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Dynamic pricing strategy to optimally allocate vaccines

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DYNAMIC PRICING STRATEGY TO OPTIMALLY ALLOCATE VACCINES

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by

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Abstract

In the United States, the Advisory Committee on Immunization Practices (ACIP) makes recommendations as to which cohorts (identified groups of individuals) ought to have higher priority access to vaccines when their supply is insufficient to immunize all susceptible individuals in the country. Typically, cohorts are determined based on susceptibility to contracting seasonal influenza and on the resulting consequences of infection for different age groups. For seasonal influenza, high-risk cohorts commonly include children, teenagers, pregnant women and people with different chronic diseases. This study proposes the application of revenue management theory to better allocate seasonal influenza vaccines among different risk-based population cohorts. Our model maximizes the number of immunized individuals by dynamically adjusting the price per dose in each cohort as to discourage vaccination in low-risk cohorts and preserve more supply for high-risk cohorts. Experimental results show that up to 12% of infections and deaths due to seasonal influenza could be avoided by implementing this price discrimination policy in hypothetical yet realistic scenarios.

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Introduction

In the United States, seasonal influenza claims over 40,000 lives every year [1]. In the case of influenza pandemics, the number of cases increases dramatically because the entire population is susceptible to new and highly infectious virus strain [2]. For example, the 1918 Spanish Flu pandemic killed 40 million people and infected nearly a quarter of the entire global population at the time [3].

Every year, about 80 million seasonal influenza vaccines are available for distribution to less than one-third of the American population [4]. Such a limited supply of seasonal influenza vaccines is due to the lack of availability of the eggs that are needed to cultivate the virus used in vaccine manufacturing. Therefore, health care authorities must determine how to distribute the limited supply of seasonal vaccines to provide the most effective protection across the population. The World Health Organization (WHO) [5], among other agencies, refers to 'herd immunity' as the minimum proportion of the population that needs to be immune to interrupt an infectious disease transmission, which is achieved by reducing the probability of infection of those individuals who have yet to develop immunity to the disease. Since the basic reproduction number, R_0, measures the rate at which the disease spreads, herd immunity is achieved when R_0 becomes less than one [5].

Several epidemiological models have been developed to describe the progression and spread of infectious diseases (See Hethcote [6] as well as Sattenspiel and Lloyd [7] for further detail.) These models are useful to plan and establish effective containment interventions, including vaccination [8, 9], behavioral interventions such as school closures [5, 10-12], or their combination [13, 14]. Most epidemiological models are compartmentalized systems that describe the disease progression resulting from having different compartmental transition rates [15, 16], in which the progression depends on a deterministic basic reproduction number (R_0), representing the average number of people that are infected

by a contagious individual [17]. However, these models have been criticized due to their reliance on R_0 which is assumed to be static. Several alternatives have been suggested; for example, Larson [18] proposes an approach that considers that R_0 is dynamic and not necessarily homogeneous even for the same population and influenza strain.

In the United States, the ACIP makes recommendations to the population on how to divide people into two distinct cohorts based on the vulnerability toward the influenza [19]. ACIP also suggests which cohort should have priority access to available vaccination [20]. Based on data from the three past influenza pandemics of the twentieth century, Meltzer, Cox and Fukuda [21] claims that an identifiable fifteen percent of the population is accountable for causing over four fifths of the infections in each pandemic.

During a pandemic scenario, the US government pays for the cost of vaccines ahead of time, and the general population only pays for the price of its delivery, often defrayed through insurance coverage. Additionally, the federal and local governments are responsible for determining the most adequate distribution of the vaccines to hospitals, clinics and medical centers [22]. During the 2009 influenza season, some health care centers denied vaccination to patients that were not in the high-risk cohorts, while many other vaccination clinics had concerns about the likelihood that those who were denied vaccination be properly vaccinated in the future [23].

In 2009, the rapid production of the H1N1 vaccine gave the population the chance to protect themselves against a strain of the virus that was unknown until that time. The CDC enforced preferential access to vaccines to those considered within the high-risk groups, as recommended by the ACIP [20]. The first vaccines delivered were, thus, destined toward vaccination centers that cater to individuals in high-risk cohorts, such as “pediatricians, ob/gyns, community health centers and private and public hospitals” [22]. However, its limited supply and fear in the population made this vaccine a commodity in high demand [24].

Mullen [20] indicates that locations that had been assigned vaccines were asked to "sign an agreement to vaccinate only people in the five groups at most risk." However, this policy was not enforced by the authorities, and anyone requesting vaccination was immunized. In this sense, Sadanand [24] notes that some corporations received vaccines for their employees prior to hospitals and clinics, resulting in an "embarrassing mistake [during the] distribution process." Nevertheless, McKay [22] concluded that most corporations promised to adhere to the CDC's guidelines, and others willingly turned over their share of doses to hospitals that had insufficient vaccine supply.

At the beginning of the influenza season, the entire population is susceptible to the virus. Vaccination is the only method that ensures avoidance of death and infections. However, the limited number of vaccines that can be produced with available methods proofs to be practically impossible to vaccinate the entire population. Alternatively, selectively vaccinating a fraction of the population to quickly achieve herd immunity can minimize the probability of infection.

This study proposes an alternative methodology to help public-health decision-makers at CDC postpone vaccine demand of low-risk individuals so that those in more at-risk cohorts have preferential access to vaccines, while trying to minimize the total number of infections and deaths caused during an influenza season. Due to the limited supply of seasonal influenza vaccine available to the population, this study assumes that health care decision-makers need to persuade cautious individuals from the low-risk cohort to opt for vaccination later in the flu season. This study considers that without an intervention from authorities, such cautious individuals are likely to use vaccines that could be used early in the season to immunize people in high-risk cohorts [25].

The proposed methodology delays vaccination of low risk individuals, and prioritizes vaccination of high risk cohorts in the early stages of the influenza season. A deterministic disease spread model is developed to replicate the effect of the influenza virus on the US population when a vaccine strategy is implemented. Specifically, this study aims to answer whether the allocation of vaccines can be more

effective if distribution rules based on the cohorts' risk levels are strictly enforced for the duration of the season.

This study proposes a price discrimination strategy to optimally allocate vaccines among the US population.

The structure of this thesis is as follows. Chapter 1 presents a literature review regarding models for analyzing the spread of contagious diseases, Discrete Event-graph simulation, Revenue Management, and Price Discrimination, which will be used to in the model formulations of Chapter 2. Two modeling approaches are explored: a simulation model and a daily optimization model to minimize the number of infections and deaths in the population, focused on enforcing the recommendations by the ACIP.

Chapter 2 introduces two compartmental stage models of a disease transmission along with its corresponding parameters. The vaccination process is presented as a compartmental stage that is integrated within the disease spread models. All models' assumptions and limitations are also discussed.

Experimental results are presented in Chapter 3. Conclusions and future work are presented in Chapter 4.

