5-2015

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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A Dissertation
Submitted to the Faculty of the
J.B. Speed School of the University of Louisville
in Partial Fulfillment of the Requirements
for the Degree of

Doctor of Philosophy in Industrial Engineering

Department of Industrial Engineering
University of Louisville
Louisville, Kentucky

May, 2015

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January 27, 2015

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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

ACKNOWLEDGMENTS

I would like to express my sincere gratitude to my advisor Dr. Gerald Evans for the continuous support of my PhD study and research, for his patience, motivation, enthusiasm, and immense knowledge. His guidance helped me in all the time of research and writing of this dissertation. I would also like to thank the other committee members, Dr. Ki-Hwan Bae, Dr. Suraj Alexander and Dr. Julio Ramirez for their comments and assistance. Additionally, my thanks goes to Dr. Sunderesh Heragu for his support and insightful comments.

ABSTRACT

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January 27, 2015

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 world wide 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. (2009a) 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, influenzas 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:

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

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

$$\frac{dR(t)}{d(t)} = A(t)I(t) \tag{2.3}$$

$B(t)$ 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.

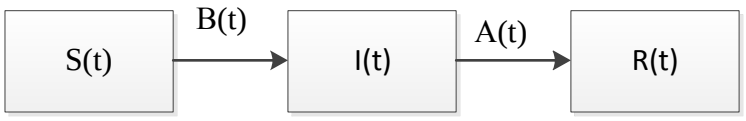

Figure 2 - 1: a compartmental epidemic model

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.

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

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

$$R(1) = R(0) + \frac{dR(0)}{d(t)} = 200 + 0.167 * 5 = 200.835$$

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, "β is the average number of infected persons per infectious subject per unit time, α is the reciprocal average latent period, and ϑ 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.

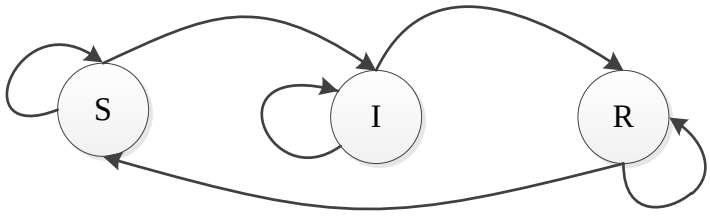

Figure 2 - 2: Markov Chain of transition probabilities in the SIR model

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)[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 pre-school, 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.

[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

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.

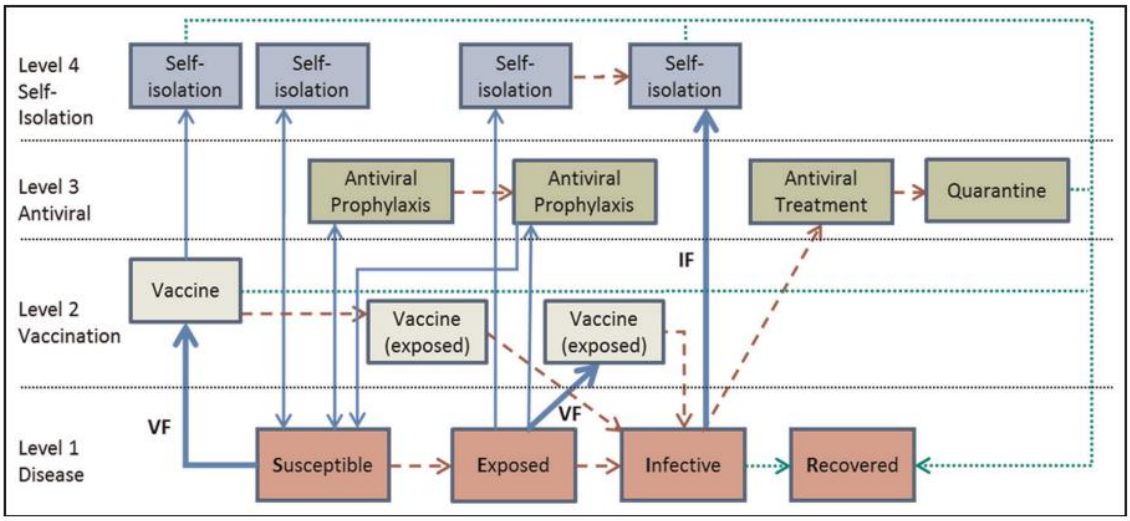

Figure 2 - 3: model transfer diagram[5]

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

[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

Simulation	Paper	Vaccination	School Closure	isolation	Travel restriction	Antiviral Prophylaxis	Wearing mask
Agent-Based simulation	Halder et al.(2014)	*					
	kelso et al. (2013)	*					
	Smieszek et al. (2011)						
	Mao et al. (2011)			*			
	Ridenhour et al. (2011)		*				
	Ventresca et al. (2013)	*					
	Potter et al. (2012)		*				
	Aleman et al. (2009a)						
	Aleman et al. (2009b)						
	Andradóttir et. al. (2010)	*	*	*		*	
	Dibble et al. (2010)	*					
	Elveback et al. (1976)	*	*				
	Ferguson et al. (2005)	*	*	*		*	
	Ferguson et al. (2006)	*	*	*		*	
	Germann et al. (2006)	*	*	*	*	*	
	Glass et al (2006)		*	*			
	Haber et al. (2007)		*	*			
	Longini et al. (2004)	*				*	
	Longini et al. (2005)	*		*		*	
	Kasaie et al. (2010)						
	Lizon et al. (2010)						
Differenti al- Equation Based Simulatio	Yarmand et al. (2013a)	*		*		*	
	Yarmand et al. (2013b)	*		*		*	
	Li et al. (2013)			*			
	Araz et al. (2013)		*				

	Carrasco et. Al.(2014)					*	
	Matrajt et al. (2013)	*					
	Chong et al. (2012)				*		
	Haimar et al. (2014)						
	Tracht et al. (2012)						*
	Lunger et al. (2012)	*					
	Xue et al. (2012)		*				
	Modchang et al. (2012)		*				
	Araz et al. (2009)		*				
	Carr et al. (2010)	*				*	
	Cooke et al. (1996)						
	Dushoff et al (2004)						
	Earn et al. (2000)						
	ferguson et al. (2003)	*				*	
	Lee et al. (2007)					*	
	Newman et al. (2002)						
	Yarmand et al. (2010)	*		*		*	
	Mills et al. (2004)						
No Model	Al-Tawfiq et al. (2013)			*			*
	Garza et al. (2013)		*				
	Berera et al. (2013)					*	
	Chowel et al. (2012)					*	

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).

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

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

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

$Y(X)$ 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, $H_1(X), H_2(X), \dots, H_w(X)$ 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 θ 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 $1-\propto$, that the solution selected has the smallest mean (in a minimization problem), if the mean of the best solution is at least δ 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.

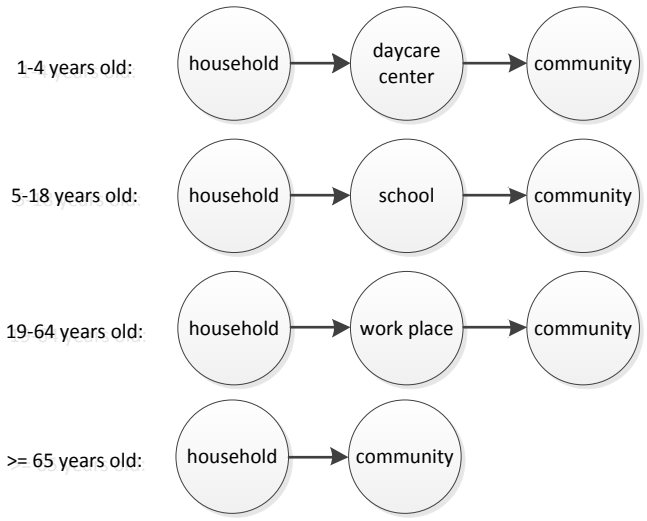

Figure 3 - 1: Mixing and age group

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.

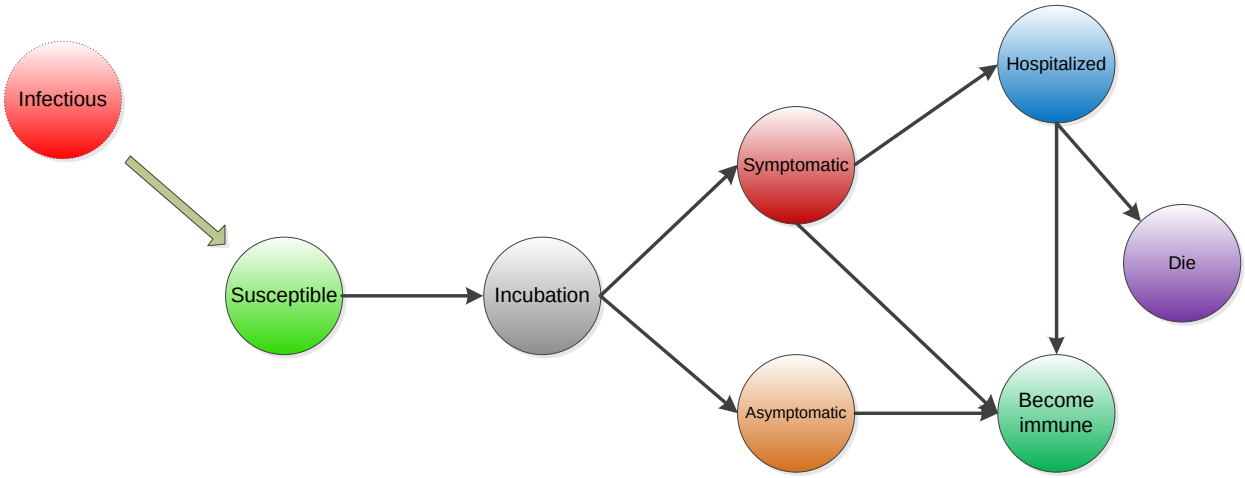

Figure 3 - 2: Progression of the disease in a susceptible person, as a result of contact with an infectious individual (Paleshi et al., 2011)

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

λ_{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 ≡ (1, 2, 3, 4)

K ≡ (1, 2, 3, 4, 5)

W ≡ (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

$\mathrm{B_{jkwt}}$: 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 $\mathrm{B_{jkwt}}$

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

$$\mathrm{P}(A_M) = 1 - \Pi_{\mathrm{k}}\Pi_{\mathrm{j}}\Pi_{w}\Pi_{\mathrm{b}\epsilon B_{jkwt}} \exp\left(-\lambda_{\mathrm{Mj}}\mathrm{d_{Mjkw}}\right) \quad (3.1)$$

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.

