May 2014

Antiviral Resistance and Dynamic Treatment and Chemoprophylaxis of Pandemic Influenza

Sandro Paz
University of South Florida, spaz@mail.usf.edu

Antiviral Resistance and Dynamic Treatment and Chemoprophylaxis of Pandemic Influenza

by

Sandro A. Paz

A dissertation submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
Department of Industrial and Management Systems Engineering
College of Engineering
University of South Florida

Major Professor: Alex Savachkin, Ph.D
Heide Castañeda, Ph.D.
Kingsley Reeves, Ph.D.
Alex Volinsky, Ph.D.
Hui Yang, Ph.D.

Date of Approval:
March 21, 2014

Keywords: Antiviral Agent, Computer Simulation, Dynamic Programming, Design of Experiments, Disease Outbreaks

Dedication

To my wife, who has been the true model of perseverance and love throughout my life since I met her. To my kids because they have reminded me how important it is to do things that you love and enjoy. To my parents, they taught me all the values that led me to this achievement. To my brother for his commitment to pursue happiness and the happiness of his daughters.

Acknowledgments

I am extremely grateful to my advisor, Dr. Alex Savachkin for his academic support and helping me to be researcher, instructor and a better professional. I would also like to thank his former students, Andres Uribe for his invaluable work in the code which has been the basis for my work and for his recommendations to be successful in the doctorate; Dayna Martinez because this research is an unpretentious complement of her work; and Alfredo Santana for the ideas that helped me to visualize the value of my research.

I would like to thank Dr. Jose Zayas-Castro, Dr. Tapas Das and Mr. Bernard Batson for their support, and the institutions that gave me financial support: Florida-Georgia Louis Stokes Alliance for Minority Participation (FGLSAMP) Bridge to the Doctorate Fellowship, USF Graduate School Diverse Student Success Fellowship, USF-IMSE Department and Pontificia Universidad Catolica del Peru.

Table of Contents

List of Tables

List of Figures

Abstract

Public health data show the tremendous economic and societal impact of pandemic influenza in the past. Currently, the welfare of society is threatened by the lack of planning to ensure an adequate response to a pandemic. This preparation is difficult because the characteristics of the virus that would cause the pandemic are unknown, but primarily because the response requires tools to support decision-making based on scientific methods. The response to the next pandemic influenza will likely include extensive use of antiviral drugs, which will create an unprecedented selective pressure for the emergence of antiviral resistant strains. Nevertheless, the literature has insufficient exhaustive models to simulate the spread and mitigation of pandemic influenza, including infection by an antiviral resistant strain.

We are building a large-scale simulation optimization framework for development of dynamic antiviral strategies including treatment of symptomatic cases and chemoprophylaxis of pre- and post-exposure cases. The model considers an oseltamivir-sensitive strain and a resistant strain with low/high fitness cost, induced by the use of the several antiviral measures. The mitigation strategies incorporate age/immunity-based risk groups for treatment and pre-/post-exposure chemoprophylaxis, and duration of pre-exposure chemoprophylaxis. The model is tested on a hypothetical region in Florida, U.S., involving more than one million people. The analysis is conducted under different virus transmissibility and severity scenarios, varying intensity of non-pharmaceutical interventions, measuring the levels of antiviral stockpile availability. The model is intended to support pandemic preparedness and response policy making.

Chapter 1: Introduction

The history of healthcare teaches us that a Pandemic Influenza (PI) is likely to reoccur and would be extremely unwelcome, since the societal and economic impact can be devastating. The historical data reveals the tragic experience of 500 thousand deaths resulting from the Spanish Flu (1918-1919) in the USA and approximately 40 or 50 million deaths worldwide. The Table 1.1 shows the impact of last pandemics influenza by number of deaths.

In a particular instance, the virus A H1N1-2009 (Swine Flu) had high morbidity but low mortality rates, which is shown by the CDC estimates: the number of infected people in US was approximately 61 million whereby 274 thousand needed to be hospitalized, and 12 thousand died; all of this occurred in the period April 2009 - April 2010 [3, 4].

The impact on society would be tremendous and in proportion to the number of population affected as well as to the specific public health policies deployed. Therefore, the policy makers need tools for selecting the best combinations of non-pharmaceutical and pharmaceutical interventions which can contain and mitigate a pandemic.

Table 1.1: Social impact: Estimated number of deaths in previous pandemic influenza.[2, 3]

Pandemic / Date	Deaths-World	Deaths-US	Virus
Spanish Flu 1918-1920	40-50 million	500-600 thousand	A (H1N1)
Asian Flu 1957-1958	2 million	70 thousand	A (H2N2)
Hong Kong Flu 1968-1969	1 million	34 thousand	A (H3N2)
Swine Flu 2009-2010	284 thousand	12 thousand	A (H1N1-2009)

When a person is infected, the first reaction might be isolation, use of sanitizers and caution when interacting with other persons. But, if an outbreak of PI starts, the policy makers could recommend non-pharmaceutical interventions (NPI) such as quarantine for family members of infected individuals since they have been exposed to the virus; they could promote the use of face masks, close schools and workplaces and also restrict travel.

On the other hand, the policy makers may select mitigation strategies based on pharmaceutical interventions (PHI) such as vaccination and the use of antiviral for treatment and prophylaxis [5].

All these alternatives for mitigating a pandemic require resources and entail complications. The extended use of NPI could cause loss of productivity in the economy, because it implies absenteeism in schools and workplaces [6]. Additionally these measures might not achieve the desired effect, as for example during H1N1-2009 pandemic when New York City opted to close schools. In this instance, the children did not stay at home because their parents needed to go to work [7]. In general, the difficulty with NPI is that the people do not comply with the requested changes in their behavior and routines.

The first issue with PHI is related to the vaccines themselves. It is necessary to detect and understand the virus in order to develop a vaccine, and usually pandemics start with a new, unknown virus; from that moment, the time to develop an appropriate vaccine and allocate the same to the vaccination centers takes from 8 to 9 months (H1N1-2009 pandemic experience). Additionally, the historical data shows us that some part of the population is vaccination-reticent, because even if the vaccine is available, it may cause uncomfortable side effects. Every season less than 30% of the population receives the vaccine, and this percentage increased from 31% to 50% during H1N1-2009 pandemic [8].