Chapter I

Literature Review

This chapter presents background information on theories that will be used throughout this study. The first section considers different epidemiological methods that have been widely used to model contagious diseases. The second section describes the use of revenue management in industry in order to assess how it can be tied to the distribution of vaccines. The final section of the chapter surveys price discrimination and discusses two different approaches, price and quantity discrimination, along with an example of the application to the influenza case.

1.1 Modeling Contagious Diseases

The 'SIR' model is the most commonly used model for explaining the spread of infectious diseases. The acronym SIR describes the different health states that an individual undergoes through an infection. Thus, in this model, an initially Susceptible (*S*) individual may become Infectious (*I*) when he or she contacts an already infected individual, and the infected individual becomes Recovered (*R*) when he or she is not infectious anymore [26]. Gani and Leach [27] incorporate two infectious stages, instead of one, as an extension of the basic SIR model. The first of such stages corresponds to an asymptomatic but contagious state; and the second one corresponds to an infectious and symptomatic stage. The modified SIR has been used to analyze the effect of social distancing (voluntary or policy-induced), which reduces the contact rate of the individuals that are diagnosed with the particular disease [14, 18, 27, 28].

Other extensions to the SIR model include alternatives to the recovery stage, which are typically used to consider highly infectious diseases [28, 29]. Modeling vaccine effects to a disease transmission

becomes crucial when establishing policies in the case of pandemics. Along with the recovery state, in which patients get healthy and acquire immunity, Cahill et al. [8], for example, adds a stage in which patients are vaccinated. He uses a differential equation approach to analyze the effect of vaccines introduced to a system, and evaluates their efficacy within it.

The transmission of an infectious diseases requires that a susceptible individual comes into contact with an infected one [30]. Such encounters are usually modeled by estimating the average number of contacts that a person may have on a particular day with infectious individuals. This contact rate assumes that the entire population is homogenous and everyone in the population has the same probability of being infected [8, 31]. While this approach has been validated when modeling the behavior of animals, heterogeneous models are preferred for human modeling because they are able to better explain the disease transmission among diverse populations and therefore yield more realistic results [32, 33].

Hethcote [34] claims that the population cohorts may be determined based on disease-related characteristics or on population-specific factors; i.e., heterogeneous groupings. Wallinga, Teunis and Kretzchmar [33] have shown through a survey study that individuals' behavior change based on their age groups and, therefore, their contact rate will be altered accordingly, and that the highest contact rate from any cohort occurs among individuals in the same age group [35]. More specifically, Stroud et al. [29] consider the differences among different groups of people –preschool, youth, adult and senior– when modeling pandemic influenza.

Ekici, Keskinocak and Swann [36] classify disease spread modeling into four groups based on their solution methodology. This study focuses on the use of discrete event and agent based simulations because both of them allow for the optimization of complex models and stochastic modeling. The other two methods, differential equations and random graphs, present significant drawbacks for the purpose of this study, such as the use of continuous modeling of time or the creation of a detailed network that have nevertheless proven useful for localized, small scale simulation [13, 37].

Revenue Management theory is briefly described in the following section.

1.2 Revenue Management

Revenue Management is loosely defined as a set of tools that companies use to optimize revenue by adjusting their supply given the demand of differentiated sets of customers [38]. The term is also used interchangeably with *yield management* [39] and can be summarized as "selling the right product to the right customer at the right time" [40].

The airline industry was first to implement Revenue Management to have more control over its reservation systems. The initial use of revenue management occurred in the 70s when some airlines began to offer different prices for passengers traveling in the same aircraft, based on early purchase decision. For the airlines, the problem was how to determine the number of seats to make available to different customer segments. In 1972, Littlewood [41] provided the solution to the problem. He stated that for a two class system, given that their demand distributions are known, no more products should be sold at a low price when selling them at a higher price yields higher expected revenue.

The main barrier to implement revenue management came down in 1978 when the airline industry was deregulated, allowing airlines to freely set their own seat prices [42]. American Airlines was the first to successfully implement Littlewood's rule in 1985 [43]. Later, in 1987, Belobaba developed the theory behind Expected Marginal Seat Revenue, which is frequently cited as one of the triggers for the popularity of revenue management [40, 44]. It is used to determine the optimal number of items that should be reserved for a particular cohort, so that revenue is maximized by applying concepts from Littlewood's rule [45].

The influenza vaccine market exhibits characteristics that favor the implementation of Revenue Management theory. First, vaccine supply is limited and expanding production capacity is expensive and physically constrained by the current availability of eggs used for vaccine development. Second, vaccine doses are perishable and cannot be stored over multiple seasons, because flu strain viruses vary from year to year. Third, the vaccine market is segmented having population cohorts with difference Willingness To

Pay (WTP). Such WTP can result from different likelihoods of infection and complications particular to each cohort, as defined by the ACIP [38-40, 46].

1.3 Price Discrimination

Price discrimination is commonly practiced by multiple industries, such as the airline or hotel industry, and even universities [47]. The main objective of price discrimination is to increase revenue by charging some consumers more than others [47]. Steinberg and Weisbrod [48] claim that in the case of nonprofit institutions, price discrimination arises out of the need to cover their costs and reach distribution and service levels goals, which is commonly observed when the price must be set below marginal cost, even zero.

According to Norman [49] there are three degrees of price discrimination. The first one, referred as "perfect" price discrimination, maximizes the firm's profit by charging the highest price the customer is willing to pay for every unit sold. It is almost exclusively applied through bargaining due to the difficulty of determining the WTP for each customer. The second degree price discrimination allows the customer to select among a set of choices that best fit the customers' preference. The last degree, also called market segmentation is the most common in the field of revenue management. Here, the seller divides the market into identifiable consumer groups who are charged a different price per unit [45, 49, 50].

Talluri and Van Ryzin [45] describe the essential features for any degree of price discrimination to be applicable. First, there has to be heterogeneity in customer preferences, as reflected by their willingness to pay. In the case of vaccines, the ACIP determines appropriate segmentation by risk group. The second condition is the inability of customers to purchase a product and then to resell it to other customers with higher willingness to pay for the item. In the case of vaccines, it is not feasible that a final user will resale the vaccines he/she has purchased, since vaccines are injected at the time of purchase. Finally, the last condition is the presence of market power which requires the companies to be able to dictate the market

price. In economic theory, market power takes place when the product is sufficiently different from others in the market and the price can be determined by the seller due to the lack of competition in the market. Therefore, a market governed by a monopoly or oligopoly is a clear example where the seller has market power [45]. The vaccine market has few manufacturers that satisfy all the market's needs, thus resulting into an oligopolistic market [51]. Additionally, almost 50% of the vaccine supply in the United States is purchased by the government, which allows for high price control.

Revenue Management theory presents two main methods to manipulate the demand of a single resource: price-based and quantity-based discrimination.