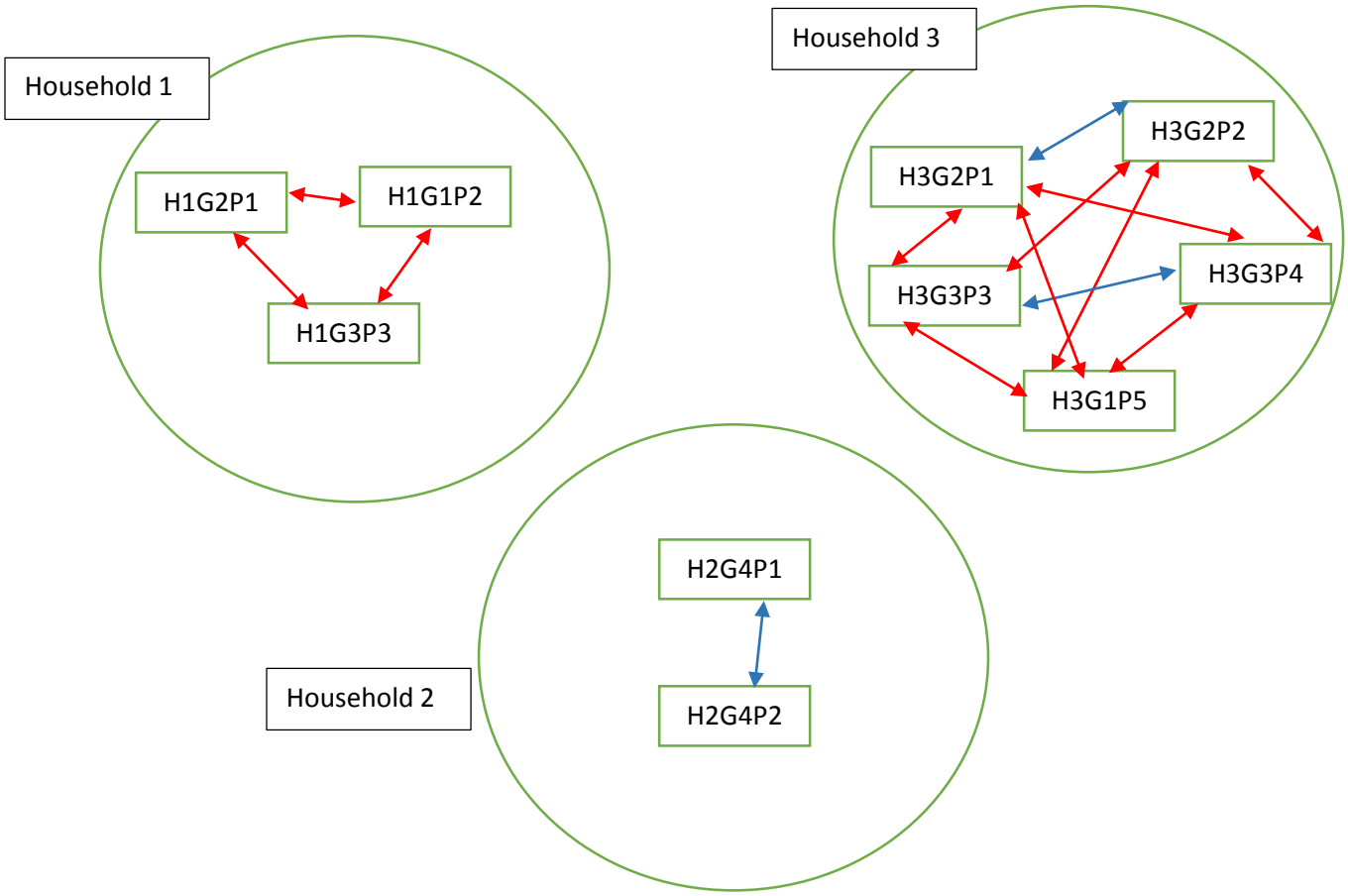

Figure 3 - 3: Contacts of the individuals in the households

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.

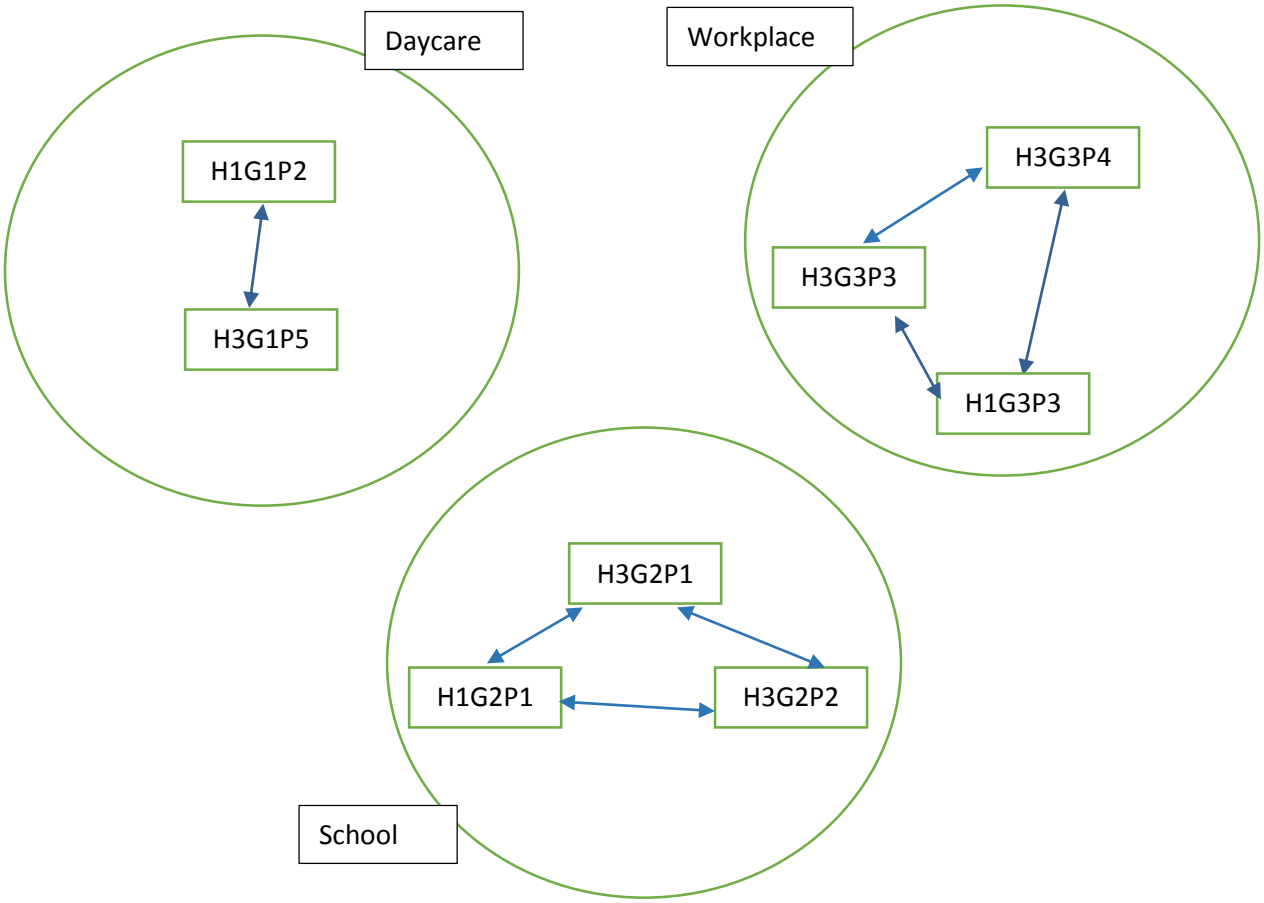

Figure 3 - 4: Contacts of the individuals in the daycare, school, and workplace

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.

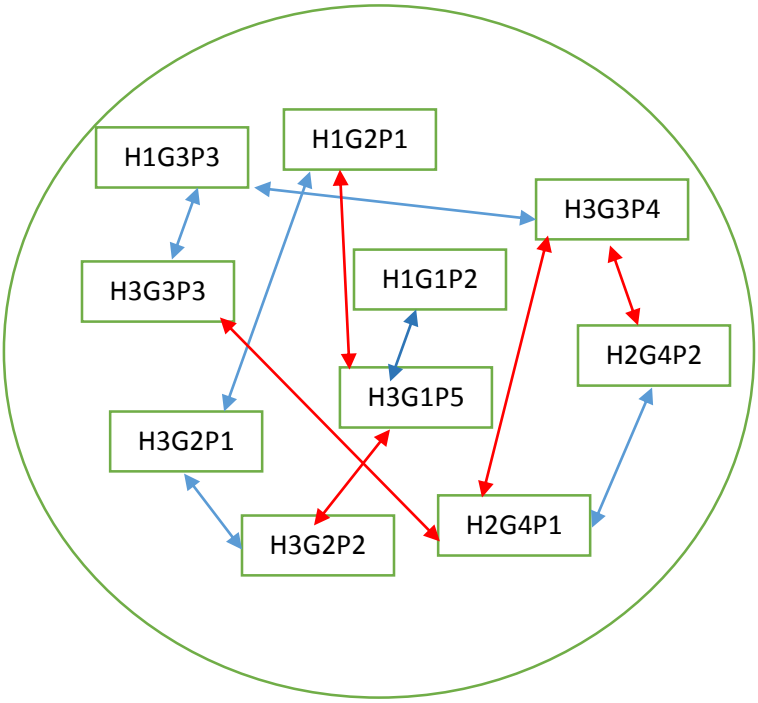

Figure 3 - 5: Contacts of the individuals in the community

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 $\beta = 1 - \exp(-0.00061 * 392) * \exp(-0.00061 * 392)$.

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 $\gamma = 1 - (1 - \alpha) * (1 - \beta) * 1 = 0.39$.

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

Incubation days	Probability
1	0.3
2	0.5
3	0.2

Table 3 - 2: Number of infectious days' distribution

Infectious days	Probability
3	0.3
4	0.4
5	0.2
6	0.1

One of the parameters used in the equation 3.1 was λ. 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

	Age group of susceptible person (m)			
Age group of infectious person (k)	0-4	5-18	19-64	>=65
0-4	0.00059	0.00062	0.00033	0.00080
5-18	0.00058	0.00061	0.00033	0.00080
19-64	0.00057	0.00053	0.00032	0.00080
>=65	0.00057	0.00054	0.00029	0.00102

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)

Age group	0-4	5-18	19-64	>=65
0-4	120	60	120	60
5-18	60	120	120	60
19-64	120	120	120	120
>=65	60	60	120	120

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

Age group	0-4	5-18	19-64	>=65
0-4	2,60	1,30	0,0	0,0
5-18	1,30	2,60	0,0	0,0
19-64	0,0	0,0	2,60	2,60
>=65	0,0	0,0	2,60	2,60

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 3 - 6: Probability of hospitalization and death given influenza infection

Age group	Hospitalization	Death
0-4	.00810	.00005
5-18	.00091	.00003
19-49	.00227	.00007
50-64	.00907	.00148
65-69	.02442	.00530
70-74	.04125	.00928
75-79	.05539	.01805
80-84	.0816	.03529
>=85	.15357	.09583

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.

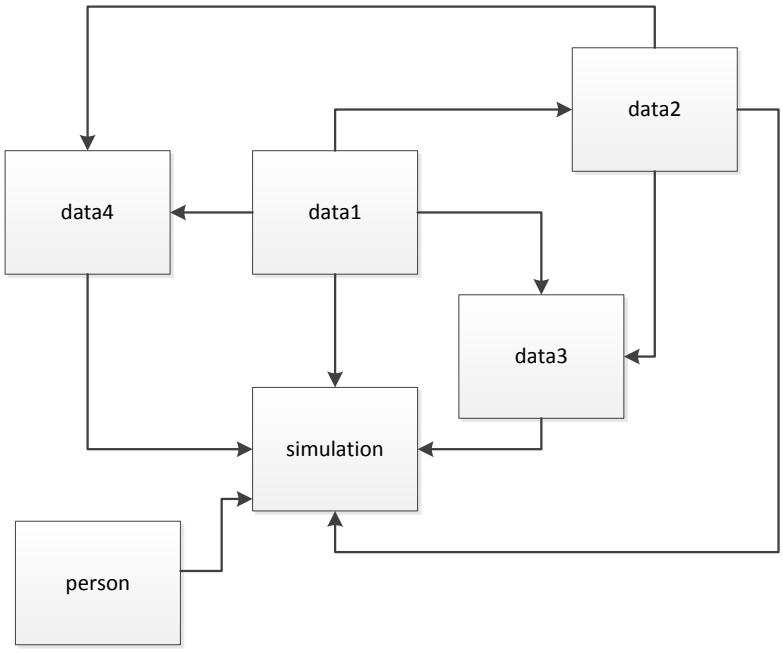

Figure 3 - 6: Relationship between the 6 classes of the simulation model

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

- *daycareg*: the group in a daycare center to which the pre-school child is assigned
- *schoolg*: the group in a school to which a school student is assigned
- *workplaceg*: 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
- *infectiousDayFinsihish*: the day on which the infectious period of the individual ends
- *numberOfIncubationDays*: duration of the incubation period for individual
- *numberOfInfeciousDays*: 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 3 - 7: data1 file

data	**Explanation**
nozipcode	Number of zip codes fully or partially located in the targeted area
maxzipp	Max. population amongst zip codes
maxnodaycare	Max. no. of daycares in a zip code
maxnoschool	Max. number of schools in a zip code
maxnoworkplace	Max. number of workplaces in a zip code.
maxnohouse	Max. number of households in a zip code
maxnodaycareg	Max. number of daycare classes (i.e. groups) in a daycare center
maxnoschoolg	Max. number of school classes in a school
maxnoworkplaceg	Max. number of workplace groups in a workplace
maxhousem	Max. number of persons in a house
maxdaycarem	Max. number of children in a daycare group
maxschoolm	Max. number of students in a school class
maxworkplacem	Max. number of persons in a workplace group
maxzage1p	Highest number of persons in the first age groups in a zip code

maxzage2p	Highest number of persons in the second age groups in a zip code
maxzage3p	Highest number of persons in the third age group in a zip code
maxzage4p	Highest number of persons in the fourth age group in a zip code
totalage1p	Total number of persons in the targeted area in the first age group
totalage2p	Total number of persons in the targeted area in the second age group
totalage3p	Total number of persons in the targeted area in the third age group

b) *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.

