ABSTRACT

RULON, CHRISTINA MARIE. Optimizing Vaccine Distribution During an Influenza Pandemic. (Under the direction of Osman Ozaltin.)

Vaccination is critical in circumventing an influenza pandemic. By its very nature, a new strain of influenza virus may develop and spread rapidly throughout spatially distributed population groups. A direct causal effect of such unfettered growth is an initial scarcity of vaccines. Accordingly, minimization of the number of vaccines needed to contain the pandemic is imperative for effective disease mitigation. Given a heterogeneous age distributed population, in the first model we develop a mixed-integer programming formulation to determine the minimal fraction of each subgroup to vaccinate such that pandemic elimination results. This formulation employs a surface threshold characterization to describe where the minimal fractions reside. Furthermore, it allows for the unique representation of contract rates, susceptibility and infectiousness for each age group. Disease elimination occurs when the reproduction number is less than or equal to one. We use the spectral radius, the largest magnitude eigenvalue of the next generation matrix, to define the reproduction number in a heterogeneous population. We analyze results from the optimization model using the parameters from the 1957 Asian influenza A pandemic. Using U.S. population projections and future age group distribution factors, we evaluate the results of the optimization model. Additionally, the evaluation of vaccines at varying levels of efficacy, provides insight into the problematic scenario of ineffective vaccines. From these results, we observe an inequitable distribution of vaccines to heterogeneous subgroups. Therefore, we consider the addition of fairness constraints to ensure equitable vaccine dissemination, and we analyze the additional vaccines needed to satisfy these constraints.

Other difficulties in vaccine distribution present as public health decisions regarding the implementation of vaccines to combat an influenza pandemic are made under a shroud of uncertainty. In this regard, decision makers face the daunting challenge of balancing competing concerns. On one side of the scale is the concern for employing proper proportions of vaccines to eliminate widespread infection. The competing predicament is the fiscal cost associated with implementing the vaccines and the health concerns of lost quality adjusted life years due to infection. Use of dynamic optimization techniques to weigh these competing objectives allow public health decision makers to consider the most recent information in determining the optimal vaccine strategy. In he second model, we employ an infinite horizon Markov Decision Process (MDP) model to provide instruction for establishing health policies regarding the proportion of susceptible individuals to vaccinate in each possible state of disease progression. The expected discounted reward optimality equations developed from this MDP are solved using a linear programming solutions approach. Furthermore, to maximize policy accuracy, we intro-

duce another layer of uncertainty through development of a two stage stochastic program to explore unpredictability surrounding vaccine efficacy. Results of this optimizations are evaluated using the parameters from an influenza outbreak at an English boarding school. These results yield insight to various facets of optimal vaccine distribution based on susceptible and infectious proportions of the population.

Optimizing Vaccine Distribution During an Influenza Pandemic

by
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DEDICATION

This thesis is dedicated to my family for their constant support and encouragement.

BIOGRAPHY

Christina Rulon graduated from the College of Mount St. Joseph in 2012 obtaining a Bachelors of Science degree in Business/Mathematics and Accounting. After working for a year in the accounting field, Christina entered North Carolina State University in the fall of 2013 pursuing a Masters of Science in Operations Research. Upon graduation, Christina will begin an Oak Ridge Institute for Science and Education (ORISE) fellowship at Wright-Patterson Air Force Base in the School of Aerospace Medicine performing biostatistics and epidemiology research.

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Chapter 1

Introduction

Influenza is an acute viral infection that is easily transmitted from person to person [51]. Although it is commonplace for influenza strains to emerge seasonally, the occasion of certain circumstances can lead to the evolution of a novel virus strain. A novel strain of influenza disseminates throughout a susceptible population of a geographic area largely due to lack of immunity from previous strains. A pandemic, which is considered a global outbreak of a disease, then develops as a result of the novel strain moving swiftly through the population due to the natural interaction between geographic areas and populations leading to rapid worldwide spread ([14] and [26]). Despite the fact that an influenza of pandemic proportions does not occur with regularity, the impact of such a pandemic can be remarkably devastating to a society in terms of its heightened illness levels, overburdened health care systems and elevated mortality rates as well as social and economic disruptions. In essence, it is these consequences that come to characterize an influenza pandemic.

The foremost characteristic of an influenza pandemic is higher illness rates. Attack rates of the virus are higher across all age groups in the population, and very often, they adversely affect age groups not usually burdened by seasonal influenza. A historical comparison of pandemics and seasonal influenza strains provide evidence for this concept. Seasonal influenza annually affects five to ten percent of adults and 20 to 30 percent of children, and it can cause serious medical complications for the following groups: children younger than two years of age, adults age 65 and over, pregnant women and people with pre-existing medical conditions [51]. However, in a pandemic, even individuals outside of the aforementioned risk groups are at an increased danger of falling prey to the higher attack rates and illness. During the 1918-1919 pandemic outbreak, commonly referred to as the Spanish flu, illness rates for the 20 to 40 percent of the worldwide population that was afflicted were highest in those aged 20 to 50 years old [27]. Furthermore, during the relatively recent 2009-2010 H1N1 influenza pandemic, people between the ages of five and 24 had the largest percentage of confirmed and probable cases as well as

41 percent of all hospitalizations [10].

In addition, another consequence of pandemic influenza is reflected in the mortality rates. During an influenza pandemic, mortality rates may be elevated for the entire population [26]. Specifically, studies have shown that even age groups not significantly impacted by seasonal influenza may have elevated mortality rates. A look at statistical evidence from the Spanish flu reveals that mortality rates were highest for individuals in the age group of 20 to 50 [27]. Also, empirical evidence from the H1N1 pandemic shows that of the approximately 12,465 deaths, none were in individuals over 65 years of age ([11] and [27]). Nonetheless, contradictions in the age-structured illness and mortality rates for seasonal influenza should not be viewed as the pandemic norm. Of the approximately 69,800 people who died from the 1957 Asian influenza pandemic, the elderly had the highest rates of death. Additionally, those over 65 years of age were the most likely to die in the 1968 Hong Kong flu virus [27].

Over and above these life threatening consequences of higher illness and mortality rates, pandemic influenza can greatly overburden health care services. With the rapid and largely unrestrained spread of illness throughout the entire population, a significantly larger number of individuals will be seeking medical care and emergency room services. As a result, resources such as staff, facilities, equipment, treatment medications and hospital beds will become quickly exhausted [26]. As an analogous consequence, an influenza pandemic can be very disruptive to the economy as skilled laborers are left with little choice but to stay home from work to care for themselves, their children or other loved ones. This workforce issue may cause some businesses to close while others find production significantly reduced. Furthermore, as a preventative measure to stop the spread of the influenza virus some businesses and schools may close during the pandemic, which increases the social and economic disorder [26].

Due to these catastrophic and often fatal consequences, mitigation of an influenza pandemic is essential to alleviate illness, reduce mortality and circumvent adverse economic performance. Yet, as a direct result of the sporadic and novel nature of the influenza strain, public health decision makers are left with little time to prepare in order to lessen and prevent these problematic effects as a new strain begins to spread. Therefore, these officials must remain mobilized in order to optimally employ the control measures at their disposal. According to the Centers for Disease Control and Prevention (CDC), influenza vaccines are the best way to prevent the spread of influenza [12]. However, since the strain is initially unknown and the time the pandemic will strike is unable to be predicted, vaccines are initially scarce in any pandemic situation. With vaccines as the most pivotal preventative element, questions arise as to the optimal distribution strategy of this scarce resource.

Throughout this thesis we will consider the fundamental question of vaccine distribution through two distinct models. In chapter two we consider the optimal distribution of vaccines to heterogeneous age-distributed subgroups in the population such that pandemic elimination

results. As evidenced by past pandemic situations, unique virus strains affect age groups in the population differently. Therefore, in this formulation, we consider subgroups with contact rates, susceptibility and infectivity differing by age group. For this model, a mixed integer programming solutions approach is developed to determine the minimal portion of each age group to vaccinate in order to eliminate the epidemic from the population. Results are evaluated based on various levels of vaccine efficacy and population distribution. Finally, we consider the consequence, in terms of additional vaccines, of the addition of fairness and equity constraints.

In chapter three we consider optimal vaccination strategies in regards to minimizing pandemic related costs through use of a Markov decision process (MDP). The MDP is solved with a linear programming solutions approach to determine optimal vaccine strategies. Further, we increase the uncertainty considered in the model by including vaccine efficacy as a stochastic parameter. Results are given for different scenarios of the stochastic model.

In chapter four we provide a summary of both models. In addition, we present final conclusions on the behavior of each formulation. Final remarks provide possible direction for future research based on these models.

Chapter 2

Optimizing Vaccine Distribution in an Age-Structured Population

2.1 Introduction

Vaccination is the critical response in circumventing an influenza pandemic. Nevertheless, when a threatening influenza pandemic emerges, vaccine availability will not meet global demand. This leaves public health officials with an immediate and challenging dilemma [19]. Namely, public health officials must determine the most effective distribution of a limited supply of vaccines among competing age groups within the population. As provided in chapter 1, pandemic influenza often presents with increased illness in age groups not normally burdened by seasonal influenza, which makes the task of deciding the most effective age group to vaccinate even more daunting. When modeling pandemic influenza, these illness related factors are often measured through the contact rate, susceptibility and infectivity, which vary immensely based upon the age group of an individual and the behavior of the circulating influenza strain. This is supported by various studies examining historical pandemics.

Let us first evaluate studies that have considered the contact rate in age-diversified populations. The number of close interactions of one individual with another over a specified period of time is known as the contact rate. The likelihood of becoming infected is strongly influenced by the number of contacts a susceptible individual has with others in the population [47]. Additionally, the ages of the contact individuals vary extensively based on the age of the susceptible individual. Consideration of the daily encounters of school-aged children in comparison with elderly individuals illuminates this concept. School-aged children come in contact with numerous individuals on a daily basis including other children in school, teachers and extracurricular activity groups. In addition, school-aged children have close interactions with their parents, who tend to be young adults, siblings and other caregivers. This is contrasted with elderly

individuals who may have relatively little close contact with others in the population on a daily basis and fewer interactions overall, even among their own age and peer groups. In fact, the article *The Shifting Demographic Landscape of Pandemic Influenza*, points to five studies, all but one of which support the theory that children have the highest rates of contact among all age groups in the population. In addition, the study associated with the article, J. Mossong [33], cites the numerous and age-diversified contact rates of children as a primary reason for disease propagation throughout the entire population. These studies provide conclusive evidence as to the importance of considering the behavior of individuals based on their age as it pertains to interactions with others when evaluating a threatening influenza pandemic.

Once contact has been established between individuals, the rates of susceptibility and infectivity play an important role in determining if the disease will be transmitted from the infective individual to the susceptible individual. Once again, these rates vary based on the disease behavior of the pandemic as it targets certain age groups. One study provides that children were twice as susceptible to infection during the 2009 H1N1 virus as adults 19 to 50 years of age living in the same household [48]. Furthermore, younger adults were more susceptible than those aged 50 and older [48]. In regards to infectivity, we can examine evidence from the Asian and the Hong Kong influenza pandemics, as well as the H1N1 pandemic influenza strain. During the Asian pandemic, children had a higher rate of infectivity than adults; however, for the Hong Kong pandemic, the infectivity was similar for all age groups [36]. Additionally, S. Cauchemez and Ferguson [48], provide that infectivity was not significantly different based on age for the H1N1 pandemic. As witnessed by these studies, it is crucial to consider the influence of the disease on certain targeted age groups in regards to heightened degrees of susceptibility and infectivity.

These studies present the need for a model that optimizes the distribution of vaccines with consideration of the age-dependent contact rates, susceptibility and infectivity for an emerging influenza strain. In section 2.2, we review literature pertaining to this topic. The next section, 2.3, provides a review of the important mathematical concepts that pertain to this chapter. In section 2.4, we develop a mixed integer programming optimization model to determine the minimum number of each heterogeneous, age-distributed subgroup to vaccinate in order to eliminate the pandemic from the population. Further, we implement a mixed integer programming solutions approach. Finally, in section 2.5, we provide results of the optimization. Additionally, as motivated by these results, we consider the addition of fairness and equity constraints in terms of the increase on the number of vaccines needed to eliminate the pandemic. In section 2.6 a conclusion is provided for this model.

2.2 Literature Review

As a result of the increase in the study of epidemiological data, rapid advancements were made in the scientific understanding of infectious disease characterization and transmission throughout the 20th century [6]. As a direct corollary of growth in scientific understanding, mathematical models became more advanced in their ability to analyze infectious disease spread and effectively recommend control measures to stifle threatening epidemics. In Adivar and Selen [1], which reviews some of this epidemiological literature from academic journals between 1971 and 2010, the studies are categorized into two groups: theoretical, focusing more on mathematical relations, and empirical research, focusing on a certain infectious disease. In this study, we will review literature in both areas. From a mathematical standpoint, we will review concepts as they pertain to the basic reproduction number and heterogeneous populations. Additionally, we will look at specific models that have been developed for the study of pandemic influenza.

2.2.1 Basic Reproduction Number and Heterogeneous Models

In the early 20th century, the critical concept of the 'net reproduction rate' began making its way from demography into the mathematical study of infectious diseases [6]. In 1952, the concept was introduced in epidemiology as the 'basic reproduction rate' by MacDonald during his work with Malaria. However, much later, in Diekmann's research in 1990, it was stated that the term 'rate' should be changed to 'basic reproduction ratio' or 'basic reproduction number' since the value is dimensionless [18]. C.P. Farrington and Gay [15] defines the basic reproduction number, symbolized as R_0, as the expected number of secondary infections in a completely susceptible population produced by a typical infected individual during its entire infectious period. This concept of considering initial spread is described as a 'branching process' where susceptible individuals are infected, while neglecting the consideration of a decrease in susceptibles [18]. This value characterizes the ability of an infectious disease to invade a population, the effort needed to control an infection that has already penetrated a geographical region and the control measures needed to prevent a pandemic [21]. For these reasons, the basic reproduction number is hailed as one of the most important concepts in the mathematical study of infectious diseases [21]. Review of developments regarding the basic reproduction number provide an important basis for subsequent concepts.

Early considerations that contributed to the development of the basic reproduction number in epidemiology can be traced to Ross in 1911 [21]. While working with Malaria, he discovered that the number of mosquitoes per individual in the population must exceed a certain number in order for the disease to persist [15]. These theories were formally defined in the work of Kermack and McKendrick as threshold criteria. The threshold theorem states that the introduction of infectious individuals into the population would give rise to an epidemic outbreak only if the

density of susceptibles is above a critical value [4]. The value of the basic reproduction number, R_0, corresponds to this theorem as it is used to describe this threshold behavior. When $R_0 \leq 1$, the epidemic does not persist; however, when $R_0 > 1$, the infectious disease can invade the population [21]. These concepts were further popularized by Dietz [17] in 1975, and further, by Anderson and May in a conference on infectious diseases in 1982 [5] (reviewed in [18]).

This early work regarding the basic reproduction number laid the foundation for another significant advancement in threshold behavior. Namely, this consideration involves the value of the basic reproduction number in a population with multiple classes of infective individuals [34]. These multiple classes are often called heterogeneous subgroups. Dividing the population into heterogeneous classes is a critical component in understanding and adequately modeling many infectious diseases. Depending on the disease characteristics and modeling objective, these disjoint classes could be based on a variety of different disease related factors, such as transmission method, infective period, latent period, and genetic susceptibility, or based on factors of age, economic status, geographic location, and cultural disposition [24].

Although heterogeneous populations were considered in early works, such as Hethcote [23] and I.M. Longini and Elveback [31], O. Diekmann and Metz [43] discover a valuable method for evaluating the basic reproduction number in a heterogeneous population. This method of determining R_0 is based on calculation of the next generation operator and can be used for any number of discrete, disjoint classes. They derive the basic reproduction number, mathematically, as the dominant eigenvalue of a positive linear operator. The value of R_0 in a heterogeneous population as the largest magnitude eigenvalue has been heavily employed in a number of studies.

One such work, Hill and Longini [28], vaccine distribution during an influenza pandemic in a heterogeneous population is analyzed and an equation is found that characterizes the surface on which the critical vaccine fractions reside. The critical vaccine fractions are defined as the minimum fraction of each subgroup to vaccinate in order to eliminate an epidemic from the population. Therefore, this surface characterization is significant as it gives all fractions that result in a R_0 of one, meaning the pandemic is eliminated. This thesis determines the vaccine fractions on this surface that minimize the total number of vaccines needed to eliminate the pandemic through a mixed integer programming optimization routine.