Regarding antiviral drugs, an important issue is the impact from massive use of antiviral agents. At present, the Strategic National Stockpile has antiviral drugs for 25% of the US population and also for assistance with other countries, which are more than 81 million courses [9]. Between 2004 and 2009, 350M antiviral treatment courses were supplied to governments worldwide [10] and the worldwide production capacity is more than 400M per year [5]. Some experts show that massive use of antiviral agents will reduce the impact of the pandemic. This is a good strategy for mitigating the pandemic, but we create a selective pressure that encourages emergence of an antiviral resistant strain [11–13]. Most of the transmissibility is stopped, but it is possible that some strong resistant strain might continue. Moreover, maintaining this

stockpile is very expensive. It should be noted that antiviral drugs, as vaccines, cause uncomfortable side effects.

As a summary, the resources are limited for various reasons, and each intervention has some non-beneficial impact, which is why the policy makers require good support tools for making intelligent decisions for this process.

Furthermore, present mitigation policies consider resource allocation based on population density without taking into account other important aspects, such as income, education, age, susceptibility, health insurance, which are all important in decision making as to how prevent the disease using vaccines or to complete the antiviral treatment in case of disease. Another problem with existing policies is that the recommendation for mitigation strategies are defined in advance and do not incorporate the current results and future posible results or changes during the pandemic itself; such policies are not dynamic. We can also find in the literature review, that most of the strategies tested in simulations are static.

In the event of a pandemic influenza reaching or initiating in the USA, the societal impact could be distressing. It is estimated that, depending on the virus transmissibility, the number of infected people could be 90 million and deaths would range between 20,000 to 2 million, depending on severity [14].

There is also an important impact on the economy which is basically caused by reduced productivity as well as medical expenses. Quantifying this loss is complicated because it depends on the interventions to mitigate and contain the pandemic and the disease characteristics. For example, voluntary or enforced workforce reduction, caused by individual decisions or mitigation policies, depends on the severity of the virus and the public health policies created by decision makers. Based on different assumptions, the researchers give some loss estimates for the USA: between 73 and 166 billions of dollars [14], or an economic impact of $187 per capita as loss to society that could be increased by approximately $2700 per capita, after adding various interventions to improve health outcomes [14, 15].

1.1 Antiviral Resistant Influenza Virus

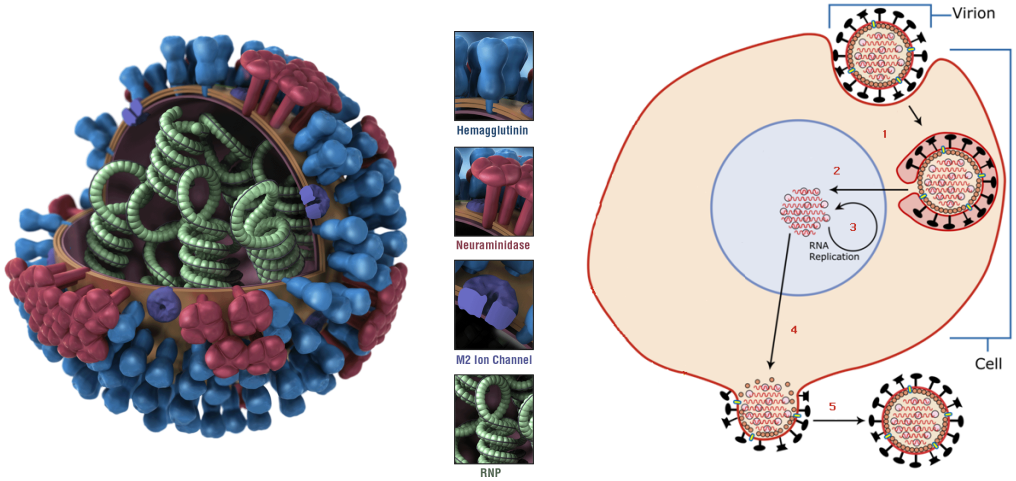
A virion, an entire virus particle as it exists outside the host cell, can replicate only in living cells. Figure 1.1 shows a virion with the proteins that cover the genetic material called Ribonucleoprotein (RNP), a compound of ribonucleic acid (RNA) and protein. These proteins contribute to the infection and replication

in a multi-step complex process, which is summarized in 5 steps: (1) the virion binds with and enters the cell; (2) it delivers its genetic material to the cell; (3) the replication begins; (4) a new virion is assembled; (5) the virion leaves the cell. At this moment, the cell dies and the virion is ready to infect the next cell [16, 17].

Each part of the virion helps in this process. The hemagglutinin contributes to the virion attaching to the cell, the M2 Ion aids in the delivery of the genetic material to start the replication process, and the neuraminidase helps the virion exit the cell. Based on these characteristics, the antiviral drug attempts to prevent this process using M2 inhibitors (avoiding steps 2 and 3), or neuraminidase inhibitors (avoiding step 5).

An important fact that can also be ascertained from this process is related to the virus mutation. The virus could be changed during this process, because the genetic material RNA gives the instructions to replicate the virus inside the cell, but it replicates without a proofreading activity (verification process that is part of the DNA replications but not of the RNA), and as a result, errors in the genetic coding could occur. This lack of proofreading influences enormously in how quickly an influenza virus mutates, and that is why it is difficult for vaccines and natural immunities to follow this excessive change [17].

Actually, the most recommended and used antiviral is oseltamivir (80% of actual Strategic National Stockpile) and that is why the response to the next PI will likely include its extensive use for prophylaxis and



(a) (b)

Figure 1.1: Influenza virion. (a) Elements [18] (b) Multi-Step Influenza Infection and Replication Process [16]

treatment. This will create an unprecedented selective pressure for the emergence and spread of antiviral resistant strains with no fitness cost, that means, with almost the same transmissibility as the original pandemic strain [19].

The Centers for Disease Control and Prevention (CDC) has kept monitoring and reporting the appearance of antiviral resistant influenza strains. Table 1.2 shows this surveillance over four seasons and for the most important virus in circulation. Notice that during these periods the use of antiviral has not been massive.

Finally, the emergence of resistant strains is a reality and could counteract the benefits of antiviral drugs. To this, we must add the practice of establishing static mitigation policies and the lack of tools to help assess dynamic policies.