nodaycare[i]: Total number of daycares in zip code i

noschool[i]: Total number of schools in zip code i

noworkplace[i]: Total number of workplaces in zip code i

c) *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 work place is imported to the simulation program.

zippop[i]: population of the zip code i

zipage1p[i]: population of the 1st age group in zip code i

zipage2p[i]: population of the 2st age group in zip code i

zipage3p[i]: population of the 3rd age group in zip code i

zipage4p[i]: population of the 4th age group in zip code i

zipdaycarep[i][j]: number of children that go to daycare center j in zip code i

zipschoolp[i][j]: number of students that go to school j in zip code i

zipworkplacep[i][j]: number of adults that go to workplace j in zip code i

d) *data4*: in this class the number of households categorized by the household size are imported to the program. These are the imported data:

house1[i]: the number of households with 1 member in zip code i

house2[i]: the number of households with 2 members in zip code i

house3[i]: the number of households with 3 members in zip code i

house4[i]: the number of households with 4 members in zip code i

house5[i]: the number of households with 5 members in zip code i

house6[i]: the number of households with 6 members in zip code i

house7[i]: the number of households with 7 members in zip code i

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

Here is a step by step explanation of the details of the *simulation* class.

1. The data captured by the classes *class1, class2, class3,* and *class4* are imported to the *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:

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

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

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

nohouse[i]: number of houses in zip code i

houseOb[i][h][j]: jth individual who lives in house h in zip code i

houseCo[i][h]: number of individuals who reside in house h in zip code i

daycareOb[i][d][j][k]: the kth person who goes to class j in daycare d in zip code i

daycareCo[i][d][j]: number of children that go to class j in daycare d in zip code i

schoolOb[i][s][j][k]: kth person who go to class j in school s in zip code i

schoolCo[i][s][j]: number of children that go to class j in school s in zip code i

workplaceOb[i][w][j][k]: kth person who go to workplace group (i.e. class) j in workplace w in zip code i

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

infectedP[i][j]: jth infected person on a particular day during simulation in zip code i

infectedC[i]: total number of infected individuals in zip code i on a particular day

infectedpeople[i]: total number of infected people on day i

symptomatic[i]: total number of ill people on day i

hospitalized[i]: total number of hospitalized people on day i

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.

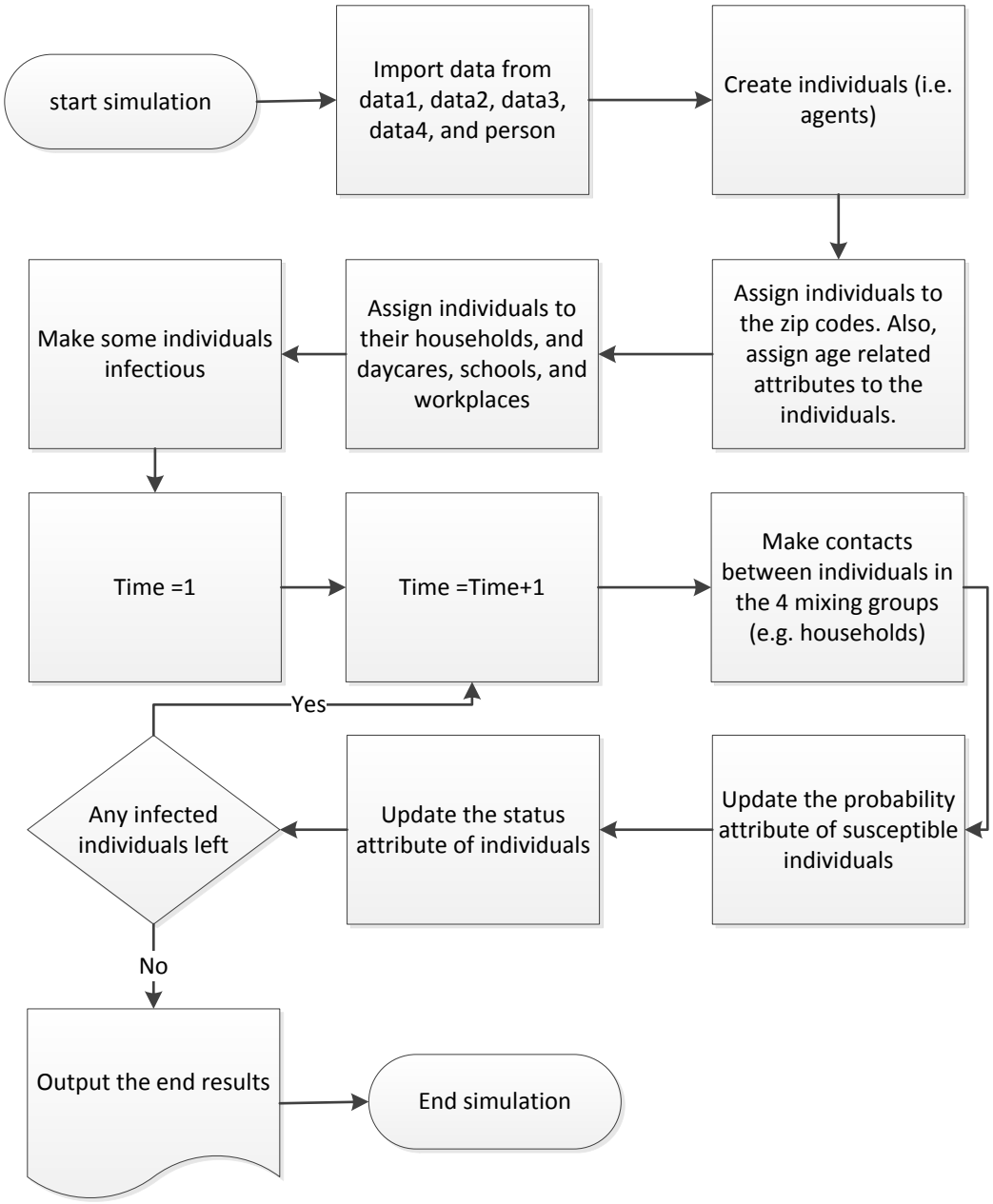

Figure 3 - 7: Flowchart of the simulation class sections

******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

Zip code	Population	Zip code	Population
40214	45291	**40218**	31658
40258	26465	**40223**	22011
40203	19694	**40228**	15743
40204	14236	**40243**	10210
40209	360	**40207**	29745
40216	40746	**40222**	21359
40205	23678	**40210**	14822
40206	18865	**40202**	6772
40208	13227	**40023**	4118
40280	303	**40245**	30109
40219	38032	**40059**	16708
40211	22612	**40299**	38371
40212	17685	**40047**	19345
40217	12507	**40291**	35427
40041	286	**40229**	36852
40220	33109	**40118**	9724
40215	22287	**40272**	37394
40213	16796	**40109**	1990
40242	10930	**40177**	1463
40025	59	**40241**	28988

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

	Number of Households (by Household size)							
Zip code	**total**	**1**	**2**	**3**	**4**	**5**	**6**	**>= 7**
40214	18573	5604	5868	3214	2315	1001	339	232
40258	10405	2650	3431	1881	1456	636	234	117
40203	9173	4841	1959	1049	666	365	151	142
40204	7417	3497	2497	795	418	133	52	25
40209	151	49	45	28	17	6	3	3
40216	16768	5113	5402	2789	2033	888	341	202
40205	10614	3944	3833	1422	979	321	81	34
40206	9488	4326	3125	1045	653	230	88	21
40208	5336	2279	1700	623	396	183	84	71
40280	91	16	53	11	7	4	0	0
40219	15331	4472	4946	2665	1869	849	334	196
40211	9064	3005	2477	1550	1020	557	258	197
40212	6839	2065	1945	1176	812	464	207	170
40217	5932	2317	2006	840	505	166	57	41
40041	151	133	17	0	0	0	1	0
40220	14512	4891	5023	2233	1502	581	191	91
40215	8786	2759	2518	1531	981	514	293	190
40213	7342	2442	2427	1225	735	329	119	65
40242	4665	1410	1716	693	534	211	68	33
40025	26	3	16	4	3	0	0	0

40218	13533	4863	4031	2114	1414	687	262	162
40223	9208	2705	3299	1368	1143	468	155	70
40228	6238	1649	2001	1114	912	375	125	62
40243	4595	1577	1602	677	483	193	44	19
40207	13905	5175	4858	1785	1343	556	139	49
40222	9898	3717	3591	1239	846	358	108	39
40210	5901	2153	1528	962	616	310	167	165
40202	2631	1775	592	173	57	23	1	10
40023	1446	156	593	269	264	104	39	21
40245	10749	1947	3773	1899	1996	828	226	80
40059	6086	1074	2210	989	1138	501	138	36
40299	15222	3745	5338	2608	2263	879	268	121
40047	7255	1399	2514	1416	1285	460	135	46
40291	14124	3363	5152	2503	1890	832	258	126
40229	13753	2924	4456	2696	2252	920	326	179
40118	3772	933	1223	738	494	234	99	51
40272	14240	3269	4817	2643	2061	921	338	191
40109	756	138	301	149	86	52	18	12
40177	617	177	216	113	59	39	9	4
40241	12201	3543	4344	1857	1622	608	173	54

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

Zip	zipage1p	zipage2p	zipage3p	zipage4p
40214	2989	7382	28669	6251
40258	1747	4314	16752	3652
40203	1300	3210	12466	2718
40204	940	2320	9011	1965
40209	24	59	228	49
40216	2689	6642	25792	5623
40205	1563	3860	14988	3267
40206	1245	3075	11942	2603
40208	873	2156	8373	1825
40280	20	49	192	42
40219	2510	6199	24074	5249
40211	1492	3686	14313	3121
40212	1167	2883	11195	2440
40217	825	2039	7917	1726
40041	19	47	181	39
40220	2185	5397	20958	4569
40215	1471	3633	14108	3075
40213	1109	2738	10632	2317
40242	721	1782	6919	1508
40025	4	10	37	8

40218	2089	5160	20040	4369
40223	1453	3588	13933	3037
40228	1039	2566	9965	2173
40243	674	1664	6463	1409
40207	1963	4848	18829	4105
40222	1410	3482	13520	2947
40210	978	2416	9382	2046
40202	447	1104	4287	934
40023	272	671	2607	568
40245	1987	4908	19059	4155
40059	1103	2723	10576	2306
40299	2532	6254	24289	5296
40047	1277	3153	12245	2670
40291	2338	5775	22425	4889
40229	2432	6007	23327	5086
40118	642	1585	6155	1342
40272	2468	6095	23670	5161
40109	131	324	1260	275
40177	97	238	926	202
40241	1913	4725	18349	4001

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.

```
Two-sample T for C2 vs C7

     N    Mean  StDev  SE Mean
C2  10  260458   1052      333
C7  10  256417    832      263


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.

```
Two-sample T for C2 vs C22

      N    Mean  StDev  SE Mean
C2   10  260458   1052      333
C22  10  273445    587      186


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.

```
Two-sample T for C2 vs C27

      N    Mean  StDev  SE Mean
C2   10  260458   1052      333
C27  10  260409    576      182


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.