2.2.2 Mathematical Models related to Pandemic Influenza

Many diverse mathematical methods have been used to consider the transmission of pandemic influenza with in a population. Additionally, mathematical methods are used to study the impact of various control measures used to terminate the infectious disease. We classify these

models based on their approach as either deterministic or stochastic. Further, some models employ optimization methods to determine the ideal control strategy. Optimization techniques provide the added capability to look beyond predetermined strategies to discover optimal control methods [42]. The addition of these optimization routines are especially useful when the goal is to determine the optimal amount of a resource to distribute based on a given objective, such as minimization of costs, illness or mortality. This concept has been particularly crucial in determining the most advantageous distribution of a limited supply of vaccines during an influenza pandemic. In the remainder of this section, we provide a review of deterministic and stochastic models in regards to the problem they evaluate. Then, we examine some articles that have employed the use of optimization approaches.

Deterministic Models

Deterministic models were one of the earliest methods used to consider the propagation and control of infectious diseases [22]. These models provide an ideal starting point for consideration of mathematical modeling in epidemiology. Some of the foundational theories discovered through these early deterministic models are still used today. Hethcote and van Ark [24] provides an overview of various deterministic models and considers models for both infectious diseases which occur quickly and those that are endemic in a population. Furthermore, this study evaluates the use of heterogeneous and homogeneous populations. Three immunization campaigns are evaluated in which the population is disseminated into cities and villages with homogeneous mixing within these geographic areas and a limited number of interactions between them. Another deterministic model, May and Anderson [39], considers the distribution of vaccines in the cities and villages structure during an outbreak of a micro parasitic infection. This research shows that for some cases fewer immunizations are required than when assuming homogeneous mixing. Both of these deterministic models highlight the importance of considering heterogeneous populations when studying infectious diseases.

Additionally, some deterministic models related to pandemic influenza consider a specific facet of the infectious disease. Examples of these studies include Matrajt and Longini [38], L. Matrajt and Longini [35], and Teytelman and Larson [50]. They address the possibility of a secondary wave, multi-dose vaccines, and differing stages of spread in geographical regions, respectively. Certainly, the vast scope of these three articles illuminates the important role of deterministic models in considering all angles of an infectious disease, which in this case is pandemic influenza.

This review of deterministic models provides evidence as to the vast considerations that can be researched through this modeling approach. Deterministic formulations have been widely used in epidemiology, especially in regards to pandemic influenza. These models have been ef-

fective in considering various subgroups in the population, especially geographically distributed regions and age-related factors. However, as scientific study becomes more advanced, practitioners are left with a need to evaluate additional factors. Consequently, a major element left to consider is the effect of uncertainty. This uncertainty can arise in many forms, such as contact rates, susceptibility, infectivity, and vaccine efficacy. Whereas, deterministic models evaluate these variables with a single estimate, stochastic models provide the ability to use probability distributions to reflect some of this uncertainty. We will next evaluate the addition of uncertainty in mathematical models by reviewing several stochastic formulations.

Stochastic Models

Stochastic models provide a useful tool to mimic the inherent uncertainty that comes with any natural process. Consequently, these models are helpful in evaluating certain unknown parameters in pandemic influenza. L.R. Elveback and Gatewood [37] is one significant work in the realm of pandemic influenza modeling which incorporates these stochastic parameters. Specifically, the stochastic variables in this model include variability in infectivity, latent, and withdrawal periods, as well as rates of susceptibility and infectivity. The results of this model are compared with historical data, and therefore, parameters from this work have been used in other models and for validation purposes [31].

Other stochastic models consider varying facets of influenza, such as, parameter estimation and control strategies. Two examples are I.M. Longini and Halloran [32] and Britton [7] which considers multiple control measures to contain an emerging pandemic and estimates R_0 from the final size of an outbreak in a community, respectively. These studies serve to illuminate the additional considerations that are incorporated into stochastic models.

Optimization Approaches

As evidenced by the previous research, deterministic and stochastic models have provided many beneficial results in epidemiology. Nevertheless, optimization is a valuable tool in Operations Research that can further aid in the consideration of finding optimal control strategies. Optimization is advantageous as it does not depend on the consideration of predetermined strategies but rather finds a mathematically optimal solution based on the model [42]. Studies have used a variety of heuristic approaches to solve optimization formulations with the goal of determining the best control strategy. We examine some of these significant studies particularly as they relate to pandemic influenza.

I.M. Longini and Elveback [31] provides one of the pioneering works in the study of optimizing vaccine distribution during an influenza pandemic. In this research an age-stratified heterogeneous mixing model is used with the population divided into five age groups, including:

preschool, school age, young adults, middle aged adults, and older adults. A deterministic model of disease spread is considered and a non-linear program is formulated. Due to the objective function structure, this study employs an iterative guessing routing based on a grid search to determine the optimal results.

In addition to the computational optimization method and deterministic model used by I.M. Longini and Elveback [31], Hethcote and Waltman [25] and Greenhalgh [20] evaluate the distribution of vaccines through use of a deterministic simulation model with dynamic programming optimization techniques. Hethcote and Waltman [25] considers a model that could be implemented for a variety of epidemic diseases with the objective of keeping the number of infectives below a fixed value. Greenhalgh [20] also examines the objective of minimizing the number infected; however, the associated model includes a heterogeneous population. Furthermore, Greenhalgh [20] considers both vaccination and removal of infectives from the population as control measures.

Other pandemic influenza research that incorporates optimization techniques include Medlock and Galvani [40] and S. Lee and Chowell [49]. The research performed in Medlock and Galvani [40] aims to effectively distribute vaccines based on five different outcome measures. This study uses an age structured compartmental model along with a non-linear simplex algorithm to determine optimal distributions. S. Lee and Chowell [49] works to find time-dependent optimal vaccination policies through an optimal control problem aimed at minimizing the number of infected individuals over the entire pandemic. This study computes a variety of optimums based on different vaccine coverage and transmission levels through the use of Pontryagins Maximum Principle.

These optimizations studies show the breadth of considerations and solution approaches that have been implemented in evaluating the optimal distribution of vaccines. This work will expand upon the previously discussed work of Hill and Longini [28] to determine optimal vaccine distribution in an age-structured heterogeneous population through a mixed integer programming solutions approach. This solution approach allows for efficient use of optimization software in order to find an optimal distribution.

2.3 Mathematical Support from Previous Articles

As the objective of this chapter is to develop a model that finds the minimum number of individuals to vaccinate to eliminate the influenza pandemic, we present some of the important contributions of Hill and Longini [28] and I.M. Longini and Elveback [31], which aid in the advancements made in this chapter. Specifically, we consider theories related to the basic reproduction number in a heterogeneous population, defined as the next generation matrix, which was a significant work of O. Diekmann and Metz [43] as discussed in section 2.2. We begin by

considering how Hill and Longini [28] utilizes this next generation matrix to consider vaccine distribution in a heterogeneous population for an influenza pandemic. Through consideration of this next generation matrix, Hill and Longini [28] develops a characterization of the surface where all vaccine fractions reside such that the reproduction number is one. Additionally, we provide some concepts from I.M. Longini and Elveback [31] that are used to calculate the entries that comprise this next generation matrix.

As a starting point, we consider the characterization of the basic reproduction number in a heterogeneous population as expressed in Hill and Longini [28]. Previously, we defined the basic reproduction number, R_0, as the number of secondary infections caused by a single infectious individual in a completely susceptible population [22]. Additionally this number is related to the reproduction number in order to consider the influence of vaccines on the population. Therefore, Hill and Longini [28] uses the reproduction number, R_f, to denote the basic reproduction number after the effect of vaccination. Consequently, in the absence of vaccines, the basic reproduction number is identical to the reproduction number, $R_0 = R_f$. Therefore, the interests reside in the value of R_f such that the disease will not persist in the population. From previous discussions, we know that if the value of $R_0 \leq 1$ the disease is eliminated. Thus, the objective of Hill and Longini [28] is to determine the value of the vaccine fractions such that $R_f = 1$.

Due to the age-structured population, the discussion of the basic reproduction number is extended to consider a heterogeneous population. As discussed in Hill and Longini [28], let m homogeneous age groups define the heterogeneous population, such that $m \in \mathcal{J}$. Additionally, let R_{ij} represent the expected number of secondary infections in unvaccinated individuals in subgroup $i \in \mathcal{J}$ caused by a single unvaccinated infectious individual in mixing group $j \in \mathcal{J}$ [28]. Then, the $m \times m$ next generation matrix, R, is:

$$R = \begin{bmatrix} R_{11} & R_{12} & \dots & R_{1m} \\ R_{21} & R_{22} & \dots & R_{2m} \\ \vdots & \vdots & \ddots & \vdots \\ R_{m1} & R_{m2} & \dots & R_{mm} \end{bmatrix}$$

From O. Diekmann and Metz [43], we know the basic reproduction number is the spectral radius of the next generation matrix, R. Therefore, Hill and Longini [28] are interested in the vaccine fractions that reduce the largest eigenvalue of the matrix to $R_f = 1$. Before considering how Hill and Longini [28] incorporated the affects of vaccines on R, we must determine the calculation of the entries, R_ij, that comprise this matrix.

The values, R_{ij}, that define the next generation matrix stem from I.M. Longini and Elveback [31]. Therefore, we define β_{ij} as the contact rate between an infectious individual in age group

$i \in \mathcal{J}$ and susceptible individuals in age group $j \in \mathcal{J}$. Additionally, let n_j be the number of individuals in age group $j \in \mathcal{J}$. With these variables defined, the following represents the average number of contacts from subgroup i to j:

$$\frac{n_i \beta_{ij}}{n_j}$$

In order to continue toward the goal of defining R_{ij}, this contact rate must take into account the susceptibility of an individual in age group j and the infectivity of an individual in age group i. Let E_j and H_i represent the relative susceptibility and infectivity, respectively, of an individual in age group $i, j \in \mathcal{J}$. Then, the total number of contacts between unvaccinated infectious individuals in subgroup i and susceptible individuals in subgroup j becomes:

$$\frac{n_i \beta_{ij} H_i E_j}{n_j}$$

In order to derive the final value of R_{ij}, we must take into account the rate of infectious individuals that are no longer circulating due to removal or recovery. Let γ_i represent the infectious removal proportion for age group i. This final calculation comprises the entries of the matrix R (for more information on this calculation, see I.M. Longini and Elveback [31]):

$$R_{ij} = \frac{n_i \beta_{ij} H_i E_j}{n_j \gamma_i} \tag{2.1}$$

Accordingly, the R_{ij} variables are now used to assist in defining when the epidemic terminates. Working towards our objective for this chapter, we now present the first formulation of the minimization problem. Let f_j be the fraction of vaccinated individuals in age group $j \in \mathcal{J}$. With this variable defined, we consider the model described by Hill and Longini [28]:

$$\min_f \sum_j n_j f_j \tag{2.2a}$$

$$\text{subject to } R_f = 1, \tag{2.2b}$$

$$0 \leq f_j \leq 1, \quad j \in \mathcal{J} \tag{2.2c}$$

Objective (2.2a) minimizes the number of individuals vaccinated. The decision variables are the fraction of individuals, f_j, that should be vaccinated in each of the m subgroups. Constraint (2.2c) guarantees that the fractions are between zero and one, while constraint (2.2b) ensures

epidemic elimination. This model discussed in Hill and Longini [28] allowed the authors to develop a surface characterization of all fractions such that a reproduction number of one would result.

With the entries of R calculated and this initial model formulated, we now discuss the integration of vaccines into R such that $R_f = 1$. To this end, Hill and Longini [28] develops a threshold surface characterizing the vaccine fractions when constraint (2.2b) is satisfied. In the remainder of this section, we present the characterization that was formulated by Hill and Longini [28]. Let θ and ϕ represent the vaccine efficacy against susceptibility and infectiousness, respectively. Furthermore, let $\psi = 1 - \theta\phi$ be the vaccine efficacy. Also, we define the auxiliary variable $d_j = 1 - \psi f_j$. Likewise, let $D = I - \psi F$, where F is a matrix with the vaccination fractions on the diagonal, $F = diag\,[f_1, f_2, \ldots f_m]$, and I is the $m \times m$ identity matrix. Then, the reproduction number after vaccination, R_f, is the spectral radius of RD.

Theorem 1 *Let A be a non-negative, indecomposable matrix and let $\rho(A)$ denote its spectral radius. The non-negative square matrix, A, has exactly one eigenvector with positive entries. Furthermore, this eigenvector corresponds to the spectral radius eigenvalue, $\rho(A)$.*

Theorem 1 is called the Perron-Frobenius theorem. Insight and explanations into this theorem, especially in regards to the terms non-negative and indecomposable, can be found in Hunter [29]. Non-negative is defined as a matrix with all positive entries. Considering the previously discussed calculation of entries in this matrix, the matrix should always be non-negative. Indecomposable, also known as irreducible, means that matrix is not capable of being reduced to the following form:

$$R = \begin{bmatrix} R_{11} & 0 \\ R_{21} & R_{22} \end{bmatrix}$$

Hill and Longini [28] assumes the matrix R is indecomposable, as does this thesis. In this assumption, the authors describe the characteristic in terms of its meaning to the pandemic influenza model stating that this assumption eliminates the possibility that some subgroups encounter major outbreaks where as other subgroups are unaffected. Hill and Longini [28] also references Anderson and Britton [3] regarding this assumption of an indecomposable matrix.

With Theorem 1 holding for the pandemic influenza model discussed, the next step is to ensure that for the next generation matrix, R, there is exactly one eigenvector, with possible scalar multiples, that corresponds to the spectral radius. In order to contain the pandemic, the post-vaccination reproduction number must be less than or equal to one, $R_f = \rho(RD) \leq 1$. When $R_f = 1$, by Theorem 1, the RD matrix must have positive left and right eigenvectors, $v = [v_1, \ldots, v_m]$, such that $\mathbf{v^T}RD = \mathbf{v^T}$.

$$\sum_{i=1}^{m} v_i R_{ij} d_j = v_j \Rightarrow d_j = \frac{v_j}{\sum_{i=1}^{m} R_{ij} v_i} = \frac{v_j}{(\mathbf{v^T} R)_j} \Rightarrow \psi f_j = 1 - \frac{v_j}{(\mathbf{v^T} R)_j} \tag{2.3}$$

Let v_j be the jth component of the eigenvector associated with the spectral radius and R_{ij} be the ijth component of the next generation matrix. Upon solving for the fractions, f_j, in (2.3) Hill and Longini [28] generate a surface characterizing all threshold solutions. (Note that scalar multiple solutions are avoided through the normalization of $\mathbf{v}$, $||\mathbf{V}|| = 1$.)

$$\begin{aligned} f_j &= \psi^{-1}\left[1 - \frac{v_j}{(\mathbf{v}^T R)_j}\right] \\ \text{such that } &||V|| = 1 \\ &v_i \geq 0 \quad \forall i \end{aligned}$$

2.4 Model Formulation

In this section, we formulate a mathematical model to determine the minimum number of vaccines needed to eliminate an epidemic from a heterogeneous, age-structured population. The results are given in the form of the fraction of each disjoint subgroup that should be vaccinated to just achieve elimination, which are denoted elsewhere as the critical vaccine fractions [28].

We are interested in the combination of fractions on the threshold surface that yields the smallest value of $\sum_j n_j f_j$. Using the work of Hill and Longini [28] and replacing the threshold surface fraction definition for f_j in formulation (2.2), returns the following:

$$\min_{v} \sum_j n_j \psi^{-1}\left[1 - \frac{v_j}{\sum_i R_{ij} v_i}\right] = \sum_j n_j \psi^{-1} - \sum_j n_j \psi^{-1}\left(\frac{v_j}{\sum_i R_{ij} v_i}\right) \tag{2.4a}$$

$$\text{subject to } 1 - \psi \leq \frac{v_j}{\sum_i R_{ij} v_i} \leq 1, j \in \mathcal{J} \tag{2.4b}$$

$$\sum_j v_j = 1 \tag{2.4c}$$

In formulation (2.4), the decision variables are the components of the eigenvector, v_j. Constraint (2.4b) is analogous to (2.2c). The new constraint (2.4c) is responsible for normalizing the components of $\mathbf{v}$. Constraint (2.2b) is no longer required as it is always true when f_j is on the threshold surface. The first term of (2.4a) is constant and can be omitted. Thus, the objective can be rewritten as a maximization:

$$\max_{v} \sum_{j} n_j \psi^{-1} \left(\frac{v_j}{\sum_i R_{ij} v_i} \right)$$

2.4.1 Mixed Integer Solutions Approach

The current problem is in the form of a fractional program. We now propose a mixed-integer programming reformulation. The first step to consider is discretization of the variables v_j. Previous discussions provide evidence that these variables must be between zero and one. Therefore, we let $v_j = \sum_{k=0}^{K} 2^{-k} x_k^j$ where K is the number of discretization variables. Then, consider the 0-1 fractional program:

$$\max_{x} \sum_{j} \frac{n_j \psi^{-1} \left(\sum_{k=0}^{K} 2^{-k} x_k^j \right)}{\sum_i R_{ij} \left(\sum_{k=0}^{K} 2^{-k} x_k^j \right)} \tag{2.5a}$$

$$\text{subject to } 1 - \psi \leq \frac{\sum_{k=0}^{K} 2^{-k} x_k^j}{\sum_i R_{ij} \left(\sum_{k=0}^{K} 2^{-k} x_k^j \right)} \leq 1, \quad j \in \mathcal{J} \tag{2.5b}$$

$$\sum_{j} \left(\sum_{k=0}^{K} 2^{-k} x_k^j \right) = 1, \tag{2.5c}$$

$$x_k^j \in \{0, 1\}, \quad j \in \mathcal{J} \quad k = 1, 2, \ldots K \tag{2.5d}$$

In (2.5), the decision variables are x_k^j. Constraint (2.5d) is added to specify x_k^j as binary, while (2.5b) and (2.5c) are equivalent to (2.4b) and (2.4c), respectively.