That is why we need to balance the benefits from the use of antiviral drugs and the consequences related to resistant strains, generating antiviral dynamic strategies for treatment and prophylaxis by taking into account this resistance. The following chapters are focused on this as follow: In Chapter 2 we analyze the status of the relevant academic literature and identify most significant gaps in two general topics: simulation and antiviral resistance. Chapter 3 describes the research objectives. Chapter 4 describes our agent-based simulation model and shows the result of the simulation considering H1N1-2009 virus and the demographic characteristics of the Hillsborough County. Chapter 5 includes design of experiments for developing a nonlinear regression model including virus attributes and mitigation strategies. This chapter ends with a sensitivity analysis for the most important factors. Chapter 6 describes the dynamic model, determines the optimal dynamic mitigation policy and compares the outcomes for this policy with the

Table 1.2: Antiviral resistance testing results on samples collected since 2007 - 2011.[20]

	2007-2008		2008-2009		2009-2010		2010-2011	
Virus Name	Virus Samples	Resistant (n)(%)	Virus Samples	Resistant (n)(%)	Virus Samples	Resistant (n)(%)	Virus Samples	Resistant (n)(%)
Seasonal A-H1N1	969	106 (10.9%)	1151	1146 (99.6%)	1	1 (100%)	0	0
A-H3N2	332	0	264	0	13	0	806	2 (0.2%)
B	290	0	654	0	23	0	723	0
2009 A-H1N1	NA	NA	2040	10 (0.5%)	4769	55 (1.3%)	4 229	39 (0.9%)

correspondent static policy. Chapter 7 summarizes the main results, contributions, and future research opportunities.

Chapter 2: Literature Review

The models for studying PI as found in specialized journals and publications can be classified into the following categories [21, 22]: statistical, dynamic compartmental, simulation-based models and combinations thereof.

With a statistical model it is possible to estimate epidemiological parameters, using maximum likelihood estimations such as Markovian analysis, linear programming or regression models. The researchers have used this model to evaluate: vaccination impact [23, 24], contact probability, and the impact of mitigation strategies [25–28], among other applications.

The dynamic compartmental models show how the subject individuals flow from one compartment into another in a model that was defined by Kermack and McKendrick in 1927 [29]. The classical SIR model (Susceptible-Infected-Recovered) considers one or more cases of infection in a closed population of susceptible cases where the infectious disease spreads based on the transmission coefficient (determined by the infectiousness and the contact probability), and each case of infection, after the disease period, is removed by recovery or death. This model functions using a system of differential equations and assumes that the population is constant and homogeneous, divided into susceptible, infected and recovery cases, with constant and independent rates of transmission. This model does not consider the latency period, asymptomatic cases, non-pharmaceutical interventions and consideration of social dynamics. Some authors have incorporated more compartments into the model (latent, infectious, non-infectious, symptomatic, asymptomatic, long term immunity, short term immunity) [7, 30–32], but the major assumptions are unaltered.

By contrast, the simulation-based models can deal with consideration of social dynamics, non-pharmaceutical as well as pharmaceutical interventions, transmissibility based on population characteristics, disease history with several stages, and all of these in a stochastic process. This research uses a simulation-based model, and therefore in the next paragraphs we analyze the most relevant publications on this subject.

2.1 Simulation-based Models for PI

With this idea for using simulation based models to find alternatives for PI mitigation, researchers have built models based on various assumptions, constraints, scenarios, and they have proven the impact of these different mitigation policies. For example, in 2004, Longini et al. [33] use stochastic epidemic simulations to test the use of antiviral for prophylaxis. The authors showed that for an influenza virus similar to H2N2, if 80% of the close contacts among infected individuals take antiviral for 8 weeks, the pandemic could be contained. One important contribution is the use of the three components of the antiviral efficacy in the simulation: (i) the antiviral efficacy for susceptibility to infection; (ii) the antiviral efficacy for symptomatic disease given infection; and (iii) the antiviral efficacy for symptomatic disease. The results were based on a population of 2000 persons. An extension of this work is presented in Longini et al. [27] where the objective is to prove that it is possible to contain more aggressive influenza strains by combining targeted antiviral prophylaxis with pre-vaccination and quarantine using a rural area in Southeast Asia as a test bed.

Ferguson et al. wrote one of the first and most important papers of simulation models for PI [34]. They show that it is possible to contain an influenza outbreak in a specific region, identifying a combination of public health interventions: the geographically targeted use of antiviral drugs, combined with social distancing measures. As a result, the probability for containing the outbreak and the stockpile size were calculated for the specific populations in Thailand. Ferguson et al. considered the rapid identification of the disease origin, the rapid and effective delivery of antiviral for treatment and prophylaxis, and the population cooperation as key factors. To obtain these conclusions, they used a stochastic, spatially structured, individual-based discrete time simulation model, incorporating demographic densities obtained from Land Scan [35], and including an infection transmission model based on lognormal distribution.

Ferguson et al. continued their research applying this previous model in Great Britain and the United States [36], using combinations of several strategies to mitigate and contain an outbreak by means of travel and border restrictions, use of antiviral for treatment and prophylaxis, isolation, household quarantine, school and workplace closure and pre-vaccination. With the results of this research paper, the authors are certain that the future research needs more detailed model validation and recent data to estimate the disease and population parameters.

Another example of a large-scale stochastic simulation model to evaluate PI in U.S. is found in German et al. [37] where various strategies are considered, including the mass vaccination with a low effectiveness vaccine, use of antiviral for treatment and a targeted prophylaxis strategy. The disease transmission is based on a contact probability that depends on the age of both the infected and susceptible individuals; the transmission probability of the virus; and the antiviral/vaccine efficacy.

The previous two groups of researchers, along with the authors in Eubank et al. [38], were included in a comparative analysis made by Halloran et al. [28] from MIDAS (Models of Infectious Disease Agent Study created by the National Institute of General Medical Sciences and the National Institutes of Health). The three groups used their own models and methodology to simulate the effectiveness of a combination of mitigation strategies against a PI in a population of 8.6 million with social dynamics similar to Chicago. The idea was to review the robustness of the results with model assumptions, considering same virus and social input variables. The three models suggest similar results for the targeted layered containment mitigation strategies, but these are to be considered as a guide for decision makers and not as prediction models for mitigation strategy effectiveness.

