n)}) + \epsilon^{(n)} \tag{4.5}$$

The final step is to make the following assumption. For each age of vaccination j ($j \in \{\otimes, 64, 65, ..., J\}$), we assume that the net benefits produced by the different values of the PSA $\{NMB(j,\theta^{(1)}), ..., NMB(j,\theta^{(N)})\}$ represent the data that can be regressed to learn about the target function: $f(j,\varphi^{(n)})$. This can be thought of as solving J total regression problems. Once a GAM model was fit for each of the J options, the fitted values were extracted. These are denoted by: $\{\hat{f}(j,\varphi^{(1)}), ..., \hat{f}(j,\varphi^{(N)})\}$. Once these values were extracted, the estimated EVPI is given by Equation 4.6 [147].

$$\widehat{EVPPI}(\varphi) = \frac{1}{N}\sum_{n=1}^{N} \max_j \hat{f}(j,\varphi^{(n)}) - \max_j \frac{1}{N}\sum_{n=1}^{N} \hat{f}(j,\varphi^{(n)}) \tag{4.6}$$

R was used to accomplish Strong's method for EVPPI. First, second order Monte Carlo PSA was performed on the forward simulation models described in the previous section. To run the PSA models, the two-loop algorithm was replaced with a single loop and 1000 samples from the same distributions used for the MDP structure and the forward simulations. Once the PSA was completed, I utilized the R code that had

been previously published online by Strong et al as part of the Sheffield Accelerated Value of Information (SAVI) tool to perform the EVPPI [150]. Mark Strong's GitHub repository provided the R code to perform regressions and EVPPI calculations (using Equations 4.4 – 4.6) with PSA output from any model. Upon deconstructing his code, I was able to modify it to determine the age of vaccination that provided the highest NMB. Using this information I was able to generate policy plots to determine what the optimal age of vaccination would be given perfect information on vaccine parameters. Given the computational efficiency of this method, I tested several starting ages from 62 – 68, with each analysis fixing vaccination at every age between the starting age – 72 (e.g., 62 – 72,..., 68 – 72). A scenario analysis was conducted which shortened the time horizon of the model from lifetime to three years for completeness.

Population EVPPI

Once all simulations had been completed, the population EVPPI was calculated. Population EVPPI is the EVPPI scaled up to the population level to determine the upper bound for the value of the information. For both the MDP and forward simulation models, the number of 64 year old men and women in the United States [8] was multiplied by the EVPPI for men and women, respectively. For results using Strong's method, multiple starting ages were tested. The EVPPI for men and women was multiplied by their respective population sizes to give the population EVPPI for different age groups.

Model Inputs

Table 4.1 provides the distributions for the EVPPI analysis. These distributions were used in both two-level Monte Carlo simulations for EVPPI and the GAM regression models.

Variable	**Distribution**	**Category**
Vaccine – Initial Efficacy**	$\mathcal{N}(0, 0.035)$	φ
Vaccine – Waning Rate*	$\mathcal{N}(1, 0.12)$	φ
Probability – HZ* – *asymp*	$ln\mathcal{N}(0, 0.099)$	ψ

Variable	Distribution	Category
Probability – PHN* – b_1	$ln\mathcal{N}(0, 0.295)$	ψ
Probability – Ocular Complications**	$\mathcal{N}(0, 0.01)$	ψ
Cost – HZ	$\Gamma(106.143, 1/18.021)$	ψ
Cost – PHN	See page 218	ψ
Cost – Ocular Complications	$\Gamma(41.961, 1/99.201)$	ψ
Cost – Vaccine	$\Gamma(23.33, 1/7.5)$	ψ
Cost – Vaccine Administration	$\Gamma(2196.6, 70)$	ψ
Cost – Vaccine Severe Reactions	$\Gamma(18, 100)$	ψ
Disutility – HZ	$\beta(24.39, 804.59)$	ψ
Disutility – PHN	See page 218	ψ
Disutility – Ocular Complications	$\beta(16.4, 254.81)$	ψ
Disutility – Common Vaccine Complications	$\beta(6, 6000) \times (30/365)$	ψ
Disutility – Severe Vaccine Complications	$\beta(2.13, 100000) \times (30/365)$	ψ

Table 4.1: Parameter distributions for EVPPI. * – A parameter was sampled and added to base case parameter value. ** – A scaling factor for the parameter was sampled and multiplied by the base value for that parameter.

4.3 Results

Results from the three EVPPI analyses will be presented in order. A comparison of the computation times of the methods will be shown at the end of the results section.

MDP Model

The EVPPI for women starting at age 64 and a WTP of $100,000 is $0.68. For men, the EVPPI is projected to be $1.52. For the cohort of all 64 year old women and men in the US the population EVPPIs are estimated to be $1,248,843 and $2,523,492, respectively. The total EVPPI is $3,772,335. Figure 4.2 shows the recommended policy for vaccination given perfect information on the vaccine, for women assuming

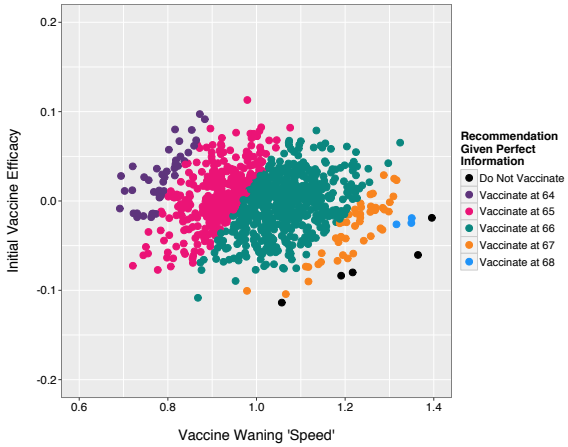

Figure 4.2: Policy Plot – Women age: 64 – MDP. Waning speed: relative change. Initial vaccine efficacy: additive change

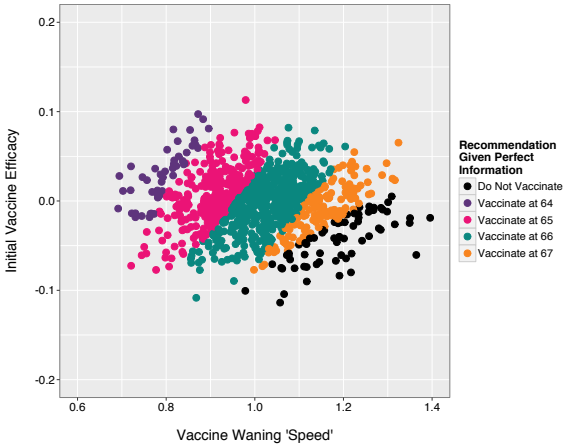

Figure 4.3: Policy Plot – Men, age: 64 – MDP. Waning speed: relative change. Initial vaccine efficacy: additive change

a WTP of $100,000. If the base case values for vaccine efficacy and waning were the "true" values (i.e., 0.00, 1.00, respectively), Figure 4.2 shows that it would be optimal to vaccinate at age 66. Only if the vaccine waning speed was very slow, approximately 30% slower than the base case, would it be optimal to vaccinate as early as 64. The figure also shows that if the vaccine was fast waning and had a lower initial efficacy, there are circumstances when it would not be optimal to vaccinate women. Under current information, for women and men, the policy would recommend vaccination at age 66.

Forward Simulation

Figures 4.4 – 4.5 show the EVPPI for 64 year old women and men at varying WTPs between $0, and $300,000, respectively. For women the highest EVPPI is at a WTP of $50,000. Here EVPPI equals $9.42. For men, EVPPI is greatest at a WTP of $70,000. At this WTP, EVPPI equals $11.19. Figure 4.6 shows the population EVPPI for men and women. At the WTP corresponding to the highest EVPPI values for women and men, the population EVPPI equals $17,070,360 and $18,504,254, respectively. For men and women, at a WTP of $100,000 the EVPPI was equivalent to the MDP

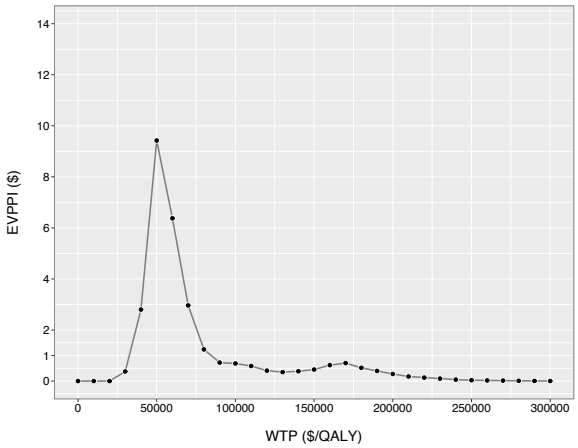

Figure 4.4: EVPPI – Women, age: 64 – forward simulation

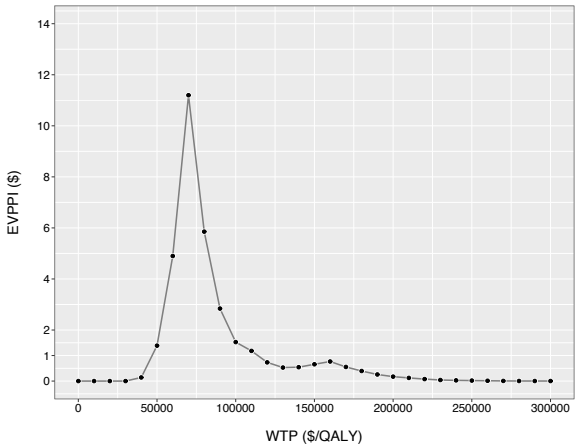

Figure 4.5: EVPPI – Men, age: 64 – forward simulation

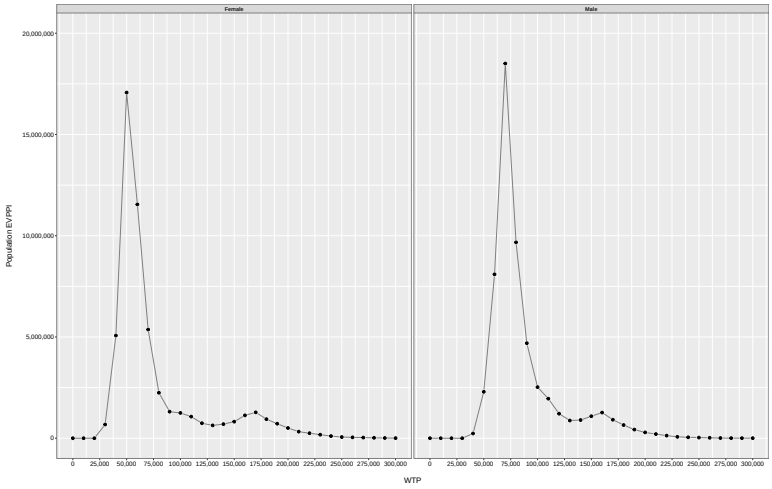

Figure 4.6: Population EVPPI – forward simulation

structure simulation at $0.68 and $1.52 for women and men, respectively.

Figure 4.7 shows the policy results of the optimal vaccination policy given perfect information for women at varying levels of WTP. It also shows the optimal policy under current information. At a WTP of $50,000/QALY for women under current information, it would be optimal to never vaccinate. Conversely, with perfect information, it would be optimal to vaccinate people as early as age 65. For vaccination to be optimal for women given a WTP of $50,000/QALY, the vaccine must have a higher initial efficacy, a slower waning rate or a combination of both. Figure 4.8 shows the policy results for men. At a WTP of $70,000/QALY it would be optimal to vaccinate at age 66 under current information. Under perfect information, if the vaccine has faster waning or lower initial efficacy, it would be optimal to never vaccinate.

Assuming a WTP of $100,000, it would be optimal to vaccinate a cohort of 64 year olds at age 66 assuming that the base case assumptions about the vaccine efficacy and waning were the "true" values. However, the policy plot also shows that a slight increase in vaccine efficacy or a slight decrease in waning speed would shift the recommendation to vaccination at age 65. Under current information, assuming a WTP of $100,000 we would recommend vaccination at age 66. The policy plots help to interpret the why the EVPPI may be higher at certain WTPs than others.

Strong's Regression Method

Individual and population EVPPI results are presented in Figures 4.9 – 4.12. Figures 4.9 – 4.10 show the individual EVPPI results for women and men at varying WTPs, respectively. The highest EVPPI for women is at a WTP of $50,000 with a value of $9.88 (vs. $9.42). For men, the highest EVPPI is $11.62 (vs. $11.19) at a WTP of $70,000. Scaled to the population level, the EVPPI is $17,910,454 and $19,216,874 for women and men, respectively. At a WTP of $100,000/QALY the EVPPI is $2.04 and $0.91 for men and women, respectively. The EVPPI results from Strong's method are marginally greater at every WTP compared to forward simulation and the MDP model.

Figure 4.11 shows the population EVPPI results for starting ages between 63 – 67

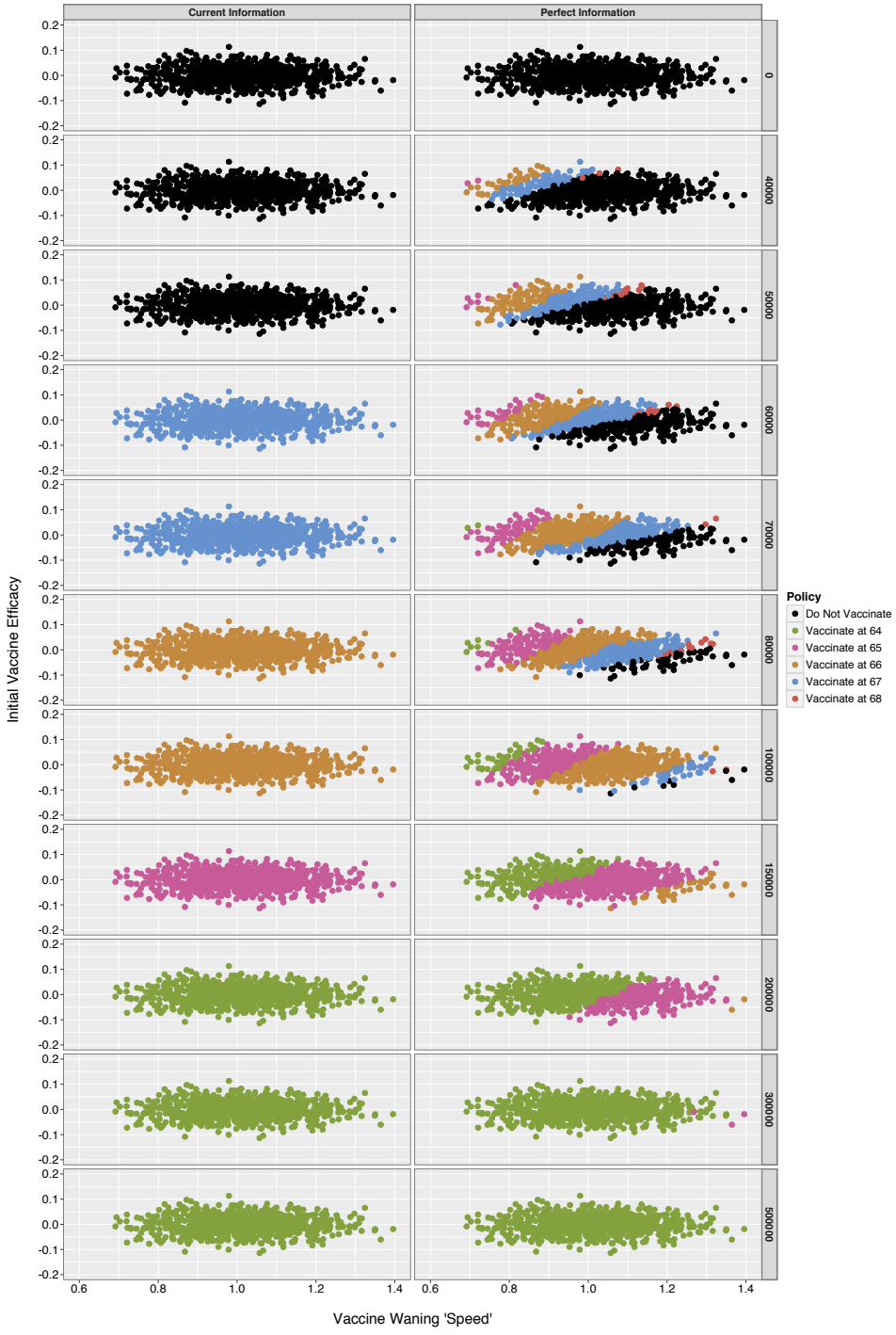

Figure 4.7: Policy Plot – Women, age: 64 – forward simulation. Waning speed: relative change. Initial vaccine efficacy: additive change.

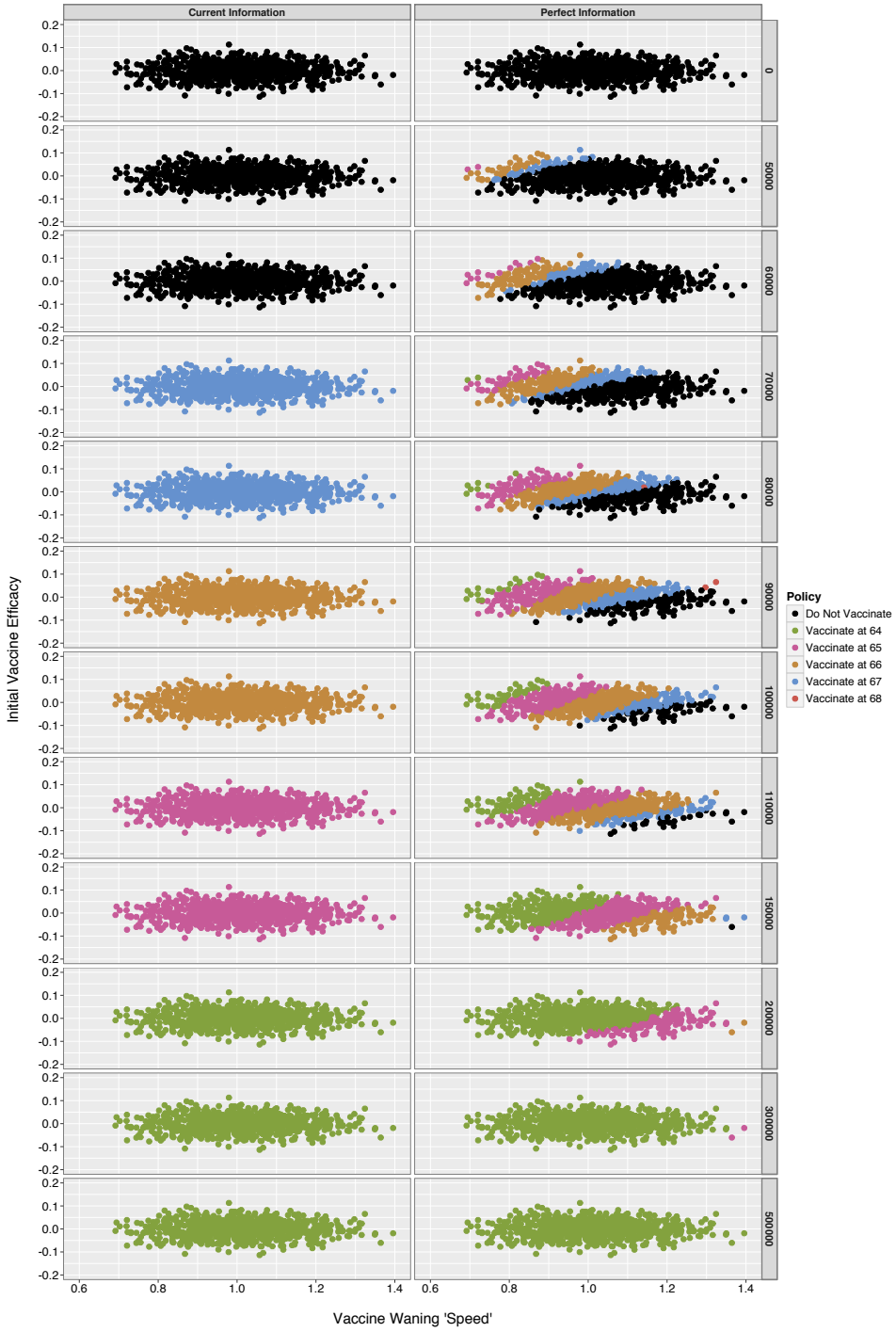

Figure 4.8: Policy Plot – Men, age: 64 – forward simulation. Waning speed: relative change. Initial vaccine efficacy: additive change.

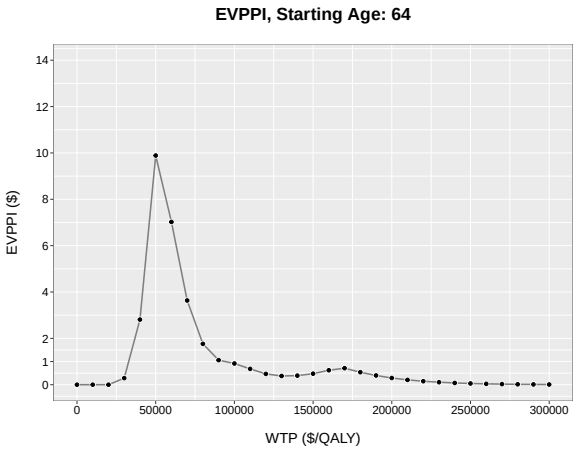

Figure 4.9: EVPPI – Women, age: 64 – Strong's Method

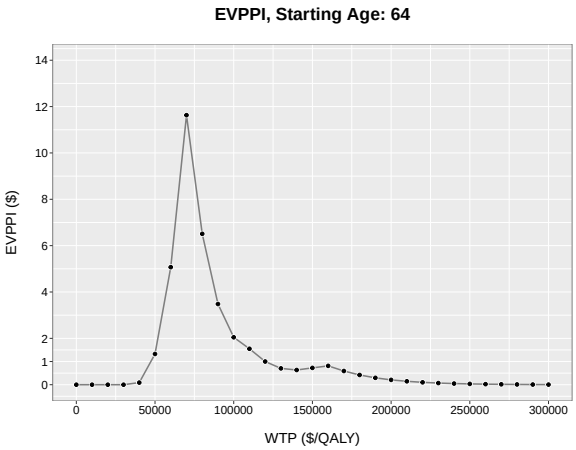

Figure 4.10: EVPPI – Men, age: 64 – Strong's Method

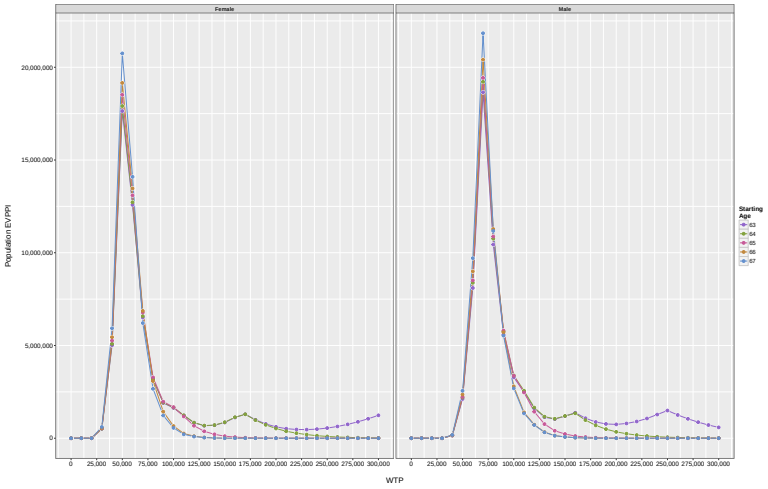

Figure 4.11: Population EVPPI – different staring ages – Strong's method

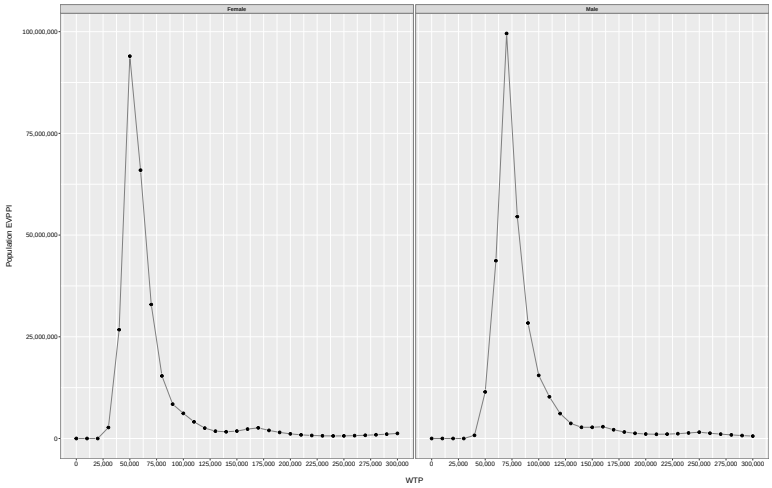

Figure 4.12: Population EVPPI – all ages combined – Strong's method

at varying levels of WTP. Results suggest information may be more valuable to men than women, and more valuable to younger ages than older ages. When combining all possible starting ages together, as shown by Figure 4.12, the highest values of population EVPPI for men and women between the ages of 63 – 67 are $99,542,341 and $93,967,997, respectively. At a WTP of $100,000 the population EVPPIs for the same groups of men and women are $15,516,265 and $6,177,378, respectively. The total population of men and women between 63 – 67 is 17,191,928, which equates to an average EVPPI of $1.26 / person at a WTP of $100,000.

Policy results for a cohort of 64 year old women are presented in Figure 4.13. Policy results for women and men starting between ages 62 – 68 can be found in Figures 4.15 – 4.27 on pages 155 – 167 in the end of chapter appendix. For a cohort of 64 year women, this figure shows nearly the same results as the Figure 4.7 from the forward simulation. The policy results indicate that under a WTP of $100,000 and assuming that the base case assumptions about the vaccine's efficacy and waning were the "true" values, that 66 would be the optimal age for vaccination. If the vaccine was more efficacious or the vaccine had a slightly slower waning rate then it would be optimal to vaccinate at age 65. Under current information, age 66 would be the optimal age for vaccination. As WTP increases, the age of vaccination under

current information decreases. Under perfect information the younger ages for optimal vaccination increase in presence on the plots, moving in from the left side. This trend can be seen on all policy plots (see Figures 4.7 and 4.15 – 4.27).

In examining Figures 4.15 – 4.27, for women, the earliest age where vaccination is recommended under current information is 63, for a cohort starting at age 62 assuming a WTP of $500,000. Under perfect information, WTP needs to be at least $500,000 for vaccination at age 62 to be included as an option. For men, vaccination at age 62 is considered optimal under current information at a WTP of $500,000. At ages 67 – 68, the current policy has nearly the same recommendation as the policy under perfect information for WTPs above $100,000.

Comparison of Method Efficiency

This section outlines the differences between the methods in terms of computation time. As mentioned previously, two-level EVPPI can be computationally and time intensive. Table 4.2 shows the computation time that was required to generate the data for each of the possible methods for this chapter. This table only presents the data generation times, not data analysis times. All computation was done on the same computer and parallel processing was used when possible (*not* used for Strong's methods). For parallel processing, eight CPU cores were used for each simulation on an Intel Core i7-2600 3.4GHz processor with 8.00GB of ram. Profiling methods used during the analysis, showed the processor working at 100% capacity; RAM was not highly utilized during computations. This indicates that the run times were limited by processor capability, not memory capability. Table 4.3 shows the computation time that would be required to process the data generated in Table 4.2.

Data generation for using a MDP model structure requires both more data generation and processing time. An important distinction about this method is that the processing times listed in Table 4.3 are for only one value of WTP. This is due to the nature of the MDP structure, where costs and QALYs must be first converted into NMB before they can be analyzed in the model; thus the MDP must be run again for each new WTP. Conversely with forward simulation, the costs and QALYs

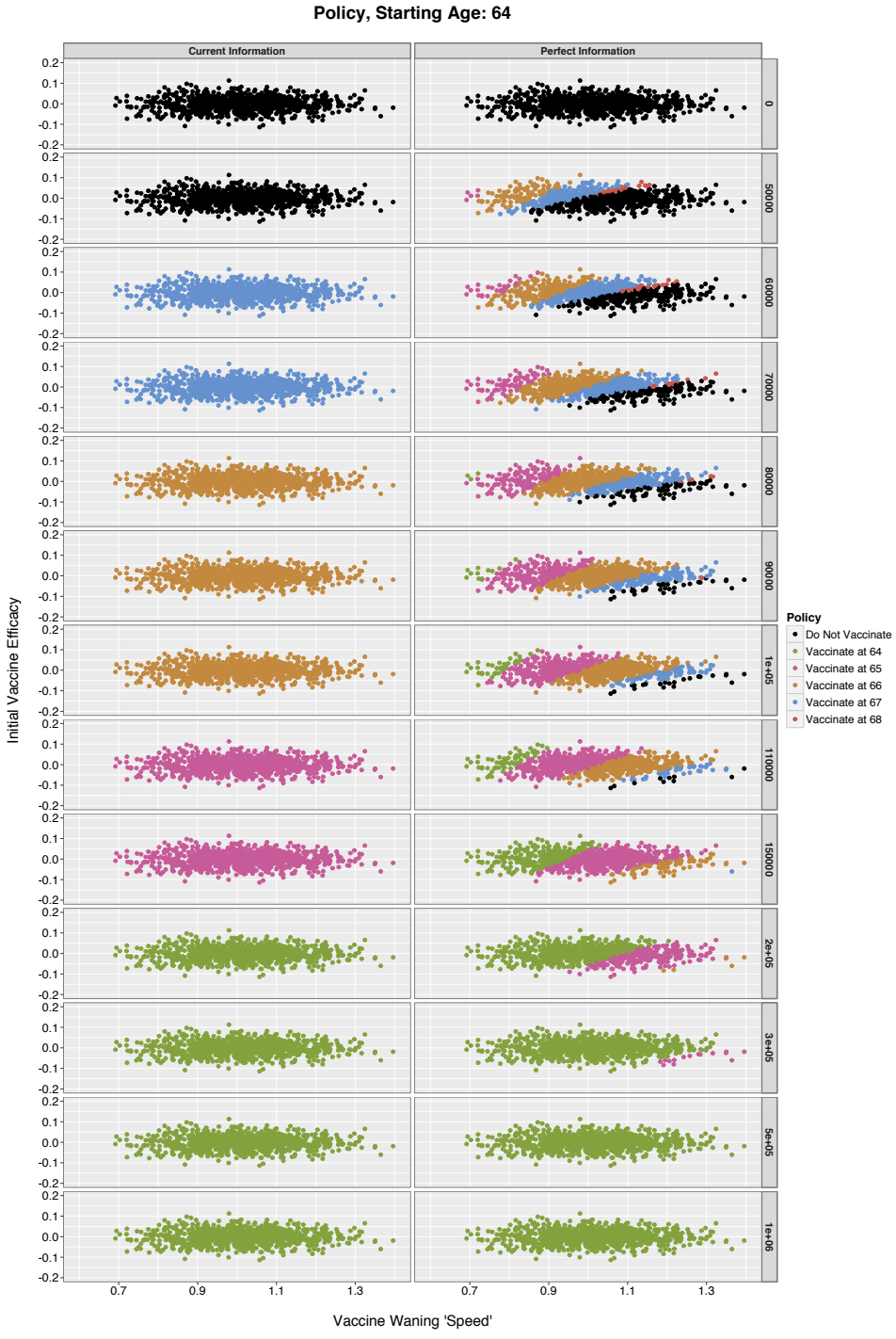

Figure 4.13: Policy Plot – Women, age: 64 – Strong's Method. Waning speed: relative change. Initial vaccine efficacy: additive change.

generated by the model reflect the lifetime costs and QALYs of cohort starting at 64 and being vaccinated at some age j. These costs and QALYs can be converted to NMBs easily. Analysis time results show that generating a 1,000 sample PSA and calculating the EVPPI using Strong's methods was more than 4 times faster than just processing the data for the 1000×1000 forward simulation (3.66 min vs. 15 min).

Method	**Model Iterations**	**CPU time**
MDP	1000×1000×37×2	52 hours
Forward simulation	1000×1000×13×2	31 hours
Strong's method	1000×13×2	3 min

Table 4.2: Computation times for data generation for EVPPI analysis

Method	**'Outer loops' for φ**	**CPU time**
MDP*	1000	7 hours
Forward simulation**	1000	15 min
Strong's method**	1000	20 seconds

Table 4.3: Computation times for data processing for EVPPI analysis. For one gender only. * – For one value of WTP ($100,000) only. ** – For 31 values of WTP ($0 – $300,000, by $10,000)

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Scenario Analysis

Figures 4.28 – 4.29 in the end of chapter appendix provide the results of the scenario analysis where the time horizon of the model was shortened to three years. In this scenario the cohort started at age 64 but only decisions to vaccinate at $\otimes$, 64, 65, and 66 were allowed (given the truncated time horizon). Results indicate that with a truncate time line, the value of information is $0 for all WTP less than $200,000 for women and $260,000 for men. Once a high enough WTP was reached ($210,000 for women, $270,000 for men) some of the simulation results suggest that there would be circumstances where it would be optimal to vaccinate at age 64. Similar to all previous results, the EVPPI was highest when the distribution of simulation results

was approximately equivalent between no vaccination and vaccination at age 64; this can be seen by examining the policy plots in Figures 4.30 and 4.31. Vaccination at 65 or 66 was never recommended under the truncated time horizon model.

4.4 Discussion

The objective of this chapter was to determine the value of additional research for two of the key parameters from both of the previous chapter analyses. Results from the cost-effectiveness and from the MDP indicated that the initial efficacy of the vaccine and its waning speed could have a substantial impact on the results. These parameters were considered to be the most important for determining the value of perfect information. In this chapter I used three different modeling techniques to assess the value of information for these parameters. The results from the analyses provide some useful insight.

The EVPPI was greatest when the simulation results were approximately equally distributed between never vaccinate or vaccinate at some age under perfect information. This can be seen by comparing the policy plot figures to the EVPPI figures. For women, the highest value of information came at a WTP of $50,000. In this situation, under current information, the recommended policy would be to not vaccinate, and under perfect information, approximately half of the points in the policy plot recommended vaccination. For men, the highest EVPPI was at a WTP of $70,000. At this WTP, the optimal vaccination strategy for (every cohort younger than age 68) was vaccination at age 67. Under perfect information, approximately half of points in the policy plot recommend no vaccination.

As WTP increases, results shift to include more simulation results in favor of vaccination vs. no vaccination. As this happens the value of information decreases. As WTP increased younger ages move in from the left hand side, "pushing" the older ages to the right. This observation has a logic to it. If the policy plots were divided into quadrants (an example is shown in Figure 4.14) the NW quadrant would be the best possible quadrant for the vaccine. Here, the vaccine is waning slowest, and has a higher initial efficacy. It is in this quadrant that younger ages for vaccination appear

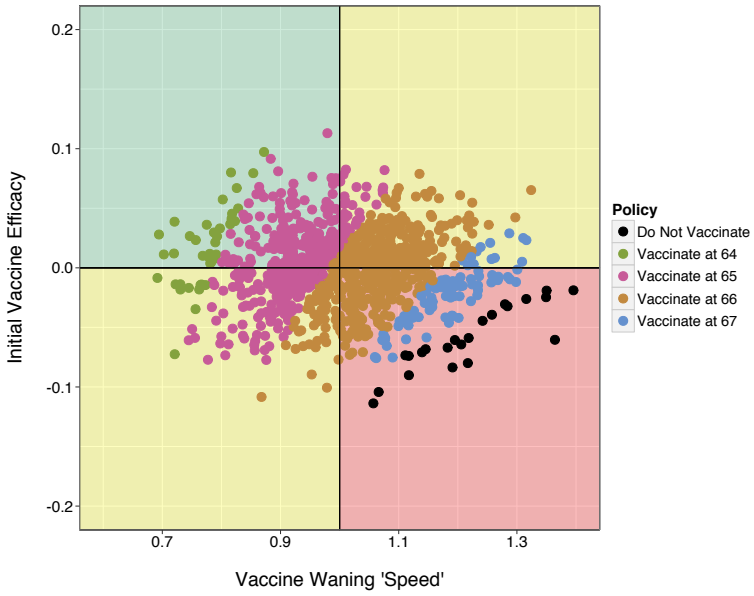

Figure 4.14: Quadrant plot – Women – Age: 64 – Strong's Method – WTP: $100,000

first. If we knew with certainty the vaccine would wane more slowly and would have a higher initial efficacy it would seem reasonable to recommend vaccination at earlier ages as the vaccine would confer more benefit for longer.

Conversely, the SE quadrant would be the worst for the vaccine. Here, the vaccine would be waning quickest and have the least initial efficacy. It is in this quadrant where the oldest ages or do not vaccinate are the most common. Given these characteristics, it would be logical to postpone vaccination until a time where the vaccine could be administered to those at higher risk. The NE and the SW quadrants assume that there fast waning with higher initial efficacy, or slower waning with lower initial efficacy, respectively. Compared to the SW, the NE quadrant has more older ages were vaccination is recommended. For example, for 64 year old women, under WTPs from $50,000 – $70,000, age 68 is recommended as an optimal policy in only the NE quadrant. This suggests that even under fast waning conditions, a higher initial efficacy could make vaccination optimal at older ages. Based only on a visual comparison of these plots it appears that the vaccines waning speed has more of an impact on recommending lower ages of vaccination than does the vaccines efficacy, as

younger ages are more frequent in the SW quadrant compared to the NE.

Analyses suggest that there is a high value in determining the uncertain information at WTPs associated with the greatest decision uncertainty. At lower WTPs under perfect information no vaccination would be recommended approximately 50% of the time (assuming vaccine characteristics in the SE quadrant). However, assuming a WTP of $100,000 or more, which is not unreasonable for the US [75, 151], the value of information about these parameters declines. Therefore, the most value occurs with the decision to vaccinate or not, not in the ability to optimize when the vaccine would be given. That is there may only be a marginal value in determining the perfect information to change the optimal recommendation by one or two years. Further, as one moves to older starting ages (e.g., 67 – 68), the VOI at higher WTP drops to near zero or zero. This is because there is not as much "room" to optimize the decision. For example at a WTP of $200,000 for women starting at age 62 there are four optimal decisions under perfect information (vaccinate between 63 – 67, depending on information). Comparatively, for women at age 67 there is only one optimal decision given perfect information (vaccinate at 67). At 67 the perfect information matches the current information, thus the information is not valuable.

Despite the value of information on an individual basis being low, the population EVPPI for this analysis was high. This is due to the population at risk for disease; with an estimated 90% or greater of the US population being at risk for HZ. For a group of 64 year olds the population EVPPI was still greater than $3.5 million at a WTP of $100,000. If we assume that the WTP in the US is at least $100,000 and decision makers were only interested in 64 year olds, the additional research would need to cost less than $3.5 million to be recommended. The type of research needed would likely be a clinical trial with several years follow-up. The price of clinical trials varies considerably, with an approximate range of $1million – $100million or more [152]. It could be possible to use observational data to answer this question. However, that could also be costly unless data collection infrastructure was already in place. Given the new vaccine on the horizon [136], there are fewer age groups where the information would be valuable. Figure 4.12 does indicate that if more ages could be affected the value of information could be quite high. Overall, while there may a

lower value of information about determining the optimal age, it does not mean this information is value-less. However, given the constraints with a new vaccine coming to market and the higher WTP in the US [75, 151], the additional research needed to be able to optimize the delivery from current information over the small $1-2$ year window would not likely be worth the investment.

A potential limitation to these conclusions is the data used for the models. VOI assumes that perfect information would be known and indeed could be known to the decision maker. The data used here encompasses a wide range or possible options and based on our understanding of the disease and the vaccine I have confidence that the 'true' value of the parameters tested would be within the distributions used. Further, the results of the policy ploys show that there are ranges within the results under perfect information, so while it may never be possible to gain perfect information, narrowing the range on what the 'true' value is would still allow for further optimization. However, narrowing the range would not provide as much value as determining perfect information and we have shown that obtaining perfect information is not likely to be worth the investment at this time.

Model Comparisons

One unique feature about this analysis was the use of three different methods to compare the EVPPI. The first method utilized was the MDP where the decisions were fixed to determine which age would produce the best age. This MDP structure did use backward induction, but it did not use the same maximization function implemented in Chapter 3, rather the model was using a fixed policy. This fixed policy was then used to determine the NMB at every age which could then be used to determine the optimal age of vaccination.

Because the MDP structure was using a fixed policy rather than an optimization policy, it was able to be replicated as a forward simulation. Turning the backward induction model into a forward simulation had several advantages. First, no additional data was needed to run the model. A MDP structure requires a large amount of data. Generating this data was the biggest time constraint in using the MDP structure as

shown by Table 4.2. To run the MDP structure for one gender required 37 vaccine STMs, each run for a two-level 1000×1000 Monte Carlo (i.e., 37,000,000 STMs). PSA was also required for the lifetime costs and QALYs of developing HZ. Once all the data was generated, it was run through the MDP structure. Therefore 1,000,000 MDPs were run for each fixed age of vaccination. Conversely, the forward simulation started a cohort of people at age 64 and then fixed the vaccination policy at some age in the future. Because this model included the chance of HZ and the benefit of vaccination, no additional data was needed. Therefore, each age of vaccination tested only required a 1000×1000 two-level Monte Carlo implementation. This drastically decreased simulation and analysis time. Another benefit of the forward simulation is that the model provided the lifetime costs and QALYs associated with the fixed vaccination policy for the cohort starting at age 64. The STM data needed for the MDP model only provided the lifetime costs and QALYs for being vaccinated at some age but did not include the prior risk of disease – that is the goal of the MDP structure to determine. Therefore, to determine the NMB for each of these are very different tasks. For the MDP structure, all input data must be converted into NMBs using a predefined threshold of WTP/QALY and then run through the MDP structure to determine the value of the fixed policy. This takes approximately 7 hours. Conversely, the forward simulation already provides the lifetime costs and QALYs of each possible policy assuming prior risks. To convert to NMB, a WTP can be applied directly to the QALYs and costs are then subtracted. This process takes less than two seconds even with a large amount of data. Because in the forward simulation this conversion is a simple multiplication and subtraction problem, many more WTPs can be tested much faster compared the MDP structure. Therefore, in comparing forward simulation the MDP structure for the purposes of EVPPI, it is evident that the forward simulation is a faster method for this problem; this is shown in Tables 4.2 – 4.3.

In comparing the forward simulation method to Strong's regression method it is obvious there is another large advantage in computation time. Strong's method is also simpler as all that is required is a second order Monte Carlo PSA; this method does not require a complicated two-level sampling algorithm. The pattern in the

results is nearly the same under the same WTP, Figures 4.7 and 4.13 are nearly identical. When comparing the results of the EVPPI analysis in terms of magnitude, Strong's method does produce a EVPPI that is higher than the EVPPI produced by the gold standard two-level Monte Carlo methods. Indeed, Strong recognizes that his method does add an upward bias to the results [145–147]. This upward bias is a limitation of this method. In this research, the maximum impact of this bias was seen at the from a WTP range of \$50,000 – \$70,000/QALY which were the WTPs that produced the largest EVPPIs. The bias resulted in population EVPPI estimates of \$700,000 and \$800,000 more than the forward simulation estimates for men and women, respectively. This difference was lower at higher WTPs. While Strong's method does introduce an upward bias into the results, it does work well for a first step in estimating the EVPPI. Given the dramatic savings in computation time, this method provides a check of the value of information and can hopefully provide fast insight into if additional research would be valuable. If the value of information is near the expected cost of the research design that would be needed to acquire that information, then the traditional two-level algorithm methods could be used, along with techniques like expected value of sample information (EVSI) to better predict the value. However if the EVPPI is very high or very low then two-level methods may not be needed. Therefore, despite the bias, I would still recommend Strong's methods as a first approach to determine the ceiling for the EVPPI.

Conclusion

In conclusion, this chapter sought to determine the value of perfect information on two key parameters in the models from the previous chapters. This research showed the benefit, in terms of time, on using efficient estimation techniques to determine the EVPPI. While these techniques may not be as accurate as the gold standard two-level Monte Carlo simulation methods, they do provide very similar results at a fraction of the computation time. For this problem, methodologically, Strong's method provided useful information and given the results could have likely been sufficient without further analysis. There has been a call for using EVPPI in

situations that involve multiple interventions or multiple decisions [153]. While this research only investigated one intervention, multiple options for vaccination timing were considered. Based on a cursory scan of the literature, EVPPI analysis has not been widely applied to the issue of treatment timing. This work also presents policy plots to assist in the interpretation of the EVPPI plots. I have not seen these types of plots used in the literature but I do feel that they add value to the analysis and provide insight to why EVPPI may be higher at certain WTP thresholds compared to others. Results suggest that there is value to this information, but that most of the value comes at WTPs that are less than the typical WTP assumed for health technologies in the US. I found that there was more value in deciding whether to use the vaccine at all rather than optimizing the age of administration. Therefore, while there would be some value in determining more about this vaccine in an effort to optimize the age of administration, it is unlikely that the research required would be worth the investment. Further, with a new vaccine on the horizon [136], the time that this information could be valuable is diminished. However, this research does lay ground work for further value of information studies on the new HZ vaccine or for other vaccines where optimal timing is important. Given the impact that the vaccines efficacy and waning make on the outcomes of the cost-effectiveness and the optimal timing of the vaccine it will be important for new studies on the new vaccine to pay close attention to these parameters.

4.A Additional Figures and Tables

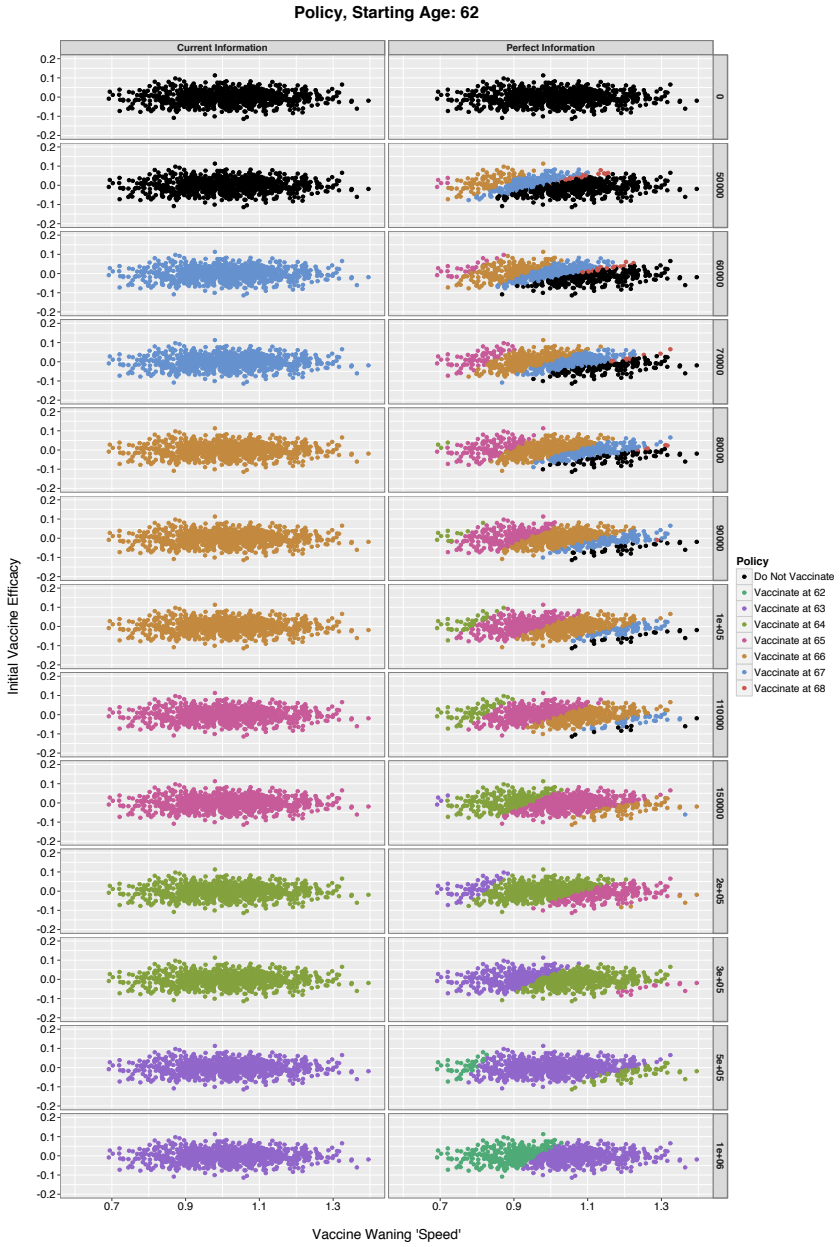

Figure 4.15: Policy Plot – Women, age: 62 – Strong's Method. Waning speed: relative change. Initial vaccine efficacy: additive change.

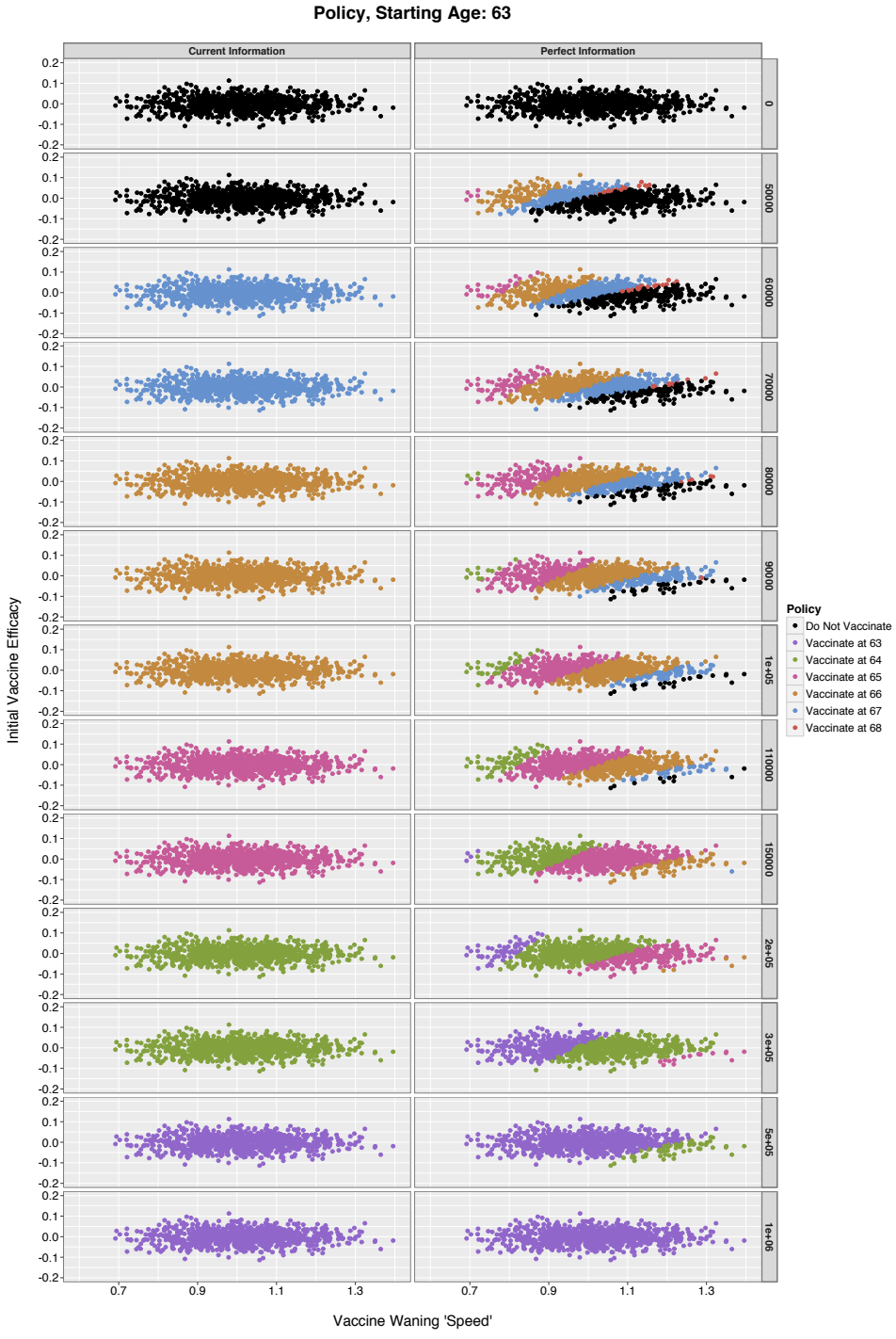

Figure 4.16: Policy Plot – Women, age: 63 – Strong's Method. Waning speed: relative change. Initial vaccine efficacy: additive change.

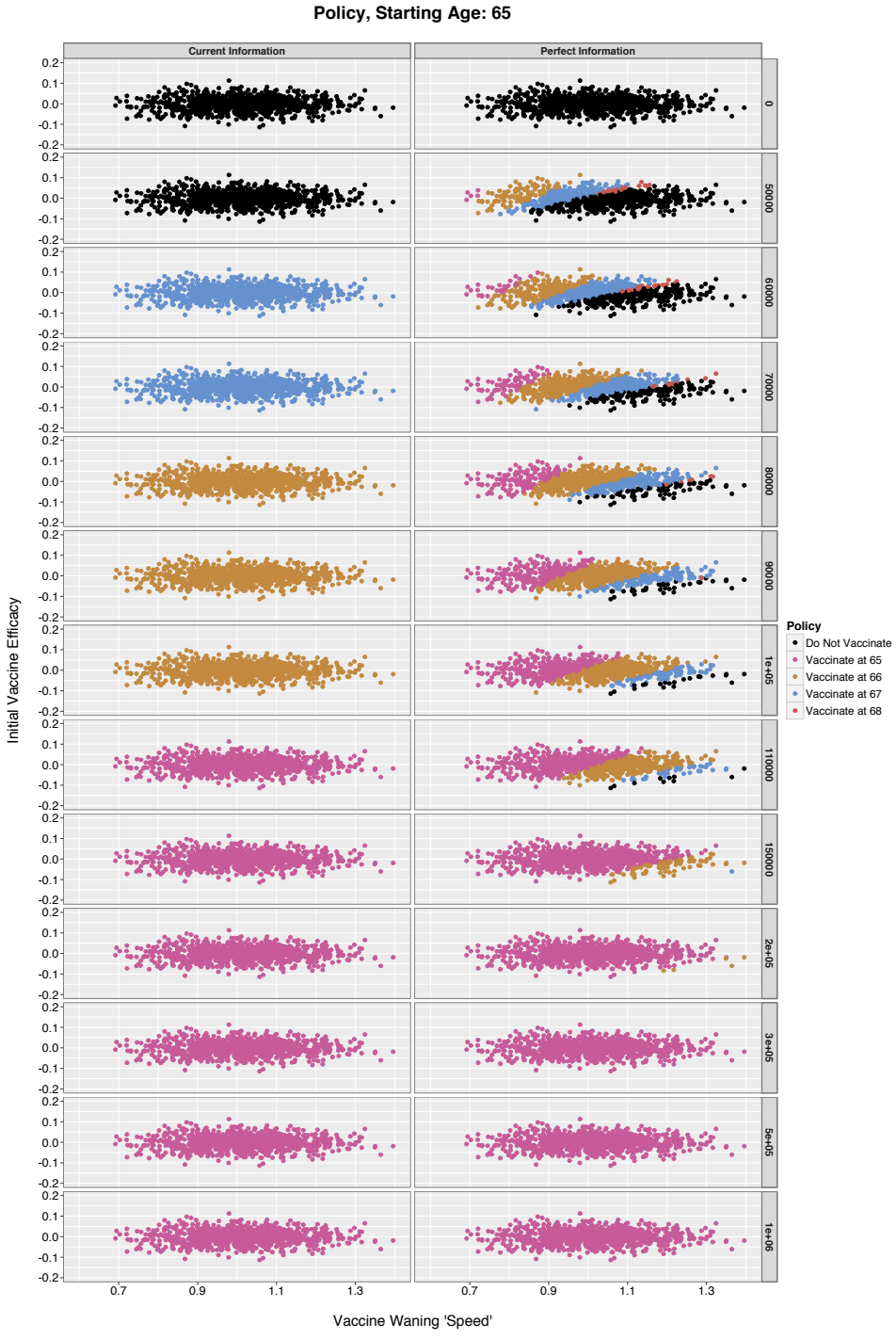

Figure 4.17: Policy Plot – Women, age: 65 – Strong's Method. Waning speed: relative change. Initial vaccine efficacy: additive change.

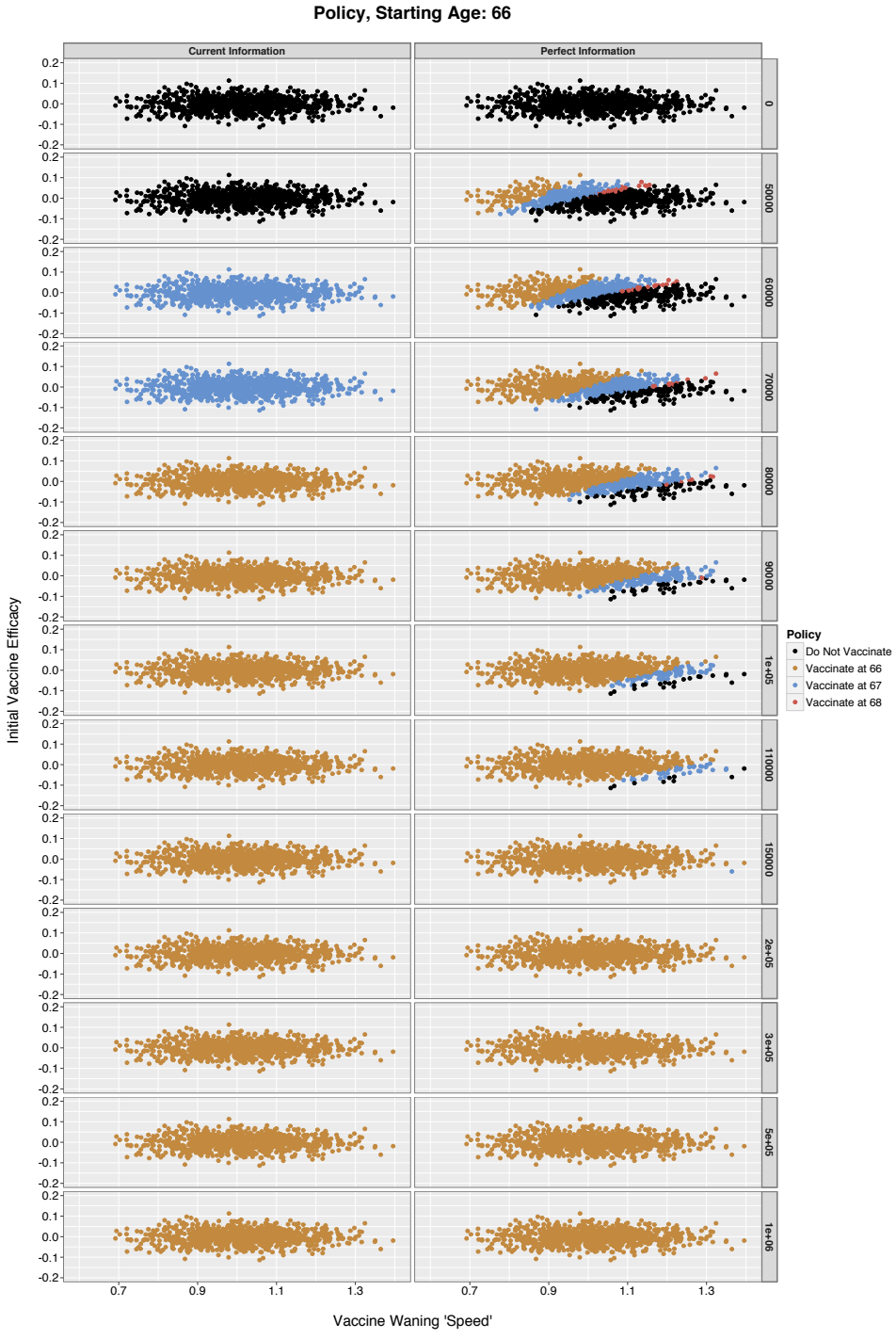

Figure 4.18: Policy Plot – Women, age: 66 – Strong's Method. Waning speed: relative change. Initial vaccine efficacy: additive change.

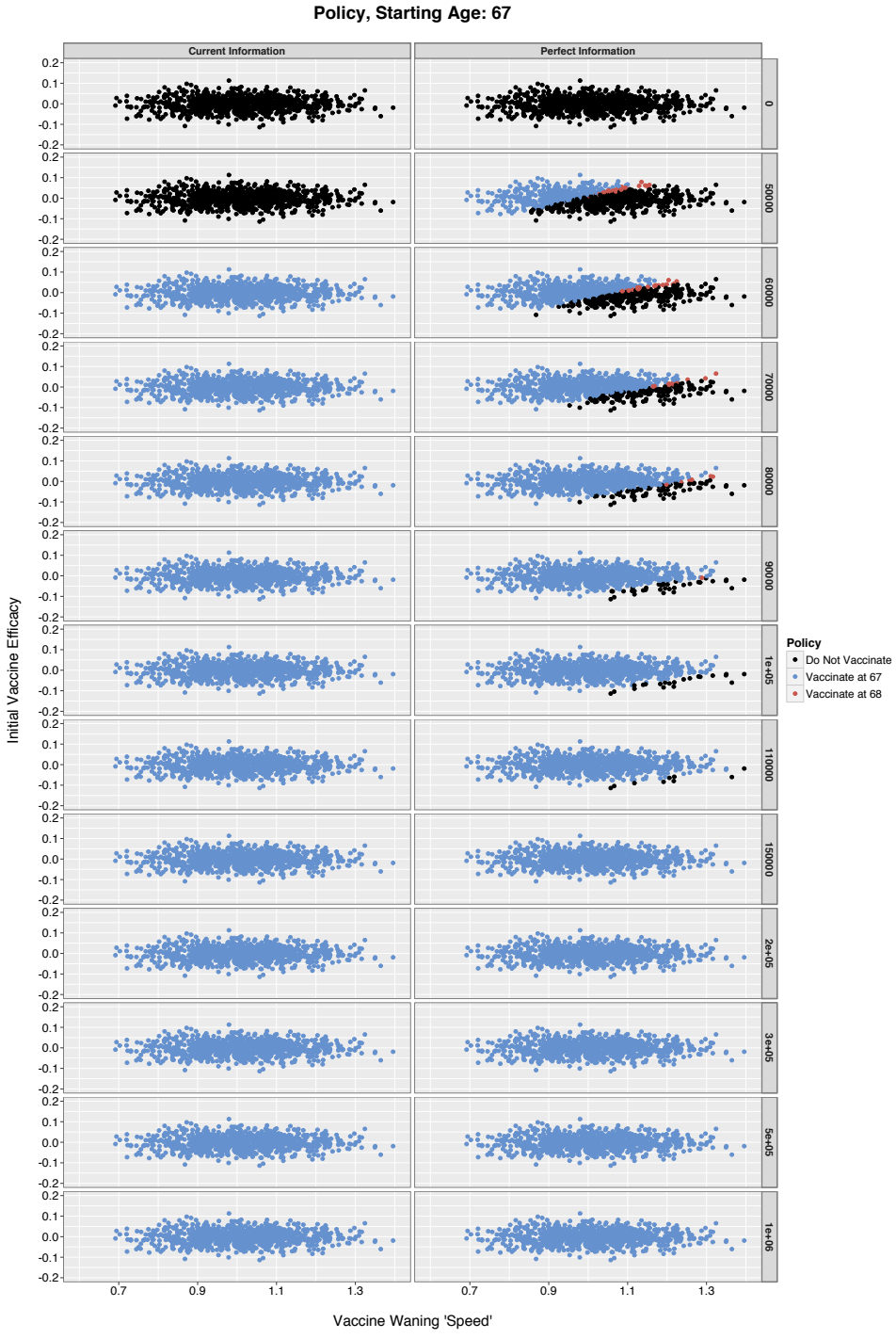

Figure 4.19: Policy Plot – Women, age: 67 – Strong's Method. Waning speed: relative change. Initial vaccine efficacy: additive change.

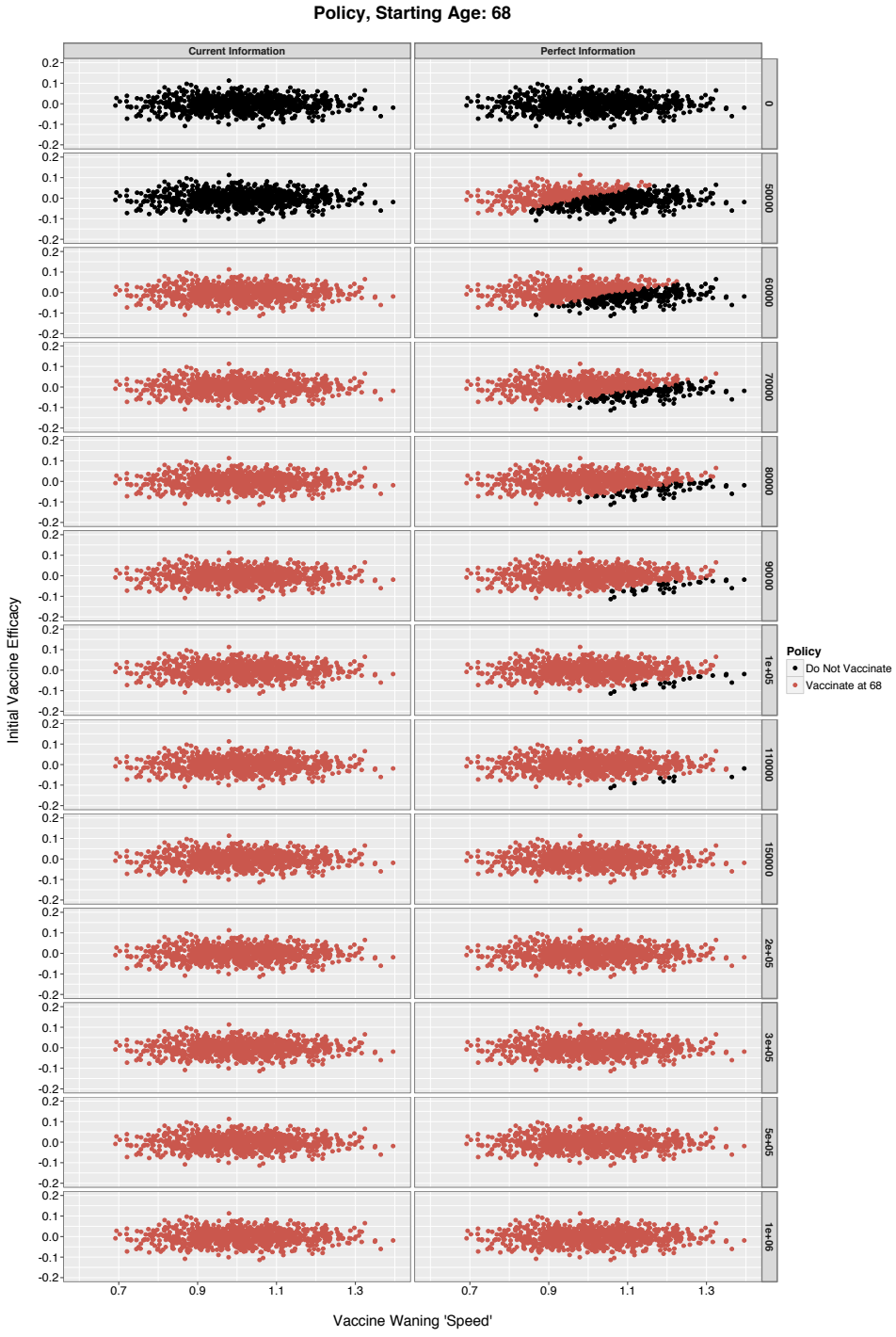

Figure 4.20: Policy Plot – Women, age: 68 – Strong's Method. Waning speed: relative change. Initial vaccine efficacy: additive change.

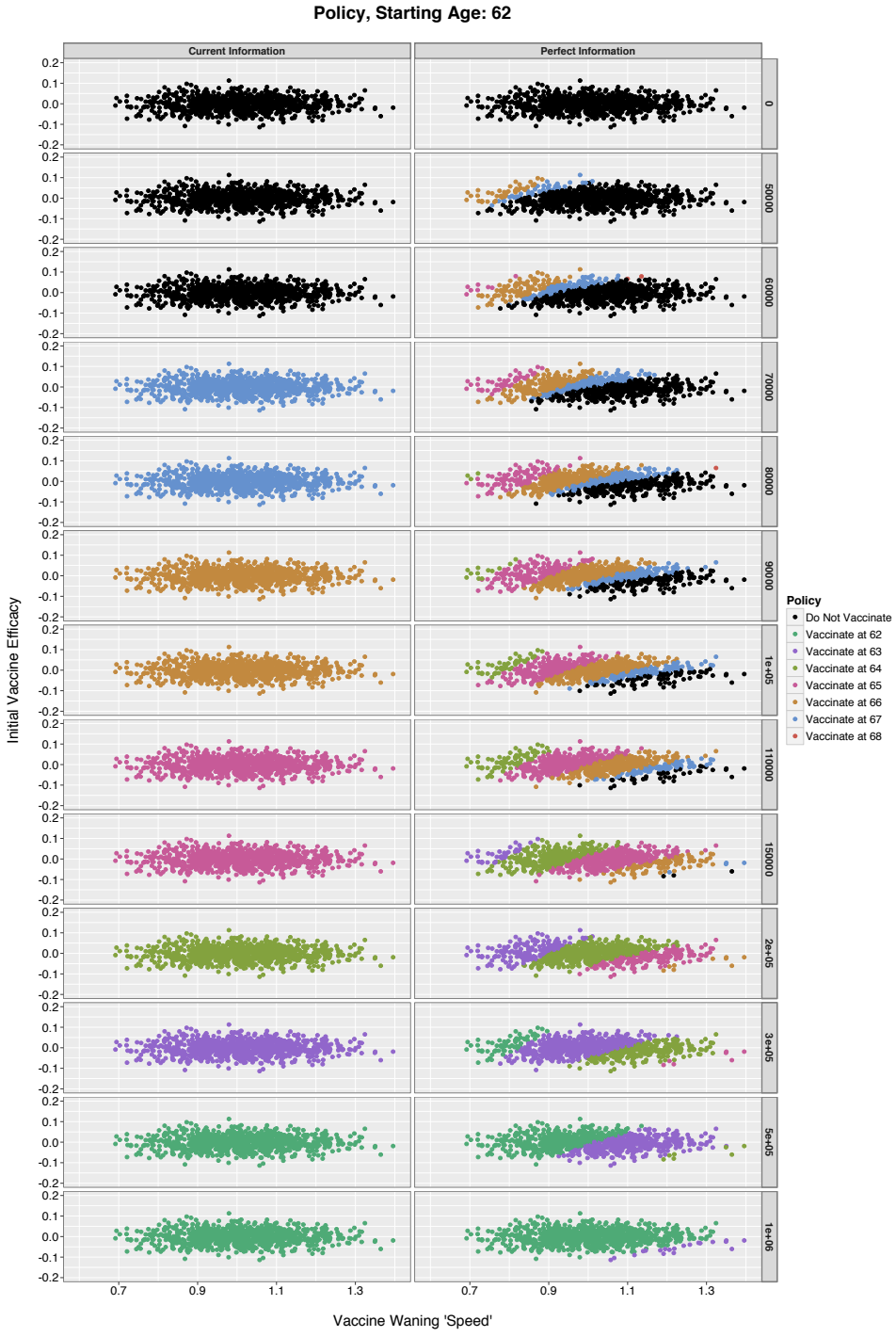

Figure 4.21: Policy Plot – Men, age: 62 – Strong's Method. Waning speed: relative change. Initial vaccine efficacy: additive change.

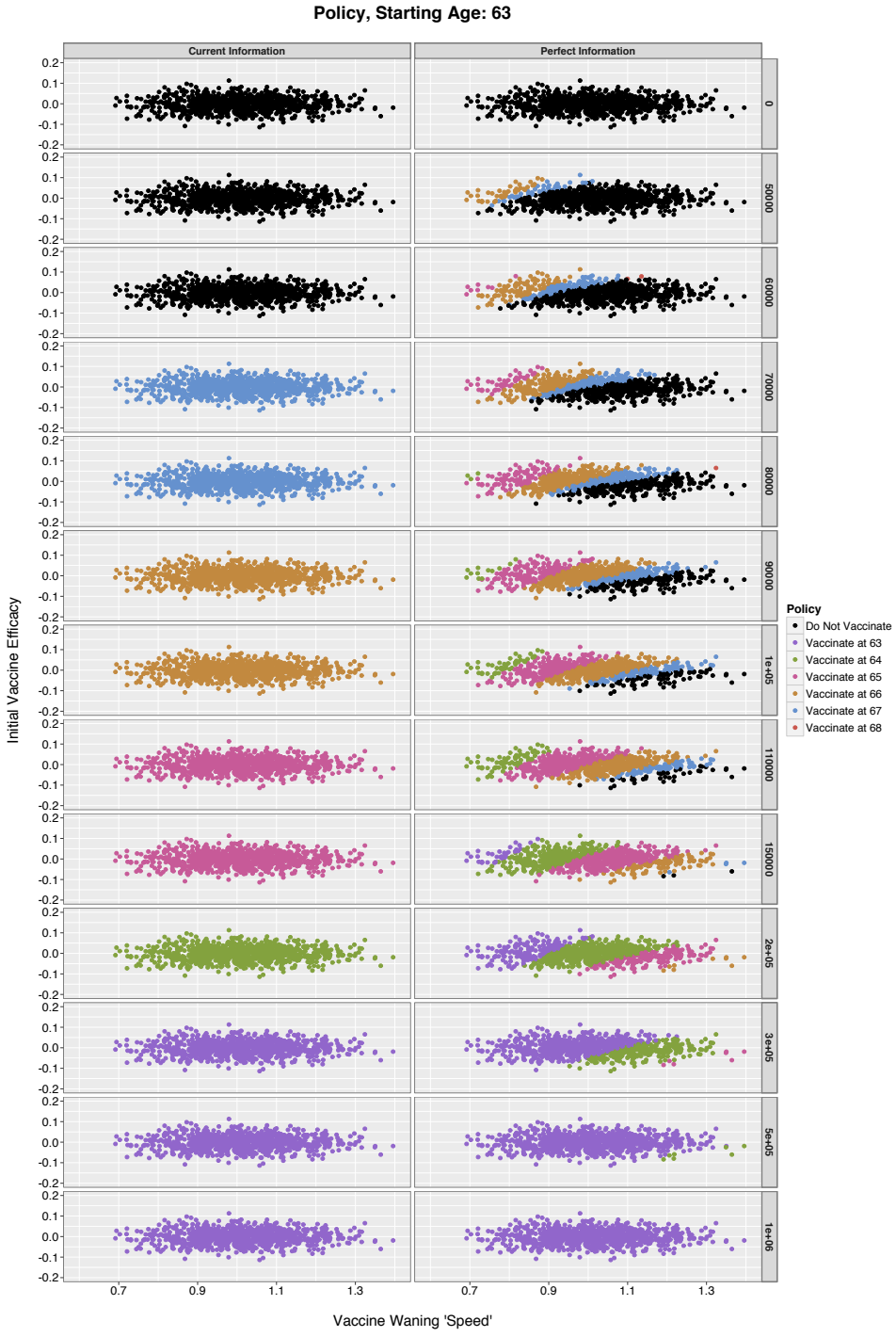

Figure 4.22: Policy Plot – Men, age: 63 – Strong's Method. Waning speed: relative change. Initial vaccine efficacy: additive change.

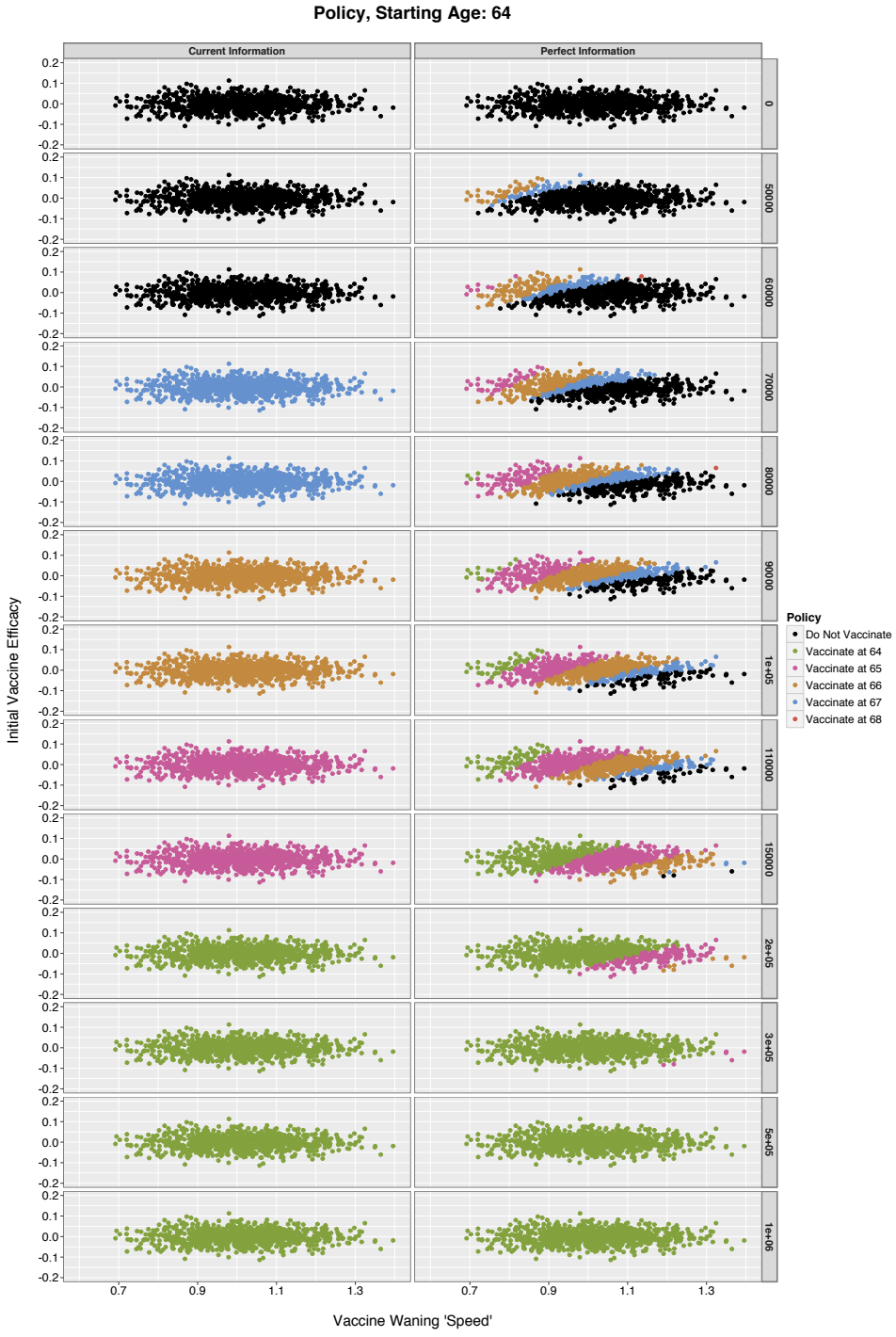

Figure 4.23: Policy Plot – Men, age: 64 – Strong's Method. Waning speed: relative change. Initial vaccine efficacy: additive change.

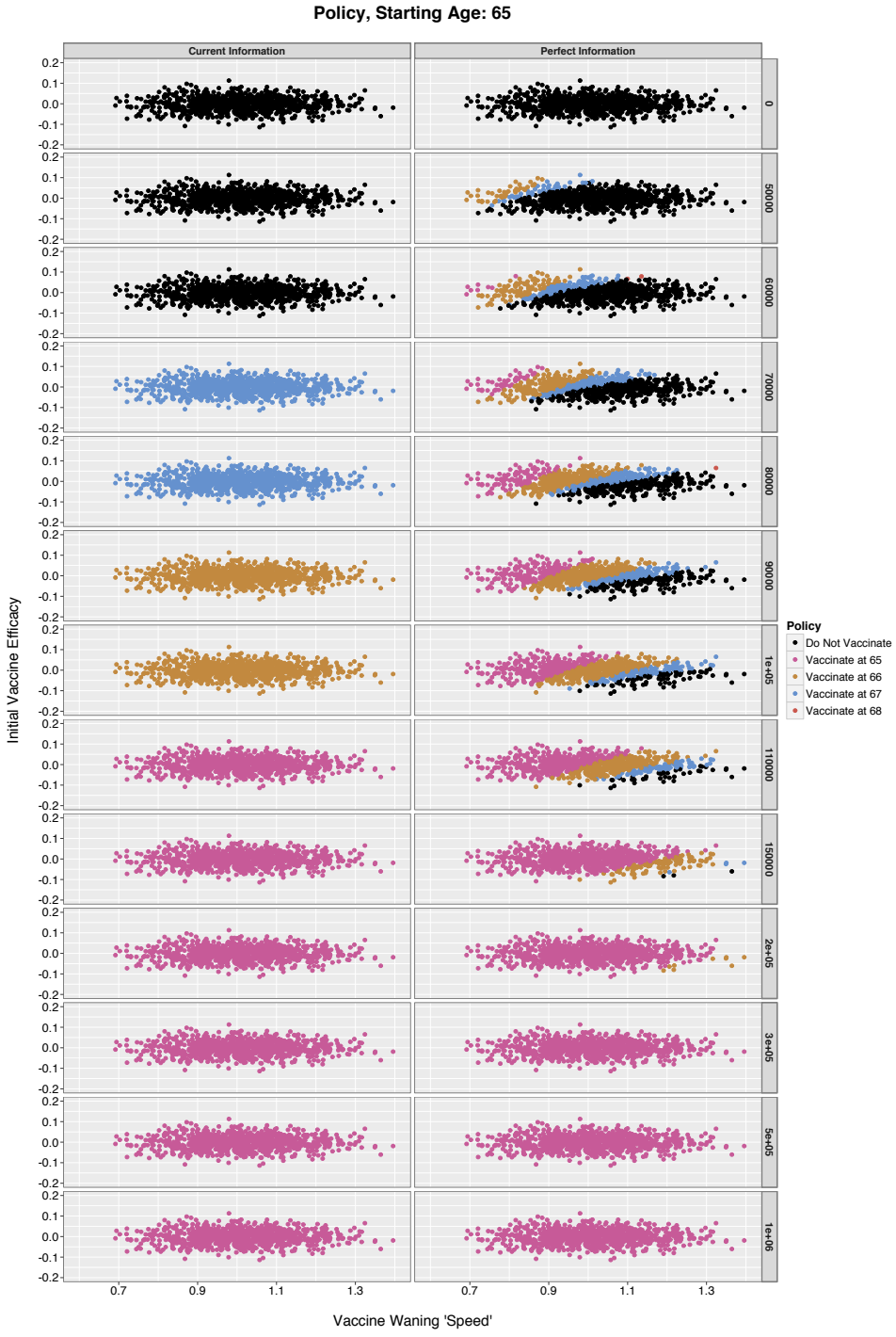

Figure 4.24: Policy Plot – Men, age: 65 – Strong's Method. Waning speed: relative change. Initial vaccine efficacy: additive change.

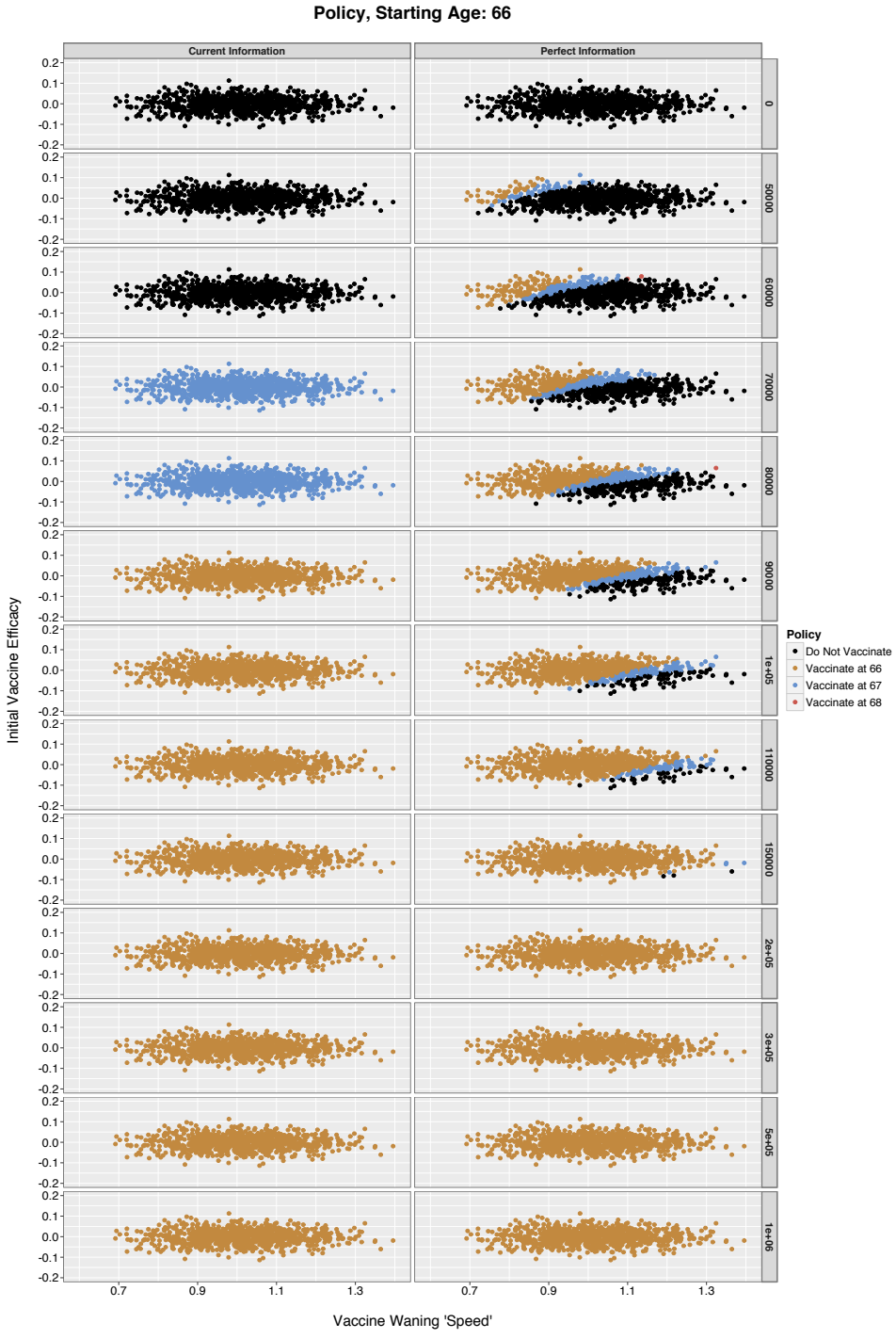

Figure 4.25: Policy Plot – Men, age: 66 – Strong's Method. Waning speed: relative change. Initial vaccine efficacy: additive change.

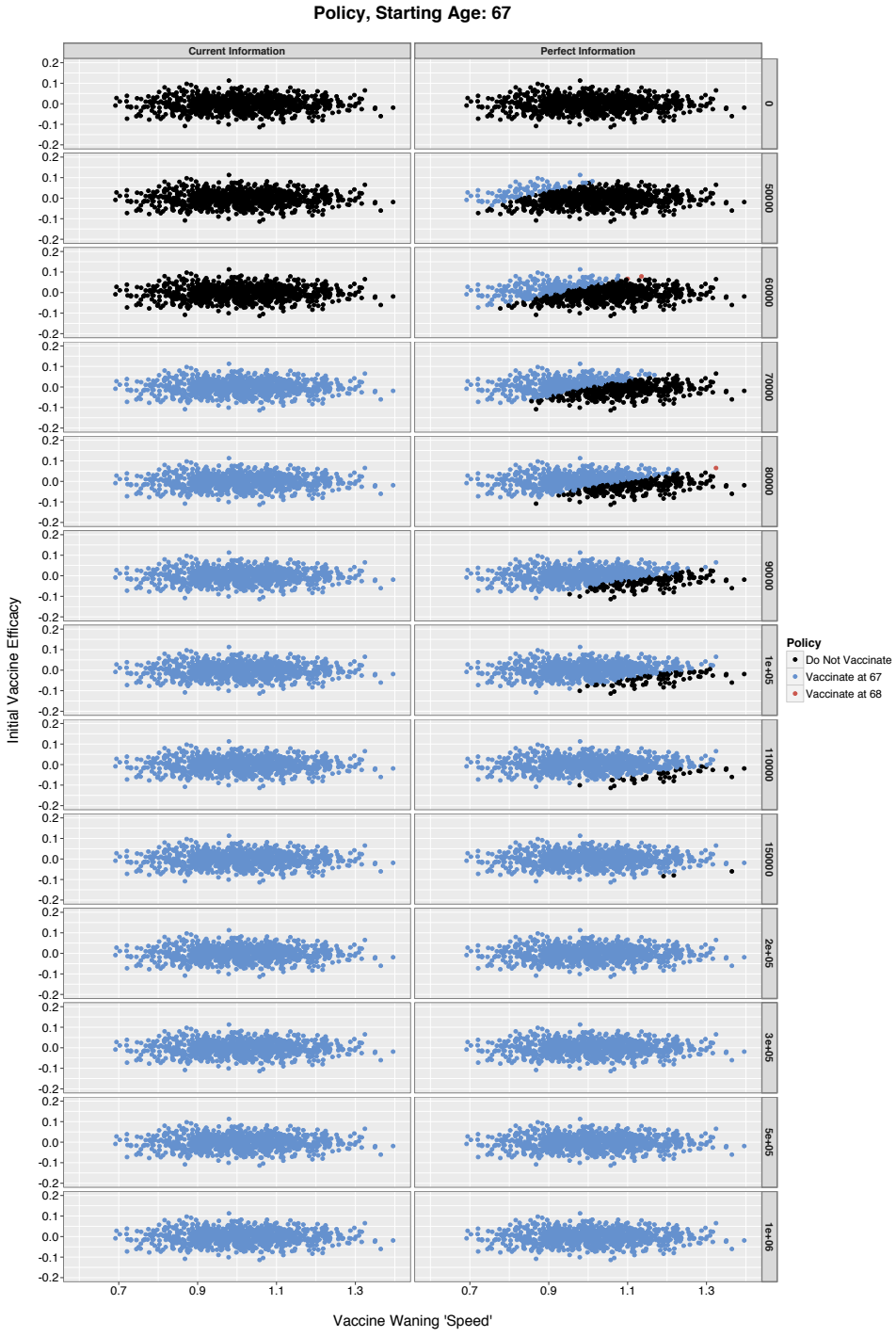

Figure 4.26: Policy Plot – Men, age: 67 – Strong's Method. Waning speed: relative change. Initial vaccine efficacy: additive change.

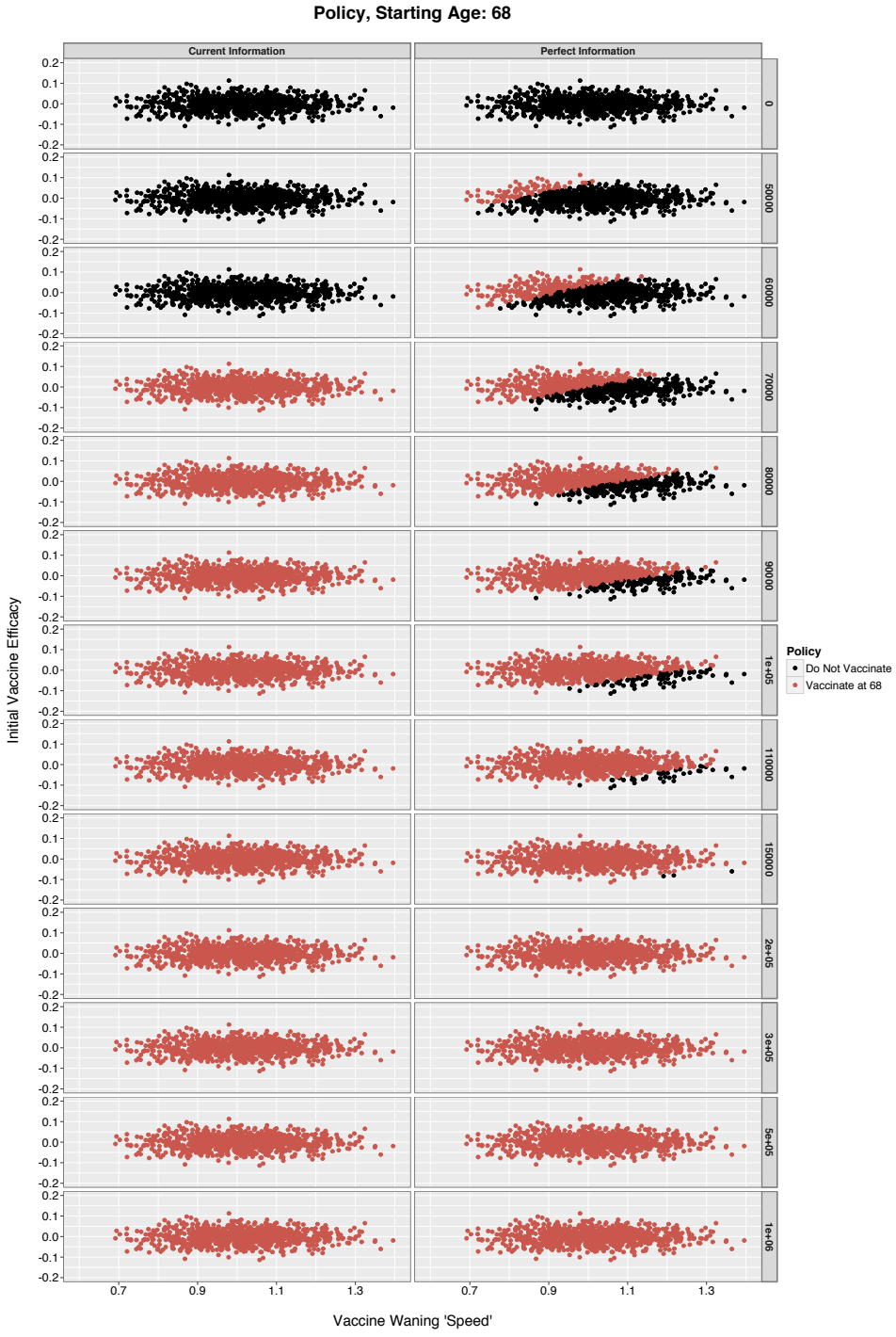

Figure 4.27: Policy Plot – Men, age: 68 – Strong's Method. Waning speed: relative change. Initial vaccine efficacy: additive change.

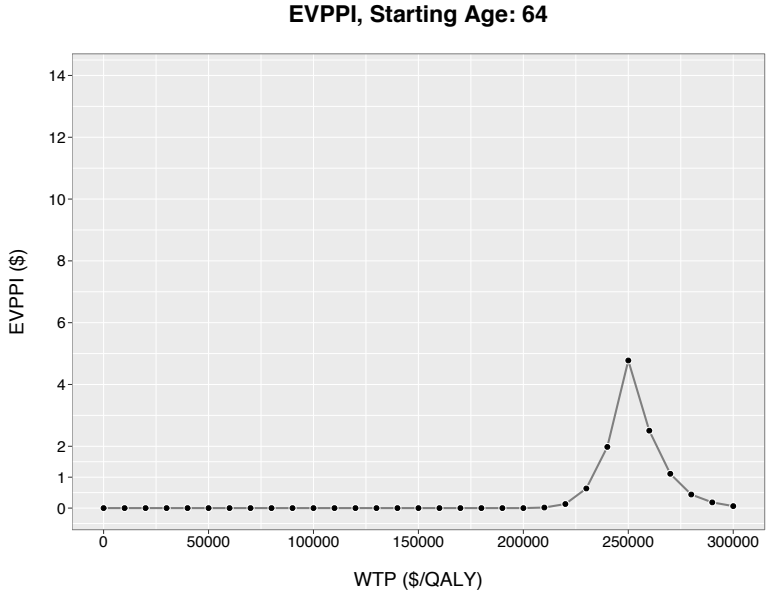

Figure 4.28: EVPPI – Women, age: 64 – Strong's Method – Scenario analysis (truncated timeline)

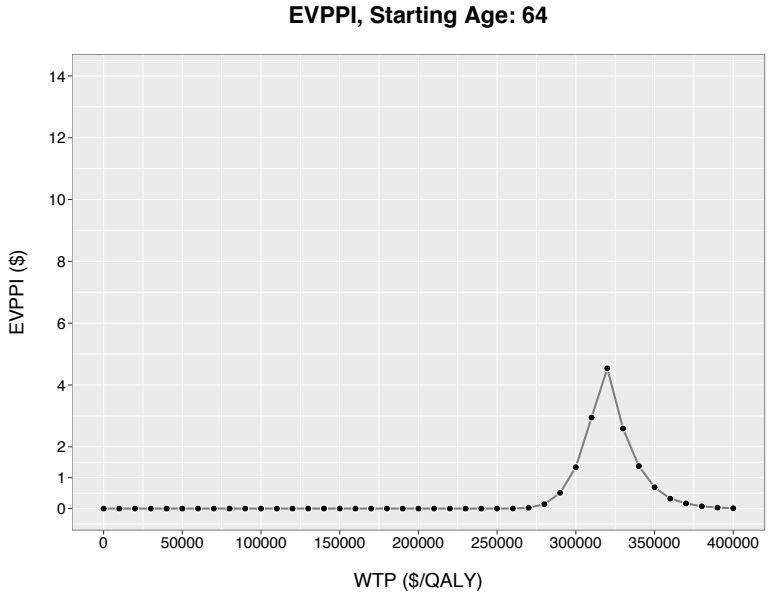

Figure 4.29: EVPPI – Men, age: 64 – Strong's Method – Scenario analysis (truncated timeline)

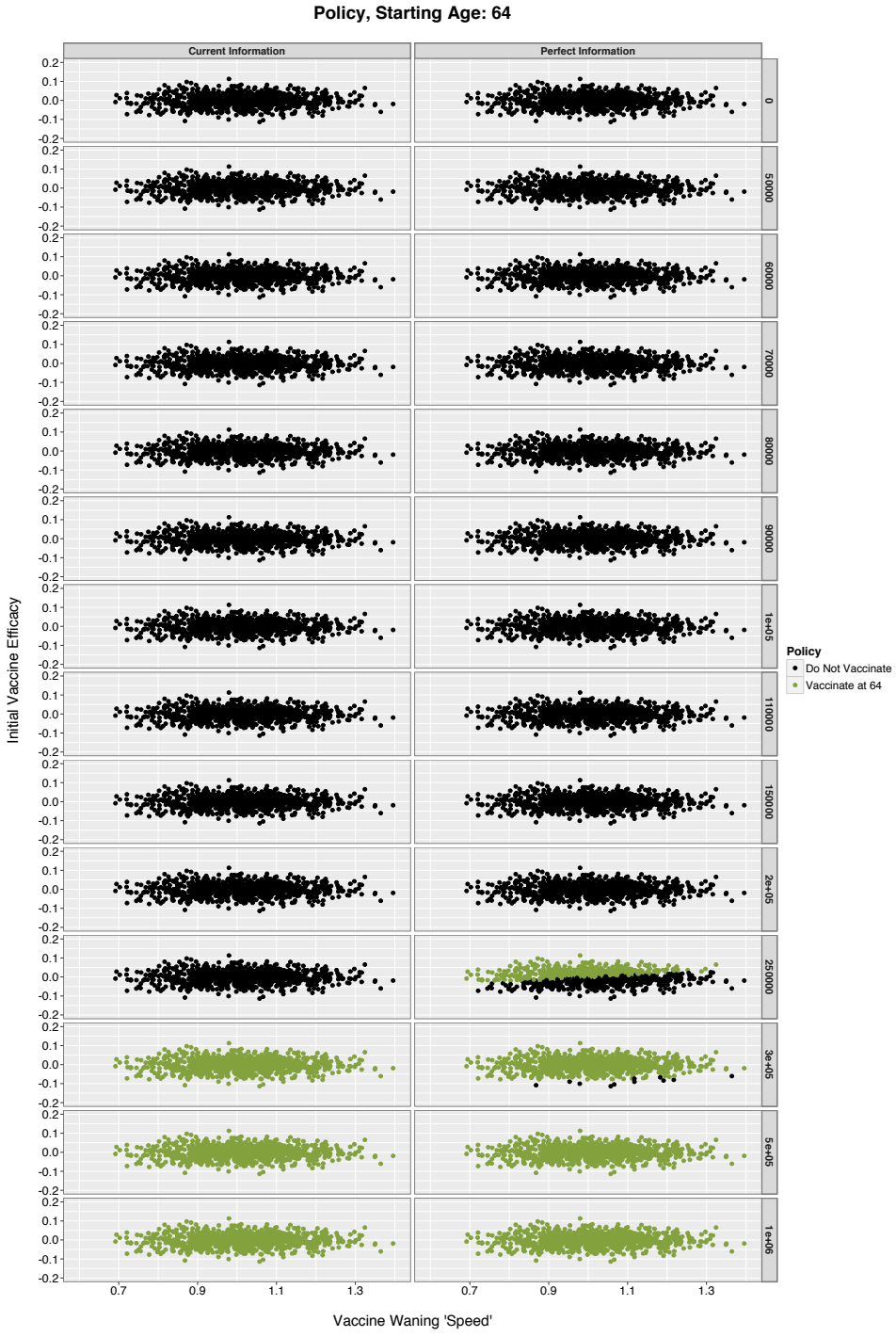

Figure 4.30: Policy Plot – Women, age: 64 – Strong's Method – Scenario analysis (truncated time line). Waning speed: relative change. Initial vaccine efficacy: additive change.

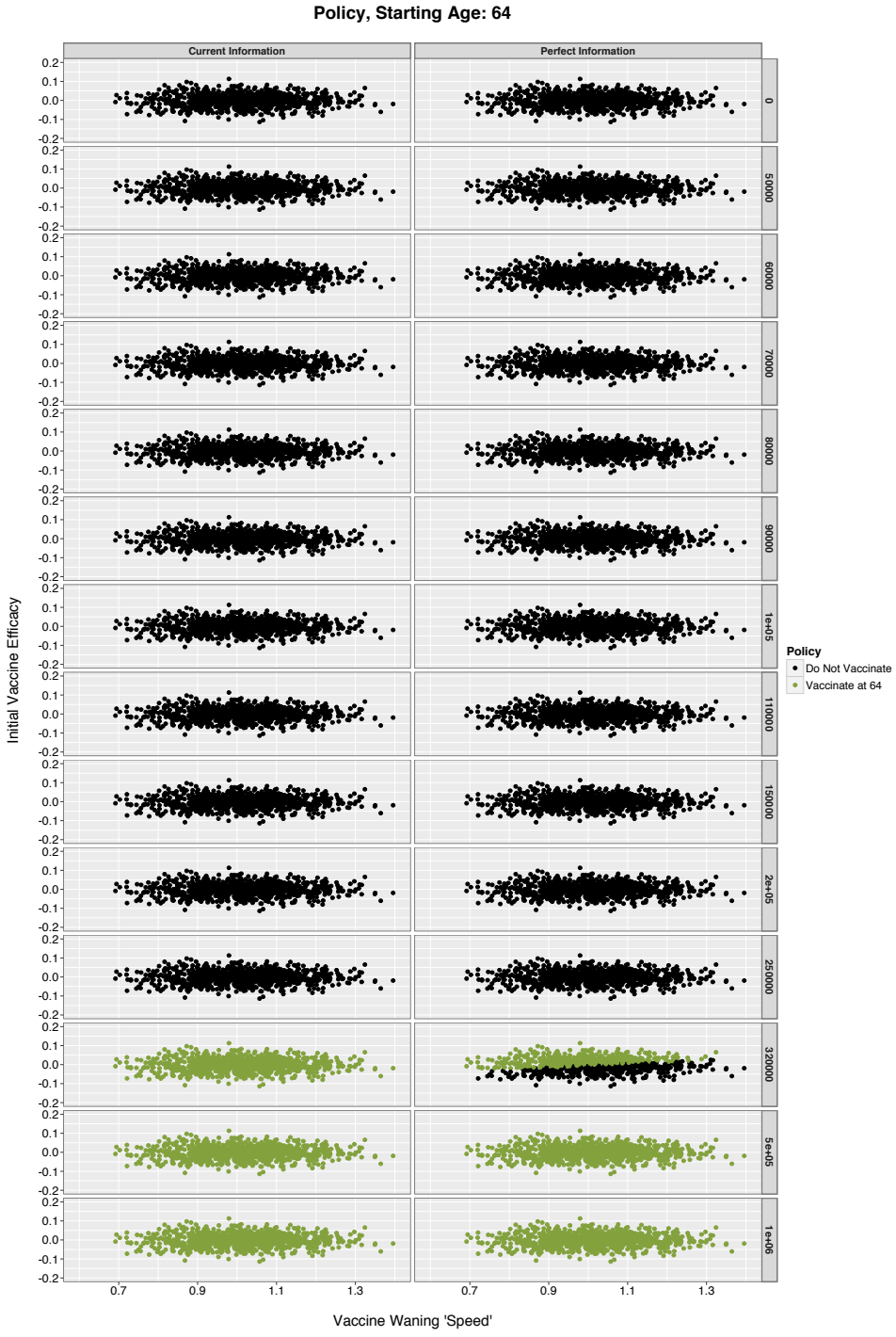

Figure 4.31: Policy Plot – Men, age: 64 – Strong's Method – Scenario analysis (truncated time line). Waning speed: relative change. Initial vaccine efficacy: additive change.

Chapter 5

Discussion & Conclusion

The aim of this dissertation was to use techniques in decision science and operations research to better determine the benefit and policies for administering the HZ vaccine. Herpes zoster is a disease that most people are at risk for [2]; it can have deleterious effects on quality of life and a high economic impact. The current vaccine is the best tool available to combat this disease. However, because the vaccine does not have a lifetime durability, it is important to make good decisions on when to use the vaccine so that we can maximize its benefits. The ACIP recommends vaccination for people ages 60 and older.

Cost-Effectiveness Analysis & Markov Decision Processes

The cost-effectiveness analysis shows the vaccine is more cost-effective for women than men at every age. The most cost-effective age to vaccinate using this model was 67 for men and women. Likewise, the MDP suggests the vaccine is likely more optimal for women than men. The MDP optimization model suggests that vaccination for both men and women should not begin until age 66, assuming only one dose will be given. The results from these models are very similar. The modeling structures were slightly different, which could explain the one year difference in the optimal recommendations. The MDP used a collapsed HZ health state that included the costs and disutilities associated with HZ and its complications, whereas the CEA

model used a more complicated structure. The MDP used annual epochs which may have slightly overestimated the benefit of the vaccine, compared to the CEA which was run in monthly cycles. While the results of the models are similar, the MDP does not recommend vaccination earlier than 66 in the base case. Comparatively, using a WTP of $100,000 in the CEA, ages younger than 67 still had ICERs less than $100,000. An important distinction between the CEA and the MDP is that the MDP tries to optimize the time when the person should get the vaccine rather than evaluate the cost-effectiveness. Therefore, it does assess the benefits of getting vaccinated at ages earlier than 66, but the model suggests that vaccinating at those earlier ages is not optimal, even if in an ICER would be less than $100,000.

Comparatively, one benefit of the MDP model is the ability to evaluate many different options quickly. Theoretically, there 2^{50} different policy options evaluated by the one dose MDP (50 epochs, 2 action options per epoch) compared to the 50 decisions that were required to be evaluated independently in the CEA model. To replicate the results of the MDP with a CEA model would have taken much more computation time. Adding the second dose option further increases the policy options, making the problem a huge computational burden through if only using standard STMs. When two doses were available, it would be optimal to vaccinate women with two doses in the base case, whereas it would never be optimal to vaccinate men with two doses in the base case. Future studies on disease modeling should consider the two dose question about when would be the optimal time to receive the new vaccine, given that a person has received the current vaccine at some time in the past.

Value of Information

Both the CEA and the MDP models showed that the results were sensitive to the waning speed and the initial efficacy of the vaccine. These two parameters had the biggest impact on the results of both models. This lead to the decision to focus on the value of additional research for these parameters. The analysis showed that the value of information was highest at lower WTPs when the decision under perfect information would be mostly split between vaccination at some age and no

vaccination at all. However, under WTPs that are more commonly used in the US (e.g., $\geq$ \$100,000) [75, 151], the value of information decreased. When converting the EVPPI to a population level estimate, the population EVPPI was high (e.g. > \$3.5million). However, the cost of the research to gain this information would also likely cost several million dollars. Therefore, while there is some benefit to being able to select the optimal age with perfect information, the benefit may be marginal, especially as there is a new vaccine that will soon be coming to market. Given the impact these parameters had on my models, these will be important parameters to focus on for research and models on the new vaccine.

Limitations

This research does have limitations. All work done is specific to the US. The disutilities used for health states were from direct elicitation time trade off study on herpes zoster. All costs for the models are from US studies. Therefore, translating the recommendations to other countries without further research on health utilities or costs for a specific country should not be done. Modeling studies are only as good as the data used. All data used in these models was collected using systematic review procedures to ensure collection of the highest quality data. However, some assumptions were made – which have been outlined in their respective chapters – when data was not available. To account for uncertainty in the data many sensitivity and scenario analyses were performed. While the sensitivity analyses do show that the models were robust to certain changes, it does highlight the impact that certain parameters can make. Like all modeling studies, the results of this research are subject to change, and indeed should be updated as new information becomes available [48]. It should also be noted that results for these analyses are only applicable to immunocompetent patients. Immunocompromised patients are known to be at a higher risk for both HZ and its complications [154]. However, event probabilities do change between different types of immunocompromised patients, which adds a further layer of complication to any analysis done for immunocompromised patients. There is also minimal data on costs and health utilities for immunocompromised

patients who experience HZ or its complications. If further epidemiology, health utility, and cost studies were done, the methods used in this dissertation could be applied to sub-groups of immunocompromised patients to determine how cost-effective the vaccine may be and when it would be best to administer it.

Future Work

Coming from this work there are several research opportunities moving forward. First, as there is a new vaccine in development [136], there will be the opportunity to repeat the cost-effectiveness analysis and the MDP analysis for the new vaccine. There will also be the opportunity to include the current vaccine in those analysis to do comparative work. One interesting question which I have already started working on in this dissertation is the question of multiple doses with both the current and upcoming vaccine. The two dose scenario analysis in Chapter 3 on the new vaccine showed that it would be optimal to administer that vaccine at age 69 and older under several assumed conditions (same cost, same safety profile, same waning, better initial efficacy). Because of the high efficacy of this vaccine, it appears that it is optimal to further delay the administration of this vaccine such that it provides the most benefit to people later in life when they are most at risk. However, it is also possible that the new vaccine will be priced higher than the current vaccine given that it is likely to be more efficacious. Therefore, once the new data is available on the new vaccine and it has been priced, future work examining a two dose question should be examined. In this work, I hope to investigate the question of it would be optimal to receive two doses of the new vaccine, or if it would be optimal to receive two doses (one current, one new) given that the current vaccine is does provide good protection at younger ages and may be priced cheaper than the new vaccine.

Data Visualization

One part of this dissertation that I would like to continue is my work with data visualization. In each chapter I have tried to think of unique ways to display data that I have not seen used in other papers. In the CEA I created the cost-effectiveness

acceptability contour (a way of displaying several cost-effectiveness acceptability curves on one plot), and the contour plots for the two-way sensitivity analysis. In the MDP analysis, I created optimal policy plots and optimal policy heat maps for the PSA. In the VOI analysis, I made policy plots to help visualize why the EVPPI may be higher at certain WTPs. These policy plots also showed all available decisions on one plot. Health economic evaluation models typically produce a large amount of data, are very complex, and often (in my anecdotal experience) are not easily understood by a general audience. I think that data visualization is a technique that helps bridge the gap between us as researchers and people with limited understanding of what we do. In my future work I plan to continue to think of new ways to display data to make results clear and easily accessible.

Conclusion

This dissertation has used advance decision modeling techniques to show that the vaccine is cost-effective for men and women at several ages. However, when accounting for risk of disease when deferring vaccination, it is likely that a policy to vaccinate people under 65 years of age is sub-optimal. While there is uncertainty about the vaccine parameters, in the US our WTP is typically great enough where there would only be a marginal benefit to gaining the information required to make optimize the decision beyond the our capabilities with current information. Vaccination is the best option available to combat this disease. It is my hope that the results of this dissertation can and will be used to make good decisions about the application of the HZ vaccine in the attempt to maximize the benefit to society while maximizing our available resources.

Appendices

Appendix A

Model Data for Dissertation

A.1 Epidemiology Data

Incidence of HZ

Data from three papers [101–103] were used to create the age-specifc incidence of HZ for men and women. These papers were selected as each provided the incidence rates for men and women separately. First, incidence rates from these selected papers were checked against other papers and systematic reviews for face validity and were deemed appropriate. To create an estimate of incidence, midpoints of the age ranges provided were plotted against reported incidence. This data was then fit using a logistic function (see Equation A.1) in R.

$$Incidence = \left(\frac{asymp}{1 + e^{\left(\frac{xmid - age}{scale} \right)}} \right) / 1000 \tag{A.1}$$

The logistic shape was selected a priori; data from a recent systematic review [13] suggests that incidence follows a logistic growth pattern. To determine the confidence interval, the asymptote parameter ($asymp$) of the logistic function was manually altered to cover the range of data extracted from the literature reviews. Figure A.1 shows the fit and the confidence interval for HZ incidence. Note, data was fit from ages 18 – 100, but only incidence data beyond age 50 was used.

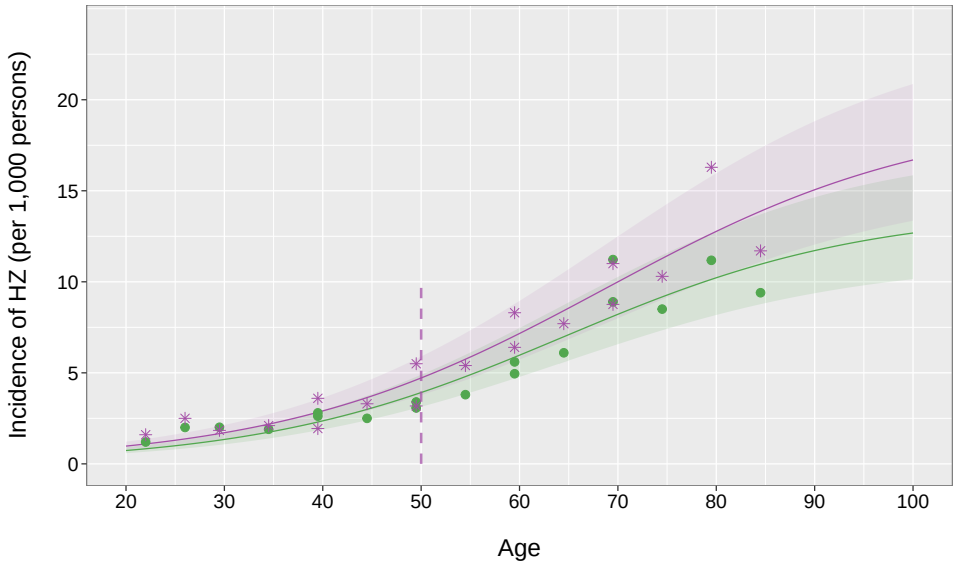

Figure A.1: Risk of HZ. Females: Data $*$, Purple fit and 95% CI region. Males: Data $\bullet$, Green fit and 95% CI region. Ages under 50 used for fitting. Data left of dashed line not used in model.

Risk of PHN

To calculate the risk of PHN given HZ, six papers from a recent systematic review [13] and one additional study from Italy were used [42, 79, 104–108]. All papers from the systematic review [13] were also found during the literature review for model inputs. Papers were selected as each provided data on at least three age groups and used a similar diagnosis strategy for PHN (risk at 90 days after infection). When available, data was preferentially used from the systematic review [13] as age categories had all been converted to the same range. Similar to HZ incidence methods, midpoints of the age ranges were plotted against the corresponding risk of PHN; shown in Figure A.2.

Different functions were fit to the data using Microsoft Excel (v.2013). The power function (see Equation A.2) was selected as it provided the highest R^2. Data when then transferred to R, and parameters from the Excel power function were used as starting values for non-linear regression. Similar to HZ incidence, data for ages 18 – 100 were used to create the fits, but only data from age 50 and above was used in the model. There is no distinction made between the risk of PHN for men and women.

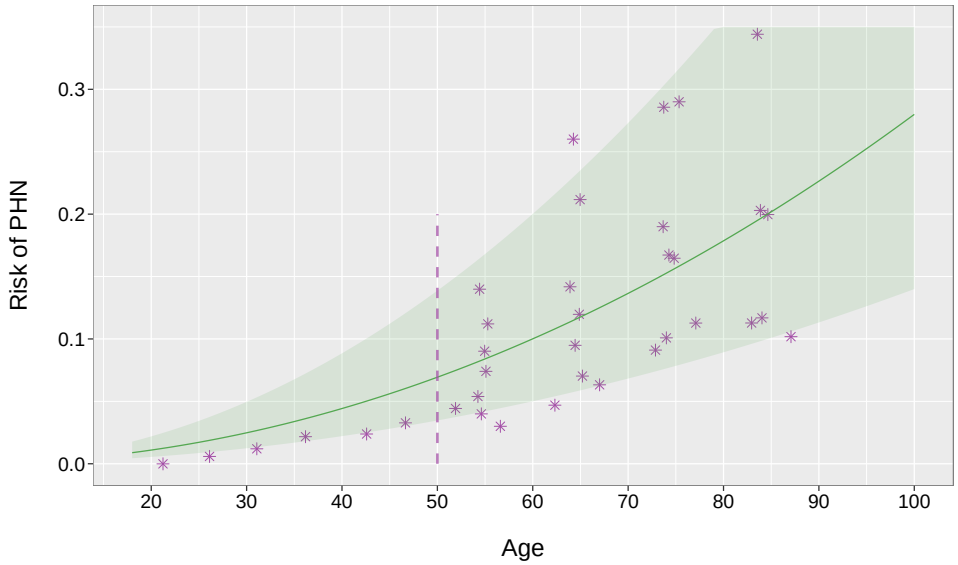

Figure A.2: Risk of PHN. Data: $*$. Solid line: Base case fit. Shaded region indicates regions used for sensitivity analysis. Upper risk limited at 35%. Ages under 50 used for fitting. Data left of dashed line not used in model.

Once the equation was fit, the b_1 parameter was altered to provide a range for the possible risk. The risk of PHN was limited to 35% at the upper bound. This limit was used as without it, the risk of PHN risk would have been outside the value of any of the literature used.

$$PHN\ Risk = b_1 \times age^{b_2} \tag{A.2}$$

PHN Time and Severity

One paper provides data for the chance of developing moderate or severe PHN as well as the duration of specific PHN health states (i.e., mild, moderate, severe) [79]. This data was used to construct probabilities for transitioning into and between different PHN health states. Data on PHN severity were extracted from the paper and fit using a linear model using the midpoints of the age ranges provided. There were no confidence estimates for these data so a range of $\pm$ 10% was used. Data on PHN time are provided in Table A.1. To use this data, it is assumed that people starting

PHN Severity	Duration	Lower CI	Upper CI	SE
Mild	6.7	6.1	7.4	0.325
Moderate	10	9.4	10.7	0.325
Severe	12.5	11.1	14.1	0.75

Table A.1: Time in PHN data. All durations in months.

in more severe PHN states must transition through all subsequent mild PHN states before reaching the disease free state. To convert the duration data into probabilities Equation A.3 was used.

$$\frac{1}{D_{PHN_j} - D_{PHN_i}} \tag{A.3}$$

j: Worse state of PHN i: Better state of PHN

A.2 Cost Data

Disease Costs

Medical expenditures related to HZ and its complications were calculated using data from one paper [14]. This paper was selected as it provided two time periods of information and the most specific data of any of the papers found in the literature. Costs were converted into 2015 US dollars using the medical care component of the consumer price index (CPI) [155]. As recommended by Briggs et al (2006) [139] costs were assumed to fit a gamma distribution. The α and β parameters were calculated using Equations A.4 – A.7 and data from Table A.2. After fitting the data to a distribution, each corresponding distribution was used to generate a confidence interval for one-way sensitivity analysis.

Parameter	Mean	SE	CI	Distribution
HZ	957	47	(867, 1,051)	Γ(414.598, 2.308)
PHN	5,831	990	(4,055, 7,963)	Γ(34.691, 168.084)
Ocular Complications	4,163	652	(2,986, 5,543)	Γ(40.767, 102.114)
Neurologic Complications	9,872	2,979	(5,520, 15,253)*	Γ(10.981, 898.950)
Cosmetic Complications	9,873	5,285	(3,036, 19,883)*	Γ(3.489, 2829.051)

Table A.2: Direct medical expenditures. SE: Standard Error of the mean. CI: 95% Confidence Intervals (* 90% Confidence Intervals used due to heavy tails). All costs in 2015 US dollars ($)

$$E[Costs] = \bar{\mu} = \alpha\beta \tag{A.4}$$

$$Var[Costs] = s^2 = \alpha\beta^2 \tag{A.5}$$

$$\alpha = \frac{\bar{\mu}^2}{s^2} \tag{A.6}$$

$$\beta = \frac{s^2}{\bar{\mu}} \tag{A.7}$$

Lost Productivity

Productivity losses for the model were calculated using data from three papers [63, 116, 117] as well as data from the U.S. Bureau of Labor Statistics (BLS) [118]. Table A.3 provides an overview of the data. Mean hours lost were extracted for each pain condition along with the percentage of the population that takes time away from work given disease. These numbers were combined to give an estimate of the mean number of working hours lost due to HZ or PHN. BLS data was used to determine mean weekly earnings for the US population. Weekly earnings were converted into hourly earnings assuming an average of 40 hours per week worked. The mean weekly earnings for the US population in 2015 was $1007.00, which equals a mean hourly earning rate of $25.20. This earning rate was multiplied by the mean number of working hours lost given disease to give an estimate of the productivity lost due to disease.

Disease	Pain State	Hours[1]	Patients(%)	Hours[2]	Cost($)	Reference
HZ	None	17.4	43	7.4	147.96	[116]
	Mild	17.4	43	7.4	147.96	
	Moderate	41.9	69	28.9	571.72	
	Severe	51.6	67	34.5	683.66	
HZ	None	–	–	–	–	[117]
	Mild	3.8	100	3.8	75.10	
	Moderate	18.4	100	18.4	363.86	
	Severe	74.2	100	74.2	1467.31	
HZ	None	48.0	4	2.1	41.57	[63]
	Mild	50.6	13	6.3	125.18	
	Moderate	50.6	39	19.9	394.35	
	Severe	93.6	78	73.0	1443.73	
PHN	Mild	49.3	9	4.5	89.51	[63]
	Moderate	91.2	33	30.4	601.10	
	Severe	153.4	53	80.7	1595.42	

Table A.3: Productivity lost data. Patients(%): proportion of patients who take time away from work. Hours[1]: Hours lost not accounting for proportion of patients who take time from work. Hours[2]: Hours lost accounting for proportion of patients who take time from work. Costs presented in 2014 US Dollars.

Vaccine Costs

Costs for the vaccine were taken from the 2015 CDC adult vaccine price list [109]. Administration costs for the vaccine were taken from three papers [110–112]. These data sources provided data on labor, supplies, and overhead costs. All data was converted in to 2015 US dollars and then averaged to provide an estimate of the administration costs for the vaccine. The main severe adverse event for the vaccine was an allergic reaction that may or may not have lead to anaphylaxis [115]. In a large cohort study (n = 193083) there were 71 cases of vaccination that required further medical care due to an allergic reaction and 9 cases that resulted in anaphylaxis [115]. Costs were sourced from one study that examined the costs associated with allergic reactions in adults [114]. Costs were converted to 2015 US dollars and then multiplied by the probability of a general allergic reaction or anaphylaxis and then summed to

estimate the costs of severe adverse reactions of the vaccine. It was assumed that the there was no costs for common adverse reactions. The vaccine is not related with increased risk of any other severe outcome [115].

A.3 QALY Data

Disease Disutilities

Data from Lieu et al (2008) [88] were selected to create the disutilities for the disease states in the model. This data was selected as it provides the only US estimate of health state disutilities using a direct elicitation time-trade off (TTO) method and includes a large sample size including community members, HZ patients, and PHN patients. Data from the paper was in a similar format to Table A.4 below. Each condition is defined by a pain score (valued from 0 – 10) and a time duration in months. The model assumes cut points in the pain scores to be: 1 – 3: Mild Pain; 4 – 6: Moderate Pain; and 7 – 10: Severe pain. Therefore, the condition 3×1 month is considered 1 month of mild pain. Any condition with 1 month period is assumed to be an HZ health state; any condition with $>$ 1 month time period is assumed to be a PHN health state.

Group	**Cmty**			**HZ**			**PHN**		
Condition	T.Mean	L.CI	U.CI	T.Mean	L.CI	U.CI	T.Mean	L.CI	U.CI
3 × 1m	15	10	21	6	4	8	18	11	27
8 × 12m	76	58	96	100	81	120	301	181	443

Table A.4: Example TTO table. Cmty: Community Members. HZ: HZ Patients. PHN: PHN Patients. T.Mean: Trimmed Mean – removal of the highest and lowest 2.5% values of the mean distribution. L.CI: Lower 95% confidence interval of the trimmed mean. U.CI: Upper 95% confidence interval of the trimmed mean.

To generate the disutilities the trimmed mean, upper, and lower confidence limits were divided by the number of days in corresponding condition (1 month = 30 days). If there was more than condition for a health state (e.g., two severe PHN

states), the utility generated from each was averaged. In the model, I elected to use the disutilities generated from the corresponding patient group. For example, the disutilities calculated from the HZ group were used to represent the disutilities for the HZ health states in the model. All disutility values were limited at a maximum value of 1.0. Lieu et al [88] also provide an estimate of the health state disutility of herpes zoster ophthalmicus (HZO); this was used to generate the health state disutility for ocular complications. For this estimate I used the estimates provided by the community members. Each of the health state disutilities were entered into the model as a decrement from a baseline QOL that corresponded with a persons age. That is, if the disutility of the health state = 0.50, it was assumed that a person would lose 0.50 utility from whatever his/her baseline health utility was at the time. The QALY Calculation Examples box provides an example of how the health state utilities were generated.

QALY Calculation Examples

- 3×1 Month = Mild HZ for 30 days
- Mean Community Member Disutility = 15/30 = 0.50

- 8×12 Month = Severe PHN for 365 Days
- Mean PHN Patient Disutility = 301/365 = 0.825
- Upper CI PHN Patient Disutility = 443/365 = 1.21 Rounded to 1.0

Vaccine Disutilities

The main severe adverse event for the vaccine was an allergic reaction that may or may not have lead to anaphylaxis [115]. In a large cohort study (n = 193083) there were 71 cases of vaccination that required further medical care due to an allergic

reaction and 9 cases that resulted in anaphylaxis [115]. Disutility values for allergic reactions were sourced from another cost-effectiveness analysis that examined allergic reactions as an outcome of treatment [119]. Values from this study were in the form of quality adjusted life days lost due to a reaction. These values were divided by 30 to estimate quality adjusted life months. The quality adjusted life month disutility was then multiplied by the probability of event to provide an estimate of the average disutility associated with receiving the vaccine. Common vaccine reactions occur approximately 30% of the time with the main symptom being bruising at the injection site [115]. It was assumed that all common reactions would not require any additional medical treatment and would resolve within 2 – 5 days.

Background Utility

Data on the background quality of life was sourced from one study [120]. Data was extracted from this study and fit using a linear regression to determine the background QOL by age. The mean value using the EQ-5D US scoring algorithm was used as the outcome variable. The predictors variables were the midpoint of the age ranges provided and gender.

A.4 Vaccine – HZ Risk Reduction

This section examines the protection benefit against HZ given vaccination. Four papers, an FDA statistical report, and a conference presentation were used to create the estimates of protection [15,20–22,51,78]. Protection against HZ is the combination of two components:

1. **Waning Efficacy:** The vaccines protection over time against HZ. This is defined as the period of protection from $t = [0, X]$, where t is measured in years and X is some number of years in the future when the vaccine reaches 0% efficacy.

2. **Initial Efficacy:** The vaccines initial protection against HZ. This is defined as the as the period of protection from $t = [0, 1)$, where t is measured in years.

For this model, the components (initial efficacy and waning) are combined using the form of a linear equation ($y = mt + b$). That is, the initial efficacy was assumed to be the intercept (b), the waning efficacy 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 form. The minimum value for vaccine efficacy was 0%; that is, the vaccine can not have a negative effect.

Waning Efficacy

The first step to determining the protection benefit of the vaccine was to determine the waning efficacy of the vaccine. Data for this step came from four sources [20–22, 78]. Data from the clinical trail and its follow-up [20–22] are given in Table A.5. Data from the large cohort study [78] is given in Table A.6. First, these data were used to generate synthetic observational data. This data was then combined and fit using statistical methods. The process of creating each of the syntheitc observational datasets will be discussed in turn.

Synthetic Data Generation – Zoster Clinical Trials

To generate the synthetic data using the clinical trial data, count data from Table A.5 were used. First, it was that these data were Poisson distributed (see Equation A.8). Twenty Poisson distributions (see Equation A.8) were created to reflect all **Trial Group** and **Years VX** combinations from Table A.5. The corresponding λ for each distribution was assumed to be the number of cases divided by the follow-up time. To create one set of data points, Y random observations (person-years) were sampled from each distribution to create 20 datasets, each corresponding to its distribution. Because of further uncertainty with this data, the number of sampled

Trial Group	Years VX	Cases	Follow-up Time	Reference
Vaccine	0–1	76	19132	[22]
	1–2	103	18827	[22]
	2–3	98	14505	[22]
	3–4	49	6264	[21, 22]
	4–5	26	3180	[21, 22]
	5–6	48	4850	[21]
	6–7	13	2243	[21]
	7–8	50	6564	[20]
	8–9	50	6280	[20]
	9–10	50	5005	[20]
Placebo	0–1	201	19081	[22]
	1–2	194	18679	[22]
	2–3	171	14327	[22]
	3–4	87	6158	[21, 22]
	4–5	42	2921	[21, 22]
	5–6	47	3295	[21]
	6–7	11	896	[21]
	7–8	66	6564	[20]
	8–9	54	6280	[20]
	9–10	57	5005	[20]

Table A.5: Data on vaccine efficacy over time – RCTs. Years VX: Years Vaccinated

observations, (person-years, Y), varied for each distribution. The number of samples was the average of the follow-up times (**Vaccine** and **Placebo Trial Groups**) for the specific years vaccinated group. After these observations were collected the sum of each dataset was taken. Equation A.9 was used to create one set of data points for efficacy over time.

$$P(X = x) = e^{-\lambda}\frac{\lambda^x}{x!} \tag{A.8}$$

The data set was split into two pieces: years 0 – 6 and years 7 – 10. For years 0 – 6, 2250 data points were generated. Each newly generated data points using the above procedure were assigned an integer value between [0,6] that corresponded with its **Years VX** group. To determine the proportion of the 2250 data points that each

year would contribute, the total person-years for each year of follow-up was divided by the total person-years follow-up for years 0 – 6 (131,219) to create the proportion. Example Box 1 provides an example of this process.

$$1 - \frac{\sum HZ\ Cases_{y_{HZ}}}{\sum HZ\ Cases_{y_{PL}}} \tag{A.9}$$

y: year
VX: Vaccine group
PL: Placebo group

A similar procedure was followed for years 7 – 10 with two modifications. First, only 250 data points were generated for years 7 – 10. This was due to uncertainty in the data presented by Morrison et al [20] due to the study design and lack of control group. Second, because no control group was present, the number of cases for the Vaccine and Placebo group had to be estimated by holding the number of vaccine cases constant and altering the number of placebo cases to correspond with the vaccine efficacies presented in the paper; shown in Table A.5. Further, as there was no control group, the number of person-years follow-up for each group was assumed be the same. This 90:10 (years 0–6: years 7–10) weighting of the synthetic data was done to weight the statistical fits more toward the first six years of data where more certainty existed. This weighting decision was based on conversations with zoster vaccine experts at the CDC.

Example 1

Years VX	PY	≈ Proportion (%)
0–1	38213	29.12
1–2	37506	28.58
2–3	28832	21.97
3–4	12422	9.46
4–5	6101	4.65
5–6	8145	6.20
6–7	2243	10.40
7–8	6564	30.44
8–9	6280	29.12
9–10	5005	23.21

Repetitions, Years 0–1: $29.12\% \times 2500 \approx 655$

Repetitions, Years 8–9: $29.12\% \times 250 \approx 72$

Synthetic Data Generation – Kaiser Observational Study

To generate the synthetic data using observational data, efficacy data from Table A.6 were used. The means were reported and the SD were estimated from the figures provided by Tseng et al [78] (see Figure A.3). It was assumed that these data were Normally distributed, due to the approximate symmetry of the confidence intervals (exceptions occur at years 6–7 and 7–8). Eight total distributions were created to correspond to reflect all **Years VX** groups from Table A.6. Each distribution randomly sampled X number of times to create X data points per **Years VX** group. In total 2500 data points were generate across all groups. To determine the number of data points per **Years VX** group (X), weighting was used. Tseng et al [78] provided the number of person-years follow-up for each year of data collection. These person-years were summed for years 0–1 through 7–8. The person-years follow-up

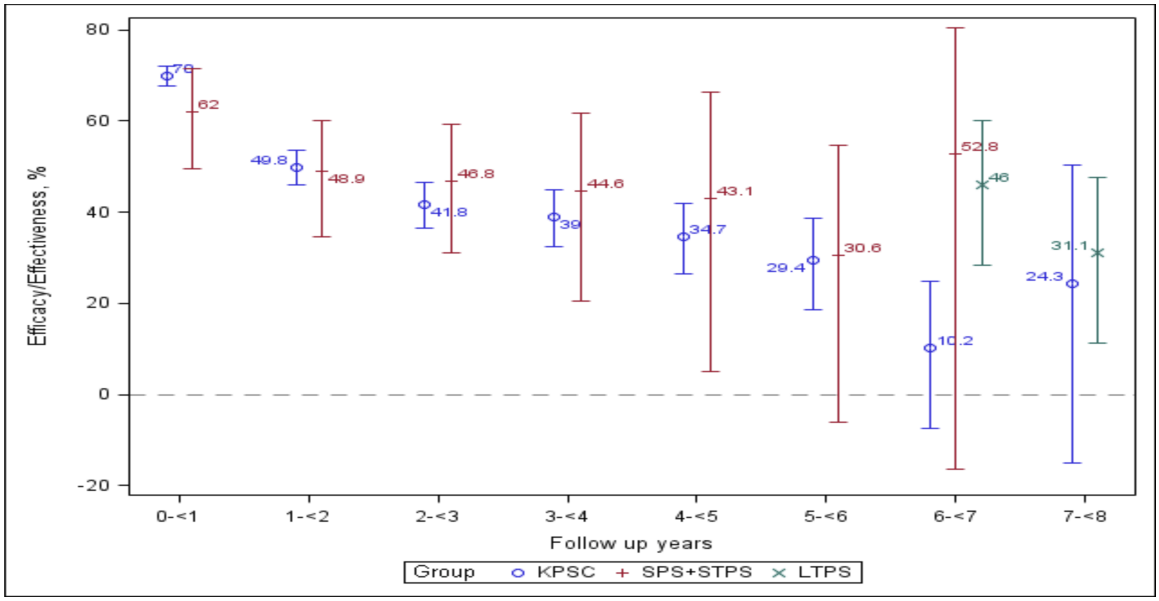

Figure A.3: Kaiser data

for the year group was divided by this sum to provide the weight (shown in Table A.6). This weight was multiplied by 2500 to determine X, the number of data points sampled for each **Years VX** group.

Years VX	Mean	SD	Weight	Follow-up Time	Reference
0–1	0.700	0.010	0.240	180620	[78]
1–2	0.498	0.022	0.208	156444	[78]
2–3	0.418	0.027	0.165	124325	[78]
3–4	0.390	0.035	0.123	92789	[78]
4–5	0.347	0.037	0.094	71092	[78]
5–6	0.294	0.050	0.078	59006	[78]
6–7	0.102	0.070	0.058	43618	[78]
7–8	0.243	0.125	0.038	29224	[78]

Table A.6: Data on vaccine efficacy over time – Kaiser. Years VX: Years Vaccinated

Synthetic Data – Statistical Fitting

Once the synthetic data was generated from both studies, it was treated as observational and combined. Each data set contained 2500 observations, so the data was assumed to be equally weighted. The decision to equally weight this data was based on a discussion with zoster vaccine experts at the CDC.

The combined data was then fit to estimate the efficacy of the vaccine over time (VE_i, where i is number of years vaccinated (0–1, 1–2, etc.)). Linear, second order polynomial, third order polynomial and restricted cubic spline (RCS) regression models were used. Based on AIC score, the RCS and third order polynomial linear regression models were selected. These models were also preferential due to the observation that there is a visibly steep decline in efficacy over the first year [20, 78]; this decline is not accounted for when using linear or second order polynomials. The form of the RCS and third order polynomial are shown by Equations A.10 and A.11, respectively. Output from the models is shown in Table A.7.

$$\begin{aligned} VE_i = \beta_0 + \beta_1 i + \beta_2 \max(i,0)^3 \\ + \beta_3 \max(i-1,0)^3 \\ + \beta_4 \max(i-2,0)^3 \\ + \beta_5 \max(i-7,0)^3 \end{aligned} \tag{A.10}$$

$$VE_i = \beta_0 + \beta_1 i + \beta_2 i^2 + \beta_3 i^3 \tag{A.11}$$

Model	β_0	β_1	β_2	β_3	β_4	β_5	AIC	adj.R^2
RCS	0.6574	-0.2083	0.0317	-0.0657	0.0344	-0.0004	-9923	0.772
Polynomial	0.6425	-0.1554	0.0273	-0.0019	–	–	-9576	0.701

Table A.7: VE_i regression output

Initial Efficacy

Data from the literature was used to estimate the initial protection of the vaccine [15, 22, 51]. Two HZ vaccine clinical trails provided this data. The initial clinical

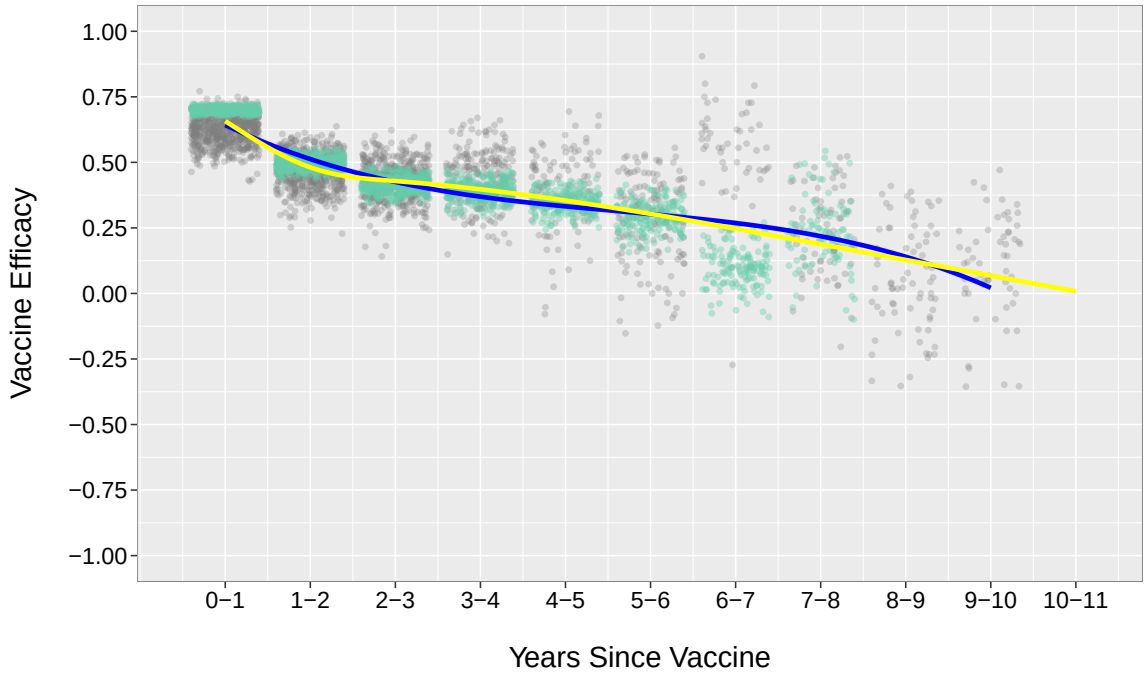

Figure A.4: Vaccine efficacy by time since vaccination. Yellow fit – RCS model. Blue fit – third order polynomial model. Grey data – synthetic RCT data. Green data – synthetic Kaiser data

trial for the HZ vaccine includes only people over age 60 [15, 22]. A subsequent trial includes people from ages 50 – 59 [51]. Data from these trials were combined to create the initial efficacy of the vaccine. To combine the data, a synthetic data set was generated, adjusted, and then fit using statistical models.

Synthetic Data Generation

First, data (shown in Table A.8) was assumed to be Poisson distributed. In total, 16 poisson distributions (see Equation A.8) were created to account for each **Trial Group** and **Age Group** combination from Table A.8. The λ for each distribution was assumed to be the number of cases divided by follow-up time. To create an estimate of the initial efficacy, 100,000 random observations (person-years) were sampled from each distribution and 16 datasets were created using these observations

Trial Group	Age Group	Cases	Follow-up Time	Reference
Vaccine	50 – 59	26	14124	[51]
	59 – 64	54	15693	[15, 22]
	65 – 69	68	15630	[15, 22]
	70 – 74	89	13830	[15, 22]
	75 – 79	67	9329	[15, 22]
	80 – 84	31	3172	[15, 22]
	85 – 89	5	498	[15, 22]
	≥ 90	1	51	[15, 22]
Placebo	50 – 59	94	14091	[51]
	59 – 64	153	15384	[15, 22]
	65 – 69	181	15569	[15, 22]
	70 – 74	158	13814	[15, 22]
	75 – 79	103	9105	[15, 22]
	80 – 84	39	3189	[15, 22]
	85 – 89	7	605	[15, 22]
	≥ 90	1	70	[15, 22]

Table A.8: Data on initial vaccine efficacy

(one dataset per distribution). The sum of each dataset was taken and efficacy was determined by using Equation A.12. This created one estimate of initial vaccine efficacy for each of the eight **Age Groups** in Table A.8. Random ages were then drawn for each age group and assigned to the newly created estimate of initial vaccine protection. The total number of person years from both trials were used to determine how many estimates of initial protection should be generated. Across both trials there were a total of 144,217 person-years follow-up. The sum the person-years for vaccine and placebo patients for each age group was divided by the number of total person-years to give a proportion of data points that were generated for each age group; Example 2 provides an example of this process. In total 2,500 data points were generated.

$$1 - \frac{\sum HZ\ Cases_{a_{VX}}}{\sum HZ\ Cases_{a_{PL}}} \tag{A.12}$$

a: Age group
VX: Vaccine group
PL: Placebo group

Example 2

Age Group	PY	≈ Proportion (%)
50 – 59	28215	19.56
59 – 64	31077	21.54
65 – 59	31262	21.67
70 – 74	27644	19.16
75 – 79	18434	12.78
80 – 84	6361	4.44
85 – 89	1103	0.076
90 – 95	121	0.008

PY: Person-years

Repetitions, Ages 59 – 64: $21.54\% \times 2500 \approx 539$
Repetitions, Ages 85 – 89: $0.076\% \times 2500 \approx 19$

Synthetic Data – Adjustment

The synthetic data generated for estimating initial efficacy provides the vaccines efficacy (VE_j) conditional upon being vaccinated at some age j. However, this data needed to be adjusted to account only for the time period of interest. Data used for people ages 60 and over was from a trial that reported three years of follow-up. Data from people ages 50 – 59 was from a trial that reported two years of follow-up. Therefore, the synthetic estimates were not specific to the time period from $t = [0, 1)$, the time period of interest. I used published methods [19] to adjust the data before fitting. This adjustment was used to determine VE_{ij}, where i is the number of years vaccinated (i.e., 0–1, 1–2, etc.), and j is the age at vaccination.

In order to make this adjustment, I made the following assumptions. First, the initial efficacy declines with age. Second, the vaccine does wane at the same rate for people of all ages. Third, the vaccine can not have less than 0% efficacy. Forth, the synthetic estimate of vaccine efficacy (VE_j) is the weighted average of waning vaccine efficacy; weights are determined by the person-years follow-up (from [19]; see Equation A.13).

$$VE_j = \frac{py0 \times VE_{ij}(i=0) + py1 \times VE_{ij}(i=1) + py2 \times VE_{ij}(i=2)}{py0 + py1 + py2} \tag{A.13}$$

To determine the age specific initial efficacy, a modification is first made the waning function (VE_i, where i is the number of years vaccinated). For the remainder of this section I will show equations assuming the vaccine wanes using the RCS function, this same procedure was repeated for the third order polynomial function. The initial waning function is shown in Equation A.14. In Equation A.14, β_0 provides the initial efficacy for the waning function ($t = [0, 1)$). Changing β_0 to β_{0j}, as shown in Equation A.15, changes VE_i to VE_{ij} as β_{0j} provides the age specific initial efficacy of the vaccine, where j is the age at vaccination. For simplicity, I will use β_{REM} (REM: Remainder; shown in Equation A.16) for the remaining the calculations.

$$\begin{aligned} VE_i = \beta_0 + \beta_1 i &+ \beta_2 \max(i, 0)^3 \\ &+ \beta_3 \max(i-1, 0)^3 \\ &+ \beta_4 \max(i-2, 0)^3 \\ &+ \beta_5 \max(i-7, 0)^3 \end{aligned} \tag{A.14}$$

$$\begin{aligned} VE_{ij} = \beta_{0j} + \beta_1 i &+ \beta_2 \max(i, 0)^3 \\ &+ \beta_3 \max(i-1, 0)^3 \\ &+ \beta_4 \max(i-2, 0)^3 \\ &+ \beta_5 \max(i-7, 0)^3 \end{aligned} \tag{A.15}$$

$$\begin{aligned}\beta_{REM} = \beta_1 i &+ \beta_2 \max(i,0)^3 \\ &+ \beta_3 \max(i-1,0)^3 \\ &+ \beta_4 \max(i-2,0)^3 \\ &+ \beta_5 \max(i-7,0)^3\end{aligned} \tag{A.16}$$

First, each synthetic data point for initial efficacy is assumed to represent one estimate of VE_j and must be adjusted to determine β_{0j} before the data can be fit and combined. Substituting Equation A.15 into Equation A.13 yields Equation A.17, where β_{0j} is the only unknown. Substituting and solving for β_{0j} adjusts the previous synthetic data to provide an age-specific estimate of the initial vaccine efficacy. These new estimates replace the estimates of initial vaccine efficacy VE_j produced by the synthetic data, to create an adjusted synthetic data set of β_{0j}s.

$$\begin{aligned}VE_j \times (py0 + py1 + py2) = py0 &\times (\beta_0 j + \beta_{REM}(i=0)) \\ + \ py1 &\times (\beta_0 j + \beta_{REM}(i=1)) \\ + \ py2 &\times (\beta_0 j + \beta_{REM}(i=2))\end{aligned} \tag{A.17}$$

To solve Equation A.17 person-years were taken from the clinical trial data [22,51]. As noted, the trial for 50 – 59 year olds only included 2 years of follow-up and the trial for people ≥ 60 included 3 years of follow-up on average. Person-years follow-up data are presented in Table A.9. For people ≥ 60, pyX was calculated from data in [22] as the person-years follow-up for specific age groups was not reported. First, total person years for years 0 - 2 were summed (19132 + 18827 + 14505 = 52464). Next the person years for each year was made a fraction by dividing the total follow-up for that year by the grand total (e.g., 19312/52464). Finally, these fractions were applied to the total person-years follow-up for each age group. Figures A.5 and A.6 show the synthetic dataset pre- and post-adjustment, respectively.

Age Group	Total py	$py0$	$py1$	$py2$	Reference
50 – 59	15040	10956	4084	0	[51]
60 – 64	15384	5610	5521	4253	[22]
65 – 69	15569	5678	5587	4304	[22]
70 – 74	13814	5038	4957	3819	[22]
75 – 79	9105	3320	3267	2517	[22]
80 – 84	3189	1163	1144	882	[22]
≥ 85	605	221	217	167	[22]

Table A.9: Person Year Inputs. pyX: person-years for year x – x+1 of trial

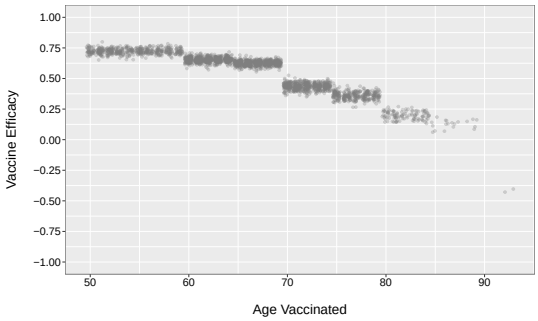

Figure A.5: Vaccine efficacy by age – pre-adjustment

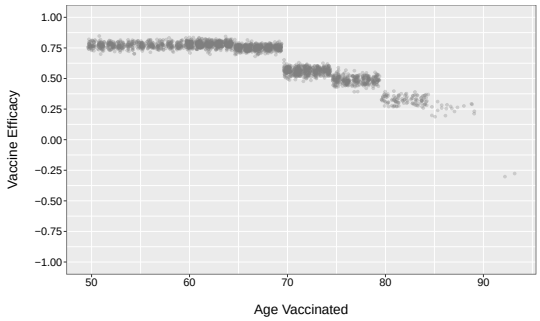

Figure A.6: Vaccine efficacy by age – post-adjustment

Synthetic Data – Statistical Fitting

Once the synthetic data on initial efficacy was adjusted it was fit using statistical methods. This fit provided the adjusted age-specific initial efficacy of the vaccine (β_{0j}, where j is the age vaccinated). Second order polynomial, and RCS linear regression models were used based on the shape of the data (see Figure A.6). The initial fits of the models are shown in Figure A.7. Based on AIC score, the RCS model was selected over the polynomial model. The form of the RCS and second order polynomial are shown by Equations A.18 and A.19, respectively. Output from the models is shown in Table A.10. Both models showed a slight increase (approximately 1 percentage point) in the age specific initial efficacy (β_{0j}) from ages 50 – 58. This is because of the adjustment and using two different data sets. This increase was manually changed so that the vaccine had the same initial efficacy from age 50 – 58.

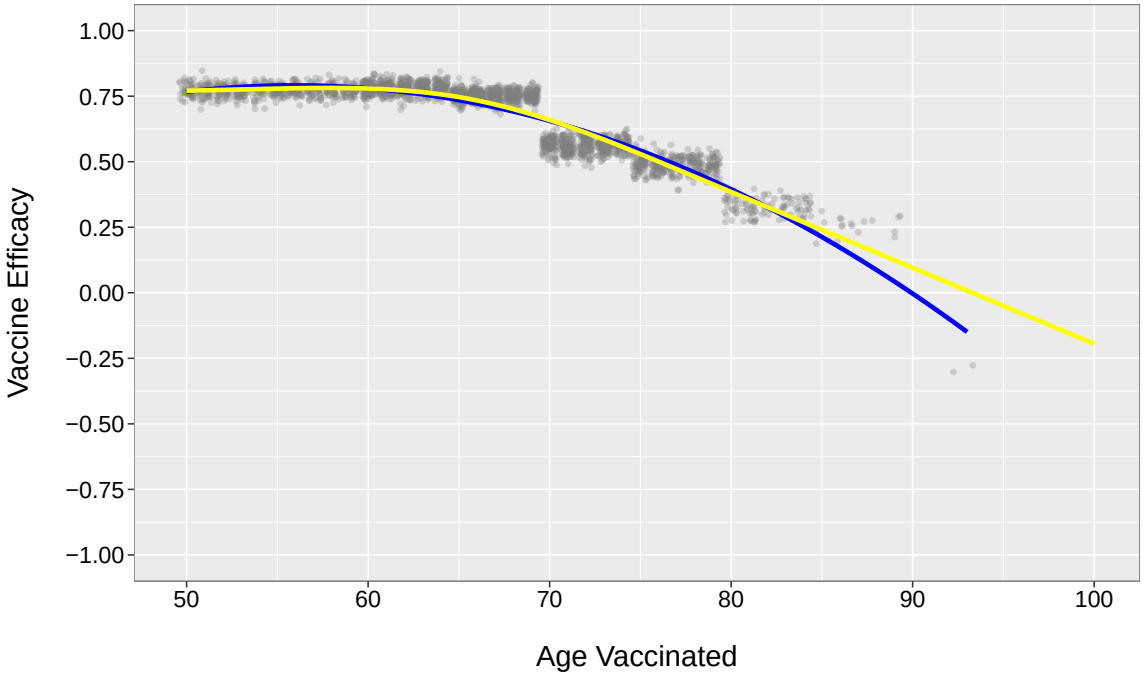

Figure A.7: Age-specific initial efficacy fits – piecewise waning. Yellow fit – Piecewise model. Blue fit – second order polynomial model.

$$\begin{aligned}\beta_{0j} = \alpha_0 + \alpha_1 j + \alpha_2 \max(j-54,0)^3 \\ + \alpha_3 \max(j-66,0)^3 \\ + \alpha_4 \max(j-77.4,0)^3\end{aligned} \tag{A.18}$$

$$\beta_{0j} = \alpha_0 + \alpha_1 j + \alpha_2 j^2 \tag{A.19}$$

Model	α_0	α_1	α_2	α_3	α_4	AIC	adj.R^2
RCS	0.6900	0.0016	-3.63e-05	7.45e-05	-3.823e-05	-8228	0.894
Polynomial	-1.351	0.0766	-0.0007	–	–	-7922	0.880

Table A.10: β_{0j} Regression Output

Synthetic Data – Combining

Once the age-specific initial efficacy was generated it was combined with the waning function to create estimates of the age-specific efficacy and waning (shown in Equation A.15). The final for the combination assuming a RCS waning and polynomial waning model are shown by Equations A.20 and A.21, respectively. Simulating these equations for values of age at vaccination, j, between 50 and 100, and different values of years vaccinated, i, plots of the age-specific waning of the vaccine were created. These are shown in Figures A.8 – A.13.

$$\begin{aligned} VE_{ij} = \beta_{0j} &+ \beta_1 i \\ &+ \beta_2 \max(i,0)^3 \\ &+ \beta_3 \max(i-1,0)^3 \\ &+ \beta_4 \max(i-2,0)^3 \\ &+ \beta_5 \max(i-7,0)^3 \end{aligned} \tag{A.20}$$

$$\begin{aligned} VE_{ij} = \beta_{0j} &+ \beta_1 i \\ &+ \beta_2 i^2 \\ &+ \beta_3 i^3 \end{aligned} \tag{A.21}$$

A.5 PHN Risk Reduction

This section examines the potential additional benefit of protection against PHN given HZ vaccination. The FDA statistical report [22] provides the only data available to examine if the HZ vaccine provides an additional protection benefit against PHN (i.e., the incidence of PHN is further reduced beyond the reduction in HZ incidence). The report provides the number of cases of HZ and PHN as well as the follow-up time for the both vaccine and placebo groups; data from the statistical report [22] is presented in Table A.11. Using Equation A.22, data in Table A.11 suggest that approximately 96% of the reduction in PHN cases in the 60 – 69 age group is attributable to the

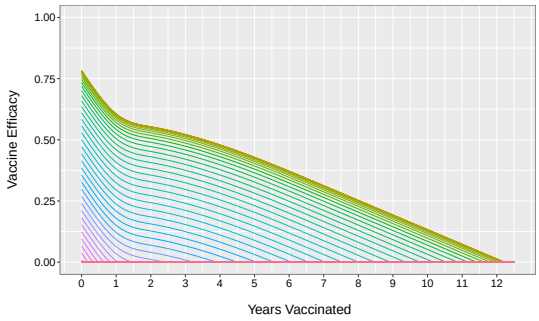

Figure A.8: RCS age-specific waning – side. Top line – Vaccination age 50. Bottom line – Vaccination age 94.

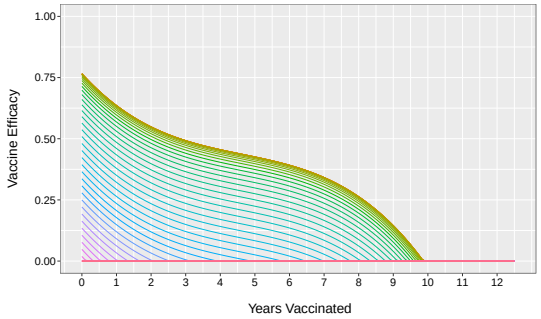

Figure A.9: Polynomial age-specific waning – side. Top line – Vaccination age 50. Bottom line – Vaccination age 94.

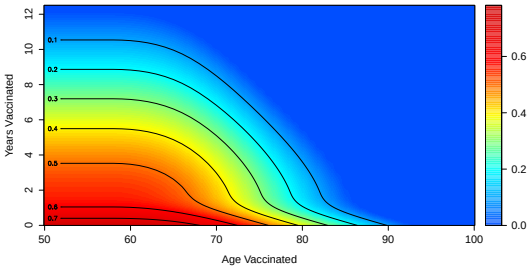

Figure A.10: RCS age-specific waning – contour.

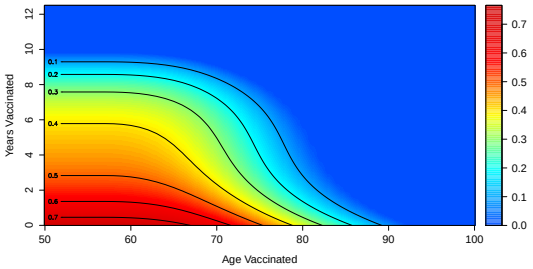

Figure A.11: Polynomial age-specific waning – contour.

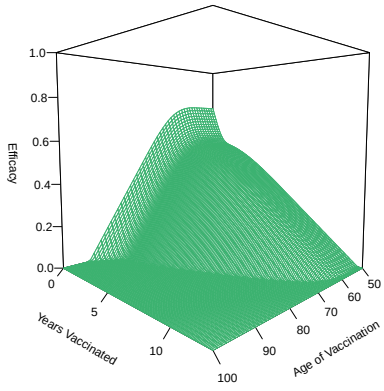

Figure A.12: RCS age-specific waning – 3D.

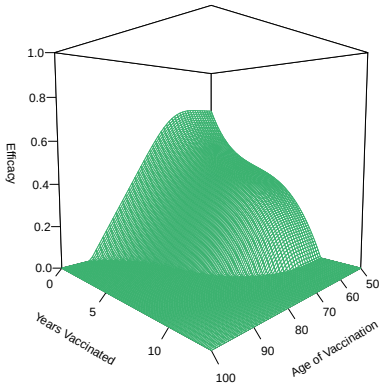

Figure A.13: Polynomial age-specific waning – 3D.

reduction in HZ incidence (i.e., a 4% additional protection benefit). Conversely, in the ≥ 70 group, approximately 51% of the reduction in PHN cases is attributable to reduction in HZ incidence (i.e., a 49% additional protection benefit). Thus data from Table A.11 suggests a discontinuity in additional protection benefit of the vaccine.

Trial Group	**Age Group**	**Disease Category**	**Cases**	**Follow-up Time**
Vaccine	60 – 69	HZ	122	31323
		PHN	8	31323
	≥ 70	HZ	193	26881
		PHN	19	26881
Placebo	60 – 69	HZ	334	30953
		PHN	23	30953
	≥ 70	HZ	308	26783
		PHN	57	26783

Table A.11: Data from FDA statistical report

As no additional data exists, simulation methods were used to create a synthetic data set to examine possible trends. To create the synthetic data, count data in Table A.11 were assumed to be Poisson distributed. Eight Poisson distributions (see Equation A.8) were created to reflect all **Trial Group**, **Age Group**, and **Disease Category** combinations from Table A.11. The corresponding λ for each distribution was assumed to be the number of cases divided by the follow-up time. To create one data point, 100,000 random observations (person-years) were sampled from each distribution to create eight datasets, (one per distribution). After these observations were collected the sum of each dataset was taken. Equation A.22 was used to create one estimate of the additional protection benefit.

$$1 - \left(\frac{\sum PHN\ Cases_{a_{VX}} / \sum HZ\ Cases_{a_{VX}}}{\sum PHN\ Cases_{a_{PL}} / \sum HZ\ Cases_{a_{PL}}} \right) \tag{A.22}$$

a: Age group
VX: Vaccine group
PL: Placebo group

A newly generated estimate of additional protection was then randomly assigned an age within its corresponding age group (e.g., 60 – 69, ≥ 70). The FDA statistical

report [22] provides data on number of patients enrolled by five-year age categories (e.g., 59 – 64, 65 – 69, ...). This data was used to determine how many people from each five year age cohort were sampled and randomly assigned to the estimates for additional protection. In total this process of generating one estimate of additional protection and assigning an age to that estimate was repeated 2500 times. This ensured a large enough sample to include people in order age groups (e.g., ≥ 85). Example 3 demonstrates the process of determining how many of the 2500 repetitions (estimates) were assigned to each age group. Figure A.14 shows the final set of synthetic data.

Data in Figure A.14 shows a discontinuity in the additional protection from age 69 – 70. Based on discussions with collaborators at the CDC, this is likely due to the way in which the data from Table A.11 is categorized, rather than some biological mechanism. In addition, the Poisson arrival process suggests that the additional impact could be negative from the ages of 60 – 69. This finding is also not supported by the understanding of how the vaccine works. Therefore, I made the following assumptions. First, the vaccine can not have an additional protection benefit below 0%. At 0% protection benefit, the reduction in PHN cases due to vaccination would be entirely attributable to the number of HZ cases reduced. Second, there is some function that represents the additional protection benefit. This assumption suggests that the discontinuity presented by Table A.11 and Figure A.14 generated by simulation of that data is an artifact of the way the data was grouped in the FDA report.

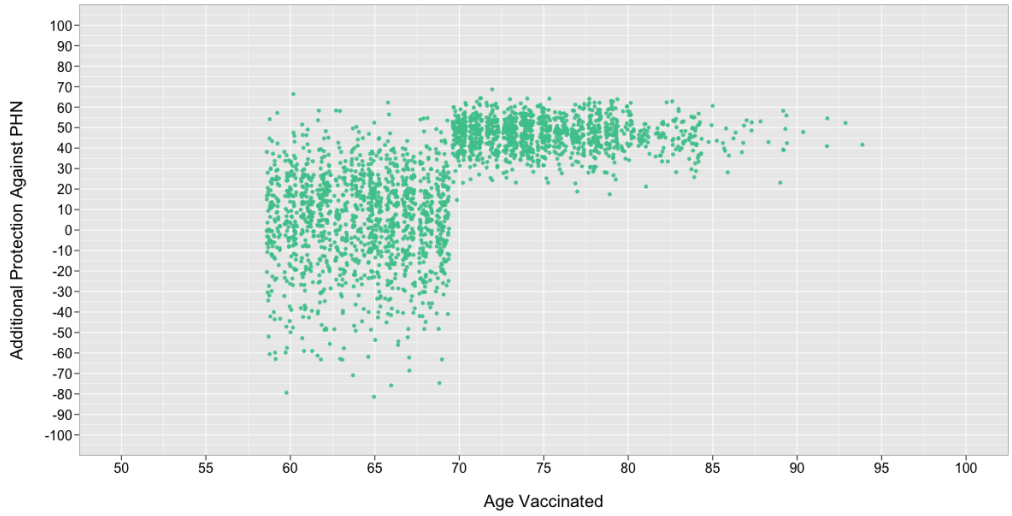

Figure A.14: Initial additional protection against PHN given vaccination – synthetic data

Example 3

Age Group	n	Proportion (%)
59 – 64	5216	50.30
65 – 59	5154	49.70
70 – 74	4545	51.16
75 – 79	3076	34.62
80 – 84	1063	11.97
85 – 89	181	2.04
90 – 95	19	0.21
59 – 69	10370	53.8
≥ 70	8884	46.2

Repetitions, Ages 59 – 64: $53.8\% \times 50.30\% \times 2500 \approx 677$

Repetitions, Ages 85 – 89: $46.2\% \times 2.04\% \times 2500 \approx 22$

Synthetic Data – Approximation Methods

Because of the discontinuity in the synthetic data shown in Figure A.14, statistical methods were found to produce models with clinically unlikely anomalies. Therefore, approximation methods methods were used to estimate linear segments at different breakpoints. Seven total approximations were generated; these are shown in Figure A.15. Data on the breakpoints and assumed additional efficacies are given in Table A.12. This method was selected as there is no further data on this additional protection. Therefore, these approximation methods provide a best guess of the additional protection without assuming some prior mathematical relationship. Based on conversations with zoster vaccine experts at the CDC, model A was chosen as the base case model to estimate the initial additional protection ($\beta 0_{j_{PHN}}$). There is unfortunately no data on how the additional protection against PHN wanes with time. Therefore, it was assumed that the additional protection against PHN would wane at the same rate as the vaccines protection against HZ. This was accomplished using Equation A.23.

$$VE_{ij_{PHN}} = \begin{cases} \beta_{0j_{PHN}} \times \frac{VE_{ij_{HZ}}}{\beta_{0j_{HZ}}} & \text{if } \beta_{0j_{HZ}} > 0 \\ 0 & \text{if } \beta_{0j_{HZ}} = 0 \end{cases} \tag{A.23}$$

Model	bp1	Efficacy bp1	bp2	Efficacy bp2	Color
A	75.4	0.4653	–	–	Grey
B	70	0.4653	–	–	Pink
C	64.2	0.0425	75.4	0.4653	Blue
D	59	0.0425	70	0.4653	Green
E	69	0.0425	81	0.4653	Red
F	64.2	0.0000	75.4	0.0000	Black
G	64.2	0.4653	75.4	0.4653	Orange

Table A.12: Additional PHN protection – approximation fits. bp: breakpoint. Ages 50 and 100, with efficacies 0.04 and Efficacy bp2, respectively, were the initial and final points for approximations in all models.

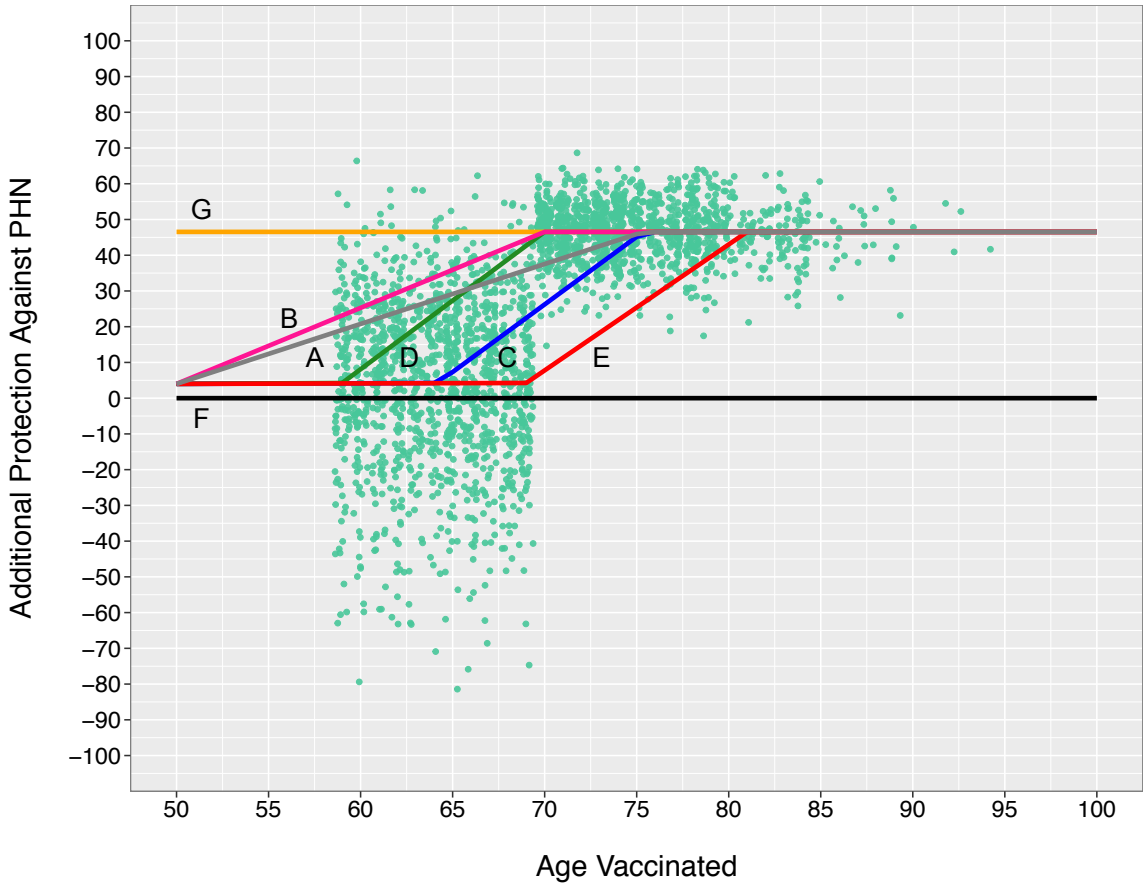

Figure A.15: Additional protection against PHN given vaccination. Model letter corresponds to Table A.12.

A.6 Literature Review

The following section presents the information and on the systematic review to collect model inputs. Systematic literature reviews were conducted to assess the published data relating to costs, health utilities, and epidemiology of herpes zoster and its complications. The search terms for each review are presented in Table A.13. Search terms were selected based on their use in similar systematic reviews. Searches were conducted by combining a **Main Term** along with a **Epidemiology**, **Cost**, or **QALY Term** using the "AND" search operator.

Main Term	**Epidemiology Term**	**Cost Term**	**QALY Term**
Herpes Zoster OR Shingles	Epidemiology	Cost	QALYs
PHN OR Postherpetic neuralgia	Incidence	Cost of Illness	Quality Adjusted Life Years
(HZ OR Shingles) neurological	Incidence of Hospitalization	Economic	Quality Adjusted
(HZ OR Shingles) (eye OR ocular OR ophthalmic)	Morbidity	Economic Burden	Quality Adjusted Cost Per Life Year
(HZ OR Shingles) complications	Mortality	Economic Impact	Cost(-)Effectiveness
(HZ OR Shingles) secondary		Societal Cost	Cost(-)Utility
(HZ OR Shingles) vaccine		Direct Cost	Utility
		Indirect Cost	
		Presenteeism	
		Absenteeism	
		Productivity	
		Productivity Loss	
		Healthcare Utilization	
		Health Expenditure	

Table A.13: Search terms from systematic review

Literature reviews focused on peer-reviewed published literature relating to herpes zoster in the US. Peer-reviewed articles relating to herpes zoster outside the US were considered (depending on data quality and transferability). Search results from the literature reviews were compiled and all duplicate articles were removed. The remaining unique entries were subjected to a title and abstract review. Results were excluded using pre-defined criteria. Any paper that was not a full scientific study, such as letters to the editor, commentaries, or conference abstracts were excluded due to a potential for selective reporting bias. A running list of all excluded studies was kept

for reference. The remaining papers were subject to a full review. Exclusion criteria for this step was also pre-defined. References for full review papers were inspected to check for any record that may have been missed during the initial searches. Each additional record was subject to the same title, abstract, and full review criteria.

Appendix B

Models and Input Data for MDPs

B.1 State Transition Models for MDP

Main STM – One Dose MDP

Data for the one dose MDP was generated from a state-transition model (STM) built in R. This model was designed to emulate the MDP (also built in R). A model overview is shown in B.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 Figure B.2). The costs and QALYs for the intra-HZ states were determined by sub-models that will be presented in the following sections of this appendix. 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 2 health state, a transient

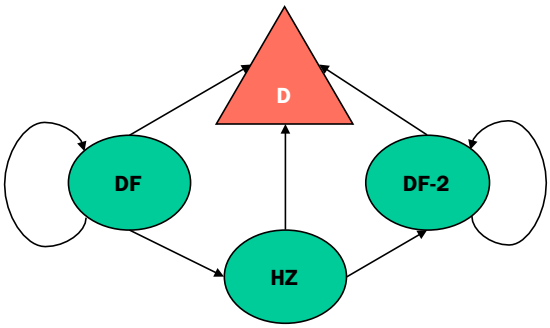

Figure B.1: MDP state-transition model

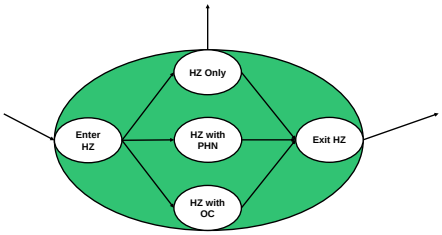

Figure B.2: Intra-HZ transition model

state where the cohort remains until death, 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.

The results from this STM, and its sub-models (described further in the following sections), were used to generate data for the base case analysis, the one-way sensitivity analysis, and the probabilistic sensitivity analysis. All data for this STM and its sub-models comes from data used in the Chapter 2 cost-effectiveness models, which can be found in Tables 2.2 – 2.4 on pages 27 – 28.

HZ Sub-model

To determine the costs and disutility due to a case of HZ a decision tree model was constructed in TreeAge. The model is shown in Figure B.3. In this model it is assumed that every person starts with HZ. HZ is first differentiated as producing pain or not. If the HZ does produce pain, the model then differentiates between mild, moderate, or severe pain. The terminal nodes for the model (denoted by triangles in Figure B.3) give both cost and disutility rewards. The result of this model produces the average costs and disutility due of a case of HZ. The cycle time for this model is assumed to be 1 month; therefore, the disutility due to HZ is divided by 12 before being implemented into the main STM.

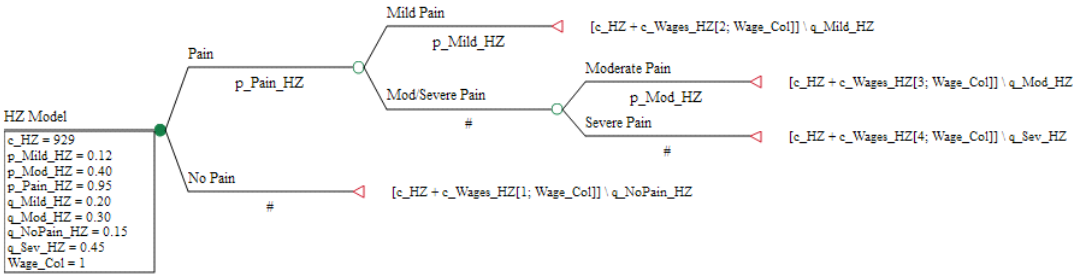

Figure B.3: HZ sub-model

PHN Sub-model

To determine the costs and disutility due to a case of PHN a Markov-like model was constructed in TreeAge, the model is shown in Figure B.4. In this model it is assumed that the cohort starts with PHN. PHN is 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). The data for these states are given in Table 2.2 on page 27. This model contains the same type of laddering structure as the cost-effectiveness model from Chapter 2, where a person must move through all better states of PHN before eventually reaching the disease free state. At each cycle, a person collects some disutility due to their PHN. There is no background QOL in this model. Simulating this model produces the average disutility and cost due of a case of PHN. The cycle time for this model is assumed to be 1 month; therefore, the disutility due to PHN was divided by 12 before being implemented into the main STM.

Ocular Complications Sub-model

To determine the disutility lost due to ocular complications given HZ, a Markov-like model was constructed in TreeAge, shown in Figure B.5. In this models it is assumed that every person starts with a complication, and has a chance of moving to disease free after each model cycle. Unlike PHN, there is no stratification for severity. That is, I assume that one complication is as bad/good as the next. While this is unlikely,

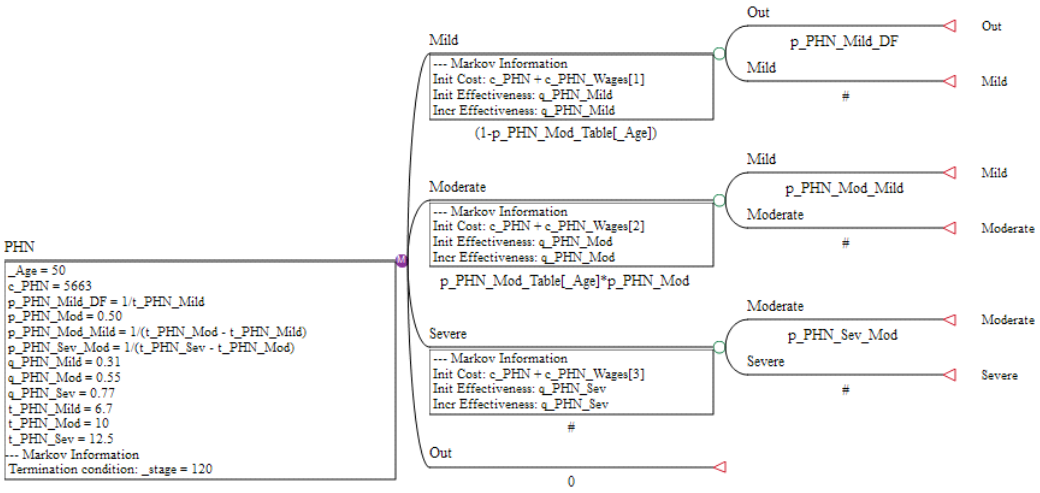

Figure B.4: PHN sub-model

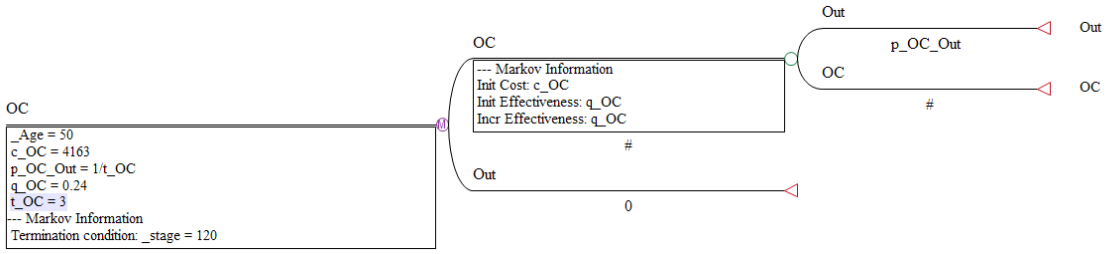

Figure B.5: Ocular complications sub-model

there is limited data on the epidemiology, costs, and disutility for differing levels of severity with ocular complications. At each cycle, the cohort collects some disutility due to their complication. There is no background QOL in this model. Simulating this model produces the average costs and disutility due an ocular complication. The cycle time for this model is assumed to be 1 month; therefore, the disutility lost due to a complication are divided by 12 before being implemented into the main STM.

Main STM Model – Two Dose MDP

Data for the two dose MDP was generated by creating a one additional STM in R. The model follows the same structure as the HZ model presented in Figure B.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. The probability of developing PHN given HZ (as occurs in the intra-HZ model, see Figure B.2), 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. At the end of the cycle, the cohort can transfer to disease free 2, a transient state where the cohort remains until death, or to death should death occur.

B.2 Sensitivity Analysis

One-way Sensitivity Analysis

To perform the one-way sensitivity analysis, first all sub-model inputs were converted to distributions. The distributions used for each sub-model were the same distributions for the cost-effectiveness analysis (available in Table 2.5). Once all sub-model inputs had been replaced with distributions, PSAs were run on each sub-model. For PHN, a PSA was run for every age between 50 – 100. The data from the PSAs was exported from TreeAge and imported into R. The raw data was used to determine the mean and confidence intervals for each of the sub-models. These means and confidence intervals were used as the data for the intra-HZ states as part of the MDP analysis. Data for PHN is presented in Table B.1, and data for HZ and ocular complications is given in Table 3.2 in Chapter 3.

PHN Data

Age	Q − M	Q − L	Q − U	$ − M	$ − L	$ − U
50	0.284	0.209	0.355	6,235	4,504	8,236
51	0.285	0.209	0.356	6,240	4,510	8,241
52	0.286	0.211	0.358	6,245	4,515	8,245
53	0.287	0.211	0.359	6,250	4,520	8,250
54	0.288	0.212	0.360	6,255	4,524	8,255
55	0.289	0.213	0.361	6,260	4,529	8,260
56	0.291	0.214	0.363	6,264	4,534	8,265
57	0.292	0.215	0.363	6,269	4,538	8,270
58	0.293	0.216	0.365	6,274	4,543	8,275
59	0.294	0.217	0.366	6,279	4,548	8,280
60	0.295	0.218	0.367	6,284	4,552	8,285
61	0.296	0.218	0.368	6,289	4,557	8,290
62	0.297	0.219	0.370	6,294	4,562	8,295
63	0.298	0.220	0.371	6,298	4,566	8,299
64	0.299	0.221	0.372	6,303	4,571	8,304
65	0.301	0.222	0.374	6,308	4,575	8,309
66	0.302	0.223	0.375	6,313	4,580	8,314
67	0.303	0.224	0.376	6,318	4,585	8,319
68	0.304	0.225	0.377	6,323	4,589	8,324
69	0.305	0.225	0.378	6,327	4,594	8,329
70	0.306	0.226	0.379	6,332	4,599	8,334
71	0.307	0.227	0.380	6,337	4,603	8,339
72	0.308	0.228	0.381	6,342	4,608	8,344
73	0.309	0.229	0.383	6,347	4,613	8,349
74	0.311	0.230	0.384	6,352	4,617	8,354
75	0.312	0.231	0.385	6,356	4,622	8,358
76	0.313	0.232	0.386	6,361	4,627	8,363
77	0.314	0.232	0.388	6,366	4,631	8,368
78	0.315	0.233	0.389	6,371	4,636	8,373
79	0.316	0.234	0.390	6,376	4,641	8,378

Age	Q − M	Q − L	Q − U	$ − M	$ − L	$ − U
80	0.317	0.235	0.391	6,381	4,645	8,383
81	0.318	0.236	0.393	6,386	4,650	8,388
82	0.319	0.236	0.394	6,390	4,655	8,393
83	0.321	0.237	0.395	6,395	4,659	8,398
84	0.322	0.238	0.396	6,400	4,664	8,403
85	0.323	0.239	0.398	6,405	4,668	8,408
86	0.324	0.240	0.399	6,410	4,673	8,413
87	0.325	0.241	0.400	6,415	4,678	8,418
88	0.326	0.241	0.402	6,419	4,682	8,423
89	0.327	0.242	0.403	6,424	4,687	8,428
90	0.328	0.243	0.404	6,429	4,692	8,433
91	0.329	0.244	0.405	6,434	4,696	8,438
92	0.331	0.245	0.407	6,439	4,701	8,443
93	0.332	0.246	0.408	6,444	4,705	8,448
94	0.333	0.247	0.409	6,448	4,710	8,453
95	0.334	0.248	0.410	6,453	4,714	8,458
96	0.335	0.249	0.411	6,458	4,719	8,462
97	0.336	0.249	0.412	6,463	4,724	8,467
98	0.337	0.250	0.413	6,468	4,728	8,472
99	0.338	0.251	0.415	6,473	4,733	8,477
100	0.339	0.252	0.416	6,477	4,738	8,482

Table B.1: MDP sensitivity analysis parameters – PHN. **Q**: QALYs. **$**: Costs. M: Mean. L: Lower limit of 95% confidence interval. U: Upper limit of 95% confidence interval.

Probabilistic Sensitivity Analysis

A probabilistic sensitivity analysis was conducted for the one and two dose MDP models. To conduct this analysis, the distributions created for the one-way sensitivity analysis sub-models were used. Using R, the STM sub-model PSA output data was analyzed to define distributions for the costs and QALY inputs for the STM. Following

recommendations [139], gamma distributions $\sim \Gamma(\alpha, \beta)$ were fit for cost data, and beta distributions $\sim \beta(\alpha, \beta)$ were fit for QALY data. Once all parameters had been converted to distributions a first 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. I 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). A visualization of the methods is shown by Figure B.6. Each of the 1000 MDP iterations produced a optimal policy over the time horizon. Each policy was converted into a binary formatted vector (1 = vaccinate, 0 = wait), where each place in the vector corresponded to an age (e.g., vector place 1 = age 100). The sum of across each vector location age was taken and divided by the total number of iterations to produce the probability that a particular age would be part of the optimal policy given a certain WTP. The two dose PSA followed the exact same procedure, I 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. Age-dependent PHN distribution data is given in Table B.2, and the remaining distributions used for the PSA analysis are given in Chapter 3 in Table 3.3.

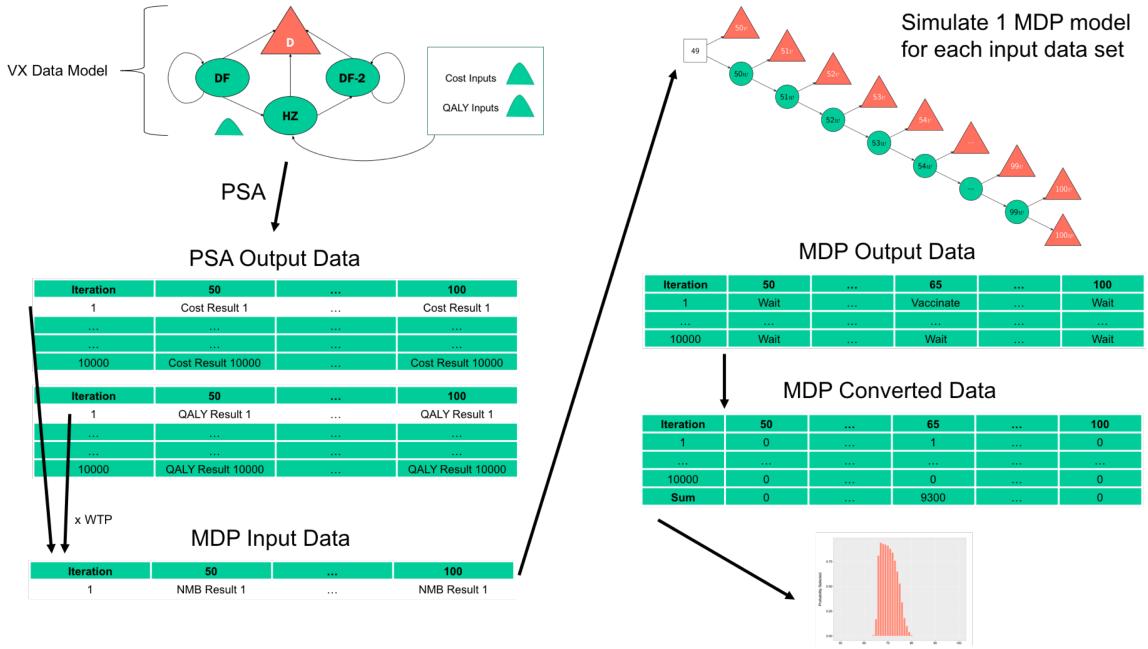

Figure B.6: MDP PSA methods diagram

PHN Data

Age	$\beta - \alpha$ Term	$\beta - \beta$ Term	$\Gamma - \alpha$ Term	$\Gamma - \beta$ Term
50	39.600	102.180	42.773	145.800
51	39.800	102.210	42.835	145.705
52	39.970	102.080	42.896	145.609
53	40.030	101.690	42.957	145.514
54	40.070	101.240	43.019	145.419
55	40.280	101.290	43.080	145.324
56	40.060	100.180	43.141	145.230
57	40.400	100.550	43.202	145.136
58	40.330	99.840	43.264	145.043
59	40.270	99.170	43.325	144.949
60	40.420	99.000	43.386	144.856
61	40.500	98.730	43.447	144.764

Age	$\beta - \alpha$ **Term**	$\beta - \beta$ **Term**	$\Gamma - \alpha$ **Term**	$\Gamma - \beta$ **Term**
62	40.480	98.160	43.509	144.671
63	40.410	97.460	43.570	144.579
64	40.460	97.120	43.631	144.487
65	40.410	96.490	43.692	144.396
66	40.460	96.100	43.753	144.305
67	40.650	96.110	43.814	144.214
68	40.760	95.910	43.876	144.123
69	40.930	95.870	43.937	144.033
70	41.170	95.990	43.998	143.943
71	41.370	95.950	44.059	143.853
72	41.380	95.480	44.120	143.764
73	41.170	94.490	44.181	143.675
74	41.320	94.410	44.242	143.586
75	41.290	93.910	44.303	143.497
76	41.260	93.350	44.364	143.409
77	41.210	92.760	44.425	143.321
78	41.290	92.560	44.486	143.233
79	41.360	92.240	44.547	143.146
80	41.260	91.490	44.608	143.059
81	41.190	90.920	44.669	142.972
82	41.000	90.040	44.730	142.886
83	41.090	89.850	44.791	142.800
84	41.120	89.490	44.851	142.714
85	41.220	89.270	44.912	142.628
86	41.110	88.630	44.973	142.543
87	41.060	88.070	45.034	142.458
88	40.990	87.480	45.095	142.373
89	41.050	87.150	45.155	142.289
90	41.010	86.690	45.216	142.205
91	41.010	86.250	45.277	142.121

Age	$\beta - \alpha$ **Term**	$\beta - \beta$ **Term**	$\Gamma - \alpha$ **Term**	$\Gamma - \beta$ **Term**
92	41.050	85.890	45.338	142.037
93	41.230	85.880	45.398	141.954
94	41.320	85.700	45.459	141.871
95	41.380	85.440	45.520	141.788
96	41.550	85.370	45.580	141.706
97	41.490	84.870	45.641	141.624
98	41.460	84.370	45.702	141.542
99	41.470	84.030	45.762	141.460
100	41.520	83.700	45.823	141.379

Table B.2: MDP probabilistic sensitivity analysis parameters – PHN. β distribution for QALYs. Γ distribution used for costs.

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