```
Two-sample T for C3 vs C28

                          SE
      N     Mean  StDev  Mean
C3   10    10490    107    34
C28  10  10007.0   91.0    29


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.

```
Two-sample T for C4 vs C29

                          SE
      N    Mean  StDev  Mean
C4   10  5250.2   89.0    28
C29  10  4999.8   67.7    21


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

$$Effectiveness = \frac{[(Baseline\ attack\ rate) - (attack\ rate\ with\ intervention)]}{(Baseline\ attack\ rate)} \quad (4.1)$$

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%, 3094% 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.

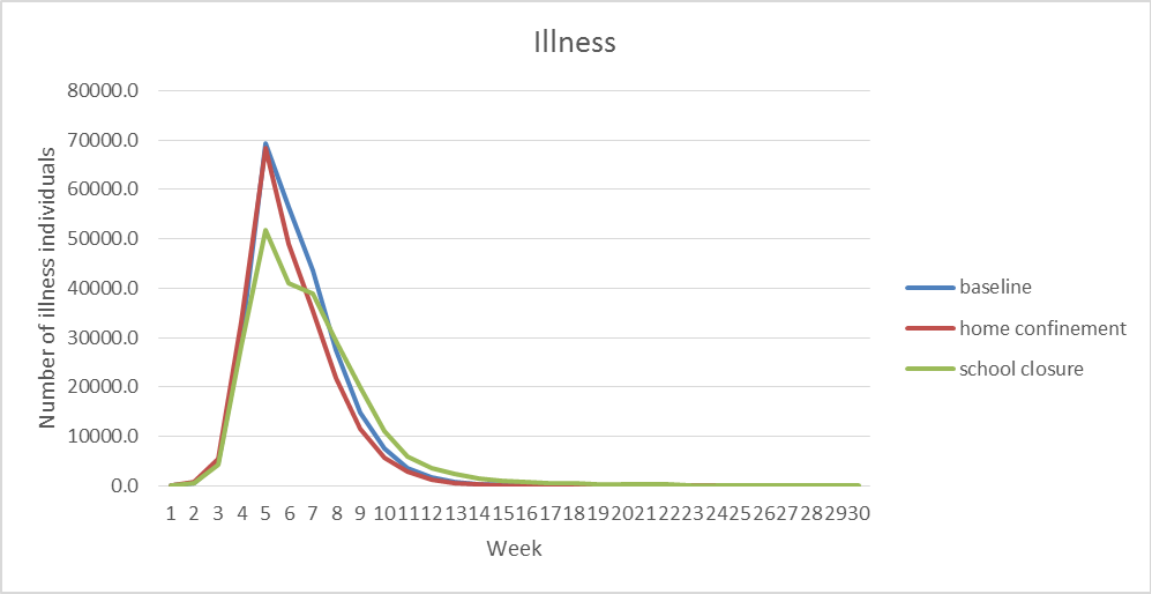

Figure 4 - 1: number of illness cases per week during the pandemic

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.

Variable	N	Mean	StDev	SE Mean	95% CI
C5	50	0.329721	0.001057	0.000149	(0.329421, 0.330022)
C6	50	0.299698	0.001156	0.000163	(0.299370, 0.300027)
C7	50	0.308304	0.004150	0.000587	(0.307125, 0.309483)

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.

```
Two-sample T for C9 vs C10

                 SE
    N    Mean  StDev  Mean
C9   50   10472    107    15
C10  50  9890.4   87.8    12


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.

```
Two-sample T for C9 vs C11

    N     Mean  StDev  SE Mean
C9   50    10472    107       15
C11  50  10404.4   69.8      9.9


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
```

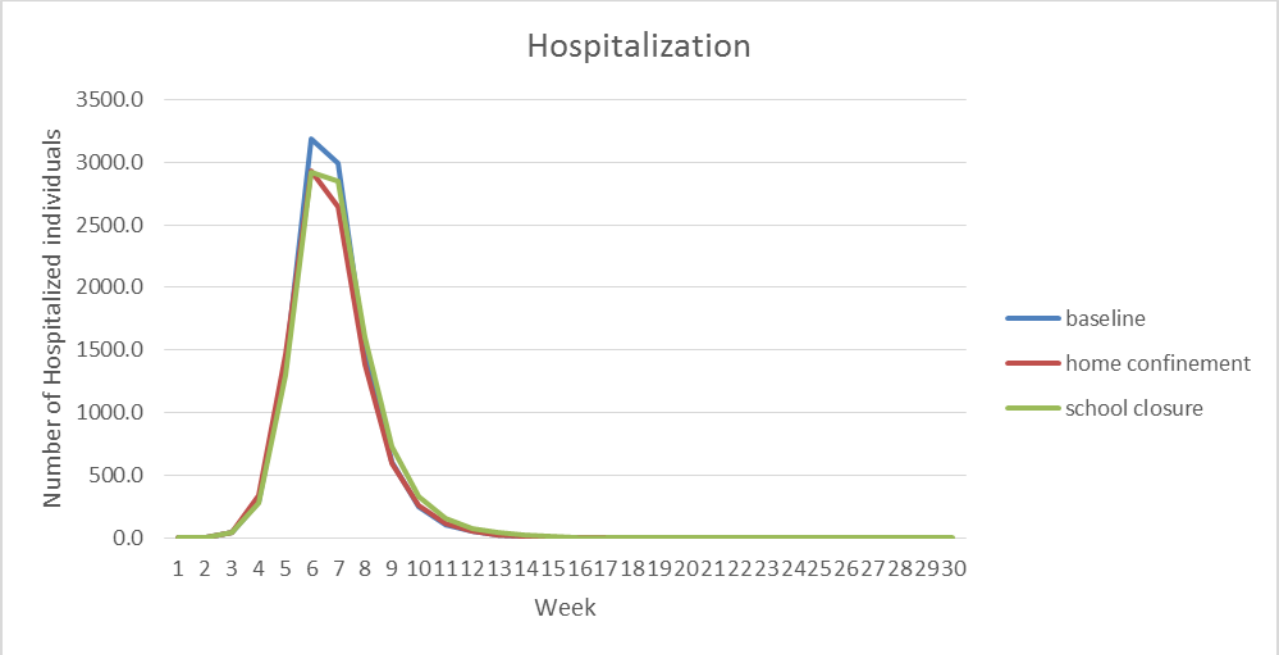

Figure 4 - 2: number of hospitalization cases per week during the pandemic

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.

Two-sample T for C13 vs C14

	N	Mean	StDev	SE Mean
C13	50	5240.6	61.2	8.7
C14	50	4982.8	60.3	8.5

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.

Two-sample T for C13 vs C15

	N	Mean	StDev	SE Mean
C13	50	5240.6	61.2	8.7
C15	50	5207.0	73.4	10

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

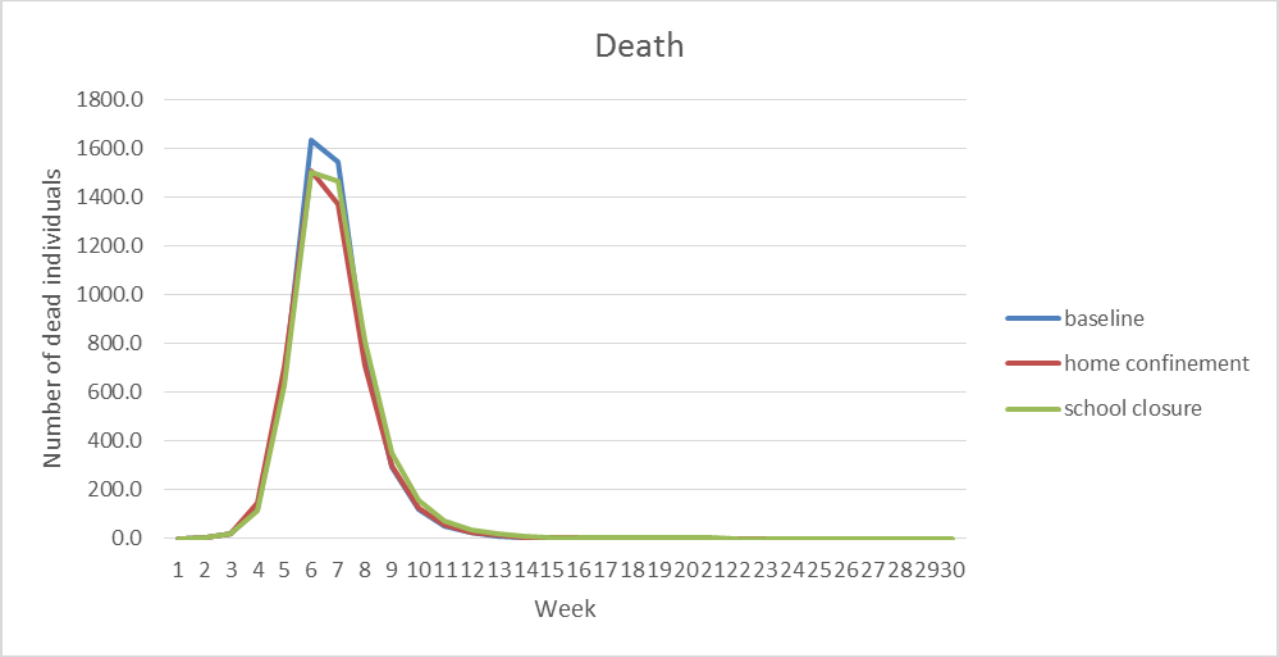

Figure 4 - 3: number of death cases per week during the pandemic

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.

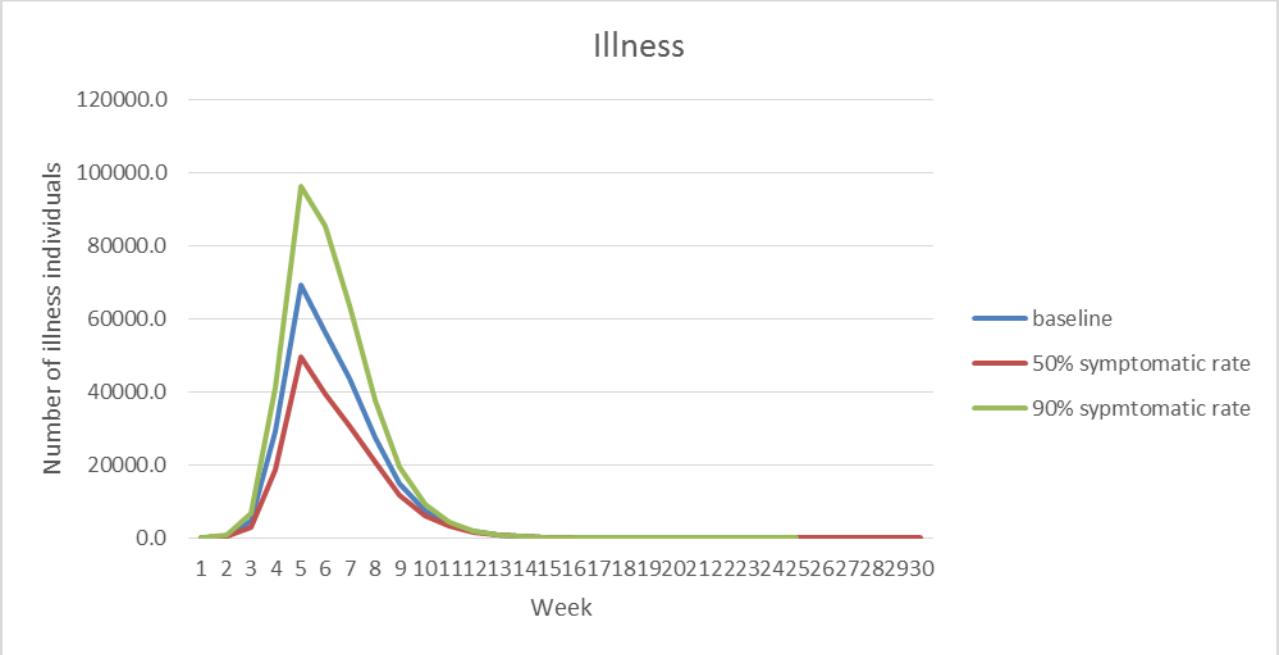

Figure 4 - 4: number of illness cases per week during the pandemic

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. $\sum_{w=1}^{W}\sum_{g=1}^{G}\alpha_g Ill_{wg}$) 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. $\sum_{w=1}^{W}\sum_{g=1}^{G}\partial_g Outp_{wg}$) 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. $\sum_{w=1}^{W}\sum_{g=1}^{G}\beta_g Hos_{wg}$). The costs associated with dead individuals is shown in the fourth term of the objective function (i.e. $\sum_{w=1}^{W}\sum_{g=1}^{G}\gamma_g Dead_{wg}$). 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, $\sum_{w=1}^{W}\delta * SCC_w/5$ and $\sum_{w=1}^{W}\sum_{g=1}^{G}\varepsilon_g CC_{wg}$, 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