Wu et al. [39] simulate different interventions scenarios in Hong Kong and include more stages in the classical Kermack and McKendrick model: S (susceptible), E (exposed), IP (infectious but not yet symptomatic), IA (infectious and asymptomatic), IS (infectious and symptomatic), IH (infectious to be hospitalized), and R (recovered). All deaths occur in the IH stage. The results show that household-based interventions are more important.

Another important study was carried out by Colizza et al, [40] using a worldwide compartmental simulation model for the pandemic spread, considering air travel networks and urban centers. Based on that, they test the use of antiviral and travel restrictions as policies to mitigate the pandemic.

A common feature of the previously discussed publications is that mitigation strategies are static, the result of each intervention being based on a policy that remains constant throughout the pandemic. Since the outbreak, the number of infected increases, based on the transmission probability until the impact of the mitigation strategy reaches more population and people develop immunity; then, the number of infected decreases after reaching a peak. If the decision makers select and maintain a policy throughout the pandemic, it could be over- or under-dimensioned for some period of time.

The next research using simulation-based models for PI considers policies with some dynamic components that suit the changes in strength of the pandemic. Uribe et al. [21] and Savachkin and Uribe [41] are of the opinion that the current fixed policy of pharmaceutical distributions among counties based on the number of inhabitants is not optimal. For that reason they simulate four counties in the State of Florida, U.S. with over four million inhabitants, in an agent based simulation model. This model features a high level of granularity, including hourly schedules for each individual and hour-by-hour interaction to simulate the contact process. At the end, a dynamic predictive strategy is developed to distribute the resources in a more efficient manner so that the cost of the outbreak is less. Another important contribution of this line of research is that they consider measures of morbidity, mortality, and social distancing, which should be included under the societal and economic costs of lost productivity and medical services.

At this point of the review of publications and journals it is important to note that none of these simulation models for PI take into account that the massive use of antiviral for chemoprophylaxis and treatment entail selective pressures on the virus to develop resistance to the antiviral drug, and therefore they do not contemplate a PI where two viruses (the sensitive or pandemic virus and the antiviral resistant virus) circulate among the population. Before analyzing some simulation models that cover this issue, in the following paragraphs we will present a discussion concerning the research on antiviral resistance.

2.2 Antiviral Resistance

Most of the studies on antiviral resistance are in the form of qualitative discussions and surveillance reports; for example Kiso et al.[42] report the case of influenza A(H3N2) collected from 50 children treated with oseltamivir in Japan, where they found neuraminidase resistance in viruses from nine patients (18%) [43]. Another case is reported by Hatakeyama et al. in the study to assess the prevalence and transmissibility of resistant influenza B viruses. They identified 1.4% of treated children with reduced drug sensitivity; as well as in 1.7% from untreated patients who were infected in their households with siblings shedding the resistant viruses [43]. Meijer et al. shows that, in Europe, during 2007-08 season, 24% of the virus A(H1N1) were oseltamivir resistant [44].

The transmission of the resistant virus is measured by its fitness cost. Most of the resistant viruses have medium or high fitness cost and that is why their transmissibility is reduced. However, Baz et al. and Le

et al. report sporadic oseltamivir-resistant A(H1N1-2009) or Swine Flu, including episodes of transmission [45, 46]. Another unusual case is reported by Mai et al., whereby the infection of students who traveled by train on a 42 hours trip and who had no contact before the trip, were infected by a special resistant mutation (H275Y) with no or very low fitness cost.

In spite of the strong relationship observed between the use of antiviral and the emergence of resistant virus, this could not be demonstrated statistically due to a lack of consistency in the collected data. Kramarz et al. tried to identify this precise relationship between antiviral use and resistance of influenza A(H1N1) but it remains uncertain because the authors only have information from antiviral prescriptions and sales. It is presumed that some of antiviral are saved in personal stockpile and never used [11]. One research project supporting the idea of a relationship is from Stephenson et al. who report resistance to oseltamivir during treatment: 27% in children with influenza A(H1N1) and 3% in children with influenza A(H3N2) [47].

Besides the studies previously discussed, there are some authors, who do not only report surveillance cases. For example, Moscona suggests that resistance to oseltamivir (the most important antiviral) is feasible based on a structural analysis of the influenza neuraminidase [13]. Boltz suggests that the rapid emergence and spread of oseltamivir resistant viruses in 2007-08 demonstrate their ability to circumvent mitigation strategies [12]. Finally Lipsitch et al. said that it is prudent to consider the possibility that resistant strains emerge during the pandemic with modest or no fitness cost, that means, with almost the same transmissibility as the sensitive strain[19].

Despite the fact that the exact relationship between the antiviral use and resistance of influenza virus to antiviral remains uncertain, some researchers analyze the impact in a PI using simulation models. In the next paragraph we show their considerations.

2.3 PI Simulation Models Under Assumption of Antiviral Resistance

The concern about the emergence of the antiviral resistant virus has been present in almost all studies on the use of antiviral as a PI mitigation strategy, but always the a priori conclusion was that it was not relevant to the study [27, 36, 37] because the emergence probability was low and/or the fitness cost of the resistant virus was high.

One of the first publications about simulation models to analyze the impact of the use of antiviral in the emergence of a resistant virus was developed by Lipsitch et al. in 2007. They developed a deterministic compartmental simulation model (Susceptible - Infected untreated - Infected treated - Infected by resistant strain - Recovered) of the transmission of oseltamivir-sensitive and -resistant influenza infections during a pandemic, which predicts that the massive use of antiviral could initiate the spread of resistant strain, despite considering only the emergence of resistant strain in 1 in 50,000 treated persons and 1 in 500,000 persons who have undergone prophylaxis. At the end, the resistant strain could be responsible for up to 10% of the disease. This magnifying effect reveals that the risk of resistance should be considered in the PI simulation models to evaluate the impact of the antiviral policies [19].