In (2.5) all fractional denominators are equivalent. Consequently, we define a new variable, $y_j = \frac{1}{\sum_i R_{ij} \sum_{k=0}^{K} 2^{-k} x_k^j}$. Consider the result of using the new variable in the following formulation:

$$\max_{x,y} \sum_j n_j \psi^{-1} \left(\sum_{k=0}^{K} 2^{-k} x_k^j y_j \right) \tag{2.6a}$$

$$\text{subject to } \sum_i R_{ij} \left(\sum_{k=0}^{K} 2^{-k} x_k^i y_j \right) = 1, \tag{2.6b}$$

$$1 - \psi \leq \sum_{k=0}^{K} 2^{-k} x_k^j y_j \leq 1 \quad j \in \mathcal{J}, \tag{2.6c}$$

$$\sum_j \left(\sum_{k=0}^{K} 2^{-k} x_k^j \right) = 1, \tag{2.6d}$$

$$x_k^j \in \{0,1\} \quad j \in \mathcal{J}, \quad k \in \mathcal{K} \tag{2.6e}$$

$$0 \geq y_j \quad j \in \mathcal{J} \tag{2.6f}$$

The decision variables in (2.6) are x_k^j and y_j. Constraint (2.6b) delineates the value of y_j. Additionally, (2.6f) is added to ensure the y_j variables are non-negative.

In three instances the binary decision variable, x_k^j, is multiplied with the continuous decision variable, y_j. In order to formulate the desired mixed integer program, the multiplication must be linearized. This is achieved through specifying an upper bound for the continuous variable, y_j. The upper bound is attained when the denominator is minimized. Therefore, we use the following optimization formulation:

$$Z = \min_v \sum_i R_{ij} v_i, \tag{2.7a}$$

$$\text{subject to } \sum_j v_j = 1, \tag{2.7b}$$

$$(1 - \psi) \sum_i R_{ij} V_i \leq v_j \leq \sum_i R_{ij} v_i \quad j \in \mathcal{J}. \tag{2.7c}$$

The decision variables in this minimization are the values of the eigenvector, v. Constraint (2.7b) is the normalization of the entries in the vector. Additionally, the Constraint (2.7c) specifies the feasible region binding v_j between zero and one.

Using this upper bound, we can reformulate the previous non-linear programming iteration. This is done by setting $z_{jk}^i = x_k^i y_j$ and $u_j = \frac{1}{Z}$. With these adjustments, we have:

$$\max_{x,y,z} \sum_j n_j \psi^{-1} \left(\sum_{k=0}^{K} 2^{-k} z_{kj}^j \right) \tag{2.8a}$$

$$\text{subject to } \sum_i R_{ij} \left(\sum_{k=0}^{K} 2^{-k} z_{jk}^i \right) = 1. \quad j \in \mathcal{J} \tag{2.8b}$$

$$1 - \psi \leq \sum_{k=0}^{K} z_{kj}^j \leq 1, \quad j \in \mathcal{J} \tag{2.8c}$$

$$\sum_j \left(\sum_{k=0}^{K} 2^{-k} x_k^j \right) = 1, \tag{2.8d}$$

$$x_k^j \in \{0,1\} \quad j \in \mathcal{J}, \quad k \in \mathcal{K} \tag{2.8e}$$

$$y_j \leq 0, \quad j \in \mathcal{J} \tag{2.8f}$$

$$z_{kj}^i \geq y_j + u_j(x_k^i - 1), \quad j \in \mathcal{J}, \quad k \in \mathcal{K}, \quad i \in \mathcal{I} \tag{2.8g}$$

$$z_{kj}^i \leq y_j, \qquad j \in \mathcal{J}, \quad k \in \mathcal{K}, \quad i \in \mathcal{I} \tag{2.8h}$$

$$z_{kj}^i \leq u_j x_k^i, \qquad j \in \mathcal{J}, \quad k \in \mathcal{K}, \quad i \in \mathcal{I} \tag{2.8i}$$

Optimization model (2.8), is a mixed-integer programming formulation that minimizes the number of vaccinations needed in a heterogeneous population while still preventing an epidemic. There are three sets of decision variables in this model, x_k^j, y_j, and z_{kj}^i. Constraints (2.8b) through (2.8f) correspond to previous constraints. The final three constraints are added in order to let the variable z_{kj}^i linearize the relationship of $x_k^j y_j$.

2.5 Results

From this model, we evaluate scenarios and perform sensitivity analysis to determine the minimum number to vaccinate. Initially, we must examine efficient values of the parameter k. After we have chosen this value for the discrete interval, we consider the effects of population increase. Final results explore repercussions of changes in vaccine efficacy on the number of people to vaccinate and the distribution of these vaccines. From these results, we are motivated to consider the effects of adding fairness and equity constraints. Results are provided for these additional considerations in terms of the increase in the number to vaccinate. The initial values are taken from I.M. Longini and Elveback [31] and Hill and Longini [28]. The specific values used can b found in Table A.1 and Table A.2 in Appendix A.1. Appendix A.2 gives the GMPL code used to create the LP file for these results. The model was then solved using cplex optimization software.

Table 2.1: Initial Values

Variable	Description
k	Number of discrete intervals
ψ	Vaccine efficacy
n_j	Population size of j
β_{ij}	Contact rates
γ_i	infectious removal proportion
H_i	Infectivity rate
E_j	Susceptibility rate

We must determine a value for the number of discrete intervals, k, before considering sensitivity to other parameters. This value must balance two conflicting objectives. As more intervals are used, we benefit from increased accuracy; however, as k increases the program will have elevated run time. We weigh the importance of this decision by considering differing values of k for the initial data. Figure (2.1) illustrates the effect of k on run time and accuracy, which is in terms of total number to vaccinate, as k increases from three to 20.

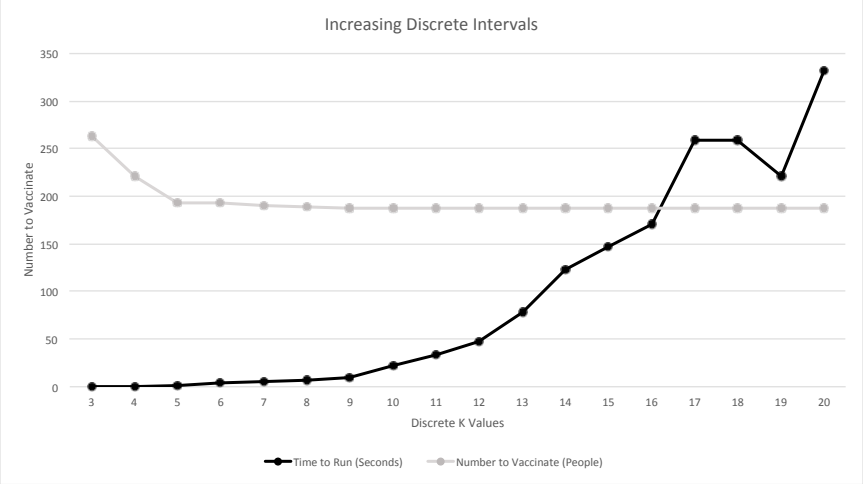


Figure 2.1: Parameter k evaulation

Examining the number to vaccinate in Figure 2.1, we witness a significant decrease when k is between three an five. Nonetheless, after the initial decrease this number remains around 190 individuals over the values of k six and greater. On the other hand, the time it takes for

the program to optimize remains low and relatively constant over the first nine values of k. However, k values of ten to 17 witness a steady increase in run time. From this analysis, we can determine that the ideal k value to use would be approximately nine. As sensitivity to other parameters is further examined in the remainder of this section, k is always chosen to be between nine and 14 so that accurate results are given and run time remains reasonable.

With a value chosen for the parameter k, we next consider changes in the size and distribution of the parameter n_j. The initial population distribution used to calculate k consist of data from the 1975 census estimates. Naturally, the distribution and the size of the population change over time. As influenza pandemics occur erratically every ten to 40 years, the population characteristics during a future epidemic are likely to be significantly different from today. In the interest of determining influences that these changes may have on the number to vaccinate, we examine future projected population growth and age structure. This projected population information is taken from the US Census Bureau for years 2015 to 2060 [8].

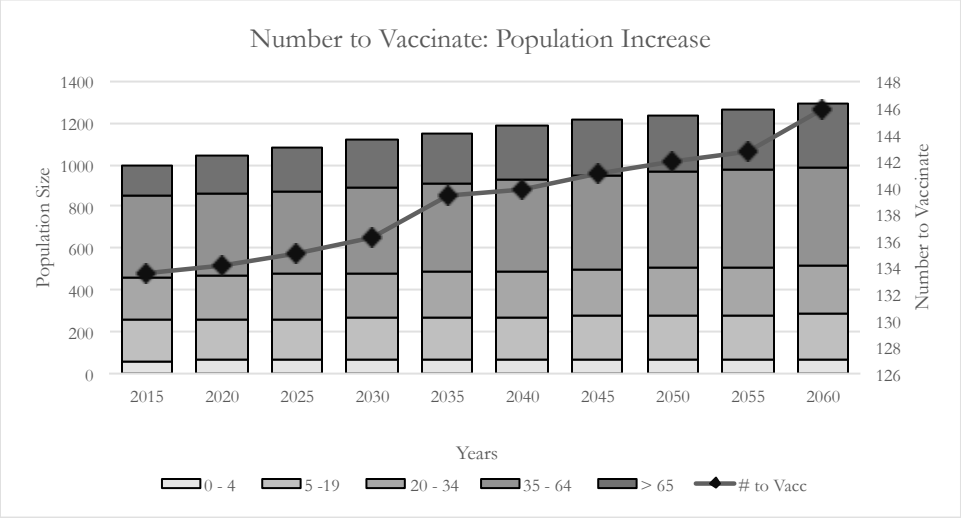


Figure 2.2: Population Increase 2015 - 2060

Figure (2.2) illustrates the influence of population increase on the number of individuals to vaccinate. The projected increase in population size is projected to subsequent years based on the initial population of 1000 individuals with the age structure proportionate to the census projections. The shades of the stacked columns indicate the proportion of the population constituting the associated age range. Consequently, figure (2.2) shows the population aging as the shaded area corresponding to age ranges 35 to 64 as well as 65 and over are gradually increasing from 2015 to 2060. During the same time frame, the population increase is 29.7 percent while

the number to vaccinate to circumvent the epidemic increases approximately 9.3 percent. The number to vaccinate does not increase equivalently with the growth of the population.

Whereas the future size and age distribution of the population can be projected by organizations such as the census bureau, vaccine efficacy is unknown until the immunization is implemented. By evaluating different levels of vaccine efficacy, we can determine sensitivity to this uncertain element. Figure Figure 2.3 evaluates efficacies from 0.5 to 0.8.

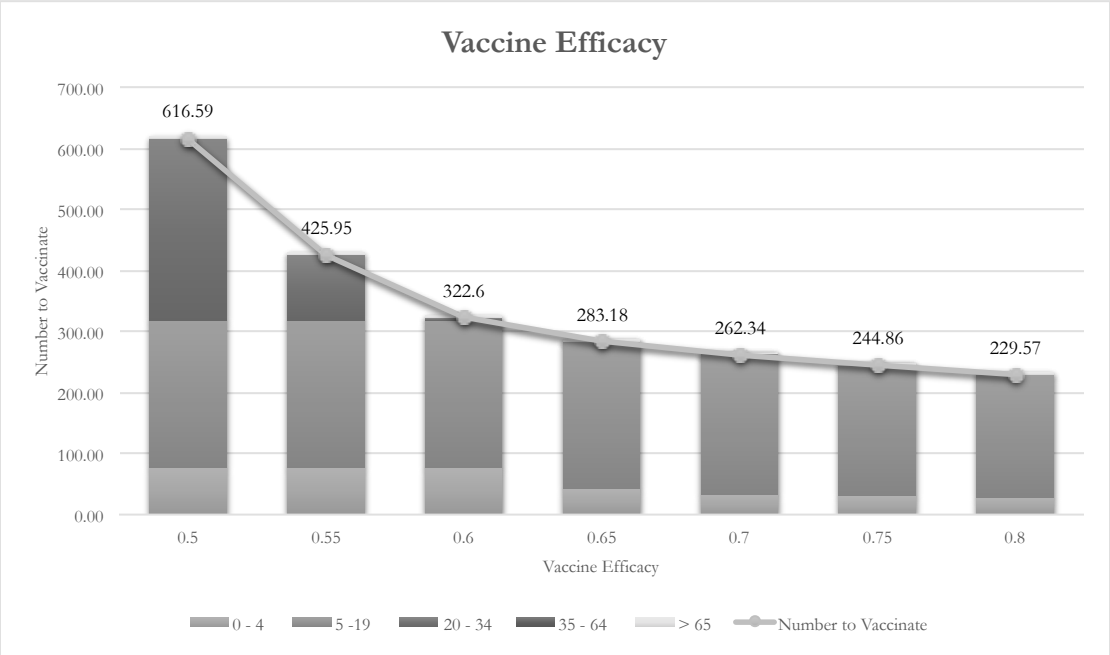


Figure 2.3: Vaccine efficacy 0.5 to 0.8

There are three important results illustrated by figure (2.3). First, when vaccine efficacy is reduced between 50 and 60 percent, there is a significant decrease in the number to vaccinate. Second, the first two age groups are always vaccinated. Finally, the fourth and the fifth age groups are never vaccinated.

These results are best understood through analysis of the values of the parameters comprising the matrix R. The parameter values used in these results were calculated based on the 1957 Asian influenza A pandemic [31]. Recall, the parameters used in calculating R include the relative susceptibility and infectiousness of an individual, E_j and H_j, respectively; the contract rate between individuals, β_{ij}; and the infectious removal proportion, γ_j. The parameter values for E_j, H_j, and γ_j are similar for all j. However, there are significant differences in the contact rate in matrix β_{ij} leading to some of these significant results.

Influence of the matrix β_{ij} is further evidenced if vaccine efficacy is decreased below 50 percent. A vaccine efficacy of 45 percent makes epidemic elimination infeasible. With $\psi = 0.45$, the reproduction number remains above one, $R = 1.025$, even if everyone in the population is vaccinated. The individuals in groups four and five contribute minimally to the spread of the disease so their vaccination is not important to the objective of eliminating the disease. This result leads to unbalanced distribution of vaccine resources among the heterogeneous subgroups in the population.

Such unbalanced vaccination fractions lead to questions and concerns regarding fairness and equity in resource distribution. The objective function and constraints given in (2.8) only aim to reduce the basic reproduction number below one by vaccinating as few individuals as possible. With current contact rates as well as levels of susceptibility and infectiousness, at most, the first three age groups will be vaccinated. As the vaccine efficacy increases vaccinating the third age group becomes less important. Adding equity constraints can provide a more even distribution of resources; however, the question arises as to the cost that these constraints will impose in terms of extra resources required.

The first equity constraints considered examines the impact of a lower bound. This lower bound states that each subgroup must have 20 percent of its individuals vaccinated. Examination of results show for vaccine efficacies under 65 percent there are significant changes with each five percent decrease in efficacy.

We compare this result with adding a constraint that specifies all fractional values must be within five percent. Adding these constraints notably alters the number of individuals to vaccinate. Comparisons of the number to vaccinate and the extreme difference when adding these constraints can be seen in figure (2.4). Since all fractions must be within five percent, we must vaccinate higher percentages of groups four and five even though they don't significantly contribute to the reduction of the reproduction number below one. Even with a vaccine efficacy of 80 percent, over half of the population is vaccinated. This corresponds to a 70 percent increase over adding only the lower bound constraint and a 143 percent increase over the original optimization without considering fairness and equity.