ρ: units of medical resources needed per hospitalized person

α_g: total cost associated with one ill person without severe symptoms in age group g

∂_g : total cost associated with one ill person with severe symptoms in age group g

β_g: total cost associated with one hospitalized person in age group g

γ_g : total cost associated with one dead person in age group g

δ : total cost associated with one class closed per week

ε_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

$Outp_{wg}$: 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:

$$Min\ Z = E\left(\sum_{w=1}^{W}\sum_{g=1}^{G}\alpha_g Ill_{wg} + \sum_{w=1}^{W}\sum_{g=1}^{G}\partial_g Outp_{wg} + \sum_{w=1}^{W}\sum_{g=1}^{G}\beta_g Hos_{wg} + \sum_{w=1}^{W}\sum_{g=1}^{G}\gamma_g Dead_{wg} + \sum_{w=1}^{W}\delta * SCC_w/5 + \sum_{w=1}^{W}\sum_{g=1}^{G}\varepsilon_g CC_{wg}\right) \quad (5.1)$$

Constraints:

$SC \in [1, 2, \dots, MSC]$ (5.2)

$CR \in [1, 2, \dots, UCR]$ (5.3)

$CT \in [1, 2, \dots, UCT]$ (5.4)

$\rho Hos_w \leq MHR_w \ for \quad w = 1,2, \dots, W$ (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 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-α: the overall desired probability of finding the best strategy where $\frac{1}{k} < 1 - \alpha < 1$

δ : 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[7] $t = t_{n_0-1,(1-\frac{\alpha}{2})^{1/(k-1)}}$, 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): $h = h(n_0, k, 1-\frac{\alpha}{2})$

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

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

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

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.

$$N_i = max\{n_0, \lceil (hS(X_i)/\delta)^2 \rceil\}$$

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 $X_B = argmin_{X_i}\bar{Y}(X_i; N_i)$ as the best system (scenario) that minimizes the objective function.

---

[7] For example, if $\alpha = 0.05$, $n_0 = 10$, 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 $\alpha = 0.05$, $n_0 = 10$, 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%[9]. Length of school closure can have 5 values, 0, 1, 2, 3, or 4[10]

[9] 10% threshold is considered as a level of severe virus spread in the school in this study
[10] 4 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

school closure threshold	2.50%	5%	7.50%	10%		
length of school closure	0	1	2	3	4	
rate of home confinement	0%	10%	20%	30%	40%	50%

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.

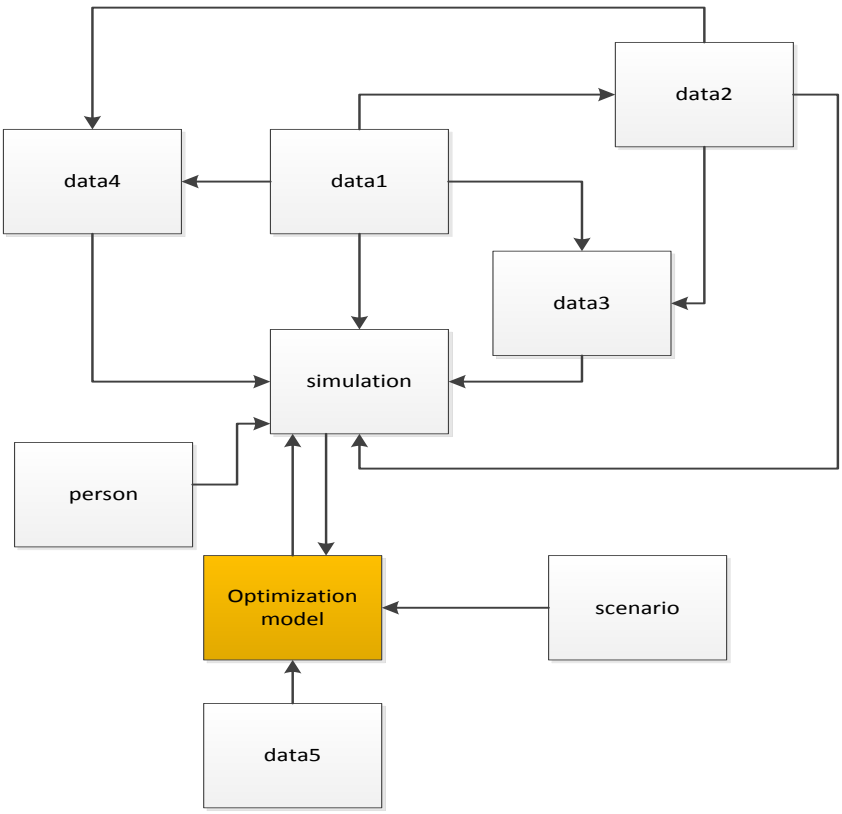

Figure 5 - 1: Structure of the JAVA program for the simulation-based optimization model

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)[12]

α_1	197	β_1	3366	ε_1	0
α_2	197	β_2	3366	ε_2	0
α_3	202	β_3	6842	ε_3	100
α_4	327	β_4	7653	ε_4	0
∂_1	300	γ_1	3435	δ[13]	500
∂_2	300	γ_2	3435		
∂_3	330	γ_3	7605		
∂_4	458	γ_4	8309		

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.

[12] There are four age groups considered in the model.
[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).

Table 5 - 3: 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

Rate of home confinement	Closure Length (week)	Closure Threshold	Infected	Ill(no severe symptoms)	Out-Patient	Hospitalized	Dead	Cost
0%	0		388859	106599	153890	10476	5258	$ 200,515,252
	1	0.025	389137	106315	154296	10488	5201	$ 204,313,970
		0.05	389677	106489	154515	10524	5245	$ 204,269,907
		0.075	390110	106666	154596	10468	5225	$ 203,294,047
		0.1	389645	106490	154654	10527	5294	$ 203,796,570
	2	0.025	381995	105120	150881	10534	5225	$ 206,872,807
		0.05	384332	105629	151802	10499	5206	$ 205,216,401
		0.075	386065	105969	152664	10502	5264	$ 204,832,821
		0.1	387098	105961	153328	10474	5208	$ 203,454,557
	3	0.025	370492	102605	145565	10395	5176	$ 206,702,894
		0.05	377419	104259	148835	10450	5182	$ 205,284,644
		0.075	381462	104721	150832	10518	5298	$ 205,429,501
		0.1	384075	105519	151633	10406	5180	$ 202,840,948
	4	0.025	364896	101329	143148	10329	5151	$ 208,095,195
		0.05	375513	103708	147891	10408	5185	$ 206,151,036
		0.075	380113	104636	149932	10428	5213	$ 204,549,118
		0.1	383426	105285	151600	10473	5207	$ 203,828,611
10%	0		376330	102247	149554	10258	5146	$ 197,257,240
	1	0.025	376721	102456	149774	10282	5169	$ 202,002,076
		0.05	376305	102351	149615	10245	5094	$ 200,176,875
		0.075	377608	102941	150203	10292	5096	$ 200,384,478
		0.1	377669	102805	150457	10387	5191	$ 201,392,091
	2	0.025	369568	101280	146364	10292	5147	$ 203,951,612
		0.05	370319	101146	146919	10283	5171	$ 202,293,712
		0.075	372186	101299	147932	10279	5133	$ 201,311,109
		0.1	374337	101891	148760	10284	5131	$ 200,692,390
	3	0.025	356336	98279	140398	10238	5086	$ 204,118,364
		0.05	364115	100016	144166	10283	5156	$ 202,945,906
		0.075	368973	100744	146402	10347	5167	$ 202,447,381
		0.1	371130	101295	147341	10329	5198	$ 201,866,517
	4	0.025	352362	97354	138775	10253	5197	$ 207,461,289

		0.05	361953	99381	143145	10302	5150	$ 204,302,003
		0.075	367281	100522	145628	10312	5163	$ 202,666,510
		0.1	370305	100890	147188	10294	5157	$ 201,366,554
20%	0		364091	98690	145379	10064	5051	$ 194,336,713
	1	0.025	364832	98716	145856	10144	5079	$ 199,690,272
		0.05	363996	98311	145489	10064	5047	$ 197,712,707
		0.075	364611	98692	145670	10078	5031	$ 197,201,219
		0.1	365762	98883	146148	10151	5083	$ 197,965,313
	2	0.025	353896	96098	140997	10091	5058	$ 200,352,690
		0.05	357124	96810	142253	10072	5045	$ 198,951,884
		0.075	359351	97624	143222	10128	5070	$ 198,715,335
		0.1	361932	98066	144532	10104	5078	$ 198,181,061
	3	0.025	342637	93985	135640	10072	5041	$ 201,329,001
		0.05	351432	96121	139437	10086	5043	$ 199,659,546
		0.075	356283	96839	141923	10098	5079	$ 198,963,950
		0.1	358954	97528	143082	10100	5085	$ 198,461,373
	4	0.025	338035	93230	133378	10005	5020	$ 203,329,776
		0.05	349117	95393	138512	10094	5083	$ 201,227,993
		0.075	353908	96188	140843	10141	5094	$ 199,760,157
		0.1	357347	96683	142816	10125	5059	$ 198,319,886
30%	0		351587	94455	141116	9888	4934	$ 190,866,203
	1	0.025	350765	94476	140388	9900	4961	$ 195,384,879
		0.05	351305	94496	140919	9890	4977	$ 194,670,888
		0.075	350903	94234	140733	9895	4933	$ 193,657,654
		0.1	351782	94334	141079	9870	4978	$ 193,452,104
	2	0.025	340126	91791	136082	9860	4997	$ 196,910,432
		0.05	342828	92552	137042	9853	4938	$ 194,911,261
		0.075	346788	93388	138821	9895	4954	$ 194,712,445
		0.1	349137	93936	139991	9845	4929	$ 193,769,689
	3	0.025	327368	89043	130112	9774	4929	$ 196,706,040
		0.05	337094	91322	134642	9820	4912	$ 195,025,254
		0.075	343230	92925	137116	9867	4946	$ 194,856,093
		0.1	344115	92623	138020	9848	4911	$ 193,369,207
	4	0.025	324010	88512	128555	9775	4929	$ 199,833,114
		0.05	335539	90798	133830	9810	4941	$ 196,534,453
		0.075	340469	92010	136205	9867	4995	$ 195,517,493
		0.1	344952	93104	138237	9873	4952	$ 194,344,717
40%	0		339376	90399	137021	9593	4847	$ 186,671,909
	1	0.025	337865	90056	136127	9636	4886	$ 191,479,178
		0.05	338226	90305	136325	9567	4838	$ 189,745,478
		0.075	338719	90299	136576	9633	4875	$ 189,901,112