Handel et al. developed a stochastic compartmental model of antiviral resistance emergence that shows different results from deterministic models. They find that a rapid intervention, based on prophylaxis, can contain an antiviral sensitive outbreak and prevent a resistant outbreak; if this is not possible; the intermediate use of antiviral gives a better result. In this model, the authors assume that all infected are symptomatic and the resistance could emerge in the treated infected, not in the susceptible individuals who have undergone prophylaxis and who are exposed to the sensitive strain [48].

Since the emergence of antiviral resistant virus is more frequent and comes with lower fitness cost, more authors are interested in analyzing this problem. That is the case of Moghadas et al. who investigate scenarios for the emergence of resistant virus using a deterministic mathematical model (an extended SIR model). They determine the optimal treatment level that minimizes the size of the outbreak and show that a treatment above the optimal level creates an outbreak of resistant strain and increases the number of infected. For this propose the emergence of antiviral resistant strain considered is around 5% of the treated patients. The researchers changed the treatment levels throughout the duration of the epidemic to reduce the number of clinical infections achieved with the static strategy, the model becoming a pseudo dynamic one [49].

Hansen and Day [50] were concerned about the static policies to mitigate a PI, and they used the optimal control theory to evaluate time-varying treatment strategies during the outbreak. Based on that, they derive analytical expressions for the optimal strategy, and they prove that the optimal solution is achieved using the maximum treatment level, after waiting a fixed period of time after the outbreak begins. This result is contrary to previous research and is based on an extended compartmental SIR simulation model with only treatment for infected individuals as a mitigation strategy.

Jaberi-Dourakia and Moghadas include the amount of antiviral stockpile in their previous model [49, 51] to find the optimal treatment profile during an influenza epidemic. Using control theory, they minimize the total number of infections during an epidemic episode and, in the end, the optimal is a function only the initial level of treatment and the timing for implementing a more aggressive use of antiviral [52].

Even though these publications measure the impact of the use of antiviral in the emergence of antiviral resistant strains, none of them consider the interaction with other mitigation policies; moreover, not all utilize antiviral for prophylaxis, only for treatment. Additionally, the models provided do not include the social dynamics because the compartmental SIR models cannot simulate the interaction and contacts in different mixing groups in society (e.g. school, workplace, shopping centers, etc.). The literature review also reveals that the authors measure the impact of their strategies in terms of the number of infected or its relationship with the number of infected under a fixed strategy using antiviral; they do not measure the economic impact [19, 34]

As a summary, (i) studies on antiviral resistance are in the form of qualitative discussions and surveillance/incidence reports; (ii) the exact relationship between antiviral use and resistance of influenza virus to antiviral remains uncertain, whereby uncertain means that we do not know when or how a resistant strain is going to emerge, but it is critical; (iii) there is a lack of simulation-based models for pandemic spread and dynamic mitigation which incorporate antiviral resistance. Models that include antiviral resistant strain are compartmental SIR models; and (iv) the simulation models include the infection attack rate and the mortality ratio (or similar variables) as output to compare the effect of each mitigation strategy and to find an optimal, preventing more comprehensive outcomes such as the cost of lost of productivity and medical expenses.

In the next chapter we will discuss how this research will cover the gaps found in current the literature.

Chapter 3: Research Objectives

The overall objective is to develop a decision-aid methodology to support the design of dynamic antiviral treatment and chemoprophylaxis strategies considering antiviral resistance. In other words, considering the gaps in the literature review, we propose to generate antiviral dynamic strategies for treatment and prophylaxis taking into account the resistance strains to antiviral drug. The challenge is balancing the benefit of antiviral drug intervention and the emergence of resistant strain. The specific aims of this research are as follows:

RO1: Develop a large-scale simulation model for PI incorporating sensitive/resistant strains and antiviral treatment and pre-/post-exposure prophylaxis.

The agent-based simulation model will mimic a community and its social interaction during a PI. The infection by a sensitive strain as the emergence and spread of resistant strain will be mitigated by implementing PHI and NPI. The model will be calibrated for different levels of transmissibility and validated with real information from the H1N1-2009 pandemic. To compare mitigations strategies, the model measures the impact in terms of economic and societal costs.

RO2: Design a set of nonlinear regression models to examine the impact of antiviral treatment and prophylaxis.

This objective will be achieved using a factorial design to select the combinations of the most relevant factors and their interactions. The results will allow the identification of the optimal mitigation strategy as a combination of controllable factors, which minimizes the cost. The combination of uncontrollable factors will define the scenarios to measure the impact of dynamic antiviral policy in the next research objective. A design of experiments will allow us to identify statistically significant controllable factors to select the action space elements to be incorporated in a dynamic mitigation policy.

RO3: Develop a DP-based methodology for dynamic antiviral treatment and prophylaxis considering antiviral resistance.

Simulating the scenarios of the PI that will be defined in RO2, we will obtain the transition probability and cost for each antiviral strategy, which will be the input to determine an optimal dynamic policy using dynamic programming optimization.

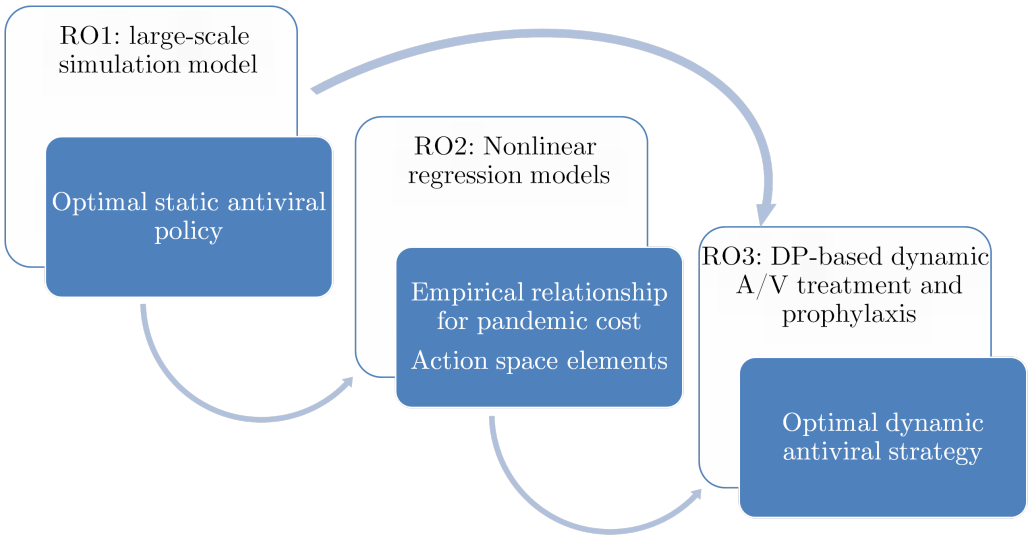


Figure 3.1: Integration of research objectives.