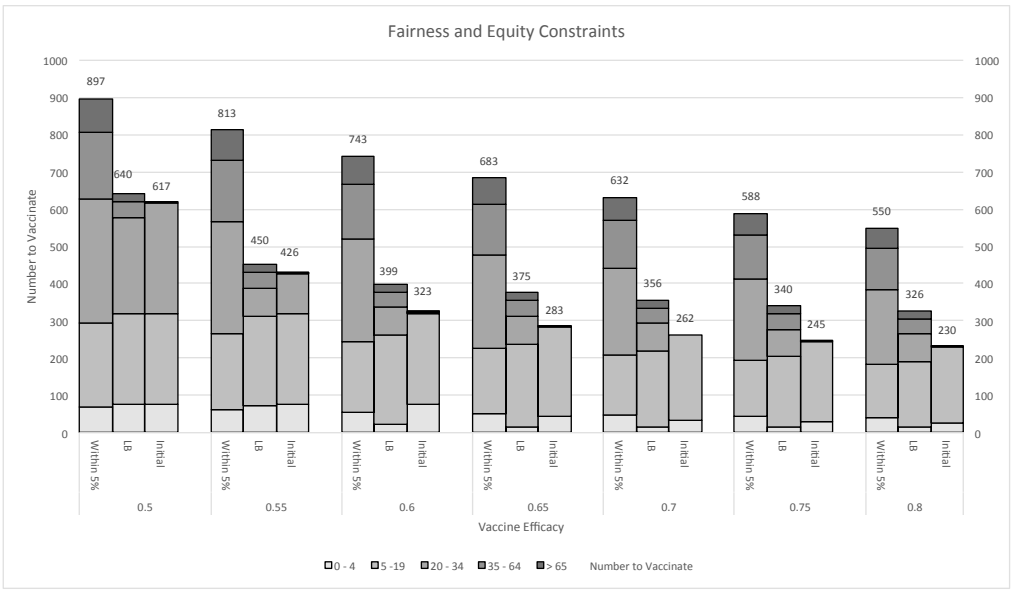


Figure 2.4: Comparison of Fairness and Equity

2.6 Conclusion

In chapter 2, we assessed the optimal distribution of vaccines in heterogeneous age distributed sub-groups in the population. We developed a model that employs the use of the surface threshold characterization of all vaccine strategies that result in epidemic elimination discovered by Hill and Longini [28]. Then, in order to minimize the number of vaccines needed, we solved the model via a mixed integer linear programming approach.

Results from this model highlights the significance of incorporating age based rates that are characteristic of pandemic influenza. For the propagation rates used in this model, the contact rate was the parameter with significant variability based on age. Consequently, the age groups actually vaccinated were those with the highest contact rates. Furthermore, for certain lower proportions of vaccine efficacy, vaccinating the entire population did not reduce the basic reproduction number below one. However, a slightly increased vaccine efficacy resulted in a vaccine distribution strategy that only included the three subgroups with the highest contact rates. Consequently, this shows that vaccinating those age group with lower contact rates contributes minimally to the decrease of the basic reproduction number below one.

The concern with such vaccine strategies suggested by this model involves fairness and equity in vaccine distribution. We considered the addition of constraints to alleviate this concern; however, these constraints come at a cost of additional vaccines. Vaccines are added since we are forcing vaccination in subgroups that contribute minimally to the overall reduction of the basic reproduction number below one. We examined two scenarios, one of which considered the

addition of constraints to ensure a minimum of 20 percent of each age group was vaccinated and the second scenario ensured all vaccination fractions were within 5 percent. Although these constraints increased equitable distribution, as expected, they significantly increased the minimal number to vaccinate across all vaccine efficacies. The addition of a lower bound increased the vaccines needed, averaged over all vaccine efficacies, by approximately 21 percent. Furthermore, the addition of constraints that specify all vaccine fractions should be within five percent doubled the average number of vaccines needed to control the epidemic. Therefore, public health decision makers must weigh the cost of equitable distribution in pandemic situations.

Nevertheless, this model provides an accurate method to determine optimal vaccine fractions while achieving the goal of pandemic elimination. It considers the age-based rates of contact, susceptibility, and infectiousness while allowing the optimal solution to be influenced by the natural variability in these propagation parameters.

Chapter 3

A Markov Decision Process for Vaccine Distribution

3.1 Introduction

Public health decisions regarding the implementation of vaccines to combat an influenza pandemic are made under a shroud of uncertainty. In part, this uncertainty is caused by the erratic nature of an influenza outbreak, as evidenced by a statement from the CDC, which provides that "shifts causing new strains occur at irregular intervals every ten to 40 years [13]." Consequently, public health officials and decision makers must remain prepared to mobilize at any given time to mitigate the spread of disease through an unsuspecting population in a cost effective manner.

In addition, fluctuating dynamics of an influenza outbreak elevate the levels of uncertainty faced by public health officials. The influenza dynamics involve the rate at which the disease propagates. The key aspect being an unknown number of susceptible individuals will become infected in a given interval of time. As a corollary, this same aspect of influenza dynamics applies to the recovery process for infected individuals. Given a certain stage of disease progression, there are multiple states in which the disease could transition during any given interval of time. Thus, the dynamics make the selection of optimal actions difficult.

A third significant cause of uncertainty in combating influenza propagation manifests itself in the varied outcomes of using control strategies such as social distancing and isolation of cases. Based on information from the CDC, vaccination is the primary and preferred control strategy used to prevent influenza spread [9]. Therefore, vaccination remains the exclusive intervention strategy considered in this study. However, even vaccination as the optimal intervention strategy contains uncertainty due to the influence of vaccine efficacy, which can only be observed in hindsight. Accordingly, this study incorporates the consideration of uncertain vaccine efficacy as a factor in this decision making process.

Moreover, in this environment of uncertainty, policy and decision makers must also balance certain objectives to achieve the optimal intervention policy regarding vaccination. These conflicting objectives are disease elimination and minimization of costs. Compounding the consideration of these objectives is the fact that influenza, if left uninhibited, will spread throughout the entire population. Consequently, this causes infection related costs, such as diagnosis and treatment, to spiral out of control. In addition, infected individuals suffer health related consequences measured in quality adjusted life years. Thus, the key components to the implementation of a vaccination policy must consider both infection based expenditures and those expenditures which directly flow from the vaccines themselves. An intervention policy that omits from consideration vaccine costs can only lead to a policy that would require immunizing all susceptibles and thus eliminating all infection related expenses. This is clearly not a cost effective analytical solution to a pandemic. Therefore, a well-balanced implementation strategy must minimize all costs related to the combination of infection and treatment during a pandemic.

Accordingly, with the aforementioned costs and uncertainties taken into consideration, a method is needed to develop strategies of intervention that prepare for an uncertain but eminent pandemic. The optimal method will model the behavior of the disease, including consideration of prior uncertainties, with the ability for behavior of the disease to be influenced through selection of courses of action. Ideally, the method will have the ability to incorporate updated pandemic dynamics to select the actions that manage behavior of the pandemic in an optimal way. Through development of this method, policy and decision makers will be prepared to select an optimal course of action to allow for rapid response when a pandemic suddenly emerges. To this end, we consider a Markov Decision Process (MDP) model which describes the natural behavior of the disease and allows for optimal intervantions to be identified based on the current degrees of disease progression in the population.

In section 3.2, we review literature pertaining to Markov Chains and MDP, which allow for characterization of a portion of this uncertainty. The next section, 3.3, provides a review of the important mathematical concepts that pertain to this chapter. In this section, we use the MDP formulated in R. Yaesoubi [45], except in regards to the actions. We let the actions be the percentage of susceptibles that should be vaccinated at each decision epoch. Additionally, in section 3.5, we use this MDP to implement a linear programming solutions approach and further consider uncertainty by formulating a stochastic programming model with vaccine efficacy as the uncertain variable. In section 3.5, we provide results of the optimization. Finally, in 3.6 we provide a concluding summary of the results of this chapter.

3.2 Literature Review

Markov processes have been influential in analyzing the stochastic behavior of a variety of systems including infectious disease propagation and control. Although these models have diverse features and immense applicability, they all contain the Markov property. The Markov property declares that future states of the system are dependent only on the present state. Further, the progression of past states to arrive at the present has no bearing on the probability of transitioning to future states. Analysis of the probability of transitioning states is performed on a discrete or continuous time scale with the modeling of infectious diseases being considered in both arenas. Next, we present some models that have considered Markov chains in the application of infectious diseases.

R.Yaesoubi [46] studies discrete time Markov chains and is highly relevant to the research conducted in this chapter. This work formulates a group of infectious disease models that have the ability to select optimal dynamic health policies. Furthermore, they address two problems that prevent the use of dynamic optimization techniques, namely, prohibitively large state spaces and unobservable states. To overcome the problem of large states spaces, they propose an aggregation method using a grid to group states together based on similar proportions of event classes. The predicament of unobservable states is alleviated through maximum likelihood estimates that have the ability to be updated over the course of the epidemic. Finally, they illustrate the susceptible-infectious-recovered (SIR) Markov chain with an example of influenza moving through an English boarding school. The critical focus of this work is the capability of the infectious disease model to select health policies using dynamic optimization techniques.

Using dynamic optimization techniques in selection of optimal dynamic health policies is a motivation for this work. Specifically, we are interested in developing a MDP. Problems modeled by an MDP involve an agent or decision maker challenged with manipulating the performance of an evolving and probabilistic system through selection of optimal actions or decisions [44]. According to I.C. White [30], MDPs are indispensable in characterizing problems which contain the following characteristics: (1) uncertainty in the environment, (2) multiple or conflicting objectives and (3) decisions with future impact. Additionally, MDPs are beneficial in problems where the intent is to optimize a system or situation [30].

These problem characteristics are readily identified in the discussion of pandemic influenza in section 3.1 and lead to development of an MDP to consider decision making in this environment. Explicitly, the characteristics of influenza that naturally lend themselves to use of an MDP include: ambiguity in the number of individuals infected and recovered, conflicting disease and intervention costs, and influence of decisions on future propagation of the disease and expenditures. Furthermore, optimization is imperative as we are interested in finding the course of action that minimizes all associated expenditures.

These considerations were prevalent in the work of R. Yaesoubi [45], which examines dynamic health policies to make real time recommendations on public health intervention strategies through the use of a Markov Decision Process (MDP). Furthermore, the MDP shows how dynamic policies allow for updated decisions in regards to changing disease dynamics, population characteristics and resource constraints. This method associates a reward with each possible action to determine the optimal policy at each possible state of disease progression. An influenza pandemic is considered as an example to portray the dynamic optimization techniques described.

This study will advance the work of R. Yaesoubi [45] in the example of pandemic influenza. Initially, we utilize the MDP formulated by R. Yaesoubi [45] which is based on a SIR compartmental model; however, we change the actions and consider the percentage of susceptibles to vaccinate in each state. The MDP formulation provides for an efficient linear programming solutions approach to find the optimal intervention strategy. From this linear program, we introduce uncertainty in regards to vaccine effectiveness by creating a two stage stochastic program. Optimal policies are then developed with this additional ambiguity realized to strengthen the dynamic policies. Results are studied for the case of the English boarding school presented in [41] and considered in [45] and [16].

3.3 Previous Mathematical Contributions

Public health policy and decision makers face numerous challenging decisions when employing an optimal number of vaccines to control disease spread in a cost effective manner. In order to inform this difficult situation, we use an MDP. To that end, we need to define several components to adequately characterize the MDP including: decision epochs, states, actions, transition probabilities, and rewards [44]. The work of R. Yaesoubi [45] forms the basis for this section. We model the decision epochs, states, transition probabilities, and rewards in the same manner as [45]; however, we are looking to determine the optimal percentage of susceptibles to vaccinate in each state as our action. In this section, we will discuss each component in the order presented above and determine its formulation for the problem of cost effective vaccine distribution in pandemic influenza as given by R. Yaesoubi [45].

3.3.1 Decision Epochs

Initially, we must determine when policy and decision makers are able to influence the natural behavior of the system through action selection. In an MDP, these actions are selected at points of time known as decision epochs. Furthermore, decision epochs are classified as either discrete or continuous and, additionally, as finite or infinite. A discrete time model involves

making decisions solely at decision epochs. In contrast, a continuous time model allows decisions after an event occurs, at opportune times chosen by the decision maker or at decision epochs. Additionally, in a model with an infinite time horizon, decisions are made for an unknown amount of time; while, in a finite model decisions are made until a certain time period is reached [44].

In R. Yaesoubi [45], a discrete time infinite horizon MDP was formulated with the time epochs as $t \in T$, where $T = \{t_0, t_1, t_2 \dots\}$. There are several significant reasons why discrete time and infinite horizon were chosen. Use of an infinite time horizon enables decision makers to influence the behavior of the influenza pandemic until the point in time when the disease is eradicated. Due to the unpredictable nature of disease propagation, there is no way to determine with certainty the time of eradication. Nonetheless, the pandemic strain will not circulate infinitely due to the closed population and disease propagation rates. Consequently, the process terminates when there are no longer infectious individuals in the population. Furthermore, public health practitioners make decisions regarding vaccination resources at certain time periods after the pandemic situation is evaluated. For this reason, R. Yaesoubi [45] implements a discrete time model. Additionally, this formulation allows for a convenient solution method to determine optimal policies. For more information on discrete verses continuous time models in epidemic situations see [46].

3.3.2 States

States characterize the condition of the system being modeled. Over time, influential events occur naturally causing the current conditions to shift. Therefore, observation of the current state occurs at the beginning of every decision epoch. Characterizing these states to adequately reflect the current condition is imperative in accurately modeling transitions [2]. Consequently, when states aren't adequately defined, the physical system may assume states not specified in the model leading to inaccurate transitions and sub-optimal action selection. In this subsection, we develop a model to adequately classify the state of disease spread in the population and determine the state space.

In defining the states R. Yaesoubi [45] uses a SIR compartmental model, which is a popular mathematical modeling approach in the study of infectious diseases. Compartmental models track the number of individuals in each class or compartment as time progresses. In an SIR compartmental model, individuals move from a susceptible class to infective and then after the infectious period they recover with permanent immunity. This characterization is indicative of a strain of pandemic influenza as individuals originate as susceptibles, become infective and then recover with perpetual immunity to that specific strain.

From the model given in R. Yaesoubi [45], we assume a fixed population size, N. This

assumption is characteristic of pandemic influenza as the time period of consideration is usually only several months, making the number of births and deaths insignificant in comparison with population size. Then, let $X_S(t)$ be the number susceptible, $X_I(t)$ the number infective and $X_R(t)$ the number recovered at decision epoch t. The relationship among the compartments can be described as follows [45]:

$$X_S(t) + X_I(t) + X_R(t) = N$$

Consequently, the current state of the system will be fully characterized by the number of individuals in any two compartments. Therefore, we specify the state space as $s_{t+\Delta t} = \{(X_S, X_I(t))|X_S(t) + X_I(t) \leq N\}$.

One final consideration, is in regards to absorbing states. When the current state reaches an absorbing state, the process terminates. In this study, the disease is completely eradicated when $s_t = (X_S(t), 0)$, thus, this set of states is considered absorbing. When this occurs there are no infective individuals capable of spreading the disease to susceptibles and, therefore, this strain of pandemic influenza is eliminated from the population [45].

3.3.3 Actions

Given the current state, the decision maker must choose whether or not to influence the natural behavior of the system through a set of pre-determined options. These options are commonly referred to as actions in the MDP. An action is selected at the beginning of every decision epoch even if it amounts to not acting to influence the behavior of the system.

In this study, we differ from the actions used in R. Yaesoubi [45]. We consider vaccination as our singular intervention strategy and allow the optimal percentage of susceptibles to vaccinate to be chosen. Let a_t be the percentage of those currently susceptible vaccinated at time t. Vaccinations are employed at the beginning of the decision epoch and provide a reduction in the number of susceptibles before transition is considered. Initially, we assume that all vaccinations are 100 percent effective so that the percentage of susceptibles is directly reduced by a_t, $(X_S(t) - (a_t X_S(t)))$.

3.3.4 Transition Probabilities

The transition probabilities are another pivotal component of the MDP formulation. Accurate probabilities are critical as they must adequately represent the probability of transitioning states in the physical system. Consequently, inaccurate transition probabilities lead to suboptimal action selection when applied to the physical system being modeled. In this subsection, we introduce the transition probabilities by means of the underlying discrete time Markov chain, given in the form of a SxS matrix. This Markov chain models the behavior of the system without

considering the affect of actions. Following this discussion, we consider the influence of vaccination on these probability distributions. Supporting analysis of these transition probabilities can be found in [45] and [46].