		0.1	338990	90227	136834	9656	4874	$ 189,706,922
	2	0.025	325580	87550	130425	9516	4814	$ 191,192,061
		0.05	329758	88319	132660	9496	4800	$ 189,821,309
		0.075	332516	88996	133687	9591	4840	$ 189,853,334
		0.1	335029	89448	135101	9599	4807	$ 189,113,645
	3	0.025	313550	84791	125224	9523	4825	$ 192,658,079
		0.05	322681	86780	129404	9595	4878	$ 191,412,015
		0.075	328635	88209	132009	9605	4862	$ 190,430,310
		0.1	331617	88776	133370	9613	4852	$ 189,580,140
	4	0.025	309705	84046	123533	9444	4757	$ 194,478,812
		0.05	322749	86911	129277	9498	4798	$ 191,637,413
		0.075	327426	87838	131569	9489	4780	$ 189,124,379
		0.1	333017	89294	133804	9571	4844	$ 189,860,668
50%	0		326471	86408	132388	9304	4706	$ 181,577,043
	1	0.025	323343	85564	131005	9309	4736	$ 185,745,926
		0.05	324196	85938	131255	9238	4698	$ 184,152,633
		0.075	325681	86396	131917	9315	4716	$ 184,588,977
		0.1	325764	85995	132314	9289	4708	$ 183,758,220
	2	0.025	310995	82981	125483	9276	4684	$ 186,533,327
		0.05	315404	83913	127452	9301	4719	$ 185,717,200
		0.075	318819	84661	129053	9264	4667	$ 184,093,127
		0.1	322899	85578	130665	9330	4720	$ 184,794,728
	3	0.025	296953	79829	119065	9135	4658	$ 186,230,913
		0.05	310127	82804	124802	9245	4651	$ 185,130,891
		0.075	314106	83430	127058	9275	4702	$ 184,452,940
		0.1	318169	84352	128846	9316	4747	$ 184,646,104
	4	0.025	296646	79976	118804	9143	4645	$ 189,525,443
		0.05	307909	82231	124010	9279	4695	$ 186,818,869
		0.075	314465	83867	126815	9267	4651	$ 184,585,790
		0.1	318210	84454	128749	9279	4701	$ 184,337,850

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), out-patient, hospitalized, and dead individuals for this scenario.

One-Sample T: C1, C2, C3, C4, C5

Variable	N	Mean	StDev	SE Mean	95% CI
C1	6	326472	1441	588	(324960, 327984)
C2	6	86408	647	264	(85729, 87087)
C3	6	132389	405	165	(131963, 132814)
C4	6	9304.2	38.2	15.6	(9264.0, 9344.3)
C5	6	4706.0	49.4	20.2	(4654.2, 4757.8)

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

Rate of home confinement	Closure Length (week)	Closure Threshold	Infected	Ill(no severe symptoms)	Out-Patient	Hospitalized	Dead	Cost
0%	0		388329	106372	153890	10476	5258	$629,130,091
	1	0.025	387574	105938	154296	10488	5201	$625,738,796
		0.05	388583	106417	154515	10524	5245	$627,645,170
		0.075	389721	106808	154596	10468	5225	$621,579,062
		0.1	389725	106739	154654	10527	5294	$632,633,554
	2	0.025	390074	106708	150881	10534	5225	$640,223,200
		0.05	390202	106855	151802	10499	5206	$631,382,930
		0.075	388309	106316	152664	10502	5264	$623,134,654
		0.1	382361	105175	153328	10474	5208	$628,875,737
	3	0.025	384505	105551	145565	10395	5176	$631,726,128
		0.05	386411	105848	148835	10450	5182	$629,755,802
		0.075	387678	106290	150832	10518	5298	$632,584,384
		0.1	389315	106633	151633	10406	5180	$622,951,784
	4	0.025	371006	102886	143148	10329	5151	$635,500,555
		0.05	377239	103989	147891	10408	5185	$630,274,223
		0.075	381632	104676	149932	10428	5213	$628,619,163
		0.1	383747	105213	151600	10473	5207	$631,755,920
10%	0		376420	102409	149707	10311	5137	$610,419,611
	1	0.025	375678	102232	149774	10282	5169	$617,210,204
		0.05	376477	102457	149615	10245	5094	$613,458,928
		0.075	376955	102541	150203	10292	5096	$619,876,805
		0.1	376409	102337	150457	10387	5191	$621,546,080
	2	0.025	377088	102448	146364	10292	5147	$622,203,527
		0.05	377818	102647	146919	10283	5171	$620,012,632
		0.075	376484	102420	147932	10279	5133	$621,085,675
		0.1	367741	100614	148760	10284	5131	$618,655,341
	3	0.025	371157	101372	140398	10238	5086	$618,752,439
		0.05	372511	101563	144166	10283	5156	$612,529,890
		0.075	374954	102123	146402	10347	5167	$621,852,139
		0.1	376061	102437	147341	10329	5198	$608,585,340
	4	0.025	356577	98208	138775	10253	5197	$616,444,284
		0.05	363740	99582	143145	10302	5150	$612,226,516

		0.075	368195	100584	145628	10312	5163	$616,323,517
		0.1	370635	100979	147188	10294	5157	$608,841,881
20%	0		363030	98063	145241	10138	5098	$601,340,507
	1	0.025	364885	98982	145856	10144	5079	$601,963,032
		0.05	363621	98367	145489	10064	5047	$594,953,358
		0.075	363948	98382	145670	10078	5031	$601,621,303
		0.1	364037	98435	146148	10151	5083	$606,974,171
	2	0.025	364517	98459	140997	10091	5058	$606,362,055
		0.05	364887	98763	142253	10072	5045	$604,663,921
		0.075	365010	98861	143222	10128	5070	$596,898,788
		0.1	354540	96522	144532	10104	5078	$603,763,977
	3	0.025	357448	97091	135640	10072	5041	$604,469,126
		0.05	359440	97502	139437	10086	5043	$600,465,302
		0.075	361175	97737	141923	10098	5079	$597,620,948
		0.1	363552	98293	143082	10100	5085	$602,899,199
	4	0.025	342706	94032	133378	10005	5020	$597,685,212
		0.05	350212	95482	138512	10094	5083	$606,410,357
		0.075	355882	96891	140843	10141	5094	$604,290,691
		0.1	358226	97312	142816	10125	5059	$599,794,153
30%	0		351485	94264	140984	9799	4965	$582,834,561
	1	0.025	351951	94530	140388	9900	4961	$588,426,900
		0.05	351770	94302	140919	9890	4977	$586,806,699
		0.075	350857	94355	140733	9895	4933	$588,963,515
		0.1	351241	94410	141079	9870	4978	$587,656,196
	2	0.025	351917	94457	136082	9860	4997	$590,864,418
		0.05	352559	94481	137042	9853	4938	$598,591,606
		0.075	351326	94337	138821	9895	4954	$583,332,340
		0.1	339071	91514	139991	9845	4929	$589,242,146
	3	0.025	343456	92760	130112	9774	4929	$580,711,820
		0.05	346629	93290	134642	9820	4912	$579,149,776
		0.075	348899	93718	137116	9867	4946	$589,602,116
		0.1	351179	94160	138020	9848	4911	$584,630,878
	4	0.025	328401	89581	128555	9775	4929	$585,862,739
		0.05	336358	91110	133830	9810	4941	$580,256,775
		0.075	342117	92300	136205	9867	4995	$583,697,195
		0.1	345120	93186	138237	9873	4952	$585,660,134
40%	0		339825	90745	137021	9593	4847	$569,354,857
	1	0.025	338623	90074	136127	9636	4886	$565,094,358
		0.05	338629	90155	136325	9567	4838	$568,390,339
		0.075	337075	90031	136576	9633	4875	$575,706,265
		0.1	337096	89863	136834	9656	4874	$569,883,237

	2	0.025	338457	90271	130425	9516	4814	$566,831,544
		0.05	338726	90257	132660	9496	4800	$567,041,238
		0.075	338817	90032	133687	9591	4840	$562,496,219
		0.1	326134	87677	135101	9599	4807	$572,688,490
	3	0.025	329607	88152	125224	9523	4825	$562,719,029
		0.05	332554	89040	129404	9595	4878	$572,546,584
		0.075	335400	89633	132009	9605	4862	$565,712,400
		0.1	338590	89952	133370	9613	4852	$567,658,993
	4	0.025	313590	84929	123533	9444	4757	$566,785,101
		0.05	322890	86844	129277	9498	4798	$564,854,846
		0.075	328403	88117	131569	9489	4780	$574,023,486
		0.1	331014	88540	133804	9571	4844	$568,351,648
50%	0		327330	86792	132584	9212	4679	$548,944,289
	1	0.025	326772	86388	131005	9309	4736	$551,143,747
		0.05	326862	86655	131255	9238	4698	$547,031,972
		0.075	323341	85543	131917	9315	4716	$543,917,975
		0.1	324014	85630	132314	9289	4708	$549,984,976
	2	0.025	324714	85853	125483	9276	4684	$552,990,474
		0.05	325137	85989	127452	9301	4719	$551,269,721
		0.075	327390	86559	129053	9264	4667	$548,883,908
		0.1	310859	82913	130665	9330	4720	$550,604,073
	3	0.025	314562	83639	119065	9135	4658	$552,747,953
		0.05	318761	84629	124802	9245	4651	$552,072,978
		0.075	321749	85255	127058	9275	4702	$549,951,070
		0.1	326943	86445	128846	9316	4747	$551,353,183
	4	0.025	298300	80447	118804	9143	4645	$541,338,280
		0.05	309303	82514	124010	9279	4695	$552,340,008
		0.075	315927	84270	126815	9267	4651	$548,538,593
		0.1	317591	84404	128749	9279	4701	$544,212,162

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.

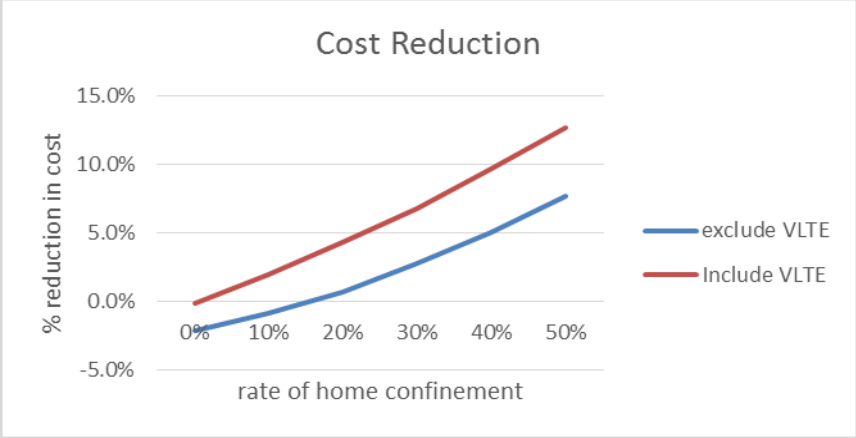

Figure 5 - 2: Percentage of reduction in cost as a result of change in the rate of home confinement

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.

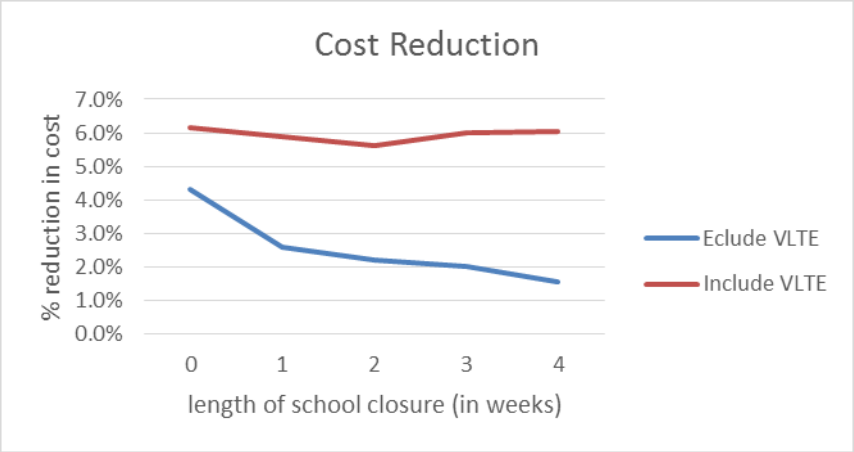

Figure 5 - 3: Percentage of reduction in cost as a result of change in the length of school closure

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.