Chapter 4: Development of an Optimal Static Antiviral Treatment and Prophylaxis Strategy

4.1 Simulation Model

The agent-based simulation model used in this research creates a population divided in mixing groups that emulate the social interaction in a community. After that, a pandemic is triggered by some infected cases, randomly selected, who spread the disease based on their contacts with other members of their mixing groups. The model evaluates every Δt (e.g., one hour) if there are new infected cases after positive contact between a susceptible and an infected individual.

Infected individuals who feel symptoms start seeking medical assistance and receive an antiviral as a treatment; also, susceptible individuals who are in the same mixing group as infected individuals or who have a critical health condition (high risk) may take an antiviral. If an infected individual does not feel symptoms, she/he continues with disease history. As a result of use of an antiviral, the simulation model creates new infected cases but with a new antiviral resistant strain. From the time that a new virus emerges, the model simulates the transmissibility and disease with two strains.

Fixed mitigation strategies, using pharmaceutical and non-pharmaceutical interventions, are implemented until the pandemic is over. A schematic of the model is shown in Figure 4.1, and the detail of this model is described in the next sections.

4.1.1 Mixing Groups and Populations Dynamics

The community simulated includes houses, schools, universities, factories, offices, shopping centers, and other places where people run errands. Inside each place, we created one or more mixing groups (small places where social interaction occurs). Each person is assigned to a set of these mixing groups considering

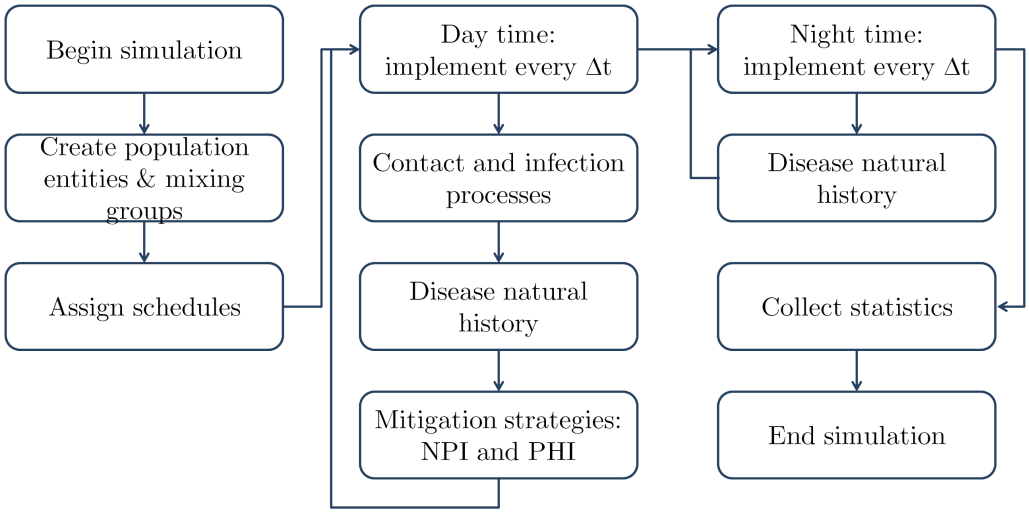


Figure 4.1: Schematic of the simulation model.

his/her age, social status, and hour of the day; she/he moves from one mixing group to another, interacting with others members, based on a specific schedule for weekdays and weekend.

Once a person is infected or a susceptible individual is in contact with an infected individual, the original schedule may change based on the mitigation strategy used. Strategies such as closing schools or household quarantines can change the schedule for all members of the mixing groups associated with the measure.

4.1.2 Contact Process and Infection Process

Every Δt (e.g., one hour) each person in a mixing group is in one of the two groups: infected or susceptible. The model tracks contacts between infected and susceptible persons, which occurs randomly and is based on the contact probability [37]. During this contact, the infected individual shares his/her viral load with the susceptible individual, who may receive the virus from more than one infected individual. The profile of infectiousness $f(t;\delta,\gamma)$ for each infected j is described by a lognormal form as follows: [34]

$$f_j(t;\delta,\gamma) = \frac{1}{t\gamma\sqrt{2\pi}}\left(e^{\frac{-(\ln t-\delta)^2}{2\gamma^2}}\right) \tag{4.1}$$

where t is the infection time andδ and γ are, respectively, the mean and standard deviation of the lognormal form defined by Ferguson [34]. Figure 4.2 shows the profile of infectiousness by the infection time.

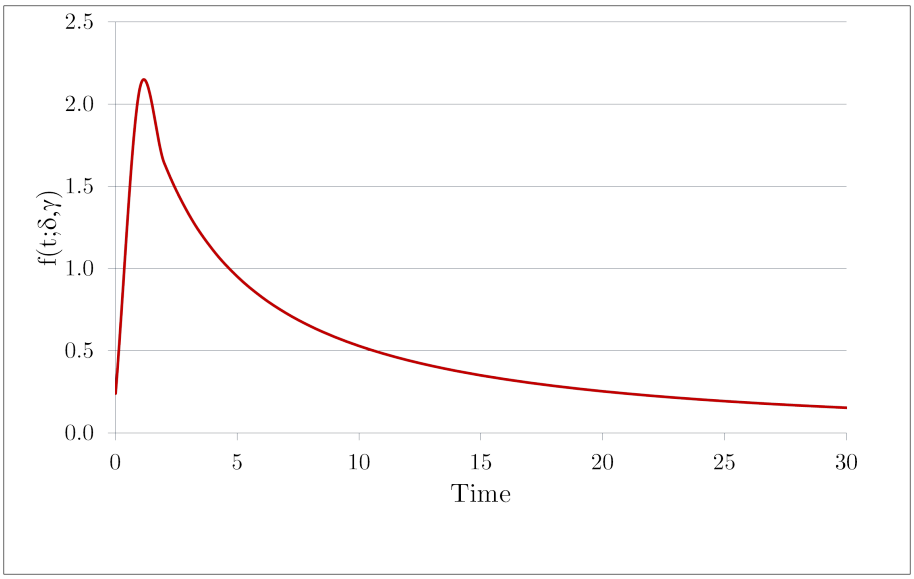


Figure 4.2: Profile of infectiousness.