In this study, the transition probabilities must reflect the disease progression through the population. We use the work of R. Yaesoubi [45] and begin by assuming the system is in state s_t at time t and s' represents the state at time $t + \Delta t$. Then, there is an associated probability for all $s' \in S$ such that $\sum_{s' \in S} p(s'|s_t) = 1$. If it is not feasible to go from the current state, s_t to state s', then the probability is zero. Similarly, for absorbing states the probability of going from the current state to the same state is one. Thus, the state of the system will never change and the process terminates.

In order to understand the calculation of all other probabilities, we must understand the events that cause a change to the system. Due to the constant population and the fact that recovering individuals never lose immunity, the only two events we consider are infections and recoveries. An infection causes an individual to move from the susceptible compartment to the infective, and therefore, the number of new infections at time t is determined by the following equation [45]:

$$I(t) = X_S(t) - X_S(t + \Delta t) \tag{3.1}$$

Likewise, recoveries cause an individual to move from the infected compartment to the recovered. However, this equation must also include the number of new infectives at time t. Therefore, the number of recoveries is given by the following equation [45]:

$$R(t) = X_S(t) - X_S(t + \Delta t) + X_I(t) - X_I(t + \Delta t) \tag{3.2}$$

With Eq. 3.1 and Eq. 3.2 defined, we can ascertain the number of infections and recoveries that must occur to transition from a current state to another specified state. However, we are interested in the probability of actually observing these numbers of infections and recoveries simultaneously during Δt. Hence, we treat the number of individuals that can become infected and those that can recover as independent random variables each with an associated probability distribution. Next, we must discuss the probability distribution of both $I(t)$ and $R(t)$ before determining the probability of transitioning [45].

The probability distribution for the random variable $I(t)$ depends on the probability of infection for a single susceptible individual. We calculate the probability of infection with an exponential distribution, $q(t)$. Let $\lambda \Delta t$ be the contact rate between a susceptible individual and

all others in the population and $\beta(t) = X_{I(t)}/N$ be the probability that a random contact of a susceptible is with an infectious individual. Then, with these two variables, we can calculate the contact rate of a susceptible person with someone who is infectious. Furthermore, let τ represent the probability that the infection is transmitted once contact has been established. Then, the probability of a susceptible person becoming infected is given by the following exponential distribution [45]:

$$q(t) = 1 - e^{-\lambda \Delta t \beta(t) \tau} \tag{3.3}$$

Now that we have established the probability of infection, we use this to calculate the probability distribution of $I(t)$ through use of a binomial distribution. This distribution is defined as [45]:

$$P_{I(t)}(i|X_S(t), X_I(t)) = \begin{cases} \binom{X_{S(t)}}{i} q(t)^i (1 - q(t))^{(X_S(t) - i)}, \text{ for } 0 \leq i \leq X_{S(t)} \\ 0, \text{otherwise} \end{cases}$$

We consider the probability distribution of the random variable $R(t)$ in a similar manner. Before defining the distribution of $R(t)$ we must know the probability that a single infected individual will recover during a given time period. Let $z(t)$ represent the probability that an infectious individual recovers, with the rate of recovery given by μ. Then, the probability that an infectious person recovers during Δt is given by the following exponential distribution [45]:

$$z(t) = 1 - e^{-\mu \Delta t} \tag{3.4}$$

We also use a binomial distribution to determine the probability of seeing $R(t)$ recoveries during Δt. The distribution is represented as follows [45]:

$$P_{R(t)}(r|X_S(t), X_I(t)) = \begin{cases} \binom{X_{I(t)}}{r} z(t)^r (1 - z(t))^{X_I(t) - r}, \text{ for } 0 \leq r \leq X_{I(t)} \\ 0, \text{otherwise} \end{cases} \tag{3.5}$$

Since infections and recoveries are the only events that occur, and further, due to their independence, we can formulate the entries in the transition probability matrix with the following probability function [45]:

$$Pr\left\{(X_S(t+\Delta t), X_I(t+\Delta t)) = (x_S, x_I) | X_S(t), X_I(t)\right\} =$$
$$\begin{cases} P_{I(t)}(i|X_S(t), X_I(t)) P_{R(t)}(r|X_S(t), X_I(t)) \\ \quad \text{for} \quad 0 \leq x_S \leq X_S(t), \quad X_S(t) \leq x_S + x_I \leq X_S(t) + X_I(t) \\ 0 \quad \text{otherwise} \end{cases} \tag{3.6}$$

Notice, in Eq. 3.6, there are two constraints that must be satisfied in order for the transition to be feasible. These constraints follow from the equations for $I(t)$ and $R(t)$, Eq. 3.1 and Eq. 3.2, respectively. Binding these two equations by zero and the number of current susceptibles and infectives, we derive the following constraints [45]:

$$0 \leq X_S(t) - X_S(t+\Delta t) \leq X_S(t) \tag{3.7}$$
$$0 \leq X_S(t) - X_S(t+\Delta t) + X_I(t) - X_I(t+\Delta t) \leq X_I(t) \tag{3.8}$$

Through algebraic manipulation of Eq. 3.7 and Eq. 3.8, we achieve the final constraints in (3.6). The analysis behind these constraints is straightforward when considering the movement of individuals during an influenza pandemic. Given N, the number infected at time $t+\Delta t$ can never be greater than the number of susceptbles in the previous time step and must be a positive number. Additionally, the number recovered at time $t+\Delta t$ is bound by zero and the number already infected in the previous time step. The second constraint implies that individuals are not permitted to move two compartments in a single time step. In other words, an individual in the susceptible compartment cannot become infected and recover in time $t + \Delta t$ [45].

With these constraints completing the model of the natural progression of influenza, we now include the influence of actions on the probability of transitioning between states. When action a_t is chosen, the susceptible compartment is reduced by $X_S(t)a_t$. This shifts the number of susceptibles to a new current state before transition is considered. We rewrite Eq. 3.6 to consider the affect of the action of vaccination as follows [45]:

$$Pr\left\{(X_S(t+\Delta t), X_I(t+\Delta t)) = (x_S, x_I) | X_S(t), X_I(t)\right\} =$$
$$\begin{cases} P_{I(t)}(i|X_S(t) - X_S(t)a_t, X_I(t)) P_{R(t)}(r|X_S(t) - X_S(t)a_t, X_I(t)) \\ \quad \text{for,} \quad 0 \leq x_S \leq X_S(t) - X_S(t)a_t, \quad X_S(t) \leq x_S + x_I \leq X_S(t) + X_I(t) \\ 0, \quad \text{otherwise} \end{cases} \tag{3.9}$$

3.3.5 Rewards

Rewards are the final element of the MDP yet to consider. A reward is given as a result of being in a certain state and taking a certain action. Consequently, they are used to quantify an

action or decision in order to compare and select the optimal action in a given state.

In the case of pandemic influenza, our objective is to minimize fiscal expenditures related to vaccination and infection. Let c be the monetary cost incurred per infection and c_v the cost per vaccination. If $a_t \in A$ is chosen at time t, then the total vaccination cost is $c_v(a_t X_S(t))$. Further, let w be the loss in health due to infections, quantified by quality adjusted life years (QALY) and p be the policy maker's willingness to pay for health per QALY. Then, we can calculate the monetary cost of health lost as wp per infection. The reward function associated with these costs is written as follows [45]:

$$r(X_S, X_I; a_t) = (c + wp)E\left[I(t)|(X_S, X_I); a_t\right] + c_v(a_t X_S) \tag{3.10}$$

With the last of these five critical elements defined, we begin to discuss how to formulate dynamic health policies such that the optimal action is selected at each decision epoch.

3.4 Optimizing Health Policies

With formulation of the MDP complete, we turn our attention to minimizing the expected costs through optimal action selection. First, we discuss decision rules in terms of the pandemic influenza vaccination problem. Next, we define a linear programming solutions approach to solve these recursive equations, which will determine optimal actions for each state. Then, we look at adding uncertainty to the model parameters through use of a two stage stochastic program. This allows consideration of variability in certain parameters that are naturally volatile. Results are analyzed from the widely studied English boarding school influenza outbreak for stochastic vaccine efficacy.

3.4.1 Decision Rules

A decision rule prescribes an optimal action for each state in every decision epoch. In this study, we implement Markovian decision rules, which considers past behaviors and actions only through the current state. Further, this process is often called memoryless as memory of past transitions to the current state are not needed. Such rules can be described by the function $d_t : S \to A$, signifying the action in $a_t \in A$ is chosen when the system assumes state $s_t \in S$ at time t [45]. Therefore, the decision rule will select a certain percentage of the population to vaccinate in every state at every decision epoch.

A policy, symbolized by π, is the compilation of the decision rules for each state at every time period, $\pi = (d_0, d_1, d_2, \dots)$. Moreover, when a the decision is the same every time a state is reached regardless of which decision epoch it is reached, $d_t = d$, the rules constitute a stationary

policy [45]. In this study we focus on characterizing a stationary policy that specifies the number of individuals to vaccinate in every state regardless of the decision epoch in which that state is reached.

3.4.2 Linear Program

We must develop a solutions approach to determine the optimal vaccination policy, $\pi*$, to implement. In order to accomplish this objective, we must determine a function for the expected total discounted reward, which results from being in a certain state and taking a certain action. In the beginning, before time $t = 0$, we assume a completely susceptible population. Initializing the epidemic, one susceptible individuals becomes infectious and begins spreading the influenza to the population. At this point vaccination can be used to stem the spread of the influenza by reducing the proportion of susceptibles. We can evaluate the expected discounted reward of a given policy, starting at $t = 1$, through the following equation [45]:

$$v^{\pi}(s_1) = E^{\pi}\left[\sum_{t=1}^{\infty} \gamma^{t-1} r(X_S, X_I; a)\right] \tag{3.11}$$

In Eq. 3.11, the discount factor is given by γ, where $0 \leq \gamma < 1$. The discount factor reduces the value of future rewards to a current value. Now assuming we are start in $t = 0$, we evaluate the expected total discount reward of a policy, $\pi = (d_0, d, d, \dots)$, through the following equation [45]:

$$\begin{aligned} V^{\pi}(s_0) &= r(X_S(0), X_I(0); a_0) + \gamma v^{\pi}(s1) \\ &= -c_v(X_S(0)a_0) + \gamma v^{\pi}(X_S(0) - X_S(0)a_0, X_I(1)) \end{aligned}$$

Let Π be the set of all possible policies such that $\pi \in \Pi$. The policy is optimal whenever [45]:

$$V^{\pi^*}(s_0) \geq v^{\pi}(s_0) \quad \text{for each} \quad s_0 \in S, \quad \text{and all} \quad \pi \in \Pi \tag{3.12}$$

Moreover, we are looking for a mechanism that chooses the optimal policy. For this purpose, we develop optimality equations, also known as Bellman equations,which are a starting point in determining optimal policies [44]. The significant work of Puterman [44] declares the optimality equations fundamental in Markov decision theory. To this end, they provide four key properties that these equations possess which makes them critical in an MDP, including: solutions that provide optimal returns from period t to the end of the decision horizon, a means for determining

optimal policies, a basis for determining an efficient procedure to compute optimal policies and determination of optimal policies and return functions. In the case of pandemic influenza, the recursive optimality equations are developed as follows:

$$v(s) = \min_{a \in A} \left\{ r(X_S, X_I; a) + \gamma \sum_{s \in S} P(s' | (X_S, S_I; a) v(s^{'}) \right\} \tag{3.13}$$

Equation (3.13) return the optimal expected total discounted value for each state as the objective is to minimize costs. However, a solutions approach is needed to solve the recursive optimality equations for the actions that constitute an optimal policy. Some methods used to solve systems of optimality equations in an MDP include value iteration, policy iteration and linear programming. In this paper we focus on a linear programming solutions method. Use of a linear programming approach allows us to employ the useful theories that come with this method. Further, additional constraints are easy to examine with this solutions approach, which could be helpful in considering vaccine availability and budget constraints.

The linear program that we develop from equation (3.13) is written as follows:

$$\min \quad v(s) \tag{3.14a}$$

$$\text{subject to} \quad v(s) \geq r(s; a) + \gamma \sum_{s' \in S} Prob(s' | s; a) v(s') \quad \forall \quad a \in A, \quad s \in S \tag{3.14b}$$

By solving Eq. 3.14a we are able to define the optimal actions for each state in the MDP formulating a policy based on minimizing the expected total discounted costs in each state. Together these actions create a policy which informs the optimal action to choose in any state at any time period.

3.4.3 Stochastic Programming

As portrayed in the introduction, uncertainty is a common theme characterizing influenza pandemics. In formulating a MDP, the first of these uncertainties was realized through the use of probability distributions to characterize the number of individuals who become infected and recover. However, there are many additional unknown parameters such as vaccine efficacy, contact rates and costs. Through development of a stochastic programming approach we can further develop this optimization model to consider varying levels of certain parameters. In this section, we formulate a two-stage stochastic programming solutions approach. In the first stage, we select optimal actions based on uncertain vaccine efficacy or disease propagation parameters. In the second stage, the uncertainty is realized and results of the action selection can be identified.

We formulate the stochastic program using formulation Eq. 3.14a as a basis. Let ω represent a scenario in the set of all scenarios, such that $\omega \in \Omega$, and ρ be the probability of a certain scenario occurring. Additionally, let $y(s;a)$ be a binary decision variable. This decision variable is needed to ensure the same action is selected under all scenarios for each state. We also need a value larger than all decision variables, $v^{\omega}(s)$, which we represent by M. Then, we develop the following stochastic programming formulation:

$$\min \sum_{\omega \in \Omega} \rho^{\omega} v^{\omega}(s) \tag{3.15a}$$

$$\text{s.t. } v^{\omega}(s) \geq r(s;a) + \gamma \sum_{s' \in S} P^{\omega}(s'|s;a) v^{\omega}(s') - (1 - y(s;a))M \quad \forall \quad a \in A, \quad s \in S, \quad \omega \in \Omega \tag{3.15b}$$

$$v^{\omega}(s) \leq r(s;a) + \gamma \sum_{s' \in S} P^{\omega}(s'|s;a) v^{\omega}(s') + (1 - y(s;a))M \quad \forall \quad a \in A, \quad s \in S, \quad \omega \in \Omega \tag{3.15c}$$

$$\sum_{a \in A} y(s;a) = 1 \quad \forall \quad s \in S \tag{3.15d}$$

In Eq. 3.15, the constraints Eq. 3.15b and Eq. 3.15c ensure that the action selected minimizes all future costs. The $(1 - y(s;a))M$ portion guarantees that the constraint is only binding for the action chosen. The constraint should be binding for the optimal action such that the value is equal to the cost in the current state plus the discounted cost of all future scenarios. Additionally, constraint Eq. 3.15d makes sure for all scenarios only one action is chosen for each state.

3.5 Results

In this subsection, we analyze results of the stochastic programming formulation. Initially, we must consider a method of state aggregation in order to make the program easier to solve with computer optimization software. Then we will evaluate various results of the stochastic program considering vaccine efficacy as the stochastic variable.

3.5.1 State Aggregation

Before solving the system to evaluate results, the size of the probability transition matrix should be considered with the aim of making the problem easier to manage. If each member of the population is considered individually as either a susceptible or infective, such as in the current state definition, the state space will be too large to handle for even small sizes of N. With every person considered individually, there are $N(N+1)/2$ feasible states in the model. Therefore, a state aggregation method is needed to combine states to make the problem more computationally tractable. We use a method similar to that of R. Yaesoubi [45].

A state in the form $\{(X_S(t), X_I(t)) : t = 1, 2, \dots\}$ is approximated with the Markov Chain $\{(\Theta_S(t), \Theta_I(t)) : t = 1, 2, \dots\}$. The new Markov chain $\{(\Theta_S(t), \Theta_I(t))\}$ is the proportion of the population in the susceptible and infective compartments at time t. These proportions take discrete values from the set $\{\theta_1, \theta_2, \dots, \theta_d\}$. In order to determine the values of $\{\theta_1, \theta_2, \dots, \theta_d\}$, the interval $[0, 1]$ is divided into d equally sized intervals. The regions are bounded by the control points $\{0 = b_0, b_1, b_2, \dots, b_d = 1\}$. Then, the state values, θ_i, are determined by $\theta_i = (b_i + b_{i-1})/2$ for $i = \{1, 2, \dots d\}$.

With the new state definition, the transition probabilities are calculated by:

$$Pr\left\{(\Theta_S(t + \Delta t), \Theta_I(t + \Delta t)) = (\theta_S, \theta_I) | \Theta_S(t), \Theta_I(t)\right\} = \sum_{(x_S, x_I) \in K_{\Theta_t}} Pr_{(X_S(t+\Delta t), X_I(t+\Delta t))}(x_S, x_I | (\lfloor N\Theta_S(t) \rfloor, \lfloor N\Theta_I(t) \rfloor) \quad (3.16)$$

In this equation, K_{Θ_t} is given by:

$$K_{\Theta_t} = \{(x_S, x_I) | \lfloor N * b_{j-1} \rfloor \leq x_S \geq \lceil N * bj \rceil, \lfloor N * b_{j-1} \rfloor \leq x_I \geq \lceil N * bj \rceil\} \quad (3.17)$$

Additionally, when considering state aggregation, the actions impact the current state of the approximated Markov chain, $(\Theta_S(t), \Theta_I(t))$. We determine the impact of actions through a range of current states after vaccination based on the interval, $bj - 1 \leq \Theta_S(t) \geq bj$, in which the current susceptibles before vaccination falls. We can calculate the range of current susceptibles after vaccination through the following equations under a certain scenario of vaccine efficacy:

$$a_L = b_{j-1} a_t \omega a_H = b_j a_t \omega \quad (3.18)$$

Depending on the action and vaccine efficacy, the new current state could span multiple intervals, meaning, $a_H - a_L > b_j - b_{j-1}$. When this occurs, we determine the current states that fall within this action range. Furthermore, we also need to determine the proportion of the action range that falls in each interval, $\{0 = b_0, b_1, b_2, \dots, b_d = 1\}$. For each current state, $(\Theta_S(t), \Theta_I(t))$, in the range, we calculate the transitions probabilities to all other states by means of Eq. 3.16. We multiply each transition probability by proportion of the action range that is encompassed by that interval. After all current states are considered, the probabilities, weighted by the percentage of the action range for that current state, are summed to determine the final transition probability matrix.

By approximating individuals with proportion ranges, some transitions may be considered in multiple states. When this occurs, that row in the transition matrix will sum to more than

one. To alleviate this concern, we normalize the row so that a proper transition matrix results.

3.5.2 Stochastic Program Results

The results presented here consider the affect of varying the vaccine efficacy, number of scenarios and the probabilities of each scenario. Initially, we present results of the stochastic programming formulation based on model Eq. 3.15 and the initial parameter values given in Table B.1 in Appendix B.1. Motivated by these results, we consider additional constraints to guarantee the percentage vaccinated is non-decreasing as infectivity increases for the same proportion of susceptibility and as susceptibility increases for the same proportion of infectives. For the optimization model with these additional constraints, we discuss the patterns of vaccination and differences in results for varying scenarios.

We evaluate varying levels of vaccine efficacy for a single scenario to determine the behavior of the model. Figure 3.1 shows the proportion of the population to vaccinate for each level of susceptibility and infectiousness. After viewing these graphs, a significant concern emerges in regards to vaccine percentages. Specifically, there are certain states in which an increase in infectivity over the same susceptible proportion may trigger a decrease in vaccination. We witness this in states $(0.35, 0.25), (0.25, 0.35)$ and $(0.15, 0.55)$ for vaccine efficacies between 40 percent and 80 percent. However, there are additional instances of this phenomena throughout the heat graphs. Furthermore, the same circumstance is apparent for increasing susceptible proportions over a constant level of infectivity. Although this is seen throughout all levels of vaccine efficacy, one can readily identify this problem in the 15 percent infective column for vaccine efficacies between 40 and 60 percent.

After careful examination of the model, we decide to consider the addition of constraints that will force the number vaccinated to be non-decreasing as both susceptibility and infectivity increase. Let $Z_S \subset S$ that includes all elements of S except those with the smallest allowable percentage of susceptibles. Analogously, let $Z_I \subset S$ be defined in the same manner for states with the smallest allowable percentage of infectives. We consider the addition of the following two constraints in 3.15:

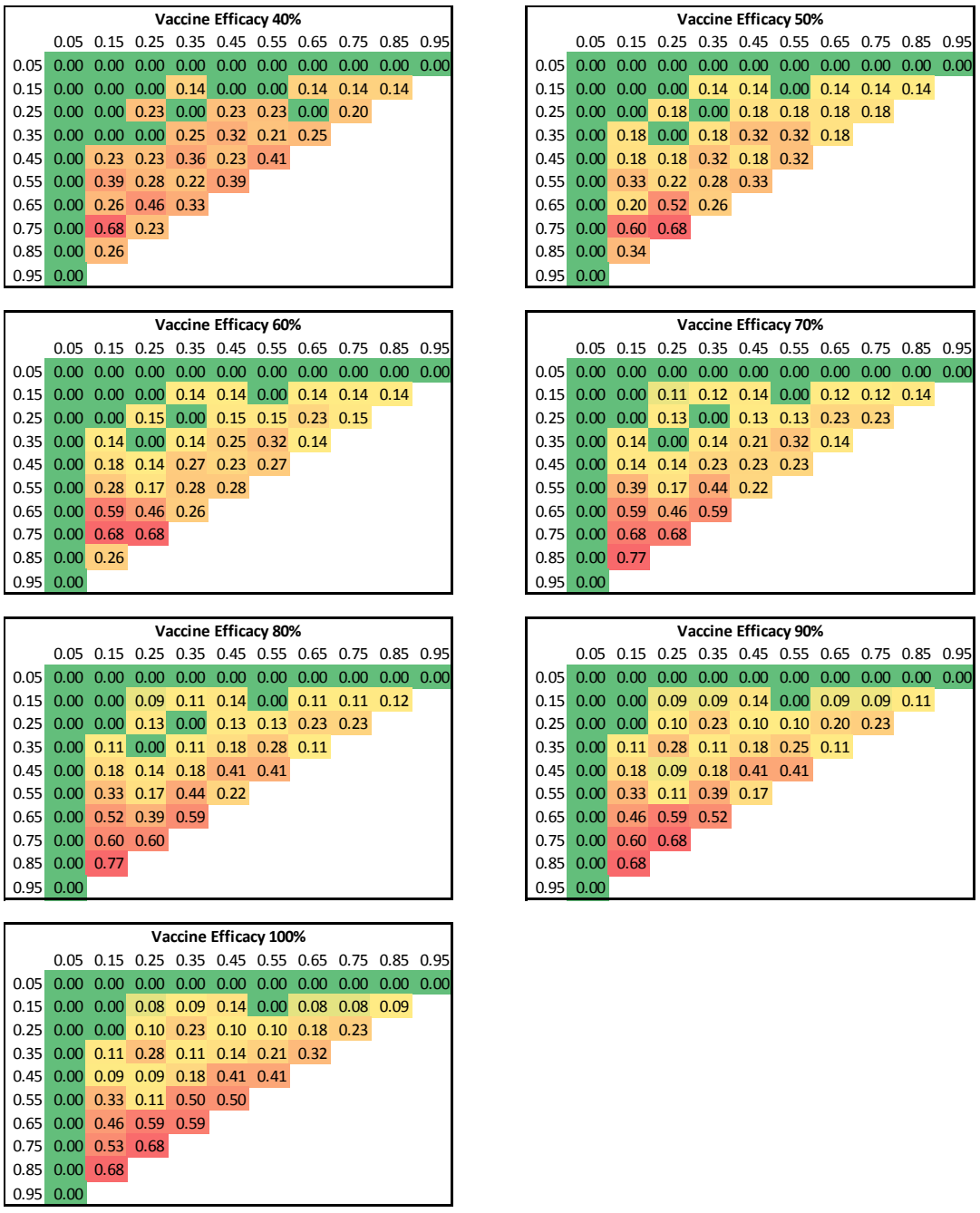
$$\sum_{a \in A} a(y(s,i;a) - y(s,i-1;a)) \geq 0 \quad \forall s \in Z_S \tag{3.19a}$$

$$\sum_{a \in A} as(y(s,i;a) - y(s-1,i;a)) \geq 0 \quad \forall s \in ZI \tag{3.19b}$$

Figure 3.2 shows the same scenarios with additional constraints. Through analysis of these graphs, we see the previously encountered concerns have been rectified.

Table 3.1: Variables for Stochastic Program Formulation

Variable	Description
K	Number of increments for state approximation
A	Number of actions
a_j	Value of actions
Ω	Number of scenarios
ω_i	Scenario values
ρ_i	Probability of each scenario
N	Population size
γ	Stochastic discount factor
λ	Contact rate
τ	Probability of infection after contact
μ	Rate of recovery
c	Cost of infection
l	Treatment length
h	Percent of health quality reduction
w	QALY Lost ($lh/365$)
c_v	Cost per vaccination
M	Large value



Vaccine Efficacy 40%

	0.05	0.15	0.25	0.35	0.45	0.55	0.65	0.75	0.85	0.95
0.05	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.15	0.00	0.00	0.00	0.14	0.00	0.00	0.14	0.14	0.14	
0.25	0.00	0.00	0.23	0.00	0.23	0.23	0.00	0.20		
0.35	0.00	0.00	0.00	0.25	0.32	0.21	0.25			
0.45	0.00	0.23	0.23	0.36	0.23	0.41				
0.55	0.00	0.39	0.28	0.22	0.39					
0.65	0.00	0.26	0.46	0.33						
0.75	0.00	0.68	0.23							
0.85	0.00	0.26								
0.95	0.00									

Vaccine Efficacy 50%

	0.05	0.15	0.25	0.35	0.45	0.55	0.65	0.75	0.85	0.95
0.05	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.15	0.00	0.00	0.00	0.14	0.14	0.00	0.14	0.14	0.14	
0.25	0.00	0.00	0.18	0.00	0.18	0.18	0.18	0.18		
0.35	0.00	0.18	0.00	0.18	0.32	0.32	0.18			
0.45	0.00	0.18	0.18	0.32	0.18	0.32				
0.55	0.00	0.33	0.22	0.28	0.33					
0.65	0.00	0.20	0.52	0.26						
0.75	0.00	0.60	0.68							
0.85	0.00	0.34								
0.95	0.00									

Vaccine Efficacy 60%

	0.05	0.15	0.25	0.35	0.45	0.55	0.65	0.75	0.85	0.95
0.05	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.15	0.00	0.00	0.00	0.14	0.14	0.00	0.14	0.14	0.14	
0.25	0.00	0.00	0.15	0.00	0.15	0.15	0.23	0.15		
0.35	0.00	0.14	0.00	0.14	0.25	0.32	0.14			
0.45	0.00	0.18	0.14	0.27	0.23	0.27				
0.55	0.00	0.28	0.17	0.28	0.28					
0.65	0.00	0.59	0.46	0.26						
0.75	0.00	0.68	0.68							
0.85	0.00	0.26								
0.95	0.00									

Vaccine Efficacy 70%

	0.05	0.15	0.25	0.35	0.45	0.55	0.65	0.75	0.85	0.95
0.05	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.15	0.00	0.00	0.11	0.12	0.14	0.00	0.12	0.12	0.14	
0.25	0.00	0.00	0.13	0.00	0.13	0.13	0.23	0.23		
0.35	0.00	0.14	0.00	0.14	0.21	0.32	0.14			
0.45	0.00	0.14	0.14	0.23	0.23	0.23				
0.55	0.00	0.39	0.17	0.44	0.22					
0.65	0.00	0.59	0.46	0.59						
0.75	0.00	0.68	0.68							
0.85	0.00	0.77								
0.95	0.00									

Vaccine Efficacy 80%

	0.05	0.15	0.25	0.35	0.45	0.55	0.65	0.75	0.85	0.95
0.05	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.15	0.00	0.00	0.09	0.11	0.14	0.00	0.11	0.11	0.12	
0.25	0.00	0.00	0.13	0.00	0.13	0.13	0.23	0.23		
0.35	0.00	0.11	0.00	0.11	0.18	0.28	0.11			
0.45	0.00	0.18	0.14	0.18	0.41	0.41				
0.55	0.00	0.33	0.17	0.44	0.22					
0.65	0.00	0.52	0.39	0.59						
0.75	0.00	0.60	0.60							
0.85	0.00	0.77								
0.95	0.00									

Vaccine Efficacy 90%

	0.05	0.15	0.25	0.35	0.45	0.55	0.65	0.75	0.85	0.95
0.05	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.15	0.00	0.00	0.09	0.09	0.14	0.00	0.09	0.09	0.11	
0.25	0.00	0.00	0.10	0.23	0.10	0.10	0.20	0.23		
0.35	0.00	0.11	0.28	0.11	0.18	0.25	0.11			
0.45	0.00	0.18	0.09	0.18	0.41	0.41				
0.55	0.00	0.33	0.11	0.39	0.17					
0.65	0.00	0.46	0.59	0.52						
0.75	0.00	0.60	0.68							
0.85	0.00	0.68								
0.95	0.00									

Vaccine Efficacy 100%

	0.05	0.15	0.25	0.35	0.45	0.55	0.65	0.75	0.85	0.95
0.05	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.15	0.00	0.00	0.08	0.09	0.14	0.00	0.08	0.08	0.09	
0.25	0.00	0.00	0.10	0.23	0.10	0.10	0.18	0.23		
0.35	0.00	0.11	0.28	0.11	0.14	0.21	0.32			
0.45	0.00	0.09	0.09	0.18	0.41	0.41				
0.55	0.00	0.33	0.11	0.50	0.50					
0.65	0.00	0.46	0.59	0.59						
0.75	0.00	0.53	0.68							
0.85	0.00	0.68								
0.95	0.00									

Figure 3.1: Results are given in terms of the percentage of the total population to vaccinate. The row specifies the percentage of the susceptibles in the population and the column gives the percentage of infectives.

Figure 3.2: Results from considering various levels of vaccine efficacy after addition of distribution constraints.

Table 3.2: Vaccine Efficacy and Probability of Occurring

Lowest Expected Vaccine Efficacy (VE)	
Vaccine Efficacy (ω)	Scenario Probability (ρ)
0.167	0.1
0.333	0.1
0.5	0.35
0.667	0.35
0.833	0.05
1	0.05
Uniform Probability of Scenario	
0.167	0.167
0.333	0.167
0.5	0.167
0.667	0.167
0.833	0.167
1	0.167
Higher Expected VE	
0.5	0.1
0.6	0.1
0.7	0.2
0.8	0.2
0.85	0.2
0.9	0.2

Next, we examine the model with multiple scenarios in each optimization. Each scenario varies in either the vaccine efficacy, ω, or the probability of scenario occurrence, ρ. Specifically, we analyze three optimizations each with six scenarios with the values for vaccine efficacy and scenario probability given in Table 3.2. The expected vaccine efficacies for the three optimizations are 55 percent, 58 percent and 76 percent and the heat graph results are shown in Figure 3.3.

Each of these scenarios was stopped after an hour of run time and there was a small gap in the optimal solution. These values are seen in Table 3.3. Also evidenced in Table 3.3, the results demonstrate that even the slight change from the lowest expected efficacy of 55 percent to 58 percent in the optimization with uniformly distributed scenario probabilities produces significant changes in the number of vaccines distributed as seen in. Furthermore, the optimization of the highest level of vaccine efficacy suggests average vaccine levels similar to that of

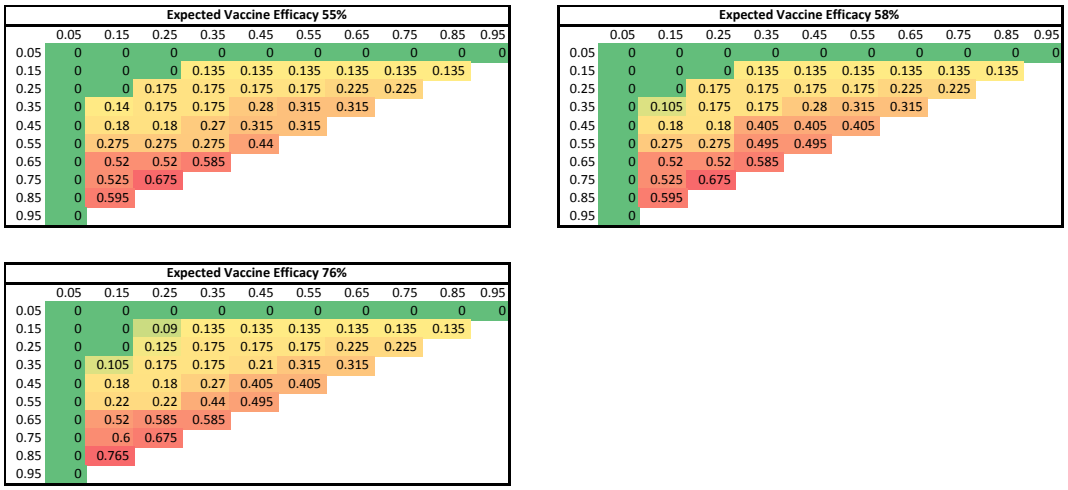


Figure 3.3: The results of considering three optimization each with six scenarios.