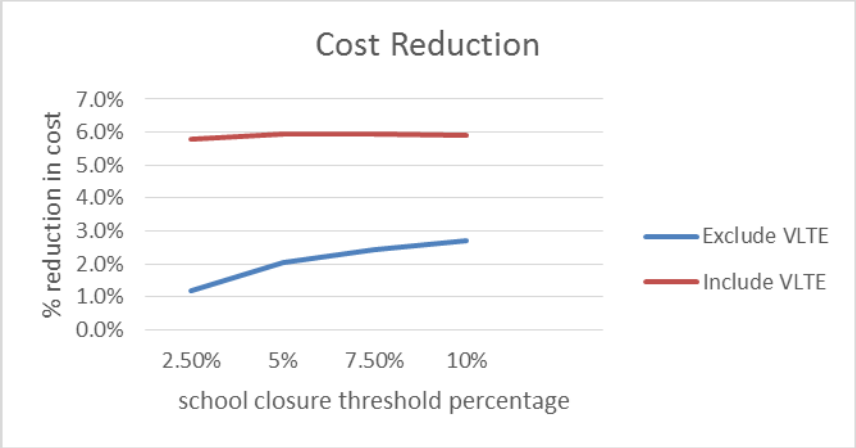

Figure 5 - 4: Percentage of reduction in cost as a result of change in the school closure threshold

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.

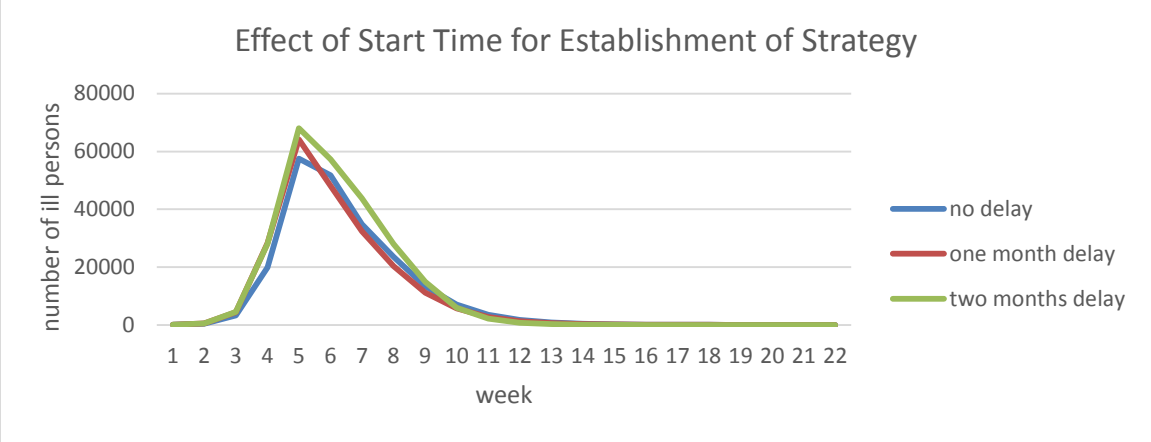

Figure 5 - 5: Effect of start time for establishment of strategy on the number of ill persons

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.

Two-Sample T-Test and CI: C2, C1

Two-sample T for C2 vs C1

	N	Mean	StDev	SE Mean
C2	5	220513	709	317
C1	5	218688	456	204

Difference = μ (C2) - μ (C1)
Estimate for difference: 1826
95% CI for difference: (903, 2748)
T-Test of difference = 0 (vs ≠): T-Value = 4.84 P-Value = 0.003 DF = 6

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.

Two-Sample T-Test and CI: C3, C1

Two-sample T for C3 vs C1

	N	Mean	StDev	SE Mean
C3	5	254401	929	415
C1	5	218688	456	204

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.

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APPENDIX A

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

Run	infected	ill	hospitalized	dead
1	386341	258962	10533	5286
2	390746	262484	10598	5370
3	388928	260719	10712	5427
4	388171	259825	10479	5220
5	388740	260167	10528	5249
6	390092	261397	10354	5179
7	389444	260531	10387	5137
8	386814	259170	10424	5222
9	389646	261129	10472	5227
10	388923	260199	10414	5185

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

Run	infected	ill	hospitalized	dead
1	383455	256572	10285	5158
2	381378	255288	10399	5221
3	382672	256420	10383	5098
4	384233	257997	10512	5304
5	382566	256528	10271	5081
6	382198	256350	10196	5127
7	384048	257342	10376	5141
8	381109	255220	10336	5114
9	382695	256391	10344	5172
10	382946	256057	10522	5230

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

Run	infected	ill	hospitalized	dead
1	408827	273894	10832	5395
2	408478	273781	10697	5369
3	407457	272670	10808	5346
4	408042	273226	10785	5339
5	408198	273977	10861	5423
6	408814	273982	10869	5459
7	408331	273549	10679	5368
8	406456	272271	10831	5454
9	407569	273269	10829	5354
10	407866	273828	10812	5417

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

Run	infected	ill	hospitalized	dead
1	389011	260408	9853	4923
2	387204	259371	10096	5026
3	388816	260322	10145	5077
4	389465	261150	10066	5033
5	389421	261171	9888	4958
6	389185	260695	10044	4911
7	387956	260400	10005	5045
8	388651	260464	9954	4907
9	387662	259588	9978	5046
10	388708	260524	10041	5072

APPENDIX B

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

Run	Dead	Hospitalized	ill	Infected
1	5151	10373	261230	390300
2	5166	10330	258996	387241
3	5221	10448	260094	388842
4	5223	10485	260528	388667
5	5146	10227	260194	388769
6	5316	10474	261920	390964
7	5211	10391	259830	387933
8	5254	10560	259256	387323
9	5300	10600	261699	389873
10	5198	10390	259867	388490
11	5168	10288	260298	388702
12	5300	10663	262311	390731
13	5267	10526	260342	388460
14	5200	10373	259771	388069
15	5275	10502	260008	387828
16	5269	10420	260012	387561
17	5221	10491	259944	387945
18	5181	10371	260079	387940
19	5163	10375	260857	389334
20	5181	10312	260201	388418
21	5262	10426	260006	387686
22	5151	10365	260892	389893
23	5201	10573	261195	389829
24	5198	10460	259569	386734
25	5239	10399	261921	390794
26	5170	10480	261412	389545
27	5243	10555	260674	389212
28	5254	10444	261335	390693
29	5160	10377	258578	386224
30	5339	10589	260970	389763

31	5322	10556	260380	389056
32	5222	10486	259883	387837
33	5340	10572	259815	388070
34	5265	10512	260457	389502
35	5229	10457	261286	389855
36	5237	10537	260621	389272
37	5159	10302	262305	390765
38	5235	10422	260473	388687
39	5264	10534	260389	388379
40	5223	10444	259411	387169
41	5312	10475	260628	389262
42	5297	10609	261127	390057
43	5173	10336	259821	387710
44	5272	10484	259402	386850
45	5254	10508	260247	387755
46	5367	10635	261857	390565
47	5397	10736	260160	387756
48	5327	10666	261143	390403
49	5236	10518	259779	387639
50	5273	10545	260437	389426

Table B - 2: number of infected, ill, hospitalized, and dead individuals for the simulation runs for home confinement scenario

Run	Dead	Hospitalized	ill	Infected
1	4944	9892	236954	354309
2	4941	9831	235434	351504
3	4901	9839	236682	353286
4	4983	9840	237156	354301
5	5008	9968	237365	354563
6	5022	9971	237257	353922
7	4973	9937	236605	353308
8	4918	9928	237395	354101
9	4952	9829	237526	354782
10	4962	9862	237002	353646

11	5025	9924	236306	354115
12	4901	9855	237192	354889
13	5060	9930	237241	353605
14	5046	9891	236826	353389
15	5063	9990	236719	353369
16	5018	9893	236139	353039
17	4932	9789	235486	352131
18	4972	9829	236294	352989
19	5093	10055	235922	351824
20	4892	9782	233080	348201
21	5102	9965	237477	354629
22	5024	9891	235664	352098
23	5034	9949	236123	352546
24	4919	9749	237002	353781
25	4989	9903	236101	352294
26	4963	9955	236815	353892
27	4997	9931	238083	354991
28	4939	9857	235854	352580
29	5045	9839	235263	352693
30	5003	10071	237356	354305
31	4984	9858	237372	354774
32	4900	9766	237285	354408
33	4975	9893	238234	355665
34	5087	9991	237640	354372
35	4964	9871	237628	354618
36	5024	9900	237179	354468
37	5023	10089	237363	354220
38	4971	9781	236574	352873
39	4968	9980	237814	355182
40	4794	9676	235389	350729
41	4936	9775	236000	352465
42	5033	10075	237127	354148
43	4924	9769	237096	354479
44	4995	9844	236551	353230
45	4965	9916	238019	355850
46	4923	9860	236080	352105
47	5051	9943	236257	353037

48	5054	9928	236955	354224
49	4941	9824	237041	353998
50	5009	9834	237809	355107

Table B - 3: number of infected, ill, hospitalized, and dead individuals for the simulation runs for school closure scenario

Run	Dead	Hospitalized	ill	Infected
1	5149	10362	240423	358954
2	5206	10324	248791	370675
3	5169	10364	240829	359620
4	5307	10496	242474	361444
5	5303	10518	242505	361957
6	5163	10371	245270	365496
7	5164	10323	249004	371570
8	5248	10385	245969	367591
9	5206	10384	250074	373045
10	5267	10520	240643	359261
11	5241	10445	244591	364775
12	5105	10351	247527	369248
13	5187	10324	241224	360255
14	5348	10437	244905	366109
15	5058	10366	244722	365438
16	5232	10461	247558	369238
17	5081	10338	249662	372428
18	5284	10386	244238	363916
19	5168	10361	241046	360214
20	5243	10391	240567	358863
21	5245	10348	238722	355935
22	5267	10498	247519	370337
23	5114	10352	240617	359683
24	5262	10493	245805	367790
25	5278	10442	248146	370581
26	5216	10317	241227	360109
27	5412	10521	246002	366893

28	5134	10363	242209	361944
29	5250	10456	239826	357698
30	5289	10508	243570	363975
31	5204	10408	241937	361261
32	5187	10350	240426	359259
33	5087	10381	249108	372006
34	5162	10419	243021	362806
35	5115	10378	242205	361372
36	5139	10450	241405	360129
37	5143	10282	240210	359116
38	5191	10391	242553	362574
39	5260	10505	245371	366066
40	5220	10487	240606	359251
41	5232	10398	241299	360207
42	5200	10340	239958	358193
43	5238	10396	244832	365205
44	5199	10364	241739	360412
45	5161	10524	247929	369970
46	5226	10431	248370	371044
47	5143	10305	237401	354766
48	5327	10480	240416	358818
49	5092	10255	241510	360268
50	5230	10470	241692	361311

Table B - 4: Weekly number of infected, ill, hospitalized, and dead individuals for baseline scenario

Week	Infected	Ill	Hospitalized	Dead
1	111.9	76.1	1.0	0.3
2	834.6	558.3	6.5	2.6
3	6959.9	4662.4	44.7	19.5
4	43662.9	29241.7	295.0	125.5
5	103536.1	69364.4	1385.0	654.4
6	84098.1	56368.4	3184.9	1633.6
7	64932.1	43492.9	2996.1	1544.4

8	41106.9	27538.7	1501.1	754.4
9	22029.5	14741.2	604.8	294.0
10	11144.9	7473.8	250.3	118.2
11	5431.3	3642.1	110.3	50.9
12	2604.2	1742.6	49.7	22.8
13	1232.2	824.3	21.6	10.4
14	587.9	394.5	11.5	5.7
15	277.8	185.8	5.0	2.2
16	124.6	84.3	2.3	1.0
17	61.8	41.6	1.1	0.3
18	30.7	20.7	0.6	0.2
19	15.4	10.0	0.3	0.1
20	6.5	4.4	0.2	0.0
21	2.6	1.5	0.1	0.0
22	1.1	0.8	0.0	0.0
23	0.9	0.6	0.0	0.0
24	0.5	0.4	0.0	0.0
25	0.7	0.4	0.0	0.0
26	0.3	0.2	0.0	0.0
27	0.1	0.1	0.0	0.0
28	0.0	0.0	0.0	0.0

Table B - 5: Weekly number of infected, ill, hospitalized, and dead individuals for home confinement scenario

Week	Infected	Ill	Hospitalized	Dead
1	124.8	84.8	1.1	0.5
2	977.6	654.4	6.8	3.0
3	8224.5	5502.8	48.9	20.2
4	49852.0	33395.4	337.7	144.5
5	102301.1	68470.1	1465.2	701.1
6	72956.2	48855.9	2932.6	1507.9
7	52997.8	35504.1	2645.1	1369.8
8	32541.6	21797.9	1388.1	707.3
9	17150.0	11478.3	598.0	300.8

10	8551.0	5723.1	257.2	125.6
11	4147.5	2771.0	113.8	55.1
12	1990.2	1334.8	51.6	25.4
13	943.4	631.4	24.1	11.6
14	441.1	294.9	11.0	5.3
15	200.9	134.4	5.0	2.8
16	95.3	64.0	2.2	1.1
17	45.1	30.0	1.0	0.4
18	22.2	15.1	0.5	0.1
19	10.6	7.0	0.2	0.1
20	4.2	2.8	0.1	0.1
21	1.9	1.4	0.0	0.0
22	0.8	0.5	0.0	0.0
23	0.3	0.1	0.0	0.0
24	0.2	0.2	0.0	0.0
25	0.1	0.1	0.0	0.0
26	0.0	0.0	0.0	0.0

Table B - 6: Weekly number of infected, ill, hospitalized, and dead individuals for school closure scenario

Week	Infected	Ill	Hospitalized	Dead
1	105.4	69.5	1.0	0.4
2	785.1	524.3	5.2	2.4
3	6553.7	4390.1	40.5	17.6
4	42290.3	28340.3	275.8	115.4
5	77355.7	51827.5	1305.0	628.9
6	61192.0	40995.7	2918.8	1506.2
7	58244.8	39001.3	2846.1	1468.3
8	43779.6	29336.5	1597.4	809.9
9	29717.5	19909.8	728.2	349.9
10	16565.9	11094.0	334.7	155.0
11	8729.3	5841.8	159.9	72.3
12	5187.9	3472.2	79.0	35.4
13	3473.3	2329.0	42.5	19.0

14	2335.9	1559.6	23.3	9.3
15	1604.0	1073.6	13.5	5.0
16	1165.0	779.4	8.2	3.1
17	896.3	600.4	5.6	2.2
18	735.0	489.9	4.4	1.5
19	609.9	408.6	3.5	1.3
20	494.0	331.1	2.6	0.9
21	396.2	265.1	2.1	0.8
22	325.5	217.0	1.8	0.5
23	262.8	175.9	1.3	0.3
24	214.0	143.9	1.3	0.4
25	169.7	114.4	1.2	0.4
26	124.7	84.3	0.6	0.2
27	97.6	64.1	0.3	0.1
28	77.2	51.5	0.3	0.1
29	56.4	37.7	0.3	0.1
30	0.0	0.0	0.0	0.0

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

	Infected	Ill	Hospitalized	Dead
baseline	19610	13147	514	257
home confinement	17805	11873	469	243
School closure	18126	12114	500	258

APPENDIX C

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

Run	Infected	Ill	Hospitalized	Dead
1	371004	185212	10157	5102
2	372647	186330	10071	5127
3	374132	186601	9999	5000
4	373734	186779	10205	5126
5	373301	186586	10138	5074
6	370637	185093	10037	5046
7	374668	187076	10166	5114
8	372347	185495	9968	4943
9	372685	186707	10059	5081
10	375284	186839	10030	4937
11	373736	187500	10077	5050
12	374294	186807	9971	4981
13	373270	186504	10074	5049
14	374751	187297	10159	5019
15	373889	186996	10124	5112
16	370505	185267	10098	5010
17	371602	185967	10189	5092
18	373437	186161	10022	4948
19	372532	186447	10149	5104
20	371419	185427	10119	5032
21	375060	187420	10259	5103
22	373125	186921	10261	5141
23	374635	187260	10180	5130
24	375416	188399	10427	5183
25	372925	186435	10032	4971
26	371483	186068	9898	4968
27	374228	186856	10044	5068

28	375079	187574	10257	5110
29	372868	186258	10135	5038
30	374328	187149	10134	5199
31	374663	187167	9955	5020
32	373495	186876	10120	5056
33	371126	185917	10011	4962
34	373661	186944	10117	4953
35	372456	186766	10129	5127
36	373286	186497	10055	5087
37	372159	186114	10227	5200
38	372640	185950	10069	4974
39	373304	186509	10029	5022
40	371512	185830	9984	4946
41	371282	185205	10159	5102
42	372334	186197	10190	5090
43	376149	188308	10136	5097
44	371173	185708	10173	5091
45	374265	187558	10003	4882
46	372679	186066	10101	5039
47	371821	186184	10143	5008
48	371278	185235	10142	5097
49	373441	186599	10154	5139
50	371420	186179	10095	5068

Table C - 2: number of infected, ill, hospitalized, and dead individuals for the simulation runs for when symptomatic rate is 90%

Run	Infected	Ill	Hospitalized	Dead
1	410751	369631	10807	5420
2	409333	368200	11020	5510
3	410461	369350	10777	5356
4	408238	367349	10809	5318
5	410588	369545	10879	5444
6	408555	367918	10871	5385
7	409336	368125	10949	5503
8	408604	367622	10835	5406
9	406050	365632	10787	5329
10	409391	368640	10826	5314

11	409750	369025	10834	5417
12	410114	368980	10965	5427
13	408507	367404	10848	5384
14	411277	370386	10871	5436
15	410082	369124	11070	5404
16	409019	367787	10817	5444
17	408962	367920	10853	5315
18	407383	366655	10720	5358
19	410381	369447	10952	5399
20	410322	369364	10881	5549
21	410294	369216	10805	5381
22	410792	369704	10756	5368
23	409019	368300	11030	5587
24	408852	367850	10885	5407
25	409378	368591	10888	5406
26	408646	367413	11099	5568
27	408165	367138	10904	5450
28	408319	367717	10874	5362
29	410419	369221	10976	5469
30	409267	368348	10888	5279
31	410650	369317	10899	5495
32	409674	368459	10818	5272
33	409606	368762	10835	5397
34	407939	367302	10819	5402
35	407952	367136	10840	5455
36	409056	368484	10950	5388
37	408094	366927	10969	5477
38	409614	368802	10898	5402
39	408930	367990	10899	5426
40	408594	367357	10874	5325
41	408337	367807	11068	5579
42	407787	366878	11002	5515
43	408705	367905	10930	5398
44	408666	367925	10964	5421
45	408217	367050	10878	5361
46	406796	365893	10723	5305
47	410552	369718	11030	5484
48	408852	367992	10841	5360
49	410861	369345	10842	5398
50	407029	365959	10813	5400

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

Week	Infected	Ill	Hospitalized	Dead
1	0	0	0	0
2	100.82	50.18	1.12	0.46
3	696.52	348.74	5.32	2.76
4	5741.36	2867.3	33.88	14.26
5	37641.2	18811.2	216.58	88.48
6	98947.64	49459.84	1062	492.7
7	78720.58	39366.22	2673.66	1356.4
8	61179.3	30557.24	2994.7	1546.42
9	41740.92	20896.9	1743.44	884.14
10	23641.88	11814.06	764.8	382.6
11	12358.68	6179.2	331.46	158.22
12	6225.92	3112.34	147.34	69.1
13	3095.66	1553.78	68.24	31.16
14	1528.72	766.2	33.72	14.94
15	746.84	374.74	16.3	7.38
16	365.54	181.84	8.66	3.92
17	173.04	87.2	3.58	1.52
18	80.72	39.74	1.86	0.96
19	38.12	18.54	1	0.56
20	18.66	9.22	0.44	0.2
21	9.18	4.66	0.2	0.06
22	5.1	2.28	0.2	0.06
23	2.88	1.46	0.06	0.04
24	1.74	0.86	0.02	0
25	1.18	0.46	0	0
26	0.58	0.36	0.04	0.02
27	0.16	0.04	0	0
28	0.14	0.06	0	0
29	0.08	0.06	0	0
30	0.1	0.04	0	0
31	0	0	0	0

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

Week	Infected	Ill	Hospitalized	Dead
1	0	0	0	0
2	120.52	108.18	1.72	0.78
3	902	811.84	8.7	3.86
4	7397.34	6659.56	59.6	26.82
5	45565.14	41003.9	382.48	173
6	106965.3	96264.2	1747.76	845.54
7	94859.86	85342	3628.04	1856.84
8	70864.02	63797.26	2970.36	1511.92
9	41879.16	37674.14	1290.58	635.06
10	21457	19307.32	478.88	222.68
11	10324.8	9292.24	185.2	79.68
12	4787.5	4309.6	75.74	32.4
13	2185.42	1965.68	31.72	13.46
14	990	894.08	15	6.24
15	447.26	402	6	2.42
16	206.34	185.38	3.26	1.42
17	93.68	84.96	1.12	0.46
18	41.74	37.06	0.6	0.26
19	21.4	19.42	0.42	0.22
20	9.04	8.02	0.08	0.02
21	3.88	3.66	0.08	0.02
22	1.22	1.08	0.02	0
23	0.42	0.36	0	0
24	0.26	0.24	0	0
25	0.02	0.02	0	0
26	0	0	0	0

CURRICULUM VITA

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EDUCATION

PhD in Industrial Engineering GPA: 3.90/4 2009 –2015
University of Louisville, Louisville, KY

- Dissertation: *Simulation-based optimization of mitigation strategies for pandemic influenza*

MBA - Entrepreneurship GPA: 3.80/4 2014 –2016
University of Louisville, Louisville, KY

MS in Social Economics System Eng. GPA: 17.66/20 2006 - 2008
Sharif University of Technology, Tehran, Iran

- Thesis: *Studying the profitability of momentum strategy and its sources in Tehran Stock Exchange*

BS in Industrial Engineering GPA: 16.33/20 2001 - 2006
Sharif University of Technology, Tehran, Iran

ACADEMIC EXPERIENCE

Research Assistant; *Logistics & Distribution Institute*, UofL, KY 2011- 2012

- Collaboration with a 30 member UofL team of a multi-million dollar healthcare project funded by Kentucky Critical Infrastructure Protection Program
- Development of simulation models to forecast the spread of pandemic influenza for Jefferson County, KY
- Establishment of simulation-based optimization models to mitigate pandemic influenza for Jefferson County, KY

Teacher Assistant; *Sharif University of Technology*, Tehran, Iran 2004- 2006

FELLOWSHIPS AND AWARDS

- Industrial Engineering Doctoral Dissertation Award; UofL 2015
- Best in Major Award; Engineering Exposition, UofL 2012
- American Society for Quality Award; The Louisville Section of American Society for Quality 2012
- University Fellowship; UofL 2009

PUBLICATIONS

- Arsalan Paleshi, Gerald W. Evans, Sunderesh S. Heragu, Kamran S. Moghaddam, "Simulation of mitigation strategies for a pandemic influenza", *Proceeding of the 2011 Winter Simulation Conference*, December 2011, Phoenix, Arizona
- Arsalan Paleshi, Gerald W. Evans, Sunderesh S. Heragu, Kamran S. Moghaddam, "Disease spread model to evaluate intervention strategies during pandemic influenza", *61th Industrial Engineering Research Conference*, May 2011, Reno, Nevada
- Arsalan Paleshi, Trivikram Rao, Gail DePuy, Bulent Erenay, "Spreadsheet decision support tool for a food bank's inventory management", 61*th Industrial Engineering Research Conference*, May 2011, Reno, Nevada
- Trivikram Rao, Arsalan Paleshi, Gail DePuy, Bulent Erenay, "A mathematical programming approach for assigning students to schools", 61*th 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