Inside each mixing group, every infected individual j contacts part of the members n_j during $[t, t+\Delta t]$; then, the amount of viral shedding applied by infected j to each contact and also by him/her self is defined by

$$VS_j(t,\Delta t) = \int_t^{t+\Delta t} \frac{\rho \cdot f_j(u;\delta,\gamma)}{n_j+1}\, du \tag{4.2}$$

where ρ, the calibration parameter, allows the simulation of different scenarios of transmissibility [34, 53] This viral load, measured in terms of the amount of virus that a susceptible individual receives, needs to consider the impact of more than one effective contact. Therefore, the viral load that receives each susceptible case i from all his/her m_i infected contacts during $[t, t+\Delta t]$ is:

$$VL_i(t,\Delta t) = \sum_{j=1}^{m_i} VS_j(t,\Delta t) \cdot (1 - AVE_{I\,j}) \tag{4.3}$$

In Equation 4.3 the viral shedding is reduced by the antiviral efficacy for infectiousness AVE_{Ij}, which could be different for each infected j. If the infected individual is taking an antiviral at the time of contact, it has a favorable impact on the transmissibility.

We assume that the amount of virus that a susceptible individual receives in each interval $[t, t+\Delta t]$ remains up to time s (e.g., 24 hours), which leads to the total viral load accumulated by susceptible i through time s starting at 0 as:

$$VLA_i(s) = \int_0^{s-\Delta t} VL_i(t, \Delta t) \cdot (1 - AVE_{Si})\, dt \tag{4.4}$$

In this case, AVE_{Si} is the antiviral efficacy for susceptibility for susceptible i and reduces the impact of virus accumulation because the susceptible individual is taking an antiviral at the time of contact.

Finally, the probability that susceptible i becomes infected during $[s, s+\Delta t]$ is

$$P(T_i(s) \leq \Delta t) = \left(1 - e^{-\int_s^{s+\Delta t} VLA_i(u)du}\right) \cdot \alpha_i \tag{4.5}$$

where $T_i(s)$ is the time required for susceptible i to get infected with exposure started at s and α_i is the age factor for susceptible i. [53]

Figure 4.3 shows the impact of antiviral efficacy. If an infected individual is taking an antiviral for treatment, the AVE_I reduces the virus transmissibility during the contact. If a susceptible individual is taking an antiviral for prophylaxis, AVE_S protects against the virus transmissibility during the contact. After the contact, if a new infected case emerges and this person is taking an antiviral for prophylaxis, she/he may not show symptoms due to antiviral efficacy by pathogenicity AVE_P.

At this point, it is important to emphasize that previous equations are written for an antiviral sensitive strain. To apply Equation 4.1 to an antiviral resistant strain, it needs to be reduced based on the fitness cost (FC), a reduction in its capacity. We assume an antiviral resistant strain is a mutation of the original virus with the same transmissibility as the antiviral sensitive strain ($FC = 0$) or less ($0 < FC \leq 0.4$) [19].

$$f_j(t; \delta, \gamma) = \frac{1}{t\gamma\sqrt{2\pi}} \left(e^{\frac{-(\ln t - \delta)^2}{2\gamma^2}}\right) \cdot (1 - FC) \tag{4.6}$$

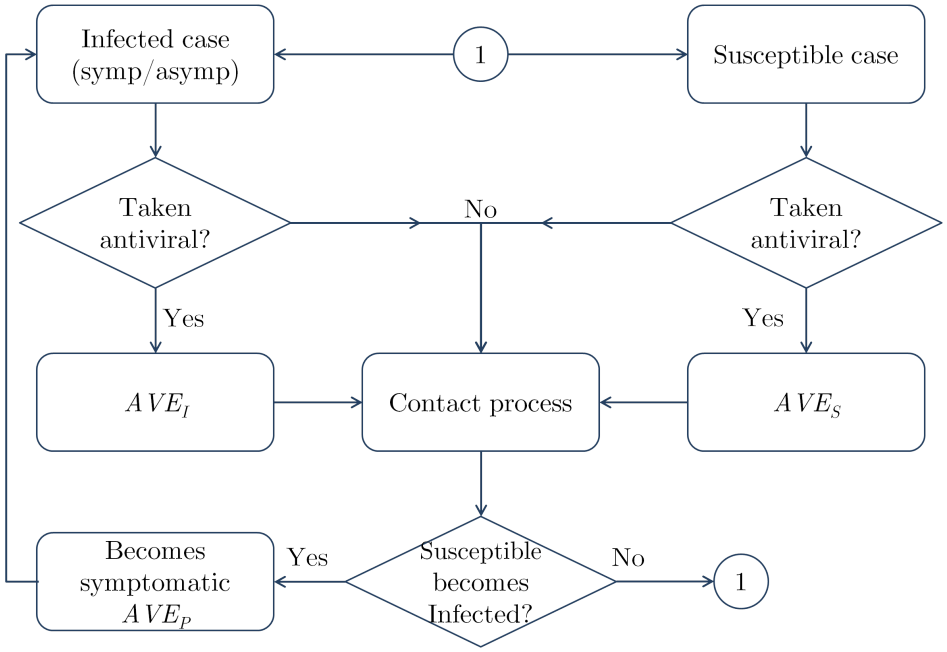


Figure 4.3: Effect of antiviral in infection transmission.

In Equations 4.3 and 4.4, the values of antiviral efficacy (AVE_{Si} and AVE_{Ij}) are zero because the antiviral has no effect on the resistant strain. Additionally, an infection could occur for one or both strains (dual infection), independently.