Price-based discrimination requires the identification of demand curves for each of the distinctly identified groups. In Economics, an indifference curve models an individual's tradeoff between two products [52]. A correlation between health and price of vaccines can be easily justified. For example, Maciosek et al. [53] estimated the savings due to vaccination based on the gains of QALYs measured by interpreting a gain in revenue as a reduction in the probability of infection among the population thus establishing a link between vaccine prices and the health of the population. When setting a price for any product, optimal pricing strategies recommend price changes at every time period if there are no pricing constraints in place [54]. While the rise of e-commerce has enabled firms to dynamically change prices [38], Gallego and van Ryzin [55] demonstrated that when limiting the number of price changes, namely to one, the solution to revenue management pricing problems is asymptotically optimal as long as the number of items is large and there is enough time to sell them. Similarly, Feng and Gallego [56] find the optimal time span for promotions to last and thus corroborate the previously stated finding.

Alternatively, quantity-based discrimination uses the concept of *allotment* to reserve a certain amount of product for a particular group of customers. The use of allotment merely sets supply for each market segment to a fixed value. One of the drawbacks of allotment is that if there is an opportunity to sell an item to a segment that is willing to pay a higher price when that particular segment has reached the allotted quantity, it will be rejected because there is only space available in the lower class.

The origins of revenue management are usually attributed to Kenneth Littlewood who introduced the probability-based two-class decision rule, nowadays known as Littlewood's Rule [38]. However, this formulation carries some important assumptions which are explained in depth by Talluri and van Ryzin [45].

In the case of influenza, the ACIP divides the US population into two distinct groups, based on their risk of becoming infected and their likelihood of complications [20]. Therefore, we propose a two-class problem as the best applicable approach to model the current seasonal influenza vaccination process.

In this study, the two-class problem considers that one class pays a discounted price p_d and that the other one pays full price $p_f > p_d > 0$. The main question that needs to be answered is what these prices are. If the prices are too high then not all vaccines may be sold. If the prices are set too low, then it is not guaranteed that the vaccines will be distributed to the intended population cohort. Thus, setting adequate prices is essential to regulate the probability of infection based on the interactions between cohorts.

Chapter II

Methodology

This study extends the disease spread model proposed by Larson [18] to allow for a wider array of cohorts and more opportunities for interaction among members of such cohorts. Furthermore, this thesis studies the effect of preferential vaccination for more risky population cohorts in order to effectively allocate vaccines to different cohorts when needed, by changing vaccine prices through an optimization mechanism. This mechanism maximizes vaccine availability for the high-risk cohorts.

Two approaches are proposed to model the progression of influenza among the population. The first one tracks the spread of the disease over the different cohorts by capturing the effect that vaccine pricing has on the number of susceptible individuals in a population, and hence, its effect on the disease's transmission rates. The model includes an optimization method that determines the fractions of each population cohort that are willing to receive vaccination at every time period, given a particular vaccine price. The proposed optimization method aims to minimize the overall number of infections and deaths occurred during an influenza season, in order to achieve a condition where $R_0 \leq 1$ is induced at the earliest possible time by dynamically adjusting the vaccine price per dose for each risk group.

The second approach uses a Monte Carlo agent-based simulation approach, which simulates the behavior of each individual in the population by introducing stochastic parameters. The pricing strategy can be guided towards optimality by adjusting the prices at every time period, however, the simulation of each time period has to be re-ran after every adjustment. Therefore, this approach is reduced to trial-and-error, which becomes very resource intensive. It is important to note that both approaches are modeled based on the same structure.

Section 2.1describes the different stages of seasonal influenza. The parameters, nomenclature and the formulas that govern the transition between stages are described in Section 2.2. Sections 2.3 and 2.4, describe each of the discrete event simulation and agent-based simulation, respectively. Finally, the models' assumptions are presented in section 2.5.

2.1 Disease Transmission Model

The disease transmission model used in this study is as an expansion of the Larson's model, which is, in turn, and expansion of the traditional SIR model with seven possible states: Susceptible (S), Exposed (E), Infectious Asymptomatic (A), Infectious Symptomatic (I), Deceased (D), Vaccinated (V) and Recovered (R). Figure 1 illustrates the transition between these states.

At the beginning of an influenza cycle, the entire population is susceptible to the seasonal influenza virus. It is only then, that a small group of people starts the infection spread. Once the infected population becomes contagious, commonly referred to as *shedding*, they mix with the s*usceptible* population and infect them. Thus, a recently infected individual will go from *susceptible* one day to *exposed* the following day, during which the individual is carrying the virus but is neither aware of it nor shedding. Normally, this period is followed by either an *infectious asymptomatic* state or an *infectious symptomatic* one. During the *asymptomatic* state, the individual may infect others but present no symptoms, while the *symptomatic* state shows signs of the disease and the individual may also infect others.

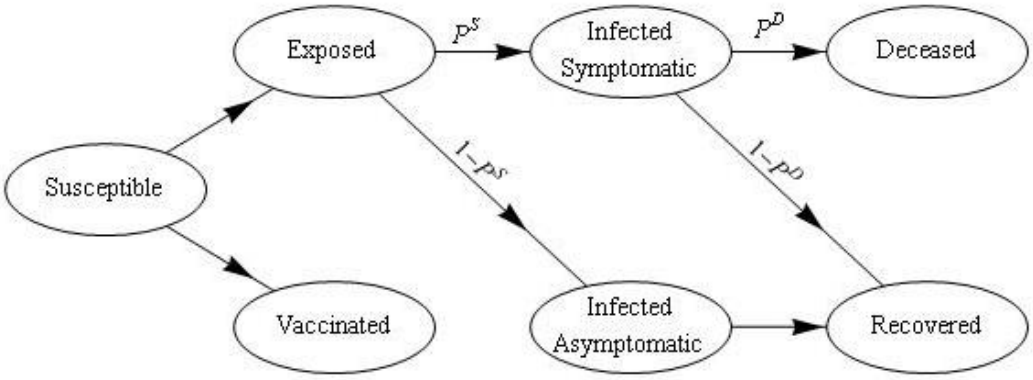

Figure 1: State Transition Diagram

The number of people who become infected by each new infected individual is a function of the number of contacts the person has during states (A) and (I), and the probability of infection. It is commonly assumed that an infectious symptomatic person undergoes a voluntary isolation [19, 57] until he or she recovers, which results in a reduction of the contact rate with susceptible individuals in the population. While isolation is not a state in the progression of the disease, it is modeled as part of the symptomatic state by reducing the number of contacts by a constant factor.

The transition into recovery from the infectious symptomatic state depends on the probability of recovery and the development of natural immunity against the virus. Additionally, to capture the effect of immunization, the proposed disease transmission model considers that immunity is also developed through vaccination. This study considers that the number of people who get vaccinated at a given point in time depends on the number of vaccines available and on the number of people willing and able to purchase a vaccine dose at the current given price. Finally, if an infected patient does not recover, his or her symptoms may worsen, which can lead to death.

The following section describes the parameters used for the experimental case being modeled.

2.2 Disease Spread Model

Models discussed in sections 2.3 and 2.4 use the following nomenclature to describe the behavior of the disease, the population, and the interaction between individuals during disease transmission.

2.2.1 Nomenclature

The following parameters are used to define the spread of the disease for the models presented in Sections 2.3 and 2.4.

$N_{i,k}(t)$ = population from cohort i in state k during time period t.

$\lambda_{i,j,r}$ = rate of contact of a person in cohort i with a person in cohort j, in r different settings where individuals i and j can meet.

$p_{i,j,r}$ = probability that a susceptible person from cohort i, given contact with an infected, contagious person from cohort j, becomes infected in setting r.

p^{D}_{i} = probability that an infected person from cohort i dies due to influenza.

Therefore, the probability that in period t a person in cohort i is in contact with an infectious individual is given by the fraction of contacts from the entire population that are infectious, and it is given by

$$\beta_{i,j,r}(t) = \frac{\sum_{k\in\{A,I\}} N_{i,k}(t) * \lambda_{i,j,r}}{\sum_{k/D} N_{i,k}(t) * \lambda_{i,j,r}} \qquad (1)$$

The probability of infection of a susceptible individual of cohort i in period t depends on the daily behavior of the individual and his or her susceptibility to the virus. Assuming Poisson-distributed interactions with means $\lambda_{i,j,r}$ and a probability of contact $\beta_{i,j,r}(t)$, the probability of infection of an individual from cohort i in period t is given by

$$P^I_i(t) = \sum_j \sum_r 1 - e^{-\lambda_{i,j,r} \bullet \beta_{j,i,r}(t) \bullet p_{i,j,r}} \qquad (2)$$

VS(t) = number of available vaccines during time period t

P^S = probability of any individual to develop symptoms after the incubation period.

P^Q = probability that any individual, given the development of symptoms, will enter into a voluntary quarantine.

The detailed model is shown on Figure 2 and includes all expressions used to describe state transitions. In particular, the population parameters include a time shift, which is related to the duration of the state for a disease. The parameters used in Figure 2 correspond to the seasonal flu and will be described in more detail in Chapter III.

The next section describes decision variable and the rationale behind it.

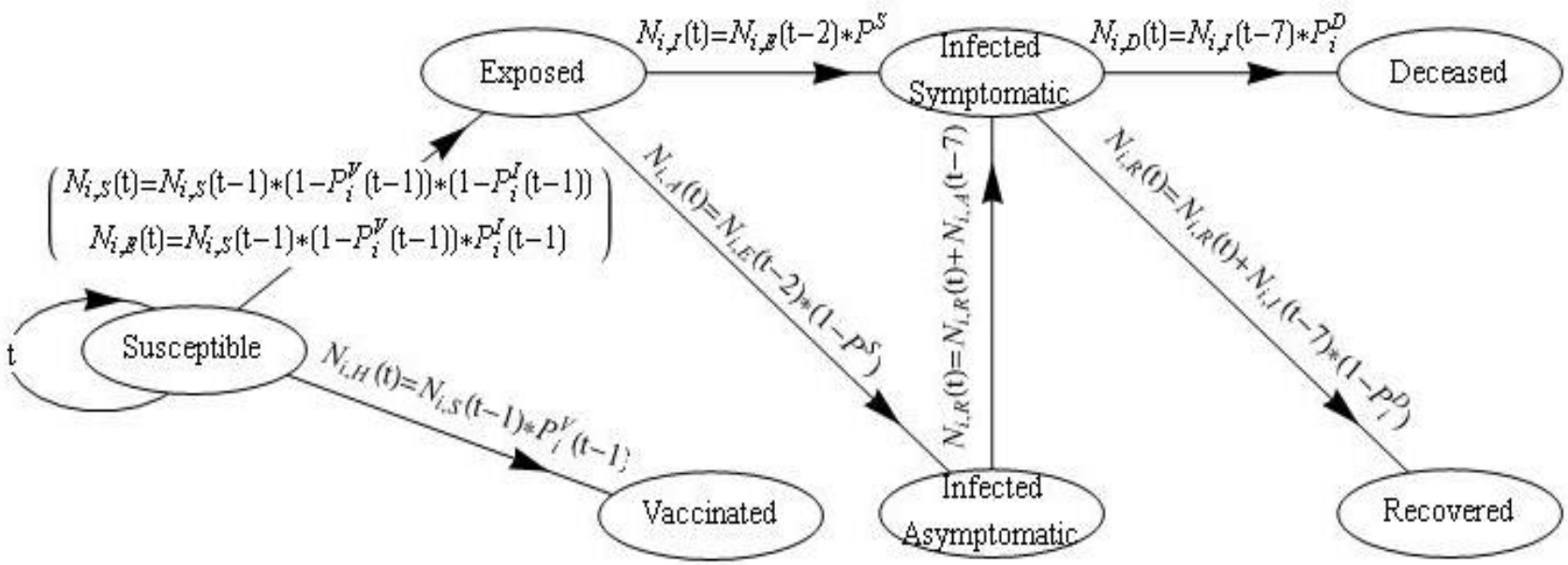

Figure 2: State transition diagram with duration of states for seasonal influenz

2.2.2 Decision Variable

The probability of an individual purchasing a vaccine is proportional to the number of people in the population that are willing and able to get vaccinated. Since this pricing model does not strictly exclude anybody from getting a vaccine –it only discourages people from early purchase—, all susceptible individuals and those unaware of having contracted the disease would be eligible for vaccination. It is assumed that anyone who has contracted the disease would develop natural immunity and, thus, not need the vaccine anymore.

In economic theory, it is commonly assumed that the willingness to pay (WTP) of each individual is known and that it can be used to price discriminate [48]. The addition of the WTP of each individual derives the market demand curve $q = d(p)$ or the demand curve for any group i of individuals $q_i = d(p_i)$, where $q = \sum_{i=1}^{n} q_i$ [49], p represents a price set on the market and q the corresponding units of the product sold at that price. The demand function can also be represented by a cumulative distribution where Q(p) indicates the percentile of the market population that is willing to pay price p for an item. Thus $d(p) = N \times Q(p)$, where N represents the total initial population [45].

Therefore, the term described below is used as a decision variable for the optimization model and as a parameter for the agent-based simulation, which is changed for every setting simulated.

$Q_i(p_i(t))$ = percentile of the population in cohort i that can get vaccinated during time t when faced with price p_i.

For ease of notation $Q_i(t) = Q_i(p_i(t))$, which is used indirectly for the optimization model in the objective function as shown by Equation (3)

$$P^{V}_{i}(t) = \frac{Q_i(t) * VS(t)}{\sum_{k \in \{S,E,A\}} \sum_i N_{i,k}(t) * Q_i(t)} \quad (3)$$

where,

$P^{V}_{i}(t)$ = probability of vaccination of a person from cohort *i* during time period *t*.

In general, given that only high-risk (H) and low-risk (L) groups of cohorts are distinguished, only one variable per risk group is defined, even if multiple cohorts belong to such group.

$$0 \leq Q_H\ t\ \leq 1, 0 \leq\ Q_L\ t\ \leq 1 \quad (4)$$

Equation (4) indicates the range of values that the variables may take. Since they represent percentiles, they have to be between zero and one, where a percentile of 0 results from prices sufficiently high that nobody in the cohort is willing to purchase the vaccine at that time period. Conversely, a value of one represents a low enough price that everybody is willing to purchase the vaccine at time *t*.

$$T^V(t) = \sum_{i \in H,L} Q_i(t) * \sum_{k \in \{S,E,A\}} N_{i,k}(t) \quad (5)$$

$$f^V = Max\left[1, \frac{QS(t)}{T^V(t)}\right] \quad (6)$$

$T^{V}(t)$ represents the number of individuals willing and able to get a vaccine during time *t*. Since only two risk groups are defined, it is assumed that the percentiles for all cohorts belonging to the risk group have the same percentile. Equation (6) shows the fraction of the population f^V

that will receive vaccination. Thus, the probability of vaccination for an individual in cohort *i* may be rewritten as depicted on Equation (7).

$$P^{V}_{i}(t) = Q_i(t) * f^{V}(t) \quad (7)$$

2.3 Optimization Model

The goal of introducing vaccination and other control strategies is to mitigate the spread of seasonal influenza among the population. R_0 measure models the number of secondary infections on a daily basis. Thus, by minimizing the value of R_0 over time, the influenza will have the least impact on the population. A similar approach has been previously studied by Tennenbaum [58], where he considers four cohorts defined by their risk and activity level and solves the formulation by using differential equations to minimize the value of R_0.

$$F = R_0(t) = \frac{\sum_{k \in E} \sum_i N_{i,k}(t+1)}{\sum_{k \in \{A,I\}} \sum_i N_{i,k}(t)} \quad (8)$$

Equation (8) provides an expression for R_0 at each period *t* that is minimized at every time-period during the duration of the influenza season. Figure 2 shows that the exposed state is related to the decision variable by Equation (9), where $P^{V}_{i}(t)$ is a function of the decision variable as described by Equation (7).

$$N_{i,E}(t+1) = N_{i,S}(t) * (1 - P_i^V(t)) * P_i^I(t) \quad (9)$$

This approach will promise more accessible vaccines to individuals in high-risk cohorts as defined by the ACIP, i.e. high-risk individuals have a higher probability of becoming infected, infecting others, and experiencing complications. Meltzer [21] calculates that fifteen percent of the population included in the highest risk cohort for influenza infection are children, who account for 4/5 of the total number of infections.

For every time period, the formulas are defined recursively with respect to the percentile variable for the current time period. Then, the minimum for the objective function is found using the *NMinimize* function from Mathematica, which determines the best approach to solve the proposed problem based on its structure. The solution to the resulting problem is used as input for the next period iteration. The process is repeated until the number of infected people or the number of susceptible people falls below one.

The next section presents the agent-based simulation logic used to represent the stochastic version of the same problem.

2.4 Agent-Based Simulation

The models from Chapter II assume a completely random mixing between individuals, allowing a person to interact with any other person based on the probability of interaction. The infectious process focuses on determining the population proportions to determine the rate of infection. This characteristic gives this model the attribute of a 'true' mass-action system as defined by de Jong et al. [59], which indicates that "the contact rate increases linearly with population density, but is independent of the total physical area, hence, of the total population size". The concept derived from the kinetics of chemical reaction holds true when the density of individuals in an area is not too high [60].

The assumptions of true mass-action indicate that as long as population proportions remain the same, all other parameters do not need to be modified to accommodate a change in population size as long as the population density for the identified region does not vary much as long as the population density remains relatively the same, all other problem parameters do not need to be modified to accommodate a change in population size. Similarly, the seed population to initiate infection should be also adjusted to reflect the proportion.

The Monte Carlo simulation experiment for modeling the spread of the disease under the effect of vaccination at different price levels uses discrete time and a reduced population size to ease the computation time. The steps involved in this experiment are described next.

The model tracks the behavior of each individual within the population, simulating their interaction. The number of contacts for each individual is generated from a random number. If the interaction is between a susceptible and a shedding individual, an infection may occur. The state of each individual is also monitored to determine the overall probability of infection and, if infected, the individual's progression through the different stages of the disease. Similarly, randomly, it is determined whether the individual develops symptoms or if she recovers from the disease.

The pseudocode for the simulation is as follows:

1. Initialize data – generate each agent and enough seeds for vaccination to begin
2. For every day *t*
    a. Randomly allocate vaccines to cohorts based on population proportions
        i. Randomly assign allocated vaccines to individuals within each cohort
    b. For every individual *n*
        i. Randomly generate –using a Poisson distribution— the number of contacts each individual will have with individuals of other cohorts

1. Update β based on the number of infectious and non-infectious from the randomly generated numbers

c. For every individual *n*

i. If individual is susceptible

1. For every contact *c*

a. Randomly determine if the contact was with an infectious individual based on probability β

b. If infectious contact

i. Randomly determine if the person got infected based on the probability of infection

ii. Else if individual is in last day of incubation

1. Randomly determine the next stage in the disease progression based on the probability of becoming symptomatic

iii. Else if individual is in last day of symptomatic state

1. Randomly determine if the individual recovers or dies

iv. Else

1. Determine the next state in the progression of the disease

2.5 Models Assumptions and Limitations

Given that influenza is modeled within a 180-day period [57], for the sake of simplicity, the model assumes that no major changes in the population occur as a consequence of its relatively short duration. Thus, births and deaths are not considered in the models presented in Sections 2.3 and 2.4. However, if needed, births could be added as a periodic increase in the susceptible population

of the youngest cohort. Likewise, since the effect of deaths due to other diseases is not considered, it may be modeled as a similar decrease in the size of each of the cohorts.

The models described in Sections 2.3 and 2.4 do not capture geographical distribution of the population and it does not account for traveling between locations. The models are not concerned with how the disease spreads between major population hubs and smaller cities, or across the country.

Other mitigation strategies, such as school closures could be considered in the model. The results of this type of policy may be implemented by defining one of the settings in the average daily contacts matrix so that it corresponds to a school.

Hospitalization can be modeled by adding an extra stage in the transmission model. Additional parameters are needed to describe the behavior of the individuals within the hospital, the probability of getting better or worsening, as well as the likelihood of transmission.

It is also assumed that one single vaccine provides perfect protection to an individual [58]. Modeling the need for a second vaccine can be accomplished by introducing a state for those individuals that have received one vaccine but not the second. Reducing the effect of the vaccine can be done by reducing the probability of infection for the people that have been vaccinated, which allows them to still become infected but at a reduced rate. Other methods of prevention such as Targeted Antiviral Prophylaxis (TAP) are deemed inaccurate, labor-intensive, and possibly only effective during the first stages of an outbreak [57]. For this reason, they are not introduced into the model.

Chapter III

Analysis

The purpose of this chapter is to describe an instance of parameters [19, 57, 61-63] that will be applied to model 2.3. The results will be tested against existing literature that uses similar modeling parameters. Section 3.1 describes features of the influenza and the population. Section 3.2 describes the experiments, followed by the results on Section 3.3.

3.1 Model Parameters

Clinical trials have been used to study the behavior of the influenza virus in humans and tried to determine its effect among different groups, commonly aged 0-5 years, 5-9 years, 10-14 years, 15-18 years, 19-64 years, and >65 years [64, 65]. Lee et al. [19] and Germann et al. [57] show that, once infected, the incubation period has an average length of two days. When the individual begins shedding, there is a 33% chance that he or she does not present symptoms. Therefore, this person is assumed to be half as likely to infect a susceptible individual than a symptomatic one [57]. Those that show symptoms are likely to enter voluntary isolation. A common assumption is that the population will be 50% compliant with such isolation [19, 57]. This means that half of the populations with symptoms will go to work or school while sick. Those that begin isolation are assumed to have no contact with people outside their household [66]. The average infection period has been found to be seven days, after which symptomatic individuals either recover or die [19, 65, 67]. We assume that those that do not develop symptoms fully recover and achieve natural immunity.

Population numbers from the U.S. Census Bureau [63] indicate that 6.8% of the population is <5 years of age, 7.3% is in the 5-9 age group, 7.3% is in the 10-14 age group, 7.2% are 15-18 years old, 59% of the population are adults aged 19-64, and 12.4% are >65 years. These numbers closely follow the work from Longini et al. [61].

This study assumes that the supply of seasonal vaccines is similar to that of the 2009 H1N1 pandemic, where 91 million vaccines were available to the U.S. population. It is important to note that the current amount of seasonal flu vaccine can only cover up to 30% of the total population [4]. The stockpile of vaccines is commonly released in large quantities throughout the duration of the infection. The model presented in this section uses the probability for the next batch of vaccines to be released on any given day.

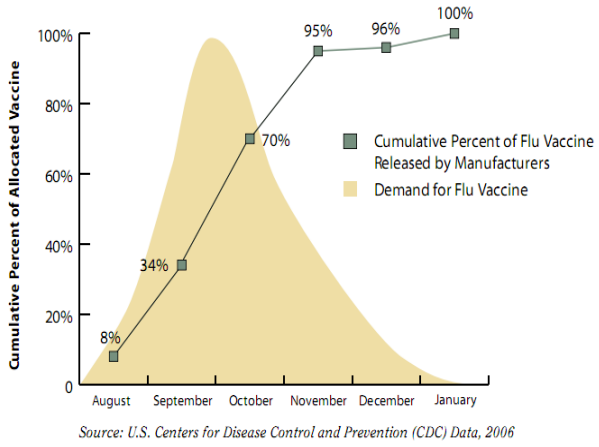

Figure 3: Sample vaccine supply curve for 2005 [68]

Based on previously CDC reported dates of distribution for influenza vaccines [68], this study suggests an equation that describes the monthly vaccine availability. This study fits a curve to the presented vaccine distribution from Figure 3 to describe a daily availability. The fitted curve keeps the number of monthly distributed vaccines equal to the data presented from previous years but

spread over all days of the month, while keeping the trend of vaccine arrival. Thus, following the data from Figure 3, 8% of the vaccines will have arrived by the end of the first month, 34% by the end of the second, and so on.

The model developed to describe the spread of the disease is described in the next section.

3.1.1 Population Interaction Parameters

The input required by both models is similar to that presented by Lee et al. [19], Germann et al. [57] and Longini et al. [61]. These authors, ran an agent-based simulation study on the proportion of the working population that need to be vaccinated to mitigate a pandemic, a simulation study based on community interactions to test the effect of combinations of intervention strategies, and an agent-based simulation study to determine the effect of targeted vaccination distribution techniques, respectively. We use population proportions for each cohort as given by the U.S. Census of the year 2000, which are presented on Table 1**Error! Reference source not found.** [63].

Cohort	Age Group	Population (%)	Category
1	0-5	6.8	Pre-school
2	5-9	7.3	Elementary School
3	10-14	7.3	Middle School
4	14-18	7.2	High School
5	19-64	59.0	Adult
	19-24	6.8	Adult
	25-44	30.2	Adult
	45-64	22.0	Adult
6	>65	12.4	Adult

Table 1: Population proportion by cohorts

We model the behavior of the population based on the average number of contacts they have with individuals from different cohorts, as seen on Table 2. The agent-based simulation generates a random number from a Poisson distribution using the mean daily contacts to generate the number of contacts each individual will have with every cohort. The optimization model feeds the average number of contacts into an equation to calculate the expected number of contacts with each cohort and estimate the likelihood that an infected individual will meet a susceptible one. In Table 1, cohorts 1-4 are represented by the 'Student' label; cohorts 5 and 6 are represented by the 'Adult' label on Table 2. The models do not differentiate between days of the week. Therefore, all weekly activities, such as Classroom, School (not classroom), and Workplace are multiplied by the number weekdays in a week (0.71). Conversely, the Weekend setting is reduced by the ratio of weekend days in a week, namely 0.29. All other setting values are described below.

Setting	Participant 1	Participant 2	Mean Daily Contacts
Classroom	Student	Student	13.5
School (not classroom)	Student	Student	15
Community	Student	Student	16.2
Weekend	Student	Student	24.3
Workplace	Adult	Adult	10
Community	All	All	32.4
Household	Student	Adult	2
Household	Student	Student	1
Household	Adult	Adult	1

Table 2: Population Mixing Parameter

A corresponding metric is based on the probability of infection given the contact between an individual that is shedding and a susceptible one. This parameter depends on who the infected individual is and his or her relation with the susceptible person. Table 3 shows the values used for the parameter in which the row label indicates the location where the infected individual from the indicated cohort becomes in contact with a susceptible one. The same labeling as Table 2 holds true for Table 3 below.

		Susceptible Cohort				
		Children				Adults
Location	Infectious Cohort	Preschool	Elementary School	Middle School	High School	
Large day-care centers	1	0.04				
Elementary School	2		0.0435			
Middle School	3			0.0375		
High School	4				0.0315	
Family						
Student	1-4	0.6	0.6	0.6	0.6	0.3
Adult	5-6	0.3	0.3	0.3	0.3	0.4
Workplace	5					0.0575
Community	1-6	0.00255	0.00255	0.00255	0.00255	0.0048

Table 3: Probability of transmission given an infectious contact

Figure 4 displays the smoothed curve representing a daily distribution and availability of vaccines. Both models are assumed to start with enough initial infected individuals among the population so that during the first day of the simulation, the population may be vaccinated. This model assumes that an individual from a particular cohort will purchase a vaccine with a probability that is proportional to the total number of individuals willing and able to pay for a vaccine.

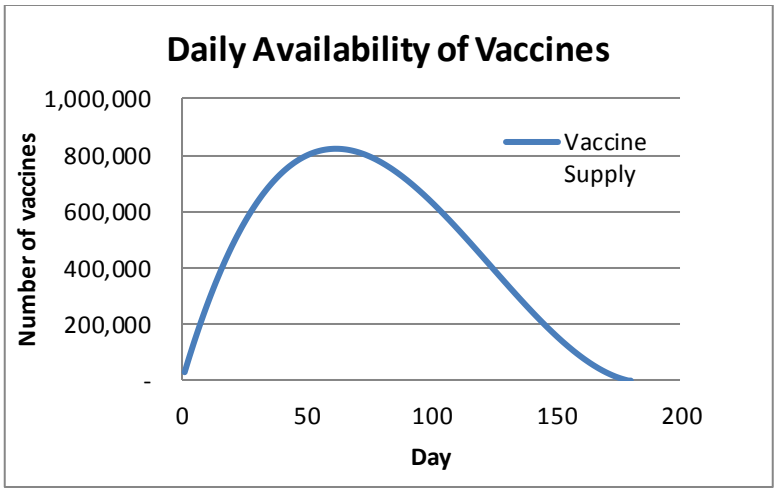

Figure 4: Assumed daily availability of vaccines

3.2 Experimentation

The models were implemented in Mathematica 7.0 at The RIT's Research Computing center. The purpose of the experiment is to determine if there are any additional gains that may be obtained by imposing a price discrimination scheme, when compared to a scenario where, depending on vaccine availability, all individuals are equally likely to get vaccinated.

Three particular models are used for experimentation. The first one, baseline experiment, assumes that no vaccines are available for the population. Therefore, the only way to get immunity to the virus is through recovery from the disease. This model is used to determine the actual effect of the disease on the population.

The second experiment assumes that vaccines are available, in accordance with Figure 4. However, this experiment assumes that vaccines are distributed throughout the population at no cost to the individual, i.e. without consideration for priority. This model allows calculating the effect of vaccination when compared to the baseline model. This model closely follows the

behavior of the population in the United States during the influenza season, where there are no price differences for cohorts. For validation, this experiment assumes that the ACIP priority, to first vaccinate individuals in high-risk cohorts, is not followed. This experiment's results are then compared against Lee's base model for validation.

In the third experiment a percentile is calculated to offset the demand of vaccines from low-risk cohorts, as described in Section 2.3. This model, when compared with the second one, allows estimating the gains from the introduction of price discrimination, thus enforcing the ACIP prioritization.

The results from the experiments run are compared in the next section.

3.3 Results

The effectiveness of the model can be shown by the decrease in the total number of infections and deaths. Table 4 presents the results from the optimization model and compares them to the two other scenarios.

Scenario	Pandemic Length (periods)	Total Infections (% population)	Total Deaths (individuals)
Model 1: No Vaccination	96	34.9%	144,582
Model 2: Free Vaccination	124	31.1%	128,499
Model 3: Priced Vaccination	123	27.4%	113,472

Table 4: Summary of results

The scenario with no vaccination shows the highest spread of the disease within the population but, in this case, the disease got under control the fastest. The majority of the population got infected and, thus, the control comes from natural immunity. The model where there is no preference in vaccination and the one we proposed in this thesis were contained in the same time. The percentage of infections and deaths under no price discrimination closely follows Lee's results. However, by better allocating the vaccines through price discrimination, the number of infections and deaths was reduced by 12%.

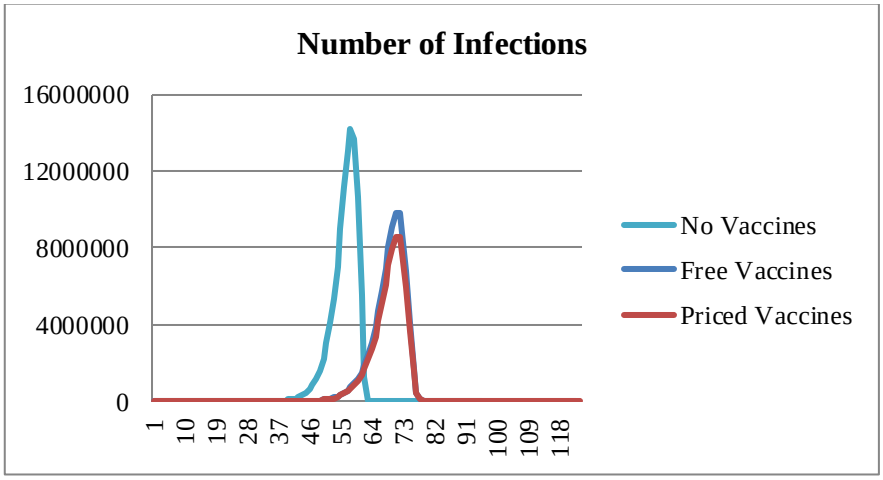

Figure 5: Spread of the disease over time

It can be noted, from Figure 5, that the infection spreads through the population at a faster rate when no vaccination is used. The peak of the disease also happens earlier than when countermeasures are presented.

On Figure 6 some interesting points can be observed. At Point A, the tradeoff for vaccination is noticed, when the value of R_0 starts rising. Here, the percentile of the high-risk population starts receiving preferential vaccination and the rise of R_0 is attenuated. Similarly, when the basic

reproduction number goes below one, at Point B, it is assumed that herd immunity is achieved [69]. This happens because most of the infections are caused by the high-risk group. At this moment, vaccines become available to the low risk population, at Point C, which still has some risk of infection. When the R_0 value tapers off, the model finds that there is no difference to allocate vaccines to any one particular group as seen at the end of the graph, at Point D.

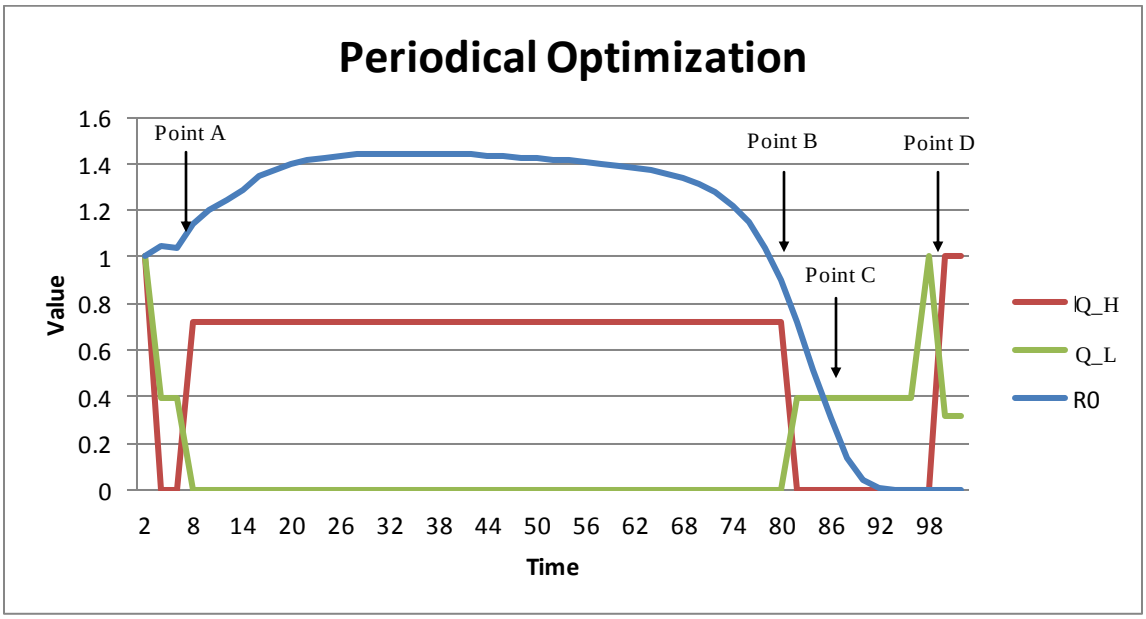

Figure 6: Relationship between R_0, Q_H and Q_L over time

Conclusions

Policy makers are constantly looking for strong evidence of effectively mitigating the spread of infectious disease. The 2009 influenza season revealed discrepancies regarding the distribution of the vaccines to people of different risk groups. Some vaccination clinics strictly enforced the recommendations from the ACIP, while others administered the vaccine at normal cost to the entire population.

This study presented two models that allow simulating the spread of a disease in a heterogeneous population setting. The model has been validated against another study and an appropriate vaccination process was introduced to the model.

An innovative approach for optimal allocation of vaccines was developed to determine appropriate vaccine distribution among different cohorts. With the given set of experimental conditions, the results clearly demonstrate a significant potential for the prevention of infections and deaths by temporarily enforcing the vaccination of high-risk individuals by postponing vaccination of those with lower risks. However, further research modeling various conditions is needed to generalize the results. Through pricing control the option of vaccination is not stripped away from the population but rather discouraged through price discrimination.

A price-discrimination policy can be enforced through cooperation with insurance companies or as a discount in pricing at the vaccination clinics. Either way, government subsidy is still heavily required to control the oligopoly of vaccines, which is also a requirement for implementing Revenue Management.

Pricing strategies particular to Revenue Management give the option of either establishing an optimal price to defer vaccination in low-risk cohorts or setting a quantity limit for each risk

group. The optimal value of either approach can be easily derived from a cumulative demand curve through the percentile approach presented.

A possible estimation for determining a demand curve is presented in the appendix section. Demand for vaccines is also estimated yearly by the CDC, which can be used to better approximate the demand curve. Further, studies should be run to better understand the effect of vaccine pricing over the duration of the disease.

Future Work

The expansion of this model makes it possible to use with other diseases since its structure is very flexible and it allows for ease of implementation with other types of pandemics. A model where the parameters and constraints can be adjusted to simulate the effects of a different disease may also be developed as it has been shown that population size minimally affects its design.

A more user-friendly environment can be helpful to promote its use and study. Through a well-designed user interface, other policies could be implemented and tested. As it was shown, the current model can accommodate other mitigation strategies such as school closures.

Mathematica allows for the development of dynamic models that can be used to test single-price models, for example. The author of this thesis has developed a small model, but the computing intensity makes its use cumbersome. In this sense, some time can be spent improving the efficiency of the code to allow for an interactive model.

Further studies can be run to more accurately depict the consumer behavior in the case of a pandemic. The Lorenz Curve approximation may serve as an initial approach to develop demand curves for each risk group or cohort. As well, a survey can be conducted to study the reaction of the population to the altruistic idea of incurring a higher risk of infection for the better of the overall population.

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Appendices

A. An Idea on Demand Curve Estimation

In economic theory it is common to assume the WTP from each individual to be known and can be used to price discriminate [48]. In this study a possibility for modeling the cumulative demand curve is presented. Hansen, Formby and Smith [70] has previously demonstrated the use of the Lorenz Curve (LC) to determine the elasticity of the housing market. Similarly, it may be feasible to estimate the optimal reservation prices for the vaccine market.

Moothathu [71] suggests the use of a Pareto distribution to generate data and plot a Lorenz curve, which describes the distribution of wealth among a particular population. The US Census Bureau has published the Gini coefficient [72], which measures the inequality of wealth distribution and placed it around 0.42.

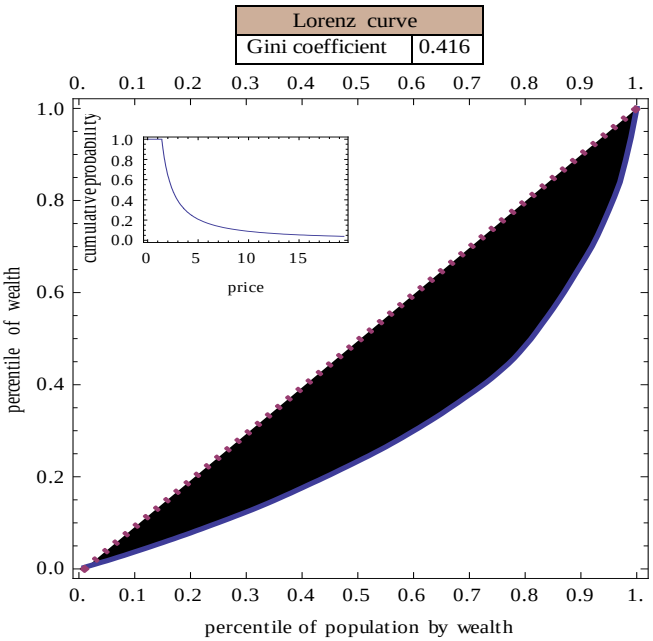

Figure 7: Wealth distribution in the United States

Figure 7 was derived with a Pareto distribution with parameters $k = 1.4$ and $\alpha = 1.23$. The graph presented on the top-left corner represents the assumed demand curve for the population. To simplify the example, we assume that all cohorts have the same cumulative probability distribution. The graph refers to the percent of the population (y-axis) that would be willing and able to purchase a vaccine dose at the set corresponding price (x-axis).