Table 3.3: Varying Scenarios

Scenario	Time (s)	Gap (%)	Objective Value	Number of States with Vaccines	Average Number of Vaccines per State	Average Vaccine Cost per State
Low VE	3600	3.40	119.93	33	129.09	$3,872.57
Uniform	3600	3.69	120	33	136.79	$4,103.55
High VE	3600	3.05	119.07	33	136.51	$4,095.23

58 percent expected efficacy; however, these vaccines are distributed differently as evidenced by Figure 3.4. In this figure, we see similar vaccine percentages across all susceptible classes less than 45 percent. However, when there are 45 and 55 percent susceptible the optimization with uniform scenarios suggest slightly higher levels of vaccines. After this point, the optimization with the highest expected vaccine efficacy requires higher percentages such that both optimizations require approximately equal average vaccines employed.

Additionally, Table 3.4 through Table 3.6 provide the Expected Value of Perfect Information (EVPI). The EVPI is the maximum value that a decision maker would want to pay in obtaining perfect information for the uncertain variables. The rewards used to calculate these results were normalized.

These results highlight the necessity of examining the states in which vaccines are employed in addition to the average levels of vaccination. Through evaluating the vaccine distribution is

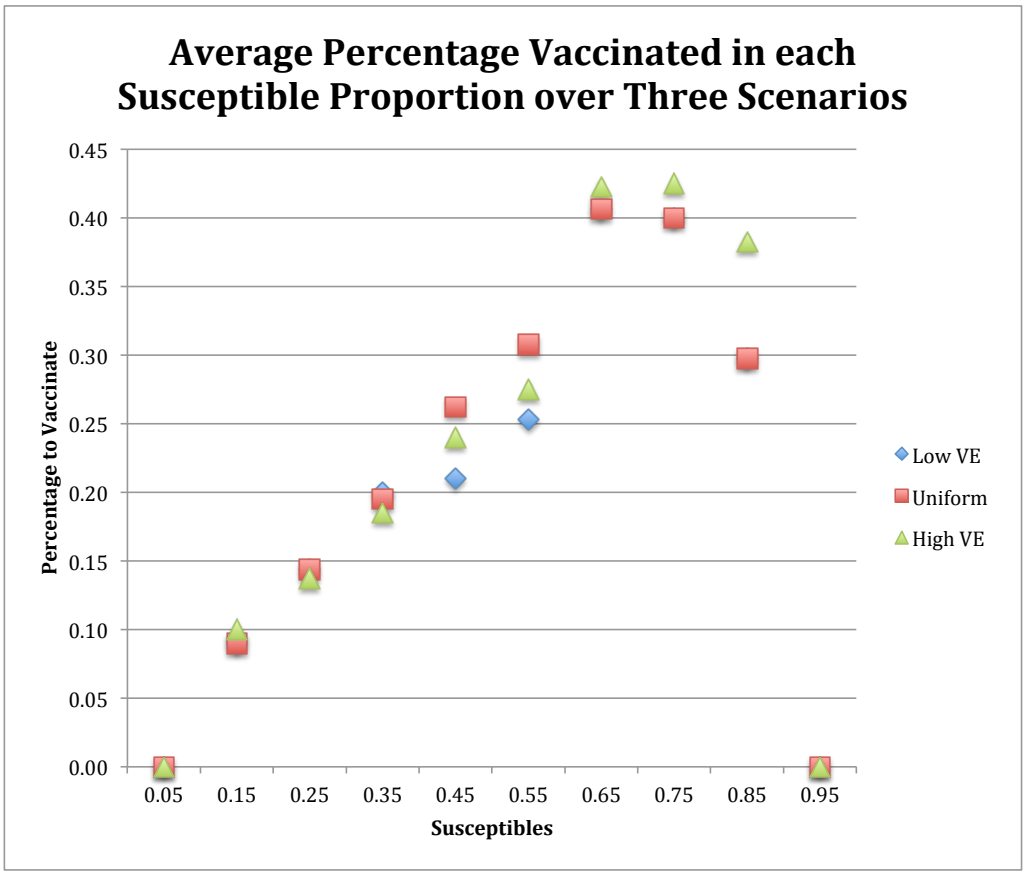


Figure 3.4: Shows average percentage to vaccinate for each susceptible state averaged over all infective states.

Table 3.4: EVPI: Lowest Expected Vaccine Efficacy

Lowest Expected Vaccine Efficacy		
Vaccine Efficacy	Objective Value	Probability
0.167	121.84	0.1
0.333	120.68	0.1
0.5	119.82	0.35
0.667	119.24	0.35
0.833	118.66	0.05
1	118.42	0.05
On Average		119.78
Low VE	119.93	
EVPI	**-0.153**	

Table 3.5: EVPI: Uniform Probability of Scenarios

Uniform Probability of Scenarios		
Vaccine Efficacy	Objective Value	Probability
0.167	121.84	0.167
0.333	120.68	0.167
0.5	119.82	0.167
0.667	119.24	0.167
0.833	118.66	0.167
1	118.42	0.167
On Average		119.78
Uniform	120	
EVPI	**-0.223**	

Table 3.6: EVPI: Highest Expected Vaccine Efficacy

Highest Expected Vaccine Efficacy		
Vaccine Efficacy	Objective Value	Probability
0.167	119.82	0.1
0.333	119.46	0.1
0.5	119.14	0.2
0.667	118.88	0.2
0.833	118.74	0.2
1	118.62	0.2
On Average		119.00
Low VE	119.06	
EVPI	**-0.056**	

given by the initial model, we learn that the distribution of vaccines does not match what is logically expected for increasing levels of susceptibility and infectiousness. Upon adding constraints, we see the importance of considering variations in the vaccine distributions when considering multiple scenarios.

3.6 Conclusion

In chapter 3 we concentrated on a discrete-time infinite horizon MDP to evaluate dynamic health policies regarding the optimal distribution of vaccines during an influenza pandemic. We defined the states to include the number of individuals susceptible and infective at time t. The actions that could be chosen at each time step were the percentage of the susceptible population in the current state that should be vaccinated. The transition probabilities were calculated based on the likelihood of observing infections and recoveries during Δt. In order to solve this problem, we used a linear programming solutions approach. Furthermore, from this linear program, we developed a stochastic model to consider variations in vaccine efficacy. The stochastic program was evaluated for a variety of scenarios.

The significance of this model formulation is its ability to suggest dynamic strategies based on proportions of susceptibility and infectiousness in the population. An additional advantage is the uncertainty naturally present in vaccine efficacy is incorporated in the model. First, we consider a single scenario in each optimization, with differing levels of efficacy. Through this analysis, we see the average number vaccinated fluctuates between 103 per state and 121 per

state, which leads to an average difference of $540 per state. This is consistent with expectations as the average number needed should fluctuate with varying degrees of efficacy. However, further examination leads us to see that vaccination does not always increase with infectivity for individuals in a single susceptible class. Due to this phenomena, we evaluate the model with additional constraints specifying that as the number of infectives increase for for a certain percentage of susceptibles, the percentage vaccinated should be non-decreasing. Additionally, we make an analogous constraint as susceptibles increase for the same proportion of infectives.

With the addition of these constraints, the model behaves as expected in terms of increases in vaccine percentages. In analyzing several scenarios with these additional constraints, we come to understand the significance of considering vaccine efficacy as a stochastic parameter. With only a three percent difference in expected vaccine efficacy, the average vaccination cost per state increases by $230. Furthermore, when we examine a higher expected vaccine efficacy, we find a negligible difference in the average number of vaccines employed per state. Nevertheless, the distribution of these vaccines differs in 18 percent of the states. Signifying the importance of examining a strategy for each state of the model.

Based on the results of stochastic vaccine efficacy, extensions of this work could consider the stochastic formulation of other parameters such as contact rate, rate of recovery and costs. Additionally, further considerations could be given to the definition of the state. An additional factor such as vaccine availability could be considered as part as the state definition as a way to consider constrained vaccines. Furthermore, considerations of other important factors such as number of infections and death could be included in future work.

Through this MDP, we have considered optimal vaccine distribution based on the current state of disease progression in the population. Further, we have determined an effective strategy that minimizes the expected cost of an influenza pandemic. This work provides a basis for future considerations in considering dynamic policies with a stochastic programming solutions approach.

Chapter 4

Conclusions

4.1 Conclusion and Future Considerations

Throughout this thesis, we evaluated two distinct models. The first considered minimizing the number of vaccines needed to eliminate an influenza pandemic in a heterogeneous age-distributed population. The model employed contributions from others regarding the next generation matrix and the characterization of the threshold surface for the vaccine fractions. In order to solve the optimization, a mixed integer linear program was implemented. Results showed an optimal policy involved vaccinating proportions of the first two subgroups (0-4 years old and 5 - 19 years old) as these individuals have higher rates of contact than other subgroups. Consequently, these results led to consideration of fairness and equity constraints. The second model, which was examined in chapter 3, employed an MDP to select optimal percentages of vaccines for various proportions of susceptible and infectious individuals comprised in the population. In this model, we use a linear program as a solution method for the MDP. As a result of the convenient formulation, we incorporated stochasticity by considering vaccine efficacy as an uncertain parameter. Then, we analyzed the result of this stochastic program. Both of these distinct models have unique advantages. Nonetheless, results of both models could be strengthened if these specific advantages were considered simultaneously.

An advantage of the model considered in chapter 2 resides in the heterogeneous age-structure. Through this structure we can represent unique age-distributed rates of infectivity, susceptibility and contact inherent in the population. However, this model fails to consider variations in unknown rates, such as vaccine efficacy. This problem could be rectified by formulating a stochastic program from the given mixed-integer linear program. This would involve considering various values in the formulation of the matrix R.

On the other hand, the MDP model, discussed in chapter 3 considers stochasticity in parameter values, but lacks the consideration of a heterogeneous age-distributed population. By

including heterogeneity in the model, an action would be selected for each age group based on the percentages of susceptibles and infectives in that age group. To achieve this aim, an additional factor must be included in the state definition, indicating the age group of for that state. Therefore, percentages of susceptible and infective individuals would be considered for each age group. The number of states would increase by the current number of states times the number of age groups in the population.

As a consequence of these future considerations, two distinct models would result each considering both heterogeneity and stochasticity. These additions allow for a more natural representation of the epidemiology of pandemic influenza. As these changes are implemented, results can be compared to the original models presented here to characterize the influence of these factors. In addition, results should be examined to determine if additional constraints are needed, such as consideration of fairness and equity.

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APPENDICES

Appendix A

Appendix A

A.1 Heterogeneous Model Initial Values

Table A.1 provides the values used in the calculation of the next generation matrix R. Table A.2 gives the initial values for the mixed integer programming optimization.

Table A.1: Values Used in the Next Generation Matrix R

Variable	**0 - 4**	**5 - 19**	**20 - 34**	**35 - 64**	**65 and over**
Contact Rates	0.305	0.132	0.205	0.099	0.041
	0.032	0.923	0.158	0.074	0.028
	0.042	0.132	0.183	0.099	0.041
	0.032	0.101	0.158	0.067	0.029
	0.032	0.101	0.158	0.074	0.032
γ	0.435	0.454	0.327	0.327	0.327
H_j	0.835	0.835	0.835	0.835	0.835
E_j	1	1	1	0.85	0.75
n	0.077	0.241	0.375	0.204	0.103

Table A.2: Initial Values for the MILP

Variable	**Value**				
k	14				
ψ	0.98				
Variable	**0 - 4**	**5 - 19**	**20 - 34**	**35 - 64**	**65 and over**
n_j	77	241	375	204	103
R	0.59	0.08	0.08	0.06	0.04
	0.18	1.70	0.19	0.14	0.09
	0.52	0.52	0.47	0.39	0.29
	0.22	0.22	0.22	0.15	0.11
	0.11	0.11	0.11	0.08	0.06

A.2 GMPL file

This section provides the GMPL code that was used to create an LP file. This LP was then solved using cplex optimization software.

```
############## INVERSE MDP MODEL ########################
param KK;
param II;
param eff;
############### SETS ##############################################
set K := 0..KK;
set I := 1..II;
############### PARAMETERS ########################################
# Next Generation Matrix
param R{i in I,j in I};   # nj=the population of subgroup j
param n{j in I};  # uj=upper bound for yj
param u{j in I};
############## VARIABLES ##########################################
var x{k in K,j in I} binary;
var y{j in I} >=0;
var z{k in K, j in I, i in I} >=0;
var f{j in I} >= 0;
############# DECISON MODEL #######################################
minimize  obj:sum{j in I}(n[j] * eff^(-1)- n[j] * eff^(-1) * (sum{k in K} z[k,j,j]*2^(-k)));
s.t. c001a{j in I}: sum{i in I} R[i,j]*(sum{k in K} z[k,j,i]*2^(-k)) >= 1.0;
s.t. c001b{j in I}: sum{i in I} R[i,j]*(sum{k in K} z[k,j,i]*2^(-k)) <= 1.0;
s.t. c002a{j in I}: sum{k in K} z[k,j,j]*2^(-k) <= 1.0;
s.t. c002b{j in I}: sum{k in K} z[k,j,j]*2^(-k) >= 1-eff;
s.t. c003a: sum{j in I} (sum{k in K} x[k,j]*2^(-k)) >= 1.0;
s.t. c003b: sum{j in I} (sum{k in K} x[k,j]*2^(-k)) <= 1.0;
s.t. c005{j in I, k in K, i in I}: z[k,j,i] >= y[j]+u[j]*(x[k,i]-1);
s.t. c006{j in I, k in K, i in I}: z[k,j,i] <= y[j];
s.t. c007{j in I, k in K, i in I}: z[k,j,i] <= u[j]*x[k,i];
s.t. c008{j in I}: f[j] = eff^(-1)*sum{k in K}(2^(-k)*x[k,j]);
end;
```

Appendix B

Appendix B

B.1 Initial Values

Table B.1 shows the initial values used in the MDP model.

Table B.1: MDP Initial Values

Variable	**Description**
K	10
A	10
a_j	$\{0, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9\}$
Ω	10
ω	$\{0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1\}$
ρ	$1/\Omega$
N	763
γ	0.97
λ	14
τ	0.105
μ	1.7
c	\$ 100
l	5 days
h	0.25
w	$(lh/365)$
c_v	\$ 30
M	5

B.2 C++ Program used to solve MDP

In this section we present the C++ code used to generate the results through cplex optimization software.

```
#include <iostream>

#include<fstream>

#include <algorithm>

#include <array>

#include <string>

#include <math.h>

#include <boost\math\distributions\binomial.hpp>
using boost::math::binomial;

using namespace std;

#include <ilcplex/ilocplex.h>

ILOSTLBEGIN;



////////////////// Initialize ////////////////////
double largeM = 5;  //Big M is used in the constraints of the stochastic program to make
constraints loose
double epsilon = 1e-6;  //Consider only probabilities greater than this number

//Initialize Increments, Actions, and Scenarios
const int Num_Increments = 10;  // Number of intervals that divide 0 and 1 to create
susceptible and infective states
const int Num_Actions = 10;  // Number of Actions that can be choosen
const int Num_Scenarios = 6;  //Number of scenarios considered -- vaccine effectiveness
const int Num_States = Num_Increments*(Num_Increments + 1) / 2;  //Number of states
calculated based on number of intervals

 // Initialize Propagation parameters
int Population = 763;  //Population size
double gamma = 0.97;  //Discount factor in Stochastic Program
double lambda = 14; //Contact Rate in the population
double tau = 0.105; //Probability of infection once contact is made with a susceptible
individual
double mu = 1.7; //Rate of Recovery

 // Initialize costs
double cost_infection = 100;  // Cost per infection
double treatment_length = 5; // days
double health_quality_reduction = 0.25; // percent reduction in health quality during
infection
double QALY_Lost = treatment_length*health_quality_reduction / 365.0;  //
double willingness_to_pay = 25000; // per QALY
double cost_vaccine = 30;  // Cost per vaccination



////////////////////////////////////////////////////////////////////
double susceptibles[Num_States];  // Portion of susceptibles for each state
double infectious[Num_States];  //Portion of infectious for each state
```

```
double Floor_Ceil_States[Num_States][4]; //Holds Floor and ceiling value for susceptible
and infection in each state
double action[Num_Actions];  //vector holding actions as percentages of susceptibles to
vaccinate
double omega[Num_Scenarios];  //vector holding values of scenarios
double rho[Num_Scenarios];   // vector holding probabilites of each scenario
double Probability[Num_Scenarios][Num_Actions][Num_States][Num_States];  //Transition
Probabilities
double Reward[Num_States][Num_Actions][Num_Scenarios]; //Rewards


  // Initialize functions in main
double expected_inf(double lambda, double tau, double INF);  // function to calculate
expected number of infections
double expected_rec(double Mu);  // function to calculate expected number of recoveries
void Prob(int numcs, int numa, int numscen, double* ProbTrans); // function to calculate
transition probabilities for a given state
double reward_func(int numstate, int numa, int numscen); // function to calculate
expected reward



int main() {


	clock_t start_time = clock();  // start clock to track time


	 ////////////////////// Fill in Arrays ////////////////////////

	// Calculate susceptible and infection array
	int t = -1;
	for (int i = 0; i < Num_Increments; i++) {
		for (int j = 0; j < Num_Increments - i; j++) {
			t++;
			susceptibles[t] = (((1 / (double)Num_Increments)*i) + ((1 /
(double)Num_Increments)*(i + 1))) / 2;
			infectious[t] = (((1 / (double)Num_Increments)*j) + ((1 /
(double)Num_Increments)*(j + 1))) / 2;
			cout << susceptibles[t] << "    " << infectious[t] << endl;
		}
	}


	//Calculate floor and ceiling of the number of susceptibles and infectious in the
population for each state
	for (int i = 0; i < Num_States; i++) {
		Floor_Ceil_States[i][0] = floor((susceptibles[i] - .5 /
Num_Increments)*Population);
		Floor_Ceil_States[i][1] = ceil((susceptibles[i] + .5 /
Num_Increments)*Population);
		Floor_Ceil_States[i][2] = floor((infectious[i] - .5 /
Num_Increments)*Population);
		Floor_Ceil_States[i][3] = ceil((infectious[i] + .5 /
Num_Increments)*Population);
	}
```

```
// Action Array
for (int i = 0; i < Num_Actions; i++) {
	action[i] = (i) / (double)Num_Actions;
}


// Value of Scenario
for (int i = 0; i < Num_Scenarios; i++) {
	omega[i] = (i + 1) / (double)Num_Scenarios;
}

// Probabilities of Scenarios
for (int g = 0; g < Num_Scenarios; g++) {
	rho[g] = 1 / (double)Num_Scenarios;
}



////////////////// Print Values calculate /////////////////
cout << endl;
cout << "Num    " << "Sus    " << "Inf    " << endl;
for (int i = 0; i < Num_States; i++) {
	cout << i << "      ";
	cout << susceptibles[i] << "     ";
	cout << infectious[i] << endl;
}

//Print Actions
cout << endl;
cout << "Actions" << endl;
for (int i = 0; i < Num_Actions; i++) {
	cout << action[i] << endl;
}

//Print Scenarios
cout << endl;
cout << "Scenarios  " << "Rho  " << endl;
for (int i = 0; i < Num_Scenarios; i++) {
	cout << omega[i] << "         ";
	cout << rho[i] << endl;
}

double RowValue[Num_Increments];
RowValue[0] = 0;
for (int i = Num_Increments; i > 1; i--) {
	RowValue[Num_Increments + 1 - i] = RowValue[Num_Increments - i] + i;
	cout << RowValue[Num_Increments + 1 - i] << endl;
}


int Row[Num_States];
for (int ss = 0; ss < Num_States; ss++) {
	Row[ss] = 0;
	for (int j = 0; j < Num_Increments; j++) {
		if (ss == RowValue[j]) {
			Row[ss] = 1;
			continue;
```

```
                }
            }
            cout << ss << "    " << Row[ss] << endl;
        }


        for (int i = 0; i < Num_Increments - 1; i++) {
            int j = 10;
            int sum = i;
            cout << "k + sum" << "         " << "sum" << endl;
            for (int k = j; k > i + 1; k--) {
                cout << k + sum << "      " << sum << endl;
                sum += k;
            }
        }



        //// determine time so far ////
        double End_Initial = double(clock() - start_time) / CLOCKS_PER_SEC;
        cout << "End_Initial = " << End_Initial << endl;


        /////// Create file for Results ///////
        ofstream myfile;
        myfile.open("Data.txt");


        ////////////////// Calculate Probabilities //////////////////////

        // Calculate Transition probabilities for all current states under each possible
scenario and action
        for (int scen = 0; scen < Num_Scenarios; scen++) {
            for (int act = 0; act < Num_Actions; act++) {
                for (int curr_state = 0; curr_state < Num_States; curr_state++) {
                    Prob(curr_state, act, scen,
Probability[scen][act][curr_state]);
                }
            }
        }


        // Determine how long it takes to calculate Probabilities
        double TimeProb = double(clock() - start_time - End_Initial) / CLOCKS_PER_SEC;
        cout << "TimeProb = " << TimeProb << endl;



        ////////////// Rewards ////////////////
        double largest_reward = 0;
        for (int state = 0; state < Num_States; state++) {
            for (int action = 0; action < Num_Actions; action++) {
                for (int scenario = 0; scenario < Num_Scenarios; scenario++) {
                    Reward[state][action][scenario] = reward_func(state, action,
scenario);
                    if (Reward[state][action][scenario] > largest_reward) {
```

```
                                largest_reward = Reward[state][action][scenario];
                        }
                }
        }
    }

    for (int state = 0; state < Num_States; state++) {
        for (int action = 0; action < Num_Actions; action++) {
            for (int scenario = 0; scenario < Num_Scenarios; scenario++) {
                Reward[state][action][scenario] =
Reward[state][action][scenario] / largest_reward;
                myfile << Reward[state][action][scenario] << endl;
            }
        }
    }



    myfile.close();

    ////////////////////////// CPLEX ///////////////////////////////

    // Create Environment and Build Model
    IloEnv env;

    try {
        //     env = IloEnv();
        IloModel model(env);


        ////////////////////// Decision Variables ///////////////////////

        // Create decision variables V_[scenario][state]
        IloArray<IloNumVarArray> V_ws(env, Num_Scenarios);
        for (int ww = 0; ww<Num_Scenarios; ww++) {
            V_ws[ww] = IloNumVarArray(env, Num_States);
            for (int ss = 0; ss<Num_States; ss++) {
                V_ws[ww][ss] = IloNumVar(env, 0, IloInfinity, ILOFLOAT);
            }
        }


        // Create Binary Decision Variable y[state]
        IloArray<IloBoolVarArray> y_sa(env, Num_States);
        for (int ss = 0; ss < Num_States; ss++) {
            y_sa[ss] = IloBoolVarArray(env, Num_Actions);

        }


        ////////// Objective function ///////////
        IloExpr  objFun(env);

        for (int ww = 0; ww < Num_Scenarios; ww++) {
            for (int ss = 0; ss < Num_States; ss++) {
                objFun += rho[ww] * V_ws[ww][ss];
            }
```

```
		}

		model.add(IloMinimize(env, objFun));
		objFun.end();



		////////////// Constraints ////////////////////

		////// First Constraint //////
		for (int ww = 0; ww<Num_Scenarios; ww++) {
			for (int ss = 0; ss<Num_States; ss++) {
				for (int aa = 0; aa<Num_Actions; aa++) {
					IloExpr sumConst1(env);
					sumConst1 += V_ws[ww][ss];
					for (int trans_state = 0; trans_state < Num_States;
trans_state++) {
						// double prob =
Probability[ww][aa][ss][trans_state];
						sumConst1 -= gamma *
Probability[ww][aa][ss][trans_state] * V_ws[ww][trans_state];
					}
					sumConst1 -= largeM * y_sa[ss][aa];
					// double reward = reward_func(ss, aa, ww);
					model.add(sumConst1 >= (Reward[ss][aa][ww] - largeM));
					sumConst1.end();
				}
			}
		}


		/////// second constraint ////////////
		for (int ww = 0; ww<Num_Scenarios; ww++) {
			for (int ss = 0; ss<Num_States; ss++) {
				for (int aa = 0; aa<Num_Actions; aa++) {
					IloExpr sumConst2(env);
					sumConst2 += V_ws[ww][ss];
					for (int trans_state = 0; trans_state < Num_States;
trans_state++) {
						// double prob = Prob(ss, trans_state, aa, ww);
						sumConst2 -= gamma *
Probability[ww][aa][ss][trans_state] * V_ws[ww][trans_state];

					}
					sumConst2 += largeM * y_sa[ss][aa];
					// double reward = reward_func(ss, aa, ww);
					model.add(sumConst2 <= (Reward[ss][aa][ww] + largeM));
					sumConst2.end();
				}
			}
		}

		//////// third constraint ////////////
		for (int ss = 0; ss<Num_States; ss++) {
			IloExpr sumConst3(env);
			for (int aa = 0; aa<Num_Actions; aa++) {
				sumConst3 += y_sa[ss][aa];
			}
```

```
                        model.add(sumConst3 == 1);
                        sumConst3.end();
                }


                /////// Fourth Constraint //////

                for (int ss = 1; ss < Num_States; ss++) {
                        if (Row[ss] == 0) {
                                IloExpr sumConst4(env);
                                for (int aa = 0; aa < Num_Actions; aa++) {
                                        sumConst4 += action[aa] * (y_sa[ss][aa] - y_sa[ss -
1][aa]);
                                }
                                model.add(sumConst4 >= 0);
                                sumConst4.end();
                        }
                }

                ////// Fifth Constraint //////////

                for (int i=0; i < Num_Increments-1; i++){
                        int j=Num_Increments;
                        int sum=i;
                        for (int k=j; k > i+1; k--){
                                IloExpr sumConst5(env);
                                for (int aa = 0; aa < Num_Actions; aa++) {
                                        sumConst5 += action[aa] * (
susceptibles[k+sum]*y_sa[k+sum][aa] - susceptibles[sum]*y_sa[sum][aa]);
                                }
                        model.add(sumConst5 >= 0);
                        sumConst5.end();
                        sum+=k;
                        }
                }




                /////////////// Cplex Model and Results ////////////


                ///// Create lp file of model ///////
                IloCplex cplex(model);
                cplex.exportModel("model.lp");



                /////// Create file for Results ///////
                ofstream myfile;
                myfile.open("Results.txt");


                //////// Output Results to file if the problem was solved /////////
```

```
		/*
		cplex.setParam(IloCplex::TiLim, 60);

		if (cplex.solve()) {

			double objectiveValue = cplex.getObjValue();

			double ResultV[Num_Scenarios][Num_States];
			for (int ww = 0; ww<Num_Scenarios; ww++) {
				for (int ss = 0; ss<Num_States; ss++) {
					ResultV[ww][ss] = cplex.getValue(V_ws[ww][ss]);
					myfile << "Variable: v_" << ww << "_" << ss << "   " <<
ResultV[ww][ss] << endl;
				}
			}

			double ResultY[Num_States][Num_Actions];
			for (int ss = 0; ss < Num_States; ss++) {
				for (int aa = 0; aa < Num_Actions; aa++) {
					ResultY[ss][aa] = cplex.getValue(y_sa[ss][aa]);
					myfile << "Variable: y_" << ss << "_" << aa << "   " <<
ResultY[ss][aa] << endl;

				}
			}


			myfile << "objective function: " << objectiveValue << endl;

		}

		myfile.close();
		*/

	}  // end try

	catch (IloException& ex) {
		cerr << "Error: " << ex << endl;
	}
	catch (...) {
		cerr << "Error" << endl;
	}

	env.end();


	////////// Output Time /////////////////
	double TimeEnd = double(clock() - start_time) / CLOCKS_PER_SEC;
	cout << "TimeEnd = " << TimeEnd << endl;
	cout << "PercentFirst = " << (End_Initial) / TimeEnd << endl;
	cout << "PercentProb = " << (TimeProb - End_Initial) / TimeEnd << endl;
	cout << "PercentConstraints = " << (TimeEnd - TimeProb - End_Initial) / TimeEnd <<
endl;
```

```
}

///////////////// Defining Functions //////////////////////




// Probability of Infection in one individual
double expected_inf(double lambda, double tau, double INF) {
	double Beta = INF / Population;   /////Infections in Population to determine
probability that contact is with infectious
	return 1 - exp(-lambda*tau*Beta);
}

// Probability of Recovery in one individual
double expected_rec(double Mu) {
	return 1 - exp(-Mu);
}




////// Function to Calculate Transition Probabilities ///////
void Prob(int numcs, int numa, int numscen, double* ProbTrans) {


	//Initialize values needed to calculate the transition probability given a certain
action is taken under a certain scenario
	// Need the high and low values of the interval for the current state
	// Need the high and low values of Current state after action and scenario are
considered
	// Need the Range of current susceptibles after vaccination and one range that
will be updated
	// Vector to Store Calculate Probabilities

	double CS_Low = susceptibles[numcs] - (.5 / (double)Num_Increments);
	double CS_High = susceptibles[numcs] + (.5 / (double)Num_Increments);
	double CSAction_Low = CS_Low - (CS_Low*action[numa] * omega[numscen]);
	double CSAction_High = CS_High - (CS_High*action[numa] * omega[numscen]);
	double TotalRange = CSAction_High - CSAction_Low;
	double UpdateRange = CSAction_High - CSAction_Low;


	// Create Vector to hold probabilities and initialize to 0
	for (int w = 0; w < Num_States; w++) {
		ProbTrans[w] = 0;
	}



	// While Loop to iterate until all current susceptible states that have values
that fall in the Range of
	// CSAction_Low to CSAction_High have been considered
	while (UpdateRange > 0) {
```

```
		// Determine the percentage of the susceptible in the range covered by the
current state interval
		double PortionRange = CSAction_High - max(CSAction_Low, CS_Low);
		double PercentInterval = PortionRange / TotalRange;



		// Current State -- CS_Current which will change as while is iterated
		double CS_Current = floor((CS_High + CS_Low) / 2 * Population);
		double CI_Current = floor((double)infectious[numcs] * Population);



		// Calculate transition probability given CS_Current and CI_Current --
		// iterates through all possible transition states
		for (int i = 0; i < Num_States; i++) {

			double ProbSum = 0;

			//Iterate through transition range based on floor and ceil of
population size for each i
			for (int g = Floor_Ceil_States[i][0]; g <= Floor_Ceil_States[i][1];
g++) {
				for (int h = Floor_Ceil_States[i][2]; h <=
Floor_Ceil_States[i][3]; h++) {


					// Constraints limiting which transitions can occur
					if (CS_Current - g <= CS_Current && h >= CS_Current - g
&& g <= CS_Current && CS_Current <= g + h && g + h <= CS_Current + CI_Current) {

						// Calculate prob of # of Infections
						double qt = expected_inf(lambda, tau,
CI_Current);
						binomial infections(CS_Current, qt);
						double prob_i = pdf(infections, CS_Current - g);


						// Calculate prob of # of Recoveries
						double y = (CS_Current - g) + (CI_Current - h);
						double rt = expected_rec(mu);
						binomial recoveries(CI_Current, rt);
						double prob_r = pdf(recoveries, y);

						// Sum the probabilities for each possible
population realization in the transition range of i
						ProbSum = ProbSum + (prob_i*prob_r);

					} // End if

					else {

						// If constraints aren't met sum stays the same
and next g and h are considered
						ProbSum = ProbSum;

					}  //End else
```

```
                        } //End For h
                    }  // End For g

                       //Insert Probability into Vector
                    ProbTrans[i] = ProbTrans[i] + (PercentInterval*ProbSum);

             } // End for i

               //Update parameters for next while loop iteration
             UpdateRange = UpdateRange - PortionRange;  //Subtract portion of range
already calculated
             CSAction_High = CS_Low;
             CS_High = CS_High - 1 / (double)Num_Increments;  //Update high value of
range for next current state
             CS_Low = CS_Low - 1 / (double)Num_Increments; //Update low value of range
for next current state
      }

      // Normalize the transition options to 1

      //Calculate the sum of all transitions in the row
      double Normalize = 0;
      for (int q = 0; q < Num_States; q++) {
             if (ProbTrans[q] < epsilon)
                    ProbTrans[q] = 0;
             Normalize = Normalize + ProbTrans[q];
      }

      // Normalize each entry in the row
      for (int p = 0; p < Num_States; p++) {
             ProbTrans[p] = ProbTrans[p] / Normalize;
      }
}


////////////// Reward function ////////////////////
double reward_func(int numstate, int numa, int numscen) {
      double reward;
      double prod = 0;
      double sum = 0;

      // Calculate Expected Number of Infections given Current State (numstate) and
Action under Scenario (
      for (int trans_state = 0; trans_state < Num_States; trans_state++) {
             prod = Probability[numscen][numa][numstate][trans_state] *
(infectious[numstate] * Population);
             sum = sum + prod;
      }

      // Calculate reward
      reward = (cost_infection + QALY_Lost*willingness_to_pay)*sum +
cost_vaccine*(floor(action[numa] * susceptibles[numstate] * Population));
      return reward;


}
```