4.1.3 Disease Natural History

Once infected, an individual follows a sequence of phases and milestones that change the phases (see Figure 4.4). Two important milestones for the simulation are (1) when an infected individual becomes infectious, because this starts all the shedding processes; and (2) when she/he becomes symptomatic, because only the symptomatic cases go to the doctor. Following the infectiousness phase, the infected person is on her/his way to recovery, or a complication could take him/her to hospital and death (period leading to a health outcome). In this sequence, the use of an antiviral reduces the infection probability (equations 4.3 and 4.4) and reduces the probability of showing symptoms (AVE_P antiviral efficacy by pathogenicity).

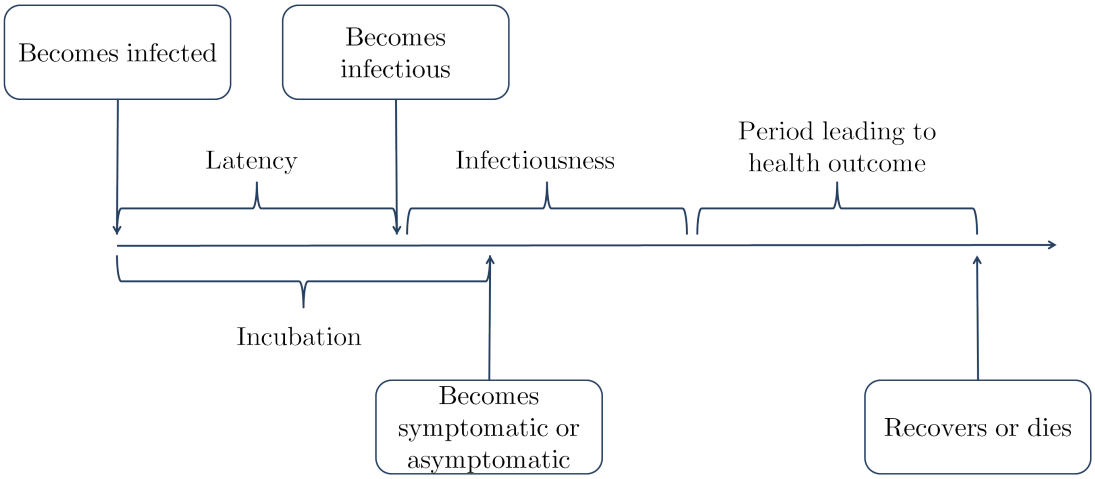


Figure 4.4: Schematic of disease natural history model.

4.1.4 Mitigation Strategies and Emergence of Antiviral Resistant Strain

Mitigation strategies start after the detection of a threshold number of confirmed infected cases, including pharmaceutical and non-pharmaceutical interventions.

The simulation considers four different non-pharmaceutical intervention strategies: case isolation, household quarantine, school closure, and workplace closure. Based on previous research, we selected a combination of these strategies and kept it fixed because the focus of this research is to study the impact of the use of an antiviral to reduce the total cost of the pandemic and the emergence of an antiviral resistant strain.

Pharmaceutical interventions include use of antiviral for treatment and pre- and post-exposure prophylaxis. The prescription of an antiviral for infected cases happens after the person becomes symptomatic and seeks medical attention. At that point, we assume that an antiviral prescription is given also for part or all the mixing group members. This is the post-exposure prophylaxis. The pre-exposure prophylaxis is given to people who have a high-risk condition such as obesity, cardiac disease, diabetes, etc. [54]

For the simulation, we assumed that the antiviral-resistant strain may emerge in an antiviral user who has been exposed to the virus. The antiviral could be used for treatment or prophylaxis. At the end, the emergence of resistant strains could counteract the benefits of antiviral treatment and prophylaxis [12, 13, 19], which is why we need to measure this impact.

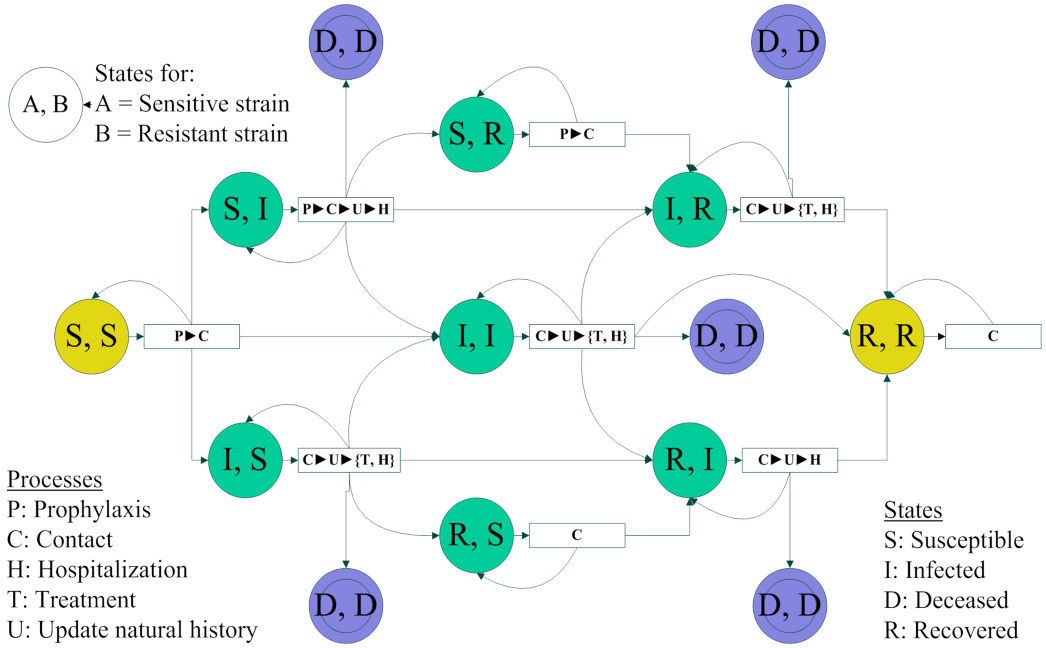


Figure 4.5: Infection states of two strains.

The consideration of two strains attacking the population independently leads to a sequence of states that describe the condition of susceptible or infected by the sensitive, antiviral-resistant, or both strains. Figure 4.5 shows that, at the beginning, a person is susceptible to be infected by either of the two strains (S,S); after the contact process (and prophylaxis, if applicable), the state could change to (I,S) or (S,I) if infected by a sensitive or resistant strain, respectively. Also, it is possible to continue as (S,S). After being infected by any strain, for example the sensