Simulation-based optimization of mitigation strategies for pandemic influenza.

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SIMULATION-BASED OPTIMIZATION OF MITIGATION STRATEGIES FOR PANDEMIC INFLUENZA

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DEDICATION

This dissertation is dedicated to

my wife, Sara, who is an angel on earth

and

my parents who are my heroes
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ABSTRACT

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Arsalan Paleshi

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Millions of people have been infected and died as results of influenza pandemics in human history. In order to prepare for these disasters, it is important to know how the disease spreads. Further, intervention strategies should be implemented during the pandemics to mitigate their ill effects. Knowledge of how these interventions will affect the pandemic course is paramount for decision makers. This study develops a simulation-based optimization model which aims at finding a combination of strategies that result in the best value for an objective function of defined metrics under a set of constraints. Also, a procedure is presented to solve the optimization model.

In particular, a simulation model for the spread of the influenza virus in case of a pandemic is presented that is based on the socio-demographic characteristics of the Jefferson County, KY. Then, School closure and home confinement are considered as the two intervention strategies that are investigated in this study and the simulation model is enhanced to incorporate the changes of the pandemic
course (e.g. the number of ill individuals during the pandemic period) as results of the establishment of different scenarios for the intervention strategies.

Finally, an optimization model is developed that its feasible region includes the feasible scenarios for establishment of intervention strategies (i.e. home confinement and school closure). The optimization model aims at finding an optimal combination of those two strategies to minimize the economic cost of the pandemic under a set of constraints on the control variables. Control variables include time, length of closure for schools, and the rate of home confinement of the individuals for home confinement strategy. This optimization model is connected to the pre-mentioned simulation model and is solved using a simulation-based optimization procedure called NSGS.

Where the results of the analysis show both home confinement and school closure strategies are effective in terms of the outputs of the model (e.g. number of illness cases during the pandemic), they show home confinement is a more cost effective one.
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CHAPTER I

INTRODUCTION

1.1. Motivation

Every year, millions of people are infected by influenza. As a result, some of them are hospitalized and/or die. Sometimes this virus affects communities on a worldwide scale and therefore infects a large proportion of the population in several countries. This situation is called pandemic influenza.

Three major influenza pandemics have occurred in recorded history. The first one, the infamous Spanish flu, occurred from 1918-20 and killed 40,000,000 people while infecting 200 million persons, which makes it the most disastrous pandemic influenza in history. The second pandemic, Asian flu, occurred during 1957 and 1958 and killed 68,900 people just in the United States. The third influenza pandemic, Hong Kong flu, occurred during 1968 and 1969 and 33,800 people died as a result in the US (Gatherer, 2009 and Hilleman, 2002).

The ill effects of pandemic influenza are not limited to mortalities; their economic costs are significant as well. These economic costs are a result of workforce absenteeism, interruption in school educational programs, and healthcare related costs, such as hospitalization of patients, and vaccination.
During the course of a pandemic influenza, healthcare systems encounter large flows of patients. As a result, there is typically a need for significant quantities of resources (e.g., beds, medicine). Healthcare systems are typically not able to support all patients. Developing emergency preparedness plans to manage the chaos during a pandemic is of great importance. Mitigation of the ill consequences of pandemic influenza can decrease the pressure on healthcare systems and the number of people infected during the course of a pandemic.

1.2. Problem Statement

Developing mitigation plans to decrease the spread of the disease can reduce the numbers of ill persons, mortalities and hospitalizations caused by the influenza pandemic. Intervention strategies such as school closure, and home confinement plans, can decrease the ill effects of a pandemic. In order to establish these intervention strategies in the case of a pandemic, their effects on the course of the pandemic need to be evaluated.

Researchers have developed various methods to reach this goal. These methods include the use of simulation models of the influenza pandemic outbreak. These models can also represent intervention strategies (e.g., school closure, home confinement, vaccination) to evaluate the effects of these strategies on the spread of the pandemic. Then, the output of the simulation models for the baseline scenario (i.e. without intervention strategies) and for the scenarios with intervention strategies can be compared.
Elveback et al. (1976) were among the first researchers to take this path to evaluate the intervention strategies and compare the effects of school closing and vaccination plans with each other and the baseline scenario. Ferguson et al. (2003), Longini et al. (2005a), Ferguson et al. (2006), Das et al. (2008), and Aleman et al. (2009) were some other studies that addressed this problem. Since these studies, other models have been developed and these models have become more detailed and consider more realistic socio-demographic characteristics of the targeted population.

The effectiveness of the intervention strategies can be evaluated with respect to performance measures, such as the numbers of ill, hospitalized, and dead persons. Also, by changing the values for some of control variables, the effects of the intervention strategies on the performance measures vary. For example, for a school closure strategy, the closure threshold (i.e., the maximum percentage of the students that can be ill on a particular day before the school is to be closed) and the length of closure are some of the control variables. Various combinations of the values for control variables result in different scenarios for the establishment of intervention strategies.

A literature review of research in this area shows that these studies usually consider a limited number of intervention scenarios, establish them and evaluate their effects on the number of infected or ill people during a pandemic. For example, for school closure, Haber et al. (2007) assumed that whenever 5%, 10%, or 20% of the students in a school are ill, that school is closed for one, two, or three
weeks. Analyzing a limited number of mitigation scenarios does not necessarily give the most effective combination of the intervention strategies.

In addition, the literature usually focuses on the effects of the intervention strategies on the number of ill people during the pandemic. However, another metric that should be considered is the highest attack rate (i.e. the percentage of people that get ill) of the virus in a short time period, such as a day. This factor allows us to estimate the required medical resources at healthcare centers (e.g., hospitals) for curing the patients during the pandemic. A smaller daily attack rate of the pandemic results in a lower pressure on the medical system.

This research involves the combination of simulation and optimization for the development of mitigation strategies. An optimization model with the objective of minimizing the ill effects (e.g., number of ill persons) of the pandemic while considering various combinations of control variables (i.e. different scenarios) will be developed. A discrete optimization via simulation (DOvS) methodology will be developed to solve the presented optimization model.

1.3. Expected Outcomes

This dissertation focuses on developing intervention strategies to mitigate a pandemic influenza’s ill effects. The expected outcomes of the dissertation are presented in this section.

A simulation-based optimization model is presented for the establishment of home confinement and school closure intervention strategies during a pandemic influenza. This model aims at finding an optimal combination of those two
strategies to minimize the economic cost of a pandemic under a set of constraints on the control variables. Control variables include time, length of closure for schools, and the rate of home confinement of the individuals for home confinement strategy. Further, the socio-demographic data for Jefferson County is used to investigate the presented model in a real world case. The simulation-based optimization model is solved using NSGS procedure. Finally, the impact of the starting point in time for establishment of these strategies on the course of pandemic is analyzed.

1.4. Research Outline

The remainder of this dissertation is as follows.

Chapter 2 provides a comprehensive literature review of the disease spread simulation models and the intervention strategies established to mitigate the ill effects of pandemics. A review of DOvS methods is also presented. In addition, the contribution of this research to the literature is explained. Chapter 3 explains the details of the disease spread model presented in this dissertation. Also, it presents the sub-sections of the simulation program and its most important variables, and a pseudo code for the main components of the simulation program. Chapter 4 presents the socio-demographic data for Jefferson County, such as zip code population, number of schools, and number of households in each zip code. Then, the simulation models presented in chapter 3 are used to simulate the pandemic influenza for a real world case (i.e. Jefferson County) and establish the intervention strategies. Chapter 5 explains the simulation-based optimization methodology used in this research to evaluate the effects of the intervention
strategies and compare them. Similar to the previous chapter, Jefferson County is used as the target community for the application of this methodology. Chapter 6 presents the conclusion and guidelines for future studies.
CHAPTER II

LITERATURE REVIEW

2.1. Introduction

This chapter contains seven sections. Section 2.2 presents a review of the influenza virus types and major pandemic influenzas. Section 2.3 reviews the studies that explore the disease spread models. Mitigation strategies for pandemic influenzas are explained in Section 2.4. In Section 2.5, the key works on DOvS methods are reviewed. Section 2.6 presents the contribution of this study to the literature. Finally, section 2.7 presents a summary of chapter 2.

2.2. Influenza

2.2.1. The Influenza Virus

Influenza viruses are live organisms made of Ribonucleic acid that cause an infectious disease called the flu, or influenza. This disease can have symptoms such as fever, sore throat, headache, and muscle pain. A review of the papers that investigated the possible models for the transmission of influenza virus shows that possible ways of transmission are direct contact, indirect contact, droplet, and airborne. Close range contact is the main mode of transmission (Brankston et al., 2007 and Nicholls, 2006).
There are three kinds of the influenza viruses: A, B, and C. These three viruses are similar in overall structure, but influenza virus A has attracted more attention than the other two. While influenza A is the most virulent type, which causes severe symptoms and can even result in death, influenza B and C usually do not have very severe symptoms, and are not much to worry about.

Influenza A is made up of eight segments or genes. One of these segments produces hemagglutinin (HA). Another gene encodes neuraminidase (NA). HA and NA are two proteins that play an important role in the structure of the virus. Epidemiologists have found 16 HA (H1 to H16) genes and 9 NA (N1 to N9) genes. A minor change in the characteristics of these two proteins is referred as antigenic drift, while a major change in the properties of them can result in an antigenic shift (Nicholls, 2006).

Influenza B does not mutate as frequently as influenza A and is genetically less diverse. It does not have the potential to cause a pandemic influenza. Influenza C is less common than influenza A and B, and can only cause a mild disease in children.

2.2.2. Influenza Pandemics

Every year, seasonal epidemics occur in different regions of the world causing medium-scale fatalities and economic losses. However, the world has also witnessed influenza pandemics affecting all of the continents in a large-scale. Webster (1998) stated that 10 to 20 pandemics have occurred over the past 250 years. The world encountered three major pandemics in the 20th century; all of
them were caused by influenza A viruses. These deadly disasters are known as the Spanish, Asian, and Hong Kong flues, which occurred in 1918, 1957, and 1968, respectively (Korteweg et al., 2010, and Barry, 2005).

The infamous Spanish flu was the most devastating. This disaster ended in 1920 and left large-scale losses behind. It affected more than 200 million people (Webster, 1998) and killed 40 million people worldwide (Gatherer, 2009). It is sometimes referred to as a worst case scenario for an influenza pandemic. Researchers declared that the so-called Spanish flu was an H1N1 subtype of the influenza A virus (Korteweg et al., 2010, and Webster, 1998).

The Asian influenza pandemic originated in China in 1957 and lasted until 1958. This pandemic was caused by the H2N2 virus and killed almost 68,900 people, in the United States alone (Hilleman, 2002).

The last major pandemic that occurred in the 20th century was the Hong Kong flu, which was an H3N2 subtype of influenza A. The economic cost of the pandemic was approximately 3.9 billion dollars in the United States and 33,800 persons died as a result from 1968 to 1969 (Hilleman, 2002).

The pandemic of 2009 H1N1 swine flu reminds the policy makers and healthcare authorities that the threat of this disaster is not over, due to the virus ability to mutate. Serologic and virologic studies show that the influenza virus has a potential to mutate and evolve into a new mutant to which the humans are still susceptible. New versions of the virus usually evolve in mammals or birds and then are transmitted to humans through contact. In some cases, they are not
transmittable from human to human, while in other cases, the virus can be transmitted from infectious persons to susceptible individuals resulting in pandemics (Hilleman, 2002, and Nicholl, 2006).

2.3. Pandemic Influenza Spread Models

Mitigating the effects of a pandemic is important. Being able to predict three metrics, namely, the numbers of ill, hospitalized, and dead individuals during a pandemic outbreak can help authorities plan intervention strategies. Influenza spread models help the decision makers estimate these metrics and evaluate the effects of intervention strategies on the course of an outbreak.

One category for influenza spread models is called differential-equation based, whose versions include SIR (Susceptible, Infectious, Recovered), SEIR (Susceptible, Exposed, Infectious, Recovered), and SEIRS (Susceptible, Exposed, Infectious, Recovered, Susceptible), and are explained in this chapter. Another category is agent-based simulation models, in which individuals are considered as agents and interact with each other in mixing groups.

2.3.1. A Simple Epidemic Model

Newman (2002) stated that Reed and Frost were the first researchers to present a class of compartmental epidemic models called susceptible/infective/removed, or SIR models. Since then, this class of models has been widely studied (Newman, 2002). An SIR model presented below provides a basic understanding of the dynamics of disease spread. The model is general and depicts the dynamics of
the spread of any infectious disease, although not as accurately applicable as desired for some situations (Lipsitch et al., 2003).

Assume a community of people divided into three classes. The first class of people is susceptible to the disease; the second class includes infectious individuals assumed to be able to spread the disease; and the third class includes the people who have been infected and cannot spread the disease as a result of death caused by the disease, or isolation from the rest of the population, or recovery with immunity. Let $S(t)$, $I(t)$, and $R(t)$ denote the number of people in each of these three groups at time $t$, respectively. One can also assume that the natural birth and death rates are negligible. The SIR model can be written as follows:

\[
\frac{dS(t)}{dt} = -B(t)S(t)I(t) \tag{2.1}
\]

\[
\frac{dI(t)}{dt} = B(t)S(t)I(t) - A(t)I(t) \tag{2.2}
\]

\[
\frac{dR(t)}{dt} = A(t)I(t) \tag{2.3}
\]

$B(t)$ denotes the rate of infection-transmitting contacts at time $t$, and $A(t)$ denotes the exit rate from the second group of people at time $t$. The model is illustrated schematically in Figure 2-1.
See Brauer et al. (2001), and Brandeau et al. (2004) for details on this model.

A numerical example of the SIR model presented above is as follows. Consider a community of people in which 1000 individuals are susceptible, 200 are immune to the virus, and 5 individuals are infectious. If $B(0)$ and $A(0)$ are 0.002 and 0.167, respectively, at the end of the first day of the pandemic, the values for the numbers of the people in these three groups are calculated as follows.

$$S(1) = S(0) + \frac{dS(0)}{dt} = 1000 - B(0)S(0)I(0) = 1000 - 0.002 \times 1000 \times 5 = 990$$

$$I(1) = I(0) + \frac{dI(0)}{dt} = 5 + 0.002 \times 1000 \times 10 - 0.167 \times 5 = 14.165$$

$$R(1) = R(0) + \frac{dR(0)}{dt} = 200 + 0.167 \times 5 = 200.835$$

This SIR model is a simplified illustration of the real world. One may add more realistic features to this model. For example, the above model is deterministic, but some recent studies have considered the probabilistic nature of the problem, and developed more realistic models (Aleman et al., 2009b, and Haber et al., 2007). Also, the presented model is homogeneous, while serologic and virologic studies have shown that influenza usually does not similarly affect individuals in different age groups. As an example, the Spanish flu targeted youths more than other age groups. Recent research has addressed this gap between reality and epidemic models and considers non-homogeneous mixing groups (Lizon et al., 2010, and Shi et al., 2010).
2.3.2. Differential Equations Based Models

The compartmental SIR model, presented by Reed and Frost, gives a foundation for all pandemic influenza models (Newman, 2002). This model and its extensions, such as SEIR (Earn et al., 2000) and SEIRS (Cooke et al., 1996) are used as the bases for the development of other spread models (Wu et al., 2006; Lee and Chen, 2007).

Yarmand et al. (2010) developed a first-order system of 16 differential equations, which was an extension of the SEIR model for the outbreak of H1N1 in 2009. The target population was the undergraduate students of North Carolina State University. Their proposed model was too complicated to be solved analytically; therefore, they used simulation methodology and ARENA simulation software (Kelton et al., 2009) in order to find the number of infected individuals over 5 months. Due to the short time span of the model, the natural birth and death rates were considered to be zero. The proposed model was deterministic. Its target population was relatively small and did not consider the heterogeneity of the population.

Araz et al. (2009) used an SEIR-based system of differential equations in order to simulate the spread of the avian influenza (H5N1) in the counties of Arizona. This model divided the population into five age groups: pre-school, elementary school, middle school, high school, and adult. The model predicted the number of infected and dead people in these age groups over the course of a pandemic influenza. People could travel between counties so that infectious individuals might transfer the disease from one county to another, but travel was
limited only to adults and the transport matrix was symmetric. In another study, Ferguson et al. (2003) developed a deterministic age-structured compartmental epidemic model and divided the population into 20 age groups.

The transmission rate of the influenza virus from an infectious person to a susceptible individual might vary throughout the months in a year. A seasonally-forced deterministic SIR model (which addressed the changes in the transmission rate of the virus) was used by Towers and Feng (2009) to predict the course of the H1N1 pandemic of 2009.

They used the data disseminated by the United States Center for Disease Control and Prevention (US CDC) from 24th of May, 2009 to 22th of August, 2009. Then, they estimated the parameters of the model and predicted a significant wave of the pandemic in fall of 2009. In contrast to Yarmand et al. (2010) and Araz et al. (2009), this model had a large target population (i.e. the United States). Yet, similar to Yarmand et al. (2010), it did not consider heterogeneity of the population.

Dushoff et al. (2004) addressed antigenic drift in the influenza virus, and thus developed a seasonally-forced SIR-susceptible (SIRS) model, which let the individuals lose their resistance to the circulating virus after a few years and become susceptible to a new version. Dushoff et al. (2004) also mentioned that seasonality of an influenza epidemic may be caused by changes in the transmission rate. Their study did not deal with influenza pandemics directly, but it was helpful to better understand their dynamics.
Li et al. (2013) evaluated the effectiveness of a mandatory quarantine that the Chinese government established in China during the 2009 H1N1 pandemic influenza. The quarantine started in May 2009 and lasted for two months. They developed a deterministic SEIR model and considered two scenarios for their model, with quarantine and without quarantine. Equations 2.4 to 2.7 show their model.

\[
\frac{dS}{dt} = -\beta \frac{I}{N} S \tag{2.4}
\]
\[
\frac{dE}{dt} = \beta \frac{I}{N} S - \alpha E \tag{2.5}
\]
\[
\frac{dI}{dt} = \alpha E - \vartheta I \tag{2.6}
\]
\[
\frac{dR}{dt} = \vartheta I \tag{2.7}
\]

where, S, E, I, and R are the susceptible, exposed, infectious, and recovered population, respectively. Also, t denotes time and N is the total population. Further, “\(\beta\) is the average number of infected persons per infectious subject per unit time, \(\alpha\) is the reciprocal average latent period, and \(\vartheta\) is the rate of recovery”\(^1\).

They limited the target population to Beijing, China, because of the heterogeneity of the population in different parts of China. The results of their study showed that the quarantine reduced the number of infected individuals at the pandemic’s peak month, but the cost effectiveness of it was low.

\(^1\) Li et al. (2013)
Differential equation-based models provide insight to pandemics’ mechanisms and are relatively fast tools for simulating pandemics. However, these models largely simplify the reality of the populations and the probabilistic nature of the disease transmission process, which affects the accuracy of the models. Also, for evaluation of influenza mitigation strategies applied to the population, or some sectors of the population, or even some pre-selected individuals, it is necessary to consider an individual as independent entity in the model.

Some studies, especially in recent years, have employed agent-based simulation in order to overcome the drawbacks of differential equation-based simulation models (Ferguson, et al. 2004 and Das et al., 2008). Section 2.3.3. presents a review of disease spread models that use agent-based simulation.

2.3.3. Agent-Based Simulation Models

Agent-based modeling and simulation (ABMS) is a relatively new approach for simulating the actions and interactions of autonomous agents. The applications of this methodology range from modeling the growth and decline of ancient civilizations to agent behavior in the stock market and in supply chains. This modeling approach was first developed in the late 1940s. However, due to its computationally-intensive procedures, researchers did not pay much attention to it until the 1990s (Macal and North, 2006).

In agent-based simulation, an agent has a set of attributes and behavioral characteristics, which define what the agent does and how it interacts with other agents. As an example, consider a sporting goods customer agent. He or she might have attributes such as age, sex, income, and goods preferences, and
behaviors such as using products, receiving services, and shopping (North and Macal, 2007).

Credit for developing the first ABS that considers people as agents goes to Thomas Schelling (North and Macal, 2007). Shelling’s model was an extreme abstraction of people and their interaction in a social system. Furthermore, it opened a new way to model one of the most sophisticated systems, namely those involving social processes (North and Macal, 2007).

The models that deal with the spread of influenza in communities of people have greatly benefited from an agent-based simulation approach (Eubank, 2005). Elveback et al. (1976) were among the first researchers that used ABSM to simulate the spread of the infectious disease by human to human contacts. They presented a stochastic simulation epidemic model, which categorized the population according to five age groups: pre-school, grade-school, high-school, young adults, and older adult. People interacted with each other in five mixing groups: families, neighborhoods, playground, school, and total community.

The model was applied to the Asian and Hong Kong pandemic strains of influenza A. Their model represented a small suburban community with 1,000 persons, 254 families, 50 neighborhoods, 30 playgrounds, and one school. Susceptible people became infected by having contacts with infectious individuals, and went through a latency period that lasted 1.9 days on average. After latency, the individual became infectious which lasted 4.1 days on average.
Elveback et al. (1976) did not specifically mention agent-based simulation in their paper, but their small model benefited from this methodology and has been insightful for other research in this area (see Haber et al., 2007).

Longini et al. (2004) simulated the spread of influenza A within a US community with 2,000 people. Demographic characteristics of the population were based on the 2,000 census data. The population was divided into four neighborhoods and had two elementary schools, one middle school, and one high school. They calibrated the model to have illness attack rates (i.e. the percentage of the people in each age group that become ill) similar to those of the 1957-1958 Asian flu. The work by Longini et al. (2004) had many similarities to Elveback et al. (1976), but it expanded the population size.

Longini et al. (2005) considered a rural area in Thailand as their target population and simulated close contacts (e.g. contacts in households or workplaces) and casual ones (e.g., contacts in temples or shops). Compared to Longini et al. (2004), Longini et al. (2005) simulated a larger population (500,000 persons). Also, they added a single regional 40-bed hospital to the model and used a distance function to assign adults to workplaces. Germann et al. (2006) was a continuation of Longini et al. (2005), but with a new sample population, the United States. They used attack rates from the 1957 Asian influenza and 1968 Hong Kong flu to calibrate their model.

Ferguson et al. (2005) developed a stochastic simulation model to simulate the spread of an emerging H5N1 pandemic in Southeast Asia at the beginning of
the current century. Their model included 85 million people in Thailand and 100-Km wide zone of contagious neighboring countries. Due to lack of sufficient data on the disease characteristics, they used sensitivity analysis to investigate the effects of changing the parameters of the model. Ferguson et al. (2006) applied an agent-based simulation model similar to Ferguson et al. (2005) for a novel influenza outbreak, using Great Britain and the Unites States as targeted populations.

As mentioned earlier, influenza A has the potential to mutate into new versions with different characteristics. In addition, some studies have hypothesized that changes in human mixing patterns, environmental humidity, and fluctuations in human immunity can cause influenza seasonality in such a way that people are more likely to get the disease in some seasons like winter.

Shi et al. (2010) addressed influenza seasonality and virus mutation in their ABSM. Their simulation model showed that a special combination of virus characteristics and seasonal effects would lead to one, two, or three separate epidemic waves. They used data from the state of Georgia to create a population structure of the model and coded the simulation in C++ programming software (Oualline, 2003).

Influenza is mostly transmitted via close contacts (within a radius of 2m) of susceptible persons and infectious individuals. The longer the contact time, the higher the probability of infection (Wallinga et al., 2006; and Haber et al., 2007).
Del Valle et al. (2007) mentioned that the transmission rate of the disease is not similar for different age groups.

Considering these facts, Aleman et al. (2009a) defined the probability of infection as a function of contact time and transmission rate between a susceptible individual and infectious person. Aleman et al. (2009a) considered the so-called SIR model as the basis for their simulation and mentioned that each individual was in one of the three states (susceptible, infectious, or removed) and could transition from one state to another with a certain probability at each time.

Figure 2-2 is an illustration of the transition probabilities in the SIR model which can be thought of as a Markov Chain. They developed a non-homogeneous agent-based simulation model to simulate the spread of influenza. Public transport simulation (which had not received much attention in previous studies) was addressed in their model. A pilot study of their model was provided for the greater Toronto area in Canada. The model was run for 30 days of a pandemic and its output (i.e. number of infected and dead individuals) was imported to a geographic information system (GIS) software.

Figure 2 - 2: Markov Chain of transition probabilities in the SIR model
2.4. Intervention Strategies for Containing Pandemic Influenza

Influenza A is the most dangerous pandemic disease threat to humankind compared to its rivals, HIV-1, Ebola, SARS, and pneumonic plague (Gatherer, 2009). It can potentially infect 30% of the people in the world, and kill around 135 million worldwide in a matter of months. As a comparison, HIV-1 killed only one fourth of this number of people in the last 30 years (Gatherer, 2009). Das et al. (2008) stated that in an avian influenza pandemic, 90 million individuals are expected to become ill in the United States. Another estimation by Haber et al. (2007) mentioned that in the next pandemic influenza, 89,000 to 207,000 people might die in the United States and according to CDC, the direct economic cost could be 72 to 166 billion dollars.

The governments at all levels (federal, state, and local) should give high priority to preparation plans for a potential pandemic. Developing some strategies to mitigate the ill effects of pandemics should be one of these plans (Yarmand et al., 2010). Some of these strategies are listed as follows:

- Antiviral drug usage (Ferguson et al., 2006; and Germann et al., 2006)
- Vaccination (Longini et al., 2005; and Patriarca and Cox, 1997)
- School closure (Haber et al., 2007; and Glass et al., 2006)
- House quarantine (Yarmand et al., 2010)
- Workplace closure (Ferguson et al., 2006)
- Restriction on travel (Germann et al., 2006)
The models presented in section 2.3. are helpful tools to simulate the spread of the virus during a pandemic. However, the main purpose for development of these models is to evaluate the effectiveness of the intervention strategies during a pandemic. As noted before, most of the studies about the mitigation strategies have been evaluated by three main metrics, namely the numbers of infected, hospitalized, and dead people during a pandemic. The remainder of this sub-section explains the studies that address mitigation strategies and their effects on the course of pandemics.

Elveback et al. (1976)\textsuperscript{2} evaluated the effects of two intervention strategies, school closure and vaccination on the attack rate of a pandemic. They developed a small agent-based model with 1000 individuals with the FORTRAN programming language (McCracken, D.D., 1972). The model contained 140 individuals in preschool, and 320 in school. Also, there were 316 young, and 224 old adults in their model. The model simulated the relationship between the individuals in the community.

They showed that in a pandemic with characteristics of the Hong Kong influenza, the attack rate of the virus decreased by 27 percent when the schools were closed throughout the outbreak. Elveback et al. (1976) also stated that the age specific attack rates for the people in preschool, school, young adult, and older adult groups decreased by 69, 49, 61, and 56 percent, respectively, as a result of vaccination of 50 percent of the people in the school group.

\textsuperscript{2} See page 17.
The basic reproductive number ($R_0$) is defined as “the average number of secondary infections caused by a single typical infected individual among a completely susceptible population” (Germann et al., 2006). $R_0$ indicates the transmissibility and severity of the influenza strain. The model presented in Germann et al. (2006) demonstrated that when $R_0 < 1.9$, a rapid vaccination could limit the number of ill people to less than 10 percent of the population. They showed that travel restriction can only delay the time course of the pandemic and does not decrease the number of ill people.

Longini et al. (2005) suggested that vaccination plans concentrate on school children because they are the population group most responsible for the transmission of influenza.

Yarmand et al. (2010)\(^3\) suggested that at the beginning of an influenza pandemic, authorities concentrate on vaccination (because it is a more cost-effective strategy versus a delayed vaccination), and if the disease continues to spread, a self-isolation strategy should be considered. Andradottir et al. (2010) suggested a combined strategy of low-coverage reactive vaccination, and limited antiviral use in conjunction with social distancing strategies.

Meltzer et al. (1999) stated that it takes 6-8 months to produce adequate vaccines for a new strain of influenza virus. Longini et al. (2004) estimated that in order to have a successful mitigation plan using antiviral agents, the United States

\(^3\) See page 13
It requires a stockpile of 1.9 billion doses of antiviral agents\(^4\). It is beyond the potential of healthcare systems to produce this amount of antiviral agents and stockpile them.

Haber et al. (2007) took the results of Meltzer et al. (1999) and Longini et al. (2004) into consideration. They suggested that public officials consider non-pharmaceutical intervention strategies such as social distancing. Inadequacy of a vaccination campaign to mitigate a pandemic flu was shown in another study by Towers and Feng (2009) as well.

Haber et al. (2007) claimed that school closing is an effective mitigation strategy. They also considered long-term care facilities (LTCF) (which has not been addressed in previous studies specifically) in their study. They added that by preventing ill seniors, who live in LTCFs, from making contacts with other residents, the numbers of ill people and deaths might be reduced by 60 percent. In another study, Aleman et al. (2010) suggested home confinement, as an effective social distancing strategy.

Halder et al. (2014) presented an individual-based simulation model to evaluate the effectiveness of a pre-pandemic vaccine. According to their study, a newly emerged pandemic virus requires 6 months to find a vaccine and by the time that the vaccine is ready the pandemic is already past its peak time. They suggested a pre-pandemic vaccination program, even if it is not completely

\(^4\) More than one dose of antiviral agents is needed for an individual.
successful. They established a simulation model and considered two scenarios for severity of the pandemic.

For the first one, they assumed that the pandemic was going to be a moderate one with transmissibility and clinical severity similar to 1957 pandemic. For the second one, it was assumed that the pandemic was very severe and had the characteristics of the Spanish flu that happened in 1918-1920.

Further, they considered four scenarios. Scenario one, no pandemic and pre-vaccination; scenario two, pandemic and pre-emptive vaccination with 0% effectiveness; scenario three, pandemic and pre-emptive vaccination with 30% effectiveness; and finally scenario four, vaccination and 75% effectiveness. Their agent-based simulation model was based on the 30,000 population of Albany, Australia. The results of their simulation showed that pre-emptive vaccination was a more effective approach compared to reactive vaccination when the pre-emptive vaccination was at least 30% effective.

Jackson et al. (2014) presented a systematic review on the simulation studies that evaluated the effectiveness of a school closing strategy during an influenza outbreak. They searched Medline and Embase databases for the studies done by October 2012 on the subject. They investigated the effects of the school closure on the total and peak attack rate of the influenza outbreak.

The results of their literature review showed that school closing mitigation strategy usually showed more effectiveness on the peak attack rate of the pandemic and less effectiveness on the total number of infections during a
pandemic. They also mentioned that this strategy was more effective when the transmissibility of the disease was higher amongst children than adults. They added that some of the studies showed up to 90% reduction in the peak attack rate of the pandemic as a result of establishment of the school closing strategy while some of the other studies showed an increase in the peak attack rate of the pandemic.

They concluded that while school closing strategies seemed to be an effective one, their effectiveness depended on the structure of the target population and characteristics of the disease and more studies needed to be done to quantify the benefits of the school closing strategy more accurately.

Similar to Jackson et al. (2014), Cachemez et al. (2014) studied the effectiveness of the school closing strategy and when and how it should be applied. They investigated different aspects of school closure strategy. According to this research, school closure can potentially happen in three ways.

1. Class Dismissal: where only the students are sent home.
2. Reactive Closure: where many of the students or staff become ill and as a result the school is closed.
3. Proactive Closure: where only very few number of students or staff become ill and as a result the school is closed.

Cachemez et al. (2014) investigated the consequences of school closing and presented three of them; the economic cost associated with school closure, the social justice and ethical issues, and the effects on the healthcare system.
According to this study, many underprivileged students especially in industrialized countries, rely on free lunch and breakfast programs and if the schools become closed, they lose this opportunity which result in ethical issues. Further, school closure forces some of the workforce in the healthcare systems to stay home and take care of their children which adds pressure on the healthcare systems in a time that they need their employees the most.

Yarmand et al. (2013a) studied the intervention strategies that can be applied at a household level in case of an epidemic and identified an optimal one. They considered vaccination, antiviral prophylaxis treatment, and isolation. They developed a cost-effectiveness and optimization model to find an optimal strategy. In addition, they considered a limit for the budget of the household for implementation of these strategies.

They considered a household with four members and assumed one of them was initially infectious and then applied the intervention strategies to them. Their analysis showed that the most effective strategy that guaranteed none of the susceptible individuals became infectious cost about $314 for the household. Also, they concluded that when the budget of the household for implementation of the strategies was limited, the most effective strategy amongst the four categories of the strategies was the vaccination, and as soon as antiviral became affordable for the family, the most effective one was using the antivirals.

While Yarmand et al. (2013a) focused on the intervention strategies in household, Yarmand et al. (2013b), on the other hand, investigated the
intervention strategies for a relatively bigger population. They considered the undergraduate students of the North Carolina State University as their target population. They developed a SEIR compartmental model and established various vaccination, treatment, antiviral prophylaxis, and isolation strategies. Their goal was to find optimal intervention strategies. Figure 2-3 shows the model transfer diagram presented in this paper.

Figure 2 - 3: model transfer diagram

Their study showed that when vaccination was combined with self-isolation, an optimal policy was created. Their model created a framework to compare several mitigation strategies.

Table 2-1 presents a list of the papers that concentrated on the intervention strategies for mitigation of the effects of the pandemic influenza. It categorizes the

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5 Reference: Yarmand et al. (2013b)
papers based on the simulation model approach (differential-equation-based or simulation-based) used in them, and the intervention strategies applied.

Table 2 - 1: Categorization of papers based on the intervention strategies and simulation model

<table>
<thead>
<tr>
<th>Simulation</th>
<th>Paper</th>
<th>Vaccination</th>
<th>School Closure</th>
<th>isolation</th>
<th>Travel restriction</th>
<th>Antiviral Prophylaxis</th>
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2.5. Discrete Optimization via Simulation

Optimization via simulation (OvS) is a methodology by which the expected value of some output of a stochastic simulation is maximized or minimized. When the decision variables are discrete, the methodology is called discrete decision-variable OvS.

In particular, discrete optimization via simulation addresses problems which aim to optimize a stochastic performance measure when the system is so complex
that it cannot be tractable analytically and numerically. The general form of the problems, which are solved via this methodology, is as follows (Nelson, 2010).

\[
\min \{c(X) = E_X[Y(X)]\} \tag{2.8}
\]

\[
X \in \theta = \emptyset \cap z^d \tag{2.9}
\]

\[
E_X[H_i(X)] \leq m_i, \; i = 1, 2, \ldots, w. \tag{2.10}
\]

\(Y(X)\) is the distribution of the performance measure, which is a function of the decision variable \(X\), where \(X\) is a vector of \(d\) integer-ordered decision variables in a feasible region \(\emptyset \subset R^d\), where \(z^d\) denotes all \(d\)-dimensional vectors with integer components. Constraints (2.10) include the expected values of additional output performance measures, \(H_1(X), H_2(X), \ldots, H_w(X)\) and we want to keep them below a certain level \(m\).

As stated in chapter one, this study aims at developing an optimization model for establishment of strategies to mitigate pandemic influenza, which can be formulized as a DOvS problem.

In the case of a disease spread model, \(X\) is a vector of control variables such as the length of school closure, and \(Y(X)\) is a performance measure such as the number of ill persons during the pandemic. Also, an example of \(H(X)\) is a performance measure such as the number of the hospitalized persons during the pandemic. An optimization model for the establishment of intervention strategies for pandemics is presented in chapter five.
Among the algorithms to solve these problems, some simulate every feasible solution and are called ranking and selection algorithms (R&S) (Chen et al., 1997).

Ranking and selection techniques are developed for problems with relatively small $|\theta|$. Another type of algorithm, called adaptive random search (ARS) techniques, are developed for situations where $|\theta|$ is relatively large. DOvS research can be categorized as follows (Andradottir, 2006).

- **Solution sampling:** the algorithms can use point-based (from one solution to the next), set-based (from solutions in an eligible set), or population-based (combining components from a set of solutions) sampling solutions.
- **Type of simulation:** algorithms can be applied for finite-horizon or infinite-horizon simulation.
- **Feasible region:** whether or not $\theta$ is finite and small enough to exhaust, or large and integer ordered.
- **Guarantee:** Algorithms can guarantee convergence to an optimal solution, or a probability of correctly selecting the optimal solution, or none of the above.

As mentioned, ranking and selection algorithms exhaust $|\theta|$ (i.e. simulate the system for all of the feasible solutions). In R&S methods, experimental design and analysis techniques are used for selecting the solution with the best (i.e. the largest or smallest) mean performance. Some statistical guarantees are given
about the quality of the solution after simulation of all the feasible solutions (Hong and Nelson, 2007).

There are two basic categories of R&S techniques: Indifference zone (frequentist) and Bayesian procedures. Indifference zone is a sequential procedure that guarantees, with confidence level greater than or equal to $1 - \alpha$, that the solution selected has the smallest mean (in a minimization problem), if the mean of the best solution is at least $\delta$ better than the second best solution. There are two categories of Bayesian procedures (Branke et al., 2007): value of information procedure (VIP) and optimal computing budget allocation (OCBA) procedure.

Nelson et al. (2001) developed an indifference-zone (IZ) selection procedure called NSGS which is capable of solving problems too large for older ranking and selection procedures.

Boesel et al. (2003) addressed the problem of finding the simulated system with the best expected performance, using an extension of the NSGS procedure which is called a cleanup procedure. This cleanup procedure takes the solutions simulated by the DOvS algorithm, eliminates without any additional simulation, the ones that are not statistically competitive, and performs just enough additional simulations on the remaining solutions.

These procedures are compared with others in the literature to estimate their efficiency, controllability, robustness, and sensitivity measurement. Branke et al. (2007) presented a thorough numerical comparison of the IZ, OCBA, and VIP procedures on a large variety of selection problems.
As opposed to R&S procedures, adaptive random search (ARS) are used to solve the problems with relatively large $|\theta|$. ARS procedures can be globally or locally convergent. Norkin et al. (1998) developed a stochastic branch and bound (SB&B) method as a globally convergent ARS method.

Similar to the deterministic branch and bound algorithm, the feasible region in SB&B is partitioned into a compact subset. However, the SB&B uses stochastic upper and lower estimates of the optimal value of the objective function in each subset. Hong and Nelson (2006) designed a framework called convergent optimization via the most-promising-area stochastic search (COMPASS) for locally convergent DOvS algorithms.

2.6. Research Contribution

Simulation models have been used to show the spread of the influenza virus in the communities of people and compare the effectiveness of the mitigation strategies on the spread of the disease and its ill effects in previous researches. However, these researches usually address a very limited number of scenarios for establishment of the intervention strategies. For example, Haber et al. (2007) considered only limited scenarios for home confinement and school closure strategies and established them separately to evaluate their effects on the number of ill, hospitalized and dead persons during a pandemic.

Another shortcoming of the research in this area is that usually the number of ill, hospitalized, or dead people are the concentration of the simulation models for comparison of the presented scenarios, not the economic impact of the intervention strategies. For example, they don’t consider the economic impact of
home confinement (i.e. cost associated with the individuals who can’t go to work because of home confinement).

As mentioned in chapter one, healthcare systems might encounter a shortage of the resources during pandemic influenza, especially when the pandemic reaches to its peak weeks. As a result, those resources might not suffice for the needs of the patients. The impact of a mitigation strategy on the reduction in the daily needs of healthcare resources throughout the influenza outbreak can be as important as the effects of them on the reduction of the total number of ill, hospitalized and dead individuals and needs to be addressed.

This research presents a model that addresses a combination of these drawbacks.

- In this study, home confinement and school closure strategies are established together and a large number of different scenarios for their establishments are presented and then compared. Simulation-based optimization methods are used for comparison of the scenarios to find the best one (i.e. scenario with the lowest cost).

- Also, the objective function for comparison of the scenarios goes beyond the number of ill, hospitalized or dead individuals and considers the economic costs associated with these three metrics (e.g. cost of a hospitalization).

- Furthermore, applying the intervention strategies such as school closing and home confinement have some economic cost associated with them. For example, in home confinement strategy, when an individual does not
have severe symptoms of disease, he or she might decide to go to work, but under the home confinement strategy he/she stays home during the illness period and as a result won’t get paid. The amount of these costs can have effects on the likeness of a strategy to be chosen as the best one. This study take these costs into consideration and adds them to the performance measures and eventually the objective function of the model.

- This research considers the daily number of the hospitalized persons during the pandemic (which is a main source of pressure on the healthcare system).

- Another main advantage of the presented model is that it gives the decision makers (i.e. healthcare authorities) the capability to subjectively create a long list of mitigation scenarios in case of a pandemic and compare them to find an optimal one. Further, since this simulation-based optimization model is an agent-based model, it enables the healthcare authorities to develop plans for a smaller area (e.g. develop mitigation plans for small population segments or schools or daycares that are located in a particular zip code in the community).

- Finally, the impact of the starting point in time for establishment of mitigation strategies on their effectiveness is analyzed.

### 2.7. Summary

A literature review of the models for influenza spread and associated mitigation strategies reveals that these researches mainly focus on simulation of the progress
of the pandemic over time. These simulation models are then used to evaluate the presented mitigation strategies.

The main goal of our study is to present a simulation-based optimization model to find the best combination of intervention strategies under a set of constraints. The optimization model minimizes performance measures such as the economic cost of ill persons during the pandemic. A DOvS methodology will be used to bridge between simulation and optimization models and solve the presented optimization model.
CHAPTER III

DISEASE SPREAD MODEL

3.1. Introduction

In this chapter, a disease spread model is described for a generic urban community. First, an explanation of the population structure, disease progress within the body of infected person, and the transmission of the disease from an infectious person to a susceptible one is described. Then, the structure of the simulation model developed to mimic the disease spread is explained in detail. For the simulation program, an agent-based simulation approach is used, which enables us to track detailed levels of connections between individuals in a population. Furthermore, the simulation model is expanded to include the establishment of the intervention strategies.

3.2. Disease Spread Model

The model consists of three components. First, population structure; second, the disease characteristics and progress of the disease within individual; and third, the transmission of the disease between people. These concepts are explained below in detail.
3.2.1. Population Structure

People are categorized into four age groups: pre-school children (less than or equal to 4 years old), students (between 5 and 18 years old), adults (between 19 and 64 years old) and seniors (65 years old or older). Each person can be a member of up to five different mixing groups: households, schools, daycare centers, workplaces, and community (e.g. stores, theaters). Each individual belongs to a household and interacts with other people in the community. Pre-school children go to daycare centers, students attend schools, and adults go to workplaces. Figure 3-1 illustrates the mixing and age groups considered in the model.

![Diagram showing mixing and age groups](image)

3.2.2. Disease Progress within the Body

The influenza virus enters a susceptible person’s body through contacts with infectious people. After the virus enters an individual’s body, there is an incubation period, after which the infectious period begins. An infectious person who does not
show symptoms is asymptomatic. An individual showing some symptoms such as fever and coughing is symptomatic. An asymptomatic individual is 50% less infectious than a symptomatic one (i.e. the transmission rate of the disease from a symptomatic infectious person to a susceptible individual is twice the transmission rate of the disease from an asymptomatic person to a susceptible individual) (Haber et al., 2007).

It is assumed that severe symptoms of the disease could result in hospitalization of the patient and even his or her death. For more information, see Longini et al. (2005). Figure 3-2 illustrates the progress of the disease within the body of a patient after he or she is infected due to contact with an infectious person.

![Figure 3-2: Progression of the disease in a susceptible person, as a result of contact with an infectious individual (Paleshi et al., 2011)](image)

### 3.2.3. Disease Transmission Process

Transmission of the disease occurs via contacts between a susceptible individual and an infectious one. It depends on parameters such as the number and duration of contacts that a person has with infectious persons as well as age specific
transmission rates of the disease from infectious individuals. Haber et al. (2007) presented a formulation for deriving a probability of getting the disease on a day.

**Notations**

**Indices and Sets**

\( i \in I \) : Set of age groups

\( k \in K \) : Set of mixing groups

\( w \in W \) : Set of types of day\(^6\)

\( t \in T \) : Set of pandemic days

**Parameters**

\( \lambda_{ij} \) : the rate of transmission per minute of contact from an infectious person in age group \( j \) to an individual who is in age group \( i \)

\( d_{ijkw} \) : the duration of contact that happens in mixing group \( k \) between a person in age group \( i \) and another persons who is in age group \( j \) on a day of type \( w \)

\( I \equiv (1, 2, 3, 4) \)

\( K \equiv (1, 2, 3, 4, 5) \)

\( W \equiv (1, 2) \)

\( T \) : total duration of the pandemic

**Inputs**

\( A_M \) : a particular susceptible individual who is in age group \( M \)

---

\(^6\) A day can be of one of two possible types, weekday or weekend day.
Variables

$B_{jkwt}$: the infectious individuals who are in age group $j$ and make contacts with individual $A_M$, in mixing group $k$, on a day type $w$, and on day $t$

$b$: an individual who is a member of $B_{jkwt}$

Then, the probability of becoming infected on day $t$ for this particular individual (i.e. $A_M$) is:

$$P(A_M) = 1 - \Pi_k \Pi_j \Pi_w \Pi_{beB_{jkwt}} \exp(-\lambda_{Mj}d_{Mjkw})$$  \hspace{1cm} (3.1)

This probability potentially varies for other individuals who are in the same age group as this particular (i.e. $A_M$), because normally they don’t meet the same individuals that individual $A_M$ meets on day $t$.

As shown in equation 3.1, the transmission rate of the disease changes, when there is a change in the age group of infectious or susceptible persons. Also, contact durations depend on the mixing and age groups of the infectious and susceptible individuals and whether the contact occurs on a week day or a weekend.

In this section, the spread of influenza virus among a small number of people is explained. This is the basic structure of the spread of the influenza pandemic in a community. In this small community, there are 10 individuals, residing in three households.

The individuals in the first age group go to a daycare center, the individuals in the second age group go to a school, and the individuals in the third age group
go to a workplace. All the individuals participate in the contacts in the community mixing group (e.g. shops, restaurants).

Figure 3-3 shows the contacts of the individuals in the households. Each circle in Figure 3-3 represents a household. Each one of the rectangular shapes inside the circles represents an individual. There are three households in this community; Household 1 has three individuals, household 2 has two individuals, and household 3 has five individuals.

The individuals are identified based on three characteristics, their household, their age group, and the number of individuals in the household. For example, individual H1G2P1 is in household 1 (H1), age group 2 (G2), and he is the first individual in the household (P1).

The number of individuals in the household doesn't have anything to do with the possibility of getting the disease and is added to the name of the individual to give him a different name than other individuals in the same household. The lines that connect the individuals demonstrate the contacts between them. The blue lines show contacts between the individuals in the same age group and the red lines show the contacts between the individuals in different age groups.
After making contacts in the households, and with household members, the individuals (based on their age groups) go to daycare, school, or workplace and make contacts in those mixing groups, too. Figure 3-4 shows the individuals in their mixing groups in daycare, school, and workplace.
Finally, the individuals make contact with others in the community mixing group and Figure 3-5 shows these contacts for these individuals.

It is assumed that amongst these individuals (on this particular day), H1G1P2, has the disease, but doesn’t show any symptoms. Further, individuals H3G2P1, and H3G2P2 are symptomatic infectious. All the other individuals are susceptible.
Since the contact network of the individuals for all the mixing groups are available, it is possible to calculate the possibility of getting the disease for each individual. These calculations are based on the equation 3.1.

![Diagram of contact networks](image)

**Figure 3 - 5: Contacts of the individuals in the community**

Here, these calculations are presented for one sample individual, H1G2P1.

By using the equation 3.1, the data provided in Tables 3-3., 3-4, and 3-5, and the network of contacts presented in Figure 3-3, 3-4, and 3-5, the probability of getting the disease at the end of the day for this particular individual is calculated.

**Individual H1G2P1:**

Household: in the household, this individual has contacts with individuals H1G1P2, and H1G3P3. The only individual in the household that has the disease
is individual H1G1P2. So, the probability of getting the disease from individual H1G1P2 is $\alpha = 1 - \exp(-0.00062 * 60 * 0.5)$.

School: Since individual H1G2P1 is in the second age group, he goes to school. Both of his classmates have the disease and show symptoms. So the probability of getting the disease from his classmates is $\beta = 1 - \exp(-0.00061 * 392) \ast \exp(-0.00061 \ast 392)$.

Community: Finally this individual has contacts with individual H3G2P1, and H3G1P5 in the community. These two individuals are not infectious, so the probability of getting the disease from them is zero.

Finally, based on the equation 3.1, the probability of getting the disease for this individual and on this day is $\gamma = 1 - (1 - \alpha) \ast (1 - \beta) \ast 1 = 0.39$.

3.3. Simulation Model

This sub-section first presents the parameters that are used in the disease spread simulation model. These parameters include transmission rates of the disease, number of days that an infected person spends in incubation and infectious period, amongst others. Then, the sub-sections of the simulation model and connection between them and the disease spread model are explained. Further, the variables of the simulation model are explained.

As mentioned before, the simulation model is developed using JAVA (Wu, 2004; Liang, 2003). JAVA is an object-oriented programming language that makes the development of agent-based simulation easier. It is platform independent, robust, secure, and multithreaded.
3.3.1 Parameters of the Model

As noted in section 3.2, each infected person goes through an incubation period during which he or she is not infectious yet. After this period, the individual becomes infectious which might include some symptoms of the disease (i.e. illness) or might not have symptoms and just be infectious. The number of days that an infected person is in incubation and infectious periods have associated distribution as presented in Table 3-1 and 3-2, respectively (Longini et al., 2005).

Table 3 - 1: Number of incubation days’ distribution

<table>
<thead>
<tr>
<th>Incubation days</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td>2</td>
<td>0.5</td>
</tr>
<tr>
<td>3</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Table 3 - 2: Number of infectious days’ distribution

<table>
<thead>
<tr>
<th>Infectious days</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>0.3</td>
</tr>
<tr>
<td>4</td>
<td>0.4</td>
</tr>
<tr>
<td>5</td>
<td>0.2</td>
</tr>
<tr>
<td>6</td>
<td>0.1</td>
</tr>
</tbody>
</table>

One of the parameters used in the equation 3.1 was $\lambda$. It is the transmission rate of the disease from an infectious person to a susceptible one. The value of this parameter differs when the age group of either of the two parties changes. Table 3-3 summarizes the value of this parameter for all 16 possible combinations (see Haber et al., 2007).
Table 3 - 3: Transmission rate of disease

<table>
<thead>
<tr>
<th>Age group of infectious person (k)</th>
<th>0-4</th>
<th>5-18</th>
<th>19-64</th>
<th>&gt;=65</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>0.00059</td>
<td>0.00062</td>
<td>0.00033</td>
<td>0.00080</td>
</tr>
<tr>
<td>5-18</td>
<td>0.00058</td>
<td>0.00061</td>
<td>0.00033</td>
<td>0.00080</td>
</tr>
<tr>
<td>19-64</td>
<td>0.00057</td>
<td>0.00053</td>
<td>0.00032</td>
<td>0.00080</td>
</tr>
<tr>
<td>&gt;=65</td>
<td>0.00057</td>
<td>0.00054</td>
<td>0.00029</td>
<td>0.00102</td>
</tr>
</tbody>
</table>

Individuals make contacts with other individuals in their households. The length of these contacts depend on the age groups of both persons having contacts (Haber et al., 2007). Table 3-4 shows the lengths of contacts in the household categorized by the age groups of individuals.

The number of contacts and their durations in the community mixing groups (e.g. stores, theaters, and restaurants) depend on the age groups of the individuals on both sides of the contact. The numbers and durations of contacts for individuals in each of the four age groups are categorized in Table 3-5 (see Haber et al., 2007).

Table 3 - 4: Total duration of contacts with household members (min/day)

<table>
<thead>
<tr>
<th>Age group</th>
<th>0-4</th>
<th>5-18</th>
<th>19-64</th>
<th>&gt;=65</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>120</td>
<td>60</td>
<td>120</td>
<td>60</td>
</tr>
<tr>
<td>5-18</td>
<td>60</td>
<td>120</td>
<td>120</td>
<td>60</td>
</tr>
<tr>
<td>19-64</td>
<td>120</td>
<td>120</td>
<td>120</td>
<td>120</td>
</tr>
<tr>
<td>&gt;=65</td>
<td>60</td>
<td>60</td>
<td>120</td>
<td>120</td>
</tr>
</tbody>
</table>

Table 3 - 5: Number of contacted persons and total duration of contacts in community (min/day)

<table>
<thead>
<tr>
<th>Age group</th>
<th>0-4</th>
<th>5-18</th>
<th>19-64</th>
<th>&gt;=65</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>2.60</td>
<td>1.30</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>5-18</td>
<td>1.30</td>
<td>2.60</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>19-64</td>
<td>0.0</td>
<td>0.0</td>
<td>2.60</td>
<td>2.60</td>
</tr>
<tr>
<td>&gt;=65</td>
<td>0.0</td>
<td>0.0</td>
<td>2.60</td>
<td>2.60</td>
</tr>
</tbody>
</table>
As mentioned in Chapter 1, some of the ill individuals might end up going to a hospital or die as a result of the severity of the disease. The probabilities of hospitalization and death for an infected person are illustrated in Table 3-6 (Haber et al. 2007).

<table>
<thead>
<tr>
<th>Age group</th>
<th>Hospitalization</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-4</td>
<td>.00810</td>
<td>.00005</td>
</tr>
<tr>
<td>5-18</td>
<td>.00091</td>
<td>.00003</td>
</tr>
<tr>
<td>19-49</td>
<td>.00227</td>
<td>.00007</td>
</tr>
<tr>
<td>50-64</td>
<td>.00907</td>
<td>.00148</td>
</tr>
<tr>
<td>65-69</td>
<td>.02442</td>
<td>.00530</td>
</tr>
<tr>
<td>70-74</td>
<td>.04125</td>
<td>.00928</td>
</tr>
<tr>
<td>75-79</td>
<td>.05539</td>
<td>.01805</td>
</tr>
<tr>
<td>80-84</td>
<td>.0816</td>
<td>.03529</td>
</tr>
<tr>
<td>&gt;=85</td>
<td>.15357</td>
<td>.09583</td>
</tr>
</tbody>
</table>

3.3.2 Structure of the simulation model’s codes

The simulation program is coded with JAVA and contains six main sub-sections (i.e. classes). These classes, the connection between them, and the main variables defined in each one of them are explained in this sub-section. Figure 3-6 shows the relationship between these classes.
The simulation methodology used in this study is an agent-based simulation and the individuals are the agents of the model. Each one of these individuals have some attributes such as age, household that they belong to, the school they attend (if they are a student) amongst other attributes. These attributes have impacts on the disease spread model at an individual level. The attributes of the individuals are defined in a class called person. Here is a list of these attributes.

- **age**: age of the individual
- **householdid**: the household number to which the individual is assigned
- **probability**: probability of not getting the disease on each day
- **contactDuration (1, 2, 3, 4)**: duration of contact with another member of the household who is in the first, second, third, and fourth age groups, respectively
• transmissionRate \((1, 2, 3, 4)\): the rate of transmission per minute of contact with a household member belonging to the first, second, third, and fourth age group, respectively

• contactDurationInDaycareCenter: duration of contact in daycare center with another pre-school child

• contactDurationInSchool: duration of contact in school with another student

• contactDurationAtWorkplace: duration of contact at workplace with another co-worker

• contactDurationInCommunity \((1, 2, 3, 4)\): duration of contact in the community, with an individual in the first, second, third, and fourth age group, respectively

• daycareno: the number of the daycare center to which the individual in the first age group is assigned

• daycarezip: the zip code that the daycare center the individual goes to is located at

• schoolno: the number of the school to which the individual in the second age group is assigned

• schoolzip: the zip code that the school the individual goes to is located at

• workplaceno: the number of the workplace to which the individual in the third age group is assigned to

• workplacezip: the zip code that the workplace the individual goes to is located at
- **daycare**: the group in a daycare center to which the pre-school child is assigned
- **school**: the group in a school to which a school student is assigned
- **workplace**: the group in a workplace to which an adult is assigned
- **symptomatic**: it is equal to 1 if the individual is infectious and symptomatic and 0.5 if the individual is infectious and asymptomatic
- **sever**: a 0-1 variable which is equal to 1 if the individual has severe symptoms; 0 otherwise
- **hospitalization**: a 0-1 variable which is equal to 1 if the individual is hospitalized after exhibiting severe symptoms and 0 otherwise.
- **dead**: a 0-1 variable which is equal to one if the individual dies after hospitalization
- **sickDay**: the day on which the individual is infected
- **infectiousDayStart**: the day on which the infectious period of the individual begins
- **infectiousDayFinish**: the day on which the infectious period of the individual ends
- **numberOfIncubationDays**: duration of the incubation period for individual
- **numberOfInfectiousDays**: duration of the infectious period for individual
- **status**: daily status of each individual: susceptible, in incubation period, infectious and asymptomatic, infectious and symptomatic, infectious with severe symptoms, hospitalized, and dead.
- **nog**: equal to 0 when the person's age is less than 65 and doesn't go to a daycare, or a school, or a workplace, otherwise 1
- **EC**: equal to 2 when the individual is infectious and **nog** is equal to 0 and it is a weekday, otherwise 1

As mentioned before, the population structure, disease progress within the body, and transmission of the disease from an infectious individual are important parts of the disease spread model. Some parts of the data about these three components of the model need to be imported to the simulation model as inputs. Four of the six previously mentioned classes, namely, **data1**, **data2**, **data3**, and **data4** are imported from four text files named **input1**, **input2**, **input3**, and **input4**, respectively.

a) **Input1**: Table 3-7 shows the data in **data1** and explains them. This data is used as input for other input files.

<table>
<thead>
<tr>
<th>data</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>nozipcode</td>
<td>Number of zip codes fully or partially located in the targeted area</td>
</tr>
<tr>
<td>maxxipp</td>
<td>Max. population amongst zip codes</td>
</tr>
<tr>
<td>maxnodaycare</td>
<td>Max. no. of daycares in a zip code</td>
</tr>
<tr>
<td>maxnoschool</td>
<td>Max. number of schools in a zip code</td>
</tr>
<tr>
<td>maxnoworkplace</td>
<td>Max. number of workplaces in a zip code</td>
</tr>
<tr>
<td>maxnohouse</td>
<td>Max. number of households in a zip code</td>
</tr>
<tr>
<td>maxnodaycareg</td>
<td>Max. number of daycare classes (i.e. groups) in a daycare center</td>
</tr>
<tr>
<td>maxnoschoolg</td>
<td>Max. number of school classes in a school</td>
</tr>
<tr>
<td>maxnoworkplaceg</td>
<td>Max. number of workplace groups in a workplace</td>
</tr>
<tr>
<td>maxhousem</td>
<td>Max. number of persons in a house</td>
</tr>
<tr>
<td>maxdaycarem</td>
<td>Max. number of children in a daycare group</td>
</tr>
<tr>
<td>maxschoolm</td>
<td>Max. number of students in a school class</td>
</tr>
<tr>
<td>maxworkplacem</td>
<td>Max. number of persons in a workplace group</td>
</tr>
<tr>
<td>maxzage1p</td>
<td>Highest number of persons in the first age groups in a zip code</td>
</tr>
<tr>
<td>maxzage2p</td>
<td>Highest number of persons in the second age groups in a zip code</td>
</tr>
<tr>
<td>-----------</td>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td>maxzage3p</td>
<td>Highest number of persons in the third age group in a zip code</td>
</tr>
<tr>
<td>maxzage4p</td>
<td>Highest number of persons in the fourth age group in a zip code</td>
</tr>
<tr>
<td>totalage1p</td>
<td>Total number of persons in the targeted area in the first age group</td>
</tr>
<tr>
<td>totalage2p</td>
<td>Total number of persons in the targeted area in the second age group</td>
</tr>
<tr>
<td>totalage3p</td>
<td>Total number of persons in the targeted area in the third age group</td>
</tr>
</tbody>
</table>

b) \textit{data2}: the number of daycares, schools, and workplaces for each zip code are imported by this class. This is a list of the imported data.

\begin{itemize}
  \item \textit{nodaycare}[i]: Total number of daycares in zip code i
  \item \textit{noschool}[i]: Total number of schools in zip code i
  \item \textit{noworkplace}[i]: Total number of workplaces in zip code i
\end{itemize}

c) \textit{data3}: in this file the population of the zip codes and the four age groups for each zip code are imported. In addition, the population of each daycare, school, and workplace is imported to the simulation program.

\begin{itemize}
  \item \textit{zippop}[i]: population of the zip code i
  \item \textit{zipage1p}[i]: population of the 1\textsuperscript{st} age group in zip code i
  \item \textit{zipage2p}[i]: population of the 2\textsuperscript{nd} age group in zip code i
  \item \textit{zipage3p}[i]: population of the 3\textsuperscript{rd} age group in zip code i
  \item \textit{zipage4p}[i]: population of the 4\textsuperscript{th} age group in zip code i
  \item \textit{zipdaycarep}[i][j]: number of children that go to daycare center j in zip code i
  \item \textit{zipschoolp}[i][j]: number of students that go to school j in zip code i
  \item \textit{zipworkplacep}[i][j]: number of adults that go to workplace j in zip code i
\end{itemize}

d) \textit{data4}: in this class the number of households categorized by the household size are imported to the program. These are the imported data:
\textit{house1[i]}: the number of households with 1 member in zip code i
\textit{house2[i]}: the number of households with 2 members in zip code i
\textit{house3[i]}: the number of households with 3 members in zip code i
\textit{house4[i]}: the number of households with 4 members in zip code i
\textit{house5[i]}: the number of households with 5 members in zip code i
\textit{house6[i]}: the number of households with 6 members in zip code i
\textit{house7[i]}: the number of households with 7 members in zip code i

The sixth class in the model is called \textit{simulation} and is the main one amongst them. All the other five classes provide inputs to the \textit{simulation} class and then this class is run.

Here is a step by step explanation of the details of the \textit{simulation} class.

1. The data captured by the classes \textit{class1}, \textit{class2}, \textit{class3}, and \textit{class4} are imported to the \textit{simulation} class. For example, the total number of zip codes in the target community or the population of each one of these zip codes are imported.

2. Based on the population of the community imported in the previous step, individuals (i.e. agents) are created. These individuals are the fundamental units of the simulation and the progress of the simulation is reliant on them and the contacts that they make with each other in the mixing groups.

3. The individuals are assigned to zip codes and their age groups in that zip code. For example, individual A is assigned to age group1 (i.e. kids) in zip
code number 4. Also, age related attributes of the individuals are assigned to them.

4. The individuals are assigned to households, daycare centers, schools, workplaces. For example, individual A is assigned to household 258, in zip code 4. Since this individual is a kid, so he or she is assigned to a daycare center, for example daycare center number 3 in zip code number 8. Further, the individual needs to be assigned to a particular class in that daycare, for example daycare center group 2 in daycare center number 3 in zip code number 8.

5. In order to start the pandemic, five individuals are made infectious, because the default value for the status of the all individuals is 2 which means susceptible. So, five individuals are chosen from the whole population and their status are changed to infectious, so that as a result of the contacts between them and other susceptible individuals, the spread of the virus in the community starts.

6. The step time of this simulation is a day. In other words, the contacts between the individuals happen during a day and then at the end of the day the change in status for each individual is calculated. The simulation model starts with making five randomly chosen individuals infectious. First, individuals make contacts in their households with their household members. Then, the probability attribute is updated for every individual.
7. Individuals who go to daycare, school, or workplace make contacts with other individuals in their mixing groups and their *probability* attributes are updated.

8. For all individuals who make contacts in the community mixing groups such as stores, the *probability* attributes are updated after making contacts.

9. For the last three steps, the simulation model only keeps track of the contacts that only one side of the contact is infectious and the other one is susceptible. Also, the duration of contacts are different in week days versus weekends, and the simulation model takes this into consideration.

10. In the last step of the simulation model, based on the last updated value of *probability* attribute for each susceptible individual and comparing that value with a random number between 0 and 1, the simulation model decides that the individual becomes infected or not. For example, if the *probability* attribute’s value is 0.2 for individuals A, and the random number generated is 0.3, (since 0.3 is greater than 0.2) the individual becomes infected. Then, based on the previous attributes assigned to the individuals such as being symptomatic or asymptomatic in case of infection, or having severe symptoms, or being hospitalized, or dead, the individuals’ *status* attribute changes to symptomatic, asymptomatic, symptomatic with severe symptoms, hospitalized or dead.
Variables

There are a number of variables and arrays that are defined and used in the programs.

This is a list of the most important variables:

\( \text{nodaycareg}[i][j] \): number of classes (daycare groups) in daycare center \( j \) in zip code \( i \)

\( \text{noschoolg}[i][j] \): number of classes (school groups) in school \( j \) in zip code \( i \)

\( \text{noworkplaceg}[i][j] \): number of classes (workplace groups) in workplace \( j \) in zip code \( i \)

\( \text{nohouse}[i] \): number of houses in zip code \( i \)

\( \text{houseOb}[i][h][j] \): \( j \)th individual who lives in house \( h \) in zip code \( i \)

\( \text{houseCo}[i][h] \): number of individuals who reside in house \( h \) in zip code \( i \)

\( \text{daycareOb}[i][d][j][k] \): the \( k \)th person who goes to class \( j \) in daycare \( d \) in zip code \( i \)

\( \text{daycareCo}[i][d][j] \): number of children that go to class \( j \) in daycare \( d \) in zip code \( i \)

\( \text{schoolOb}[i][s][j][k] \): \( k \)th person who goes to class \( j \) in school \( s \) in zip code \( i \)

\( \text{schoolCo}[i][s][j] \): number of children that go to class \( j \) in school \( s \) in zip code \( i \)

\( \text{workplaceOb}[i][w][j][k] \): \( k \)th person who goes to workplace group (i.e. class) \( j \) in workplace \( w \) in zip code \( i \)

\( \text{workplaceCo}[i][w][j] \): number of adults that go to group (i.e. class) \( j \) in workplace \( w \) in zip code \( i \)

\( \text{infectedP}[i][j] \): \( j \)th infected person on a particular day during simulation in zip code \( i \)
\( \text{infectedC}[i] \): total number of infected individuals in zip code i on a particular day

\( \text{infectedpeople}[i] \): total number of infected people on day i

\( \text{symptomatic}[i] \): total number of ill people on day i

\( \text{hospitalized}[i] \): total number of hospitalized people on day i

\( \text{deadpeople}[i] \): total number of dead people on day i

A high level flowchart of the sub-sections of the simulation class explained above is shown in Figure 3-7. As mentioned before, this is the main class of the simulation model.

### 3.4. Pseudo code

In this section, a pseudo code for the main part of the simulation model is presented. The pseudo code contains the daily contacts of the individuals on each day in the mixing groups (i.e. household, daycares, schools, workplace, and community). Also, it shows how the status of the individuals are updated as a result of having contacts with infectious individuals. Further, it shows how the number of ill, hospitalized, or dead individuals are recorded at the end of each day, so that they can be used for further analysis by the program.
start simulation

Import data from data1, data2, data3, data4, and person

Create individuals (i.e. agents)

Make some individuals infectious

Assign individuals to their households, and daycares, schools, and workplaces

Assign individuals to the zip codes. Also, assign age related attributes to the individuals.

Time = 1

Time = Time + 1

Make contacts between individuals in the 4 mixing groups (e.g. households)

Update the status attribute of individuals

Update the probability attribute of susceptible individuals

Any infected individuals left

Yes

No

Output the end results

End simulation

Figure 3 - 7: Flowchart of the simulation class sections
******Pseudo code

For each day of the simulation

***update the status attributes of the individuals

For each individual in the population

Update the status attribute of the individual based on the results of the contacts of the individual with other individuals that had contact with the individual last day

List of possible status: Hospitalized, Dead, Ill with severe symptoms, Ill without severe symptoms, in incubation period, Infectious but not ill, Susceptible, Recovered

For all zip codes of the targeted area

For all the infectious individuals residing in the zip code

***Contacts in households

For all of the susceptible individuals that live in the same household as the infectious individual

Update the probability attribute of the susceptible individual

***Contacts in daycare centers

If the infectious individual is less than five years old and goes to a daycare center

For all susceptible individuals that go to the same daycare class as the infectious individual

Update the probability attribute of the susceptible individual

***Contacts at schools

Else If the infectious individual is less than 18 years old and goes to a school

For all susceptible individuals that go to the same school class as the infectious individual

Update the probability attribute of the susceptible individual

***Contacts at workplaces

Else If the infectious individual is less than 65 years old and goes to a workplace
For all susceptible individuals that go to the same workplace group as the infectious individual

Update the probability attribute of the susceptible individual

***Contacts in the community

For all the susceptible individuals that have contacts with the infectious individual

Update the probability attribute of the susceptible individual

*** Calculation of the probabilities at the end of the day

For all the susceptible individuals in the population

double r = Math.random();

If r > value of the individual’s probability attribute

Individual’s incubation period starts from tomorrow

Increase the number of infected individuals by one

IF individual’s hospitalization attribute is equal to one

Increase the total number of hospitalized individuals by one

IF individual’s dead attribute is equal to one

Increase the total number of dead individuals by one

IF individual’s symptomatic attribute is equal to one

IF individual’s sever attribute is equal to one

Increase the total number of outpatient individuals by one

ELSE

Increase the total number of onlyill individuals by one
3.5. Intervention Strategies

In Chapter 1 several intervention strategies were introduced that might be helpful during the course of pandemic influenza. In this research, we focus on two of these strategies, namely home confinement and school closure, which are explained as follows.

3.5.1. School Closure

According to this strategy, whenever the percentage of ill students in a school reaches to a threshold, that school is closed for a predefined number of weeks (e.g. two weeks). During school closure, household contact durations of the students are equal to the weekend values of those parameters. Duration of contacts in the household and community on weekends are twice their values on weekdays. Also, the number of contacts in community on weekends are twice their values on weekdays. However, household contact duration between these students and their household members who continue to go to a daycare center, a school and a workplace do not change.

3.5.2. Home Confinement

Based on this strategy, an infectious person with symptoms stays home until he or she recovers. Home confinement begins one day after showing symptoms. Duration of contacts between the confined person and his or her household members who stay home and do not go to work or school are equal to the weekend values of those parameter.
CHAPTER IV

DISEASE SPREAD SIMULATION FOR JEFFERSON COUNTY

4.1. Introduction

In this chapter an agent-based simulation is presented for an influenza disease spread in Jefferson County, Kentucky. The objective of this simulation is to demonstrate the pattern of the disease spread amongst the persons in a society using the socio-demographic data of Jefferson County.

In addition, three metrics of the effects of the pandemic on the target population, and the numbers of ill, hospitalized, and dead persons during the course of pandemic are evaluated. Then, two intervention strategies, school closing and home confinement that were mentioned in Chapter 3 are applied during the course of the pandemic in the simulation model to evaluate their effects on the three pre-mentioned metrics.

The influenza pandemic model consists of three components as described in Chapter 3. First, population structure; second, the disease characteristics and progress of the disease within the body; and third, the transmission of the disease between people. The same structure for these three components is considered for the models in this chapter.
The parameters of the simulation models such as the number of incubation days’ distribution or transmission rate of the disease are the same as the ones in Chapter 3.

4.2. Socio-Demographic Data of Jefferson County

Jefferson County is used as a real world case to demonstrate the pandemic influenza spread. Hence, socio-demographic data of Jefferson County is needed for the input of simulation and this section summarizes and explains this data. It is based on 2010 US Census and Department of Education database.

According to 2010 US Census the population of Jefferson County is 741,096. Further, 6.6%, 16.3%, 63.3%, and 13.8% of this population are in the first, second, third, and fourth age groups, respectively. In addition, there are 40 zip codes completely or partially located in this county. The population residing in these zip codes varies from a maximum of 45291 in zip code 40214 to a minimum of 59 in zip code 40025 with an average of 19749. A list of these zip codes and their populations are presented in Table 4-1. The total population of these 40 zip codes is 789977 which is more than the population of Jefferson County, because some of them are not completely within the borders of the county.

One of the data sets needed as the input of the simulation is the number of households in each zip code. Table 4-2 summarized the total number of households in each zip code and seven categories by household size; which range from one person in the household to seven and more persons in it. There are 326749 households as a total in these 40 zip codes, with a maximum of 18573 households in zip code 40214.
Table 4 - 1: Zip codes completely or partially located in Jefferson County

<table>
<thead>
<tr>
<th>Zip code</th>
<th>Population</th>
<th>Zip code</th>
<th>Population</th>
</tr>
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<tbody>
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<td>40059</td>
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</tr>
<tr>
<td>40025</td>
<td>59</td>
<td>40241</td>
<td>28988</td>
</tr>
</tbody>
</table>

Table 4 - 2: Total number of households categorized by household size in every zip code

<table>
<thead>
<tr>
<th>Zip code</th>
<th>total</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>&gt;= 7</th>
</tr>
</thead>
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<td>4</td>
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</table>
Another data set is the zip codes and the number of people in each of the four age groups in these zip codes that are shown in Table 4.3.

<table>
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<td>40109</td>
<td>756</td>
<td>138</td>
<td>301</td>
<td>149</td>
</tr>
<tr>
<td>40177</td>
<td>617</td>
<td>177</td>
<td>216</td>
<td>59</td>
</tr>
<tr>
<td>40241</td>
<td>12201</td>
<td>3543</td>
<td>4344</td>
<td>1857</td>
</tr>
</tbody>
</table>

Table 4 - 3: number of people in age groups 1, 2, 3, and 4 in every zip code
4.3. Verification

In this section, verification of the simulation model is done. Three categories of input parameters of the simulation model are changed, and the simulation program is run for each one of the three altered models, separately. Then, the outputs of the simulation runs are examined and compared with the baseline simulation model. Scenarios for changing the input parameters are as follows: duration of contact with household members (scenario 1), transmission rate of the disease between infectious and susceptible people (scenario 2), and hospitalization rate of the infected individuals (scenario 3).

**Duration of contact with household members**

Table 3-4 shows the duration of contacts with other household members for each person depending on his/her age group. These values are decreased by 5% and
the simulation is run for 10 replications. Then, the number of ill individuals for this scenario is compared with the baseline model results (see Table A-1 and A-2 in Appendix A for the detailed results of simulation runs for baseline scenario and scenario 1). Table 4-4 shows the result of t-test for comparison of the means for the number of ill individuals for the two scenarios. The results of t-test show that the average number of ill individuals slightly decreased as a result of the 5% decrease in the duration of the contacts between individuals in the households.

Table 4 - 4 : two sample t-test results for comparison of the average number of ill individuals for baseline scenario and scenario 1. C2 and C7 represent baseline scenario and scenario 1, respectively.

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Mean</th>
<th>StDev</th>
<th>SE Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>C2</td>
<td>10</td>
<td>260458</td>
<td>1052</td>
<td>333</td>
</tr>
<tr>
<td>C7</td>
<td>10</td>
<td>256417</td>
<td>832</td>
<td>263</td>
</tr>
</tbody>
</table>

Difference = μ (C2) - μ (C7)
Estimate for difference: 4042
95% CI for difference: (3147, 4937)
T-Test of difference = 0 (vs #): T-Value = 9.53  P-Value = 0.000  DF = 17

**Transmission rate of the disease**

Table 3-3 shows the transmission rate of the disease between an infectious individual and a susceptible one, depending on their age groups. These values are increased by 5% and the simulation is run for 10 replications. Then, the number of ill individuals for this scenario is compared with the baseline model results (see Table A-3 in Appendix A for the detailed results of simulation runs for scenario 2). Table 4-5 shows the results of t-test for comparison of the means for the number of ill individual for the two scenarios. The results of t-test show that the average
number of ill individuals slightly increased as a result of the increase in the transmission rate of the disease.

Table 4 - 5: two sample t-test results for comparison of the average number of ill individuals for baseline scenario and scenario 2. C2 and C22 represent baseline scenario and scenario 2, respectively.

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Mean</th>
<th>StDev</th>
<th>SE Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>C2</td>
<td>10</td>
<td>260458</td>
<td>1052</td>
<td>333</td>
</tr>
<tr>
<td>C22</td>
<td>10</td>
<td>273445</td>
<td>587</td>
<td>186</td>
</tr>
</tbody>
</table>

Difference = μ (C2) - μ (C22)
Estimate for difference: -12986
95% CI for difference: (-13803, -12169)
T-Test of difference = 0 (vs ≠): T-Value = -34.09  P-Value = 0.000  DF = 14

Hospitalization rate of the ill individuals

Table 3-7 shows the hospitalization rate of the infected individuals for an individual depending on his/her age group. These values are decreased by 5% and the simulation is run for 10 replications for this scenario (see Table A-4 in the Appendix A for the results of the simulation runs for scenario 3). It is expected that changing these values should only change the number of hospitalized and dead people during the pandemic and not the number of ill people.

Then, the number of ill, hospitalized and dead individuals during the pandemic for baseline scenario and scenario 3 are compared. Table 4-6, 4-7, and 4-8 show the results of the comparison of the means of the number of ill, hospitalized, and dead individuals for baseline scenario and scenario 3, respectively.
As shown in Table 4-6, the difference between the number of ill individuals for baseline scenario and scenario 3 is not statistically significant.

Table 4 - 6: two sample t-test results for comparison of the average number of ill individuals for baseline scenario and scenario 3. C2 and C27 represent baseline scenario and scenario 3, respectively.

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Mean</th>
<th>StDev</th>
<th>SE Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>C2</td>
<td>10</td>
<td>260458</td>
<td>1052</td>
<td>333</td>
</tr>
<tr>
<td>C27</td>
<td>10</td>
<td>260409</td>
<td>576</td>
<td>182</td>
</tr>
</tbody>
</table>

Difference = μ (C2) - μ (C27)
Estimate for difference: 49
95% CI for difference: (-770, 868)

T-Test of difference = 0 (vs ≠): T-Value = 0.13  P-Value = 0.899  DF = 13

Table 4-7 and 4-8 show that the number of hospitalized and dead individuals are smaller for scenario 3 compared to baseline scenario.

Table 4 - 7: two sample t-test results for comparison of the average number of hospitalized individuals for baseline scenario and scenario 3. C3 and C28 represent baseline scenario and scenario 3, respectively.

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Mean</th>
<th>StDev</th>
<th>SE Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>C3</td>
<td>10</td>
<td>10490</td>
<td>107</td>
<td>34</td>
</tr>
<tr>
<td>C28</td>
<td>10</td>
<td>10007.0</td>
<td>91.0</td>
<td>29</td>
</tr>
</tbody>
</table>

Difference = μ (C3) - μ (C28)
Estimate for difference: 483.1
95% CI for difference: (389.2, 577.0)

T-Test of difference = 0 (vs ≠): T-Value = 10.85  P-Value = 0.000  DF = 17
Table 4 - 8: two sample t-test results for comparison of the average number of dead individuals for baseline scenario and scenario 3. C2 and C29 represent baseline scenario and scenario 3, respectively.

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Mean</th>
<th>StDev</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>C4</td>
<td>10</td>
<td>525.2</td>
<td>89.0</td>
<td>28</td>
</tr>
<tr>
<td>C29</td>
<td>10</td>
<td>4999.8</td>
<td>67.7</td>
<td>21</td>
</tr>
</tbody>
</table>

Difference = μ (C4) - μ (C29)
Estimate for difference: 250.4
95% CI for difference: (175.4, 325.4)
T-Test of difference = 0 (vs ≠): T-Value = 7.08  P-Value = 0.000  DF = 16

4.4. Simulation Setup

In this section, three simulation scenarios, baseline (without intervention strategy), school closing, and home confinement are established and the computational results of the simulations are analyzed.

In the school closure scenario, a school is closed for three weeks when the threshold for ill students is 3% and in the home confinement scenario 30% of the ill persons stay home until recovery.

In order to calculate the effectiveness of each strategy, we use

\[
Effectiveness = \frac{[\text{Baseline attack rate} - \text{attack rate with intervention}]}{\text{Baseline attack rate}}
\]  

For example, if the population of a community is 100,000, and the total number of illness cases during a pandemic is 30,000 individuals without establishment of interventions strategies, and 25,000 while intervention strategies are applied, the effectiveness of the intervention strategies is \((30,000/100,000 - 25,000/100,000)/(30,000/100,000) = 16.6\%\).
The simulation model is run for 50 replications for each scenario. On the first day of the simulation five individuals are set as infectious and the simulation continues day by day until there is no more infected individual left in the community.

### 4.5. Results of the Simulation

Tables B-1, B-2, and B-3 in Appendix B show the number of infected, ill, hospitalized, and dead individuals for each of the 50 simulation runs for baseline, home confinement, and school closure strategies, respectively. Further, Tables B-4, B-5, and B-6 in Appendix B show the average weekly number of infected, ill, hospitalized, and dead individuals for baseline, home confinement, and school closure strategy, respectively.

Figure 4-1 shows the results for ill (symptomatic infectious) people per week for the three scenarios. Results of the simulation runs show that 32.97% (32.94%, 33.00% with 95% CI) of the population were ill during the pandemic for baseline scenario. Further, 29.96% (29.93%, 30.00% with 95% CI) and 30.83% (30.71%, 30.94% with 95% CI) of the population were ill during the pandemic when the home confinement and school closing strategies were established, respectively (see Table 4-9 for more detailed results from Minitab software output). These two particular intervention strategies show 9.1% and 6.5% effectiveness regarding the number of ill people, respectively.
Figure 4 - 1: number of illness cases per week during the pandemic

The maximum weekly illness cases during the school closure show a reduction compared to home confinement and baseline scenarios. The maximum weekly illness during the baseline and home confinement scenarios are 69364 and 68470 persons, respectively, whereas it is 51827 during school closure scenario.

Table 4 - 9: one – sample T test results for the illness rate of the pandemic for three scenarios: C5, C6, and C7 indicate the baseline, home confinement, and school closure strategies, respectively.

<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
<th>Mean</th>
<th>StDev</th>
<th>SE Mean</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>C5</td>
<td>50</td>
<td>0.329721</td>
<td>0.001057</td>
<td>0.000149</td>
<td>(0.329421, 0.330022)</td>
</tr>
<tr>
<td>C6</td>
<td>50</td>
<td>0.299698</td>
<td>0.001156</td>
<td>0.000163</td>
<td>(0.299370, 0.300027)</td>
</tr>
<tr>
<td>C7</td>
<td>50</td>
<td>0.308304</td>
<td>0.004150</td>
<td>0.000587</td>
<td>(0.307125, 0.309483)</td>
</tr>
</tbody>
</table>

Figure 4-2 shows the weekly number of hospitalized persons during the pandemic for the three scenarios. The results of the simulation runs show that 10472, 9890, and 10404 individuals were hospitalized during the baseline, home confinement, and school closure scenarios, respectively. The results of t-test in Table 4-10 show statistically significant reduction in the hospitalization when the
home confinement strategy was established (see Table B-2 and B-5 in Appendix B for more details).

Table 4 - 10: The output of two-sample t-test for comparison of the means of the number of hospitalization cases for baseline and home confinement scenarios. C9, and C10 indicate the baseline and home confinement scenarios, respectively.

<table>
<thead>
<tr>
<th></th>
<th>SE</th>
<th>N</th>
<th>Mean</th>
<th>StDev</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>C9</td>
<td>50</td>
<td>10472</td>
<td>107</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>C10</td>
<td>50</td>
<td>9890.4</td>
<td>87.8</td>
<td>12</td>
<td></td>
</tr>
</tbody>
</table>

Difference = μ (C9) - μ (C10)
Estimate for difference: 581.7
95% CI for difference: (542.8, 620.5)
T-Test of difference = 0 (vs ≠): T-Value = 29.74  P-Value = 0.000  DF = 94

Also, the results of t-test in Table 4-11 show statistically significant reduction in hospitalization rate for the school closing strategy at 95% confidence level (see Table B-3 and B-6 in Appendix B for more details). However, the amount of reduction is not as much as the one for home confinement strategy.

Table 4 - 11: The output of two-sample t-test for comparison of the means of the number of hospitalization cases for baseline and school closure scenarios. C9, and C11 indicate the baseline and school closure scenarios, respectively.

<table>
<thead>
<tr>
<th></th>
<th>SE</th>
<th>N</th>
<th>Mean</th>
<th>StDev</th>
<th>SE Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>C9</td>
<td>50</td>
<td>10472</td>
<td>107</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>C11</td>
<td>50</td>
<td>10404.4</td>
<td>69.8</td>
<td>9.9</td>
<td></td>
</tr>
</tbody>
</table>

Difference = μ (C9) - μ (C11)
Estimate for difference: 67.6
95% CI for difference: (31.7, 103.5)
T-Test of difference = 0 (vs ≠): T-Value = 3.75  P-Value = 0.000  DF = 84
Figure 4-2: number of hospitalization cases per week during the pandemic

Figure 4-3 shows the weekly death rate during the pandemic. Simulation results show on average 5241, 4982, and 5207 individuals died during the pandemic under the baseline, home confinement, and school closure scenarios. The results of t-test in Table 4-12 show statistically significant reduction in the death rate when the home confinement strategy was established (see Table B-2 and B-5 in Appendix B for more details).

Table 4-12: The output of two-sample t-test for comparison of the means of the number of death cases for baseline and home confinement scenarios. C13, and C14 indicate the baseline and home confinement scenarios, respectively.

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Mean</th>
<th>StDev</th>
<th>SE Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>C13</td>
<td>50</td>
<td>5240.6</td>
<td>61.2</td>
<td>8.7</td>
</tr>
<tr>
<td>C14</td>
<td>50</td>
<td>4982.8</td>
<td>60.3</td>
<td>8.5</td>
</tr>
</tbody>
</table>

Difference = μ (C13) - μ (C14)
Estimate for difference: 257.8
95% CI for difference: (233.7, 281.9)
T-Test of difference = 0 (vs ≠): T-Value = 21.22  P-Value = 0.000  DF = 97
Also, the result of t-test in Table 4-13 show statistically significant reduction in the death rate for the school closing strategy at 95% confidence level (see Table B-3 and B-6 in Appendix B for more details). However, the amount of reduction is not as much as the one for home confinement strategy.

Table 4 - 13: The output of two-sample t-test for comparison of the means of the number of death cases for baseline and school closure scenarios. C13, and C15 indicate the baseline and school closure scenarios, respectively.

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Mean</th>
<th>StDev</th>
<th>SE Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>C13</td>
<td>50</td>
<td>5240.6</td>
<td>61.2</td>
<td>8.7</td>
</tr>
<tr>
<td>C15</td>
<td>50</td>
<td>5207.0</td>
<td>73.4</td>
<td>10.0</td>
</tr>
</tbody>
</table>

Difference = μ (C13) - μ (C15)
Estimate for difference: 33.6
95% CI for difference: (6.8, 60.4)
T-Test of difference = 0 (vs ≠): T-Value = 2.49  P-Value = 0.015  DF = 94

Figure 4 - 3: number of death cases per week during the pandemic
4.6. Sensitivity Analysis

A sensitivity analysis is conducted on the probability of being symptomatic (PBS) when a person is infected with the disease. This value is considered to be equal to 67% in the literature. Here, two other values for PBS, 50% and 90%, are considered and the illness rates during the pandemic are evaluated for these rates and then compared with the baseline scenario with 67% PBS.

The simulation is run for 50 replications for each of the two values for PBS, 50%, and 90%. The detailed results of the simulation runs are presented in Table 1 to 4 in Appendix C. Figure 4-4 shows the weekly number of ill people during the pandemic for three scenario, baseline scenario with 67%, 50%, and 90% PBS. The total number of ill individuals under the baseline scenario with 67% PBS is 260472 whereas this value is 186505 and 368172 when PBS is 50% and 90%, respectively. The attack rate of the pandemic decreases by 28.3% when PBS decreases to 50%, and increases by 41.3% when PBS increases to 90%. The results of the simulations show that changes in the value of PBS can have a drastic effect on the attack rate of the pandemic.
Figure 4 - 4: number of illness cases per week during the pandemic

4.7. Summary

In this chapter, an agent-based model was presented that simulates the spread of the pandemic influenza in a real world community (i.e. Jefferson County, KY). Two intervention strategies, home confinement and school closure were established and the effects of them on the number of illness, hospitalization, and death cases were compared with the baseline scenario. Both of the intervention strategies show a reduction on the number of illness cases during the pandemic.
CHAPTER V

SIMULATION-BASED OPTIMIZATION

5.1. Introduction

In Chapter 4, a simulation model was presented to evaluate the effects of two intervention strategies on the illness, hospitalization, and death rates during a pandemic in Jefferson County. The intervention strategies applied in Chapter 4 were established for particular values of the control variables. For example, the length of school closure for school closure strategy was three weeks. However, one might change the values for these control variables and find different results for the output metrics of the simulation for every set of control variables.

For home confinement and school closure strategies presented in previous chapters, rate of home confinement, length of school closure, and closure threshold are the control variables. Depending on the range defined for each of these control variables, hundreds of scenarios can be generated for strategies which have different effects on the desired output metrics.

In this chapter, simulation-based optimization models are presented which aim at finding a combination of the strategies (i.e. set of control variable values) that result in the best value for an objective function of the defined metrics under
a set of constraints. Also, a procedure is presented to solve the optimization models.

5.2. Optimization Model

Illness of an individual in an influenza pandemic can have some cost associated with it. This cost is even bigger for hospitalization and death. Meltzer et al. (1999) presents the costs associated with illness, hospitalization, and death for an individual in case of a pandemic.

In the following model, the first term of the objective function (i.e. $\sum_{w=1}^{W} \sum_{g=1}^{G} \alpha_g \text{Ill}_{wg}$) includes the cost associated with ill individuals that don’t show severe symptoms. An ill person can show severe symptoms of disease and visit a hospital or clinic as an outpatient. The second term of the objective function (i.e. $\sum_{w=1}^{W} \sum_{g=1}^{G} \delta_g \text{Outp}_{wg}$) includes the cost associated with outpatients. The costs associated with hospitalized individuals that are required to stay in the hospital is shown in the third term of the objective function (i.e. $\sum_{w=1}^{W} \sum_{g=1}^{G} \beta_g \text{Hos}_{wg}$). The costs associated with dead individuals is shown in the fourth term of the objective function (i.e. $\sum_{w=1}^{W} \sum_{g=1}^{G} \gamma_g \text{Dead}_{wg}$). Applying home confinement and school closure strategies have some cost associated with them. For example, in a home confinement strategy, if a person is withdrawn from work, the cost associated with absenteeism from work might be also under consideration. The last two terms, $\sum_{w=1}^{W} \delta \times \text{SCC}_w/5$ and $\sum_{w=1}^{W} \sum_{g=1}^{G} \epsilon_g \text{CC}_{wg}$, of the objective function consider the costs associated with establishing the school closure and home confinement strategies, respectively.
As shown in Figure 4-1, the maximum weekly values for the number of ill, hospitalized, and dead persons for school closure strategy were smaller than these in the other two scenarios. The healthcare systems usually encounter scarcity of the medical resources and lowering the maximum weekly value of the metrics can have a significant impact on the healthcare systems. Constraint 5.5 addresses these restrictions.

Finally, the cost associated with one ill, hospitalized, or dead person is different from one age group to another one. In addition, the cost associated with home confinement varies in different age groups. These details are considered in all parts of the objective function.

**Notations**

**Indices and Sets**

\( g \in G \) : Set of age groups

\( w \in W \) : Set of days of the pandemic

**Parameters**

\( MSC \) : upper limit on the number of weeks that a school is closed in school closure strategy

\( UCT \) : upper limit on the school closure threshold when establishing school closure strategy

\( UCR \) : upper limit on the rate of home confinement when establishing home confinement strategy
\( MHR_w \): units of medical resources (e.g. beds) available at the healthcare centers for hospitalized individuals in day \( w \)

\( \rho \): units of medical resources needed per hospitalized person

\( \alpha_g \): total cost associated with one ill person without severe symptoms in age group \( g \)

\( \partial_g \): total cost associated with one ill person with severe symptoms in age group \( g \)

\( \beta_g \): total cost associated with one hospitalized person in age group \( g \)

\( \gamma_g \): total cost associated with one dead person in age group \( g \)

\( \delta \): total cost associated with one class closed per week

\( \varepsilon_g \): total cost associated with one day home confinement per person in age group \( g \)

\( W \): Total duration of pandemics in days

\( G \equiv (1, 2, 3, 4) \)

**Variables:**

\( SC \): length of school closure (in week)

\( CR \): rate of home confinement

\( CT \): school closure threshold

**Outputs:**

\( Ill_w \): number of persons who got ill in day \( w \)

\( Hos_w \): number of persons who got hospitalized in day \( w \)

\( Dead_w \): number of persons who died in day \( w \)

\( SCC_w \): number of classes in closure status on day \( w \)
\( \text{Outp}_{wg} \): number of persons who got ill with severe symptoms in age group g and day w

\( CC_{wg} \): number of person-day confinement in age group g and day w

**Objective function:**

\[
\text{Min } Z = E \left( \sum_{w=1}^{W} \sum_{g=1}^{G} \alpha_g \text{Ill}_{wg} + \sum_{w=1}^{W} \sum_{g=1}^{G} \delta_g \text{Outp}_{wg} + \sum_{w=1}^{W} \sum_{g=1}^{G} \beta_g \text{Hos}_{wg} + \sum_{w=1}^{W} \sum_{g=1}^{G} \gamma_g \text{Dead}_{wg} + \sum_{w=1}^{W} \delta \cdot \text{SCC}_w / 5 + \sum_{w=1}^{W} \sum_{g=1}^{G} \epsilon_g \text{CC}_{wg} \right)
\]  

(5.1)

**Constraints:**

\( SC \in [1,2,...,MSC] \)  

(5.2)

\( CR \in [1,2,...,UCR] \)  

(5.3)

\( CT \in [1,2,...,UCT] \)  

(5.4)

\( \rho_{Hos_w} \leq MHR_w \) for \( w = 1,2,...,W \)  

(5.5)

Constraint (5.2) shows that the number of weeks that a school can be closed is limited to 1, 2, ..., up to \( MSC \) weeks. Constraint (5.3) shows that the rate of home confinement is 1%, 2%, ..., up to \( UCR \) of the population. Constraint (5.4) shows that the school closure for a school starts on a particular day after 1% or 2%, ..., up to \( UCT \) of the population of that school are ill. Constraint (5.5) shows that the medical resources available for hospitalized persons on each day is less than an upper value amount, \( MHR_w \).
5.3. NSGS Procedure

In order to solve the models presented in previous sections, the NSGS procedure (see Nelson et al., 2001a) mentioned in Chapter 2 is used. This approach has some advantages compared to the standard ranking and selection procedures. Standard R&S procedures are popular because they are easy to apply and interpret, but they are usually practical to use when the number of comparing systems are relatively small, say less than 20. The NSGS approach presented in Nelson et al. (2001a) tackles the problems that have a larger number of feasible solutions (e.g. hundreds of solutions) and solve them in a reasonable amount of time.

In this section the NSGS approach is explained in more details. Also, it is explained how this procedure makes changes to the standard R&S procedures to be practical for solving larger problems.

Procedure NSGS:

Step 1: Set the below values:

1-\(\alpha\): the overall desired probability of finding the best strategy where \(\frac{1}{k} < 1 - \alpha < 1\)

\(\delta\) : called indifference zone (IZ) parameter and shows the smallest value that is practically significant in the objective function where \(\delta > 0\)

\(n_0\) : a common initial number of replication which is typically \(n_0 \geq 2\)

\(k\) : initial number of competing systems or in other words the number of scenarios that are compared with each other.
Also set \( t = t_{n_0 - 1, (1 - \frac{\alpha}{2})^{1/(k-1)}} \), which is the \((1 - \frac{\alpha}{2})^{1/(k-1)}\) quantile of the \( t \) student distribution with \( n_0 - 1 \) degree of freedom.

Obtain Rinott’s constant\(^8\) \( h = h(n_0, k, 1 - \frac{\alpha}{2}) \)

**Step 2**: take \( n_0 \) replication for each scenario and calculate the sample means \( \bar{Y}(X_i; n_0) \) and variances \( S(X_i)^2 = (\frac{1}{n_0-1}) \sum_{j=1}^{n_0} (y_j(X_i) - \bar{Y}(X_i; n_0))^2 \) for \( i = 1,2, ..., k \)

**Step 3**: calculate the quantity

\[
W_{ij} = t(S(X_i)^2 + S(X_j)^2)/n_0)^{1/2}
\]

for all \( i \neq j \). Form the screening subset \( I \), that contains every feasible solution (i.e. scenario) \( X_i \) where \( 1 \leq i \leq k \) and

\[
\bar{Y}(X_i; n_0) \leq \bar{Y}(X_j; n_0) + W_{ij} \quad \text{for all } i \neq j
\]

**Step 4**: if |\( I \)| = 1, then the system in \( I \) is the best solution which minimizes the objective function. Otherwise, compute for all \( i \in I \), second sample size.

\[
N_i = \max\{n_0, \lceil hS(X_i)/\delta \rceil \}
\]

where \( \lceil . \rceil \) is the ceiling function.

**Step 5**: Take \( N_i - n_0 \) additional replications from all systems \( i \in I \)

**Step 6**: compute the overall sample means \( \bar{Y}(X_i; n_0) \) for all \( i \in I \).

**Step 7**: select the system \( X_B = \arg \min_{X_i} \bar{Y}(X_i; N_i) \) as the best system (scenario) that minimizes the objective function.

---

\(^7\) For example, if \( \alpha = 0.05, n_0 = 10, \text{ and } k = 3 \), then \( t_{n_0 - 1, (1 - \frac{\alpha}{2})^{1/(k-1)}} = t_{9,(0.975)^{1/2}} = 2.68 \).

\(^8\) For example, \( h = h \left( n_0, k, 1 - \frac{\alpha}{2} \right) = h(10,3,0.975) = 3.72 \), when \( \alpha = 0.05, n_0 = 10, \text{ and } k = 3 \).
The Step 3 in the NSGS procedure is the major change presented by this procedure. In other words, Nelson et al. (2001a) presented a simple screening procedure that can be used to eliminate the noncompetitive systems after the first step (i.e. the first round of simulation that is done for all of the competing systems), thereby saving the number of observations that would be taken in the second stage of simulation (i.e. Steps 4 and 5). This procedure is the combination of a sub-set selection procedures that eliminate competitive solutions, and a ranking procedure applied to the competitive systems remaining in the system.

5.4. Simulation-based Optimization Model

In this sub-section, the model presented in Section 5.2 is used to establish a mathematical model to compare a range of intervention scenarios. After developing the mathematical model, a simulation-based optimization model (i.e. an integration of the NSGS procedure and the simulation model presented in Chapter 4) is established with JAVA. Then, the model is run to compare the intervention strategies and find the one with the smallest value for objective function.

The values for cost coefficients in the objective functions are based on Meltzer et al. (1999) and are summarized in Table 5-1. There are 102 competing scenarios in this model. School closure threshold can have 4 values, 2.5%, 5%, 7.5%, and 10%.

Length of school closure can have 5 values, 0, 1, 2, 3, or 4. A threshold is considered as a level of severe virus spread in the school in this study. A week is considered as the maximum tolerable length of school closure (every time a school is closed), without too much side effect on the education of the students, in this study.
weeks. Finally, rate of home confinement has 6 values, 0, 10, 20, 30, 40, or 50\%^{11}.

Table 5-1 summarizes these values.

Table 5 - 1: The values for school closure threshold, length of school closure and rate of home confinement considered for the model

<table>
<thead>
<tr>
<th>school closure threshold</th>
<th>2.50%</th>
<th>5%</th>
<th>7.50%</th>
<th>10%</th>
</tr>
</thead>
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<tr>
<td>length of school closure</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>rate of home confinement</td>
<td>0%</td>
<td>10%</td>
<td>20%</td>
<td>30%</td>
</tr>
</tbody>
</table>

According to the health authorities in Louisville Metro Area, one of the main healthcare resources at the time of a pandemic is the number of available hospital beds. There are approximately 2980 acute care hospital beds in Louisville Metro that could be used to treat patients with influenza if hospitalized. This constraint is also considered in the model.

The model presented in Chapter 3 and used in Chapter 4 needs to be modified to make a connection between the optimization model and simulation program. Figure 5-1 shows a high level view of this connection.

*Optimization model* is a class added to the model presented in Chapter 3 which makes a bridge between the above mathematical model and the simulation model (i.e. *simulation* class) and apply the NSGS procedure.

---

^{11} According to one of the Louisville Metro authorities, the maximum level for the rate of home confinement applicable in an urban area similar to Louisville is about 50\% of the population for an influenza outbreak.
There are two more classes that feed data to the *optimization model* class, *scenario* and *data5*. *Scenario* class provides information on the number of scenarios that are being compared together and the number of values for the control variables. The *data5* class provides data on the parameters and variables related to the NSGS procedure (e.g. Rinott’s constant) and the coefficients of the performance measures of the objective function that are summarized in Table 5-2.
Table 5 - 2: cost coefficients’ values in formula (5.1) (values in dollar)\textsuperscript{12}

<table>
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<tr>
<th></th>
<th>$\alpha_1$</th>
<th>$\beta_1$</th>
<th>$\delta_1$</th>
<th>$\gamma_1$</th>
<th>$\epsilon_1$</th>
<th>$\delta_2$</th>
<th>$\gamma_2$</th>
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<td>3435</td>
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<td>6842</td>
<td>300</td>
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</tr>
</tbody>
</table>

The program continues to run for each scenario as long as there is at least one infected individual left in the population.

5.5. Results of Simulation-Based Optimization

The simulation-based optimization model is run for six replications for the first step of the NSGS procedure for each scenario. Table 5-3 summarizes the output of the program for the first step of the NSGS procedure.

The highlighted scenario (i.e. the one with 50% rate of home confinement, and no school closure) in Table 5-3 is the only scenario that meets the criteria of NSGS procedure to go to the second step. Hence, there is no need for the second step and this scenario is the best one. The cost associated with it is $181,577,043.

\textsuperscript{12} There are four age groups considered in the model.
\textsuperscript{13} The cost of one week school closure for a school class is considered equal to the five days of pay rate for the teacher. Daily pay rate of a teacher is considered equal to $100 (see Meltzer et al. (1999) for average daily payment of adults).
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<th>Rate of home confinement</th>
<th>Closure Length (week)</th>
<th>Infected</th>
<th>Ill (no severe symptoms)</th>
<th>Out Patient</th>
<th>Hospitalized</th>
<th>Dead</th>
<th>Cost</th>
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Table 5 – 4 shows the t-test results for the outputs of the simulation model for the optimal scenario.
Table 5-4: t-test for the results of the simulation for the optimal scenario. C1, C2, C3, C4, and C5 are the number of infected, ill (only the ill persons without severe symptoms), outpatient, hospitalized, and dead individuals for this scenario.

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5.6. Sensitivity analysis

Table 5-2 shows $3435, $3435, $7605, and $8309 as the costs associated with one dead person in age group one, two, three, and four, respectively. These cost coefficients include the medical expenses, but don’t consider the future earning of the dead person. If the average present value of the life time earning of the dead individuals be included in the cost coefficients of the dead persons, the coefficients increase to $1,019,536, $1,019,536, $1,045,278 and $74,146, respectively. In this section, the effects of adding this portion of death cost is analyzed. The cost coefficients of the dead individuals are changed in the objective function of the model and then the NSGS procedure is applied to the simulation-based optimization model.

Table 5-5 shows the results of the first step of the NSGS procedure.
Table 5 - 5: number of infected, out-patient, ill with no severe symptoms, hospitalized, and dead individuals and cost per scenario for the first round of NSGS process

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</table>

The highlighted scenarios are the ones that go to the second step. All of the scenarios that considered 50% for the rate of home confinement are selected to go to the second step. The only scenario with a rate of home confinement different from 50% that goes to the second step is the scenario with 40% rate of home confinement and two weeks of school closure with 7.5% of school closure threshold.
The results from the second step in the NSGS procedure show that the scenario with 50% of the home confinement and 10% of school closure threshold and four weeks for school closure length is the best scenario.

Figures 5-2, 5-3, and 5-4 show the categorized average percent changes in the cost of pandemic as a result of applying the scenarios shown in Table 5-3 and Table 5-5. Figure 5-2 takes the average cost of all of the scenarios in Tables 5-3 and 5-5 for which the rate of home confinement control variable is the same and shows the percentage of change in cost compared to the baseline scenario. The blue line is for the model excluding the value of the life time earnings (VLTE) from the dead person’s cost and the red line is for the model including this cost in the analysis. For example, the red line in this graph shows that the average reduction in the cost across all the scenarios with the rate of home confinement equal to 40% is 9.7% compared to baseline scenario. For both cases, the percentage of reduction in cost increases as the rate of home confinement increases.

![Cost Reduction](image)

Figure 5 - 2: Percentage of reduction in cost as a result of change in the rate of home confinement
Figure 5-3 takes the average cost of all of the scenarios for which the length of school closure is the same and shows the percentage of change in cost compared to the baseline scenario. The model that includes VLTE is more sensitive to the length of school closure.

![Cost Reduction Graph](image)

**Figure 5 - 3:** Percentage of reduction in cost as a result of change in the length of school closure

Figure 5-4 takes the average cost of all of the scenarios for which the school closure threshold is the same and shows the percentage of change in cost compared to the baseline scenario. The model that include VLTE is more sensitive to the school closure threshold.

As shown in these three graphs, cost function is more sensitive to the rate of home confinement compared to the school closure’s control variables.
5.7. Effect of start time of strategy

After the influenza outbreak starts, the authorities have the option to respond with mitigation strategies. The starting point in time that the authorities apply these mitigation strategies can affect the degree of effectiveness of a strategy.

In this section, the best scenario chosen in section 5.5, starts to apply in three point in time, namely at the beginning, with one month, and two months delay after the start of the pandemic. The effects of these delays are analyzed and summarized in Figure 5-5.
Results of t-student test for one month and two month delay show significant difference in the number of ill persons compared to the one with no delay at 95% confidence interval. The number of ill persons for the scenarios with one month and two months delay increased by 1%, and 16% compared to the scenario with no delay, respectively. See Tables 5-6 and 5-7 for more details.

Table 5 - 6: The results of t-test for comparing the difference of the number of ill individuals for two scenarios; C1, the strategy with 50% comply rate for home confinement which starts at the beginning of the pandemic and C2, the strategy with 50% comply rate for home confinement which starts after one month delay.

<table>
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<td>709</td>
<td>317</td>
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<tr>
<td>C1</td>
<td>5</td>
<td>218688</td>
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<tr>
<td>Difference = μ (C2) - μ (C1)</td>
<td>Estimate for difference: 1826</td>
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<td></td>
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<tr>
<td></td>
<td>95% CI for difference: (903, 2748)</td>
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<tr>
<td>T-Test of difference = 0 (vs ≠): T-Value = 4.84 P-Value = 0.003 DF = 6</td>
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</tbody>
</table>

**Two-Sample T-Test and CI: C2, C1**
Table 5 - 7: The results of t-test for comparing the difference of the number of ill individuals for two scenarios, C1, the strategy with 50% comply rate for home confinement which start at the beginning of the pandemic and C2, the strategy with 50% comply rate for home confinement which starts after two months delay.

<table>
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<td>C1</td>
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<td>218688</td>
<td>456</td>
<td>204</td>
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</table>

Difference = μ (C3) - μ (C1)
Estimate for difference: 35713
95% CI for difference: (34524, 36903)
T-Test of difference = 0 (vs ≠): T-Value = 77.20 P-Value = 0.000 DF = 5

5.8. Summary

In this chapter a simulation-based optimization model was presented to evaluate the effectiveness of the school closure and home confinement mitigation strategies for pandemic influenza. The results of the analysis show that a home confinement strategy is more effective than baseline and school closure strategies. When the rate of home confinement is 50% and the school closure threshold is 10% and the length of school closure is 4 week, the cost of the pandemic shows a reduction of 12.7%.
CHAPTER VI

CONCLUSION AND FUTURE STUDY

Influenza pandemics are among the most damaging disasters for human being. Hundreds of thousands of people become ill, hospitalized, and dead during an influenza outbreak, leading to heavy costs to healthcare systems. Economic organizations lose billions of dollars as a result of work absenteeism and lower productivity of personnel.

Healthcare authorities are always looking for some preparedness or mitigation plans to reduce the ill effects of the pandemics, and vaccination, school closure, and home confinement are some of the mitigation strategies that are considered. Much research has been done to evaluate the effectiveness of the mitigation strategies in the past.

This research focuses on school closure and home confinement strategies. A simulation-based optimization model is presented that compares different scenarios for establishment of these strategies under a set of constraints and finds the best scenario based on the economic costs associated with them.
Jefferson County, KY is the target community in this research and considered to develop a real world case for the models presented in this study.

The results of the models show that home confinement is more effective relative to the school closure strategy. The economic costs of the pandemic are reduced by 12.7% when the rate of home confinement is 50% and the school closure threshold is 10% and the length of closure is four weeks.

This study expands the knowledge about the mitigation strategies. However, the horizon of knowledge in this area can be further expanded and here are some of the suggestions for future research:

- This study presents a framework for combining the optimization and simulation for evaluating the mitigation strategies in the case of a pandemic influenza. There are two mitigation strategies considered in this research. However, other mitigation strategies such as vaccination can be added to the considered strategies under this simulation-based optimization methodology in combination with home confinement and school closure.
- For the school closure strategies, only the cost associated with teacher's payment is considered in the analysis. One might consider the indirect educational impact of the closure and expand the model from that standpoint.
- In this research, we converted the performance over multiple measures (e.g. number of hospitalized or dead individuals) to a scalar measure using costs. If cost is not a suitable measure for healthcare authorities to use (for
example, if the importance of the lives of the individuals or limiting the number of dead people is critical in the decision making process), converting multiple performance measure to a scalar performance measure using multiple attribute utility (MAU) theory is another way to expand this study.
REFERENCES


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of the National Academy of Sciences of the United States of America, 101(48), 16915-16916.


645-653. Piscataway, New Jersey: Institute of Electrical and Electronics Engineers, Inc.


APPENDIX A

Table A - 1: number of infected, ill, hospitalized, and dead individuals for the simulation runs for baseline scenario

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Table A - 2: number of infected, ill, hospitalized, and dead individuals for the simulation runs for scenario 1

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Table A - 3: number of infected, ill, hospitalized, and dead individuals for the simulation runs for scenario 2

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Table A - 4: number of infected, ill, hospitalized, and dead individuals for the simulation runs for scenario 3

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APPENDIX B

Table B - 1: number of infected, ill, hospitalized, and dead individuals for the simulation runs for baseline scenario

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Table B - 4: Weekly number of infected, ill, hospitalized, and dead individuals for baseline scenario
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Table B - 7: number of infected, ill, hospitalized, and dead individuals for baseline, home confinement, and school closure scenarios for zip code 40214
APPENDIX C

Table C - 1: number of infected, ill, hospitalized, and dead individuals for the simulation runs for when symptomatic rate is 50%

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Table C - 3: Weekly number of infected, ill, hospitalized, and dead individuals when symptomatic rate is 50%

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Table C - 4: Weekly number of infected, ill, hospitalized, and dead individuals when symptomatic rate is 90%  

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# CURRICULUM VITA

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<tr>
<th>ARSALAN PALESHI</th>
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<tbody>
<tr>
<td>3325 AUDUBON RIDGE DR, LOUISVILLE, KY, 40213</td>
</tr>
<tr>
<td>Phone: (502)7771328</td>
</tr>
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<td><a href="mailto:paleshi@gmail.com">paleshi@gmail.com</a></td>
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## EDUCATION

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<td>PhD in Industrial Engineering</td>
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<td>University of Louisville, Louisville, KY</td>
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<tr>
<td>• Dissertation: <em>Simulation-based optimization of mitigation strategies for pandemic influenza</em></td>
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<tr>
<td>University of Louisville, Louisville, KY</td>
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<tr>
<td>MS in Social Economics System Eng.</td>
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<td>2006 - 2008</td>
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| Sharif University of Technology, Tehran, Iran | | *
| • Thesis: *Studying the profitability of momentum strategy and its sources in Tehran Stock Exchange* |
| BS in Industrial Engineering | 16.33/20 | 2001 - 2006 |
| Sharif University of Technology, Tehran, Iran | | |

## ACADEMIC EXPERIENCE

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<th>Years</th>
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<td>Research Assistant; Logistics &amp; Distribution Institute</td>
<td>UofL, KY</td>
<td>2011- 2012</td>
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<tr>
<td>• Collaboration with a 30 member UofL team of a multi-million dollar healthcare project funded by Kentucky Critical Infrastructure Protection Program</td>
<td></td>
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<td>• Development of simulation models to forecast the spread of pandemic influenza for Jefferson County, KY</td>
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<td>• Establishment of simulation-based optimization models to mitigate pandemic influenza for Jefferson County, KY</td>
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<tr>
<td>Teacher Assistant; Sharif University of Technology</td>
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## FELLOWSHIPS AND AWARDS

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<td>Industrial Engineering Doctoral Dissertation Award; UofL</td>
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<td>Best in Major Award; Engineering Exposition, UofL</td>
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<tr>
<td>American Society for Quality Award; The Louisville Section of American Society for Quality</td>
<td>2012</td>
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<tr>
<td>University Fellowship; UofL</td>
<td>2009</td>
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• Trivikram Rao, Arsalan Paleshi, Gail DePuy, Bulent Erenay, “A mathematical programming approach for assigning students to schools”, 61th Industrial Engineering Research Conference, May 2011, Reno, Nevada

• Arsalan Paleshi, Gerald W. Evans, Sunderesh S. Heragu, Kamran S. Moghaddam, “Disease Spread Model to evaluate the effectiveness of home confinement strategy during pandemic influenza, 3rd Health and Humanitarian Logistics Conference, March 2011, Atlanta, Georgia

• Hamid Foroughi, Arash Agha Gholizade Khiavi, Shahram Abyari Ali Abad, Arsalan Paleshi, “How price fluctuations is influenced by the response of intermediaries to different sales methods: A Case study in Automotives”, 26th International Conference of System Dynamics Society, July 2008, Athens, Greece

**Computer Skills**

- Programming: JAVA, VB
- Optimization: LINGO, GAMS, MATLAB
- Statistical Analysis: MINITAB, EVIEWS
- Geographic Information System: ArcGIS
- Project Management: MS-Project
- Simulation: ARENA, VENSIM
- Database Management: MS-Access
- Risk Analysis & Decision Making: DPL
- Design: CAD

**Extra-Curricular Activities**

- President, INFORMS Student Chapter, UofL 2011 –2012
- Vice-President, INFORMS Student Chapter, UofL 2010 - 2011
- Officer, American International Relations Club, UofL 2010 - 2011
- Webmaster, INFORMS Student Chapter, UofL 2009 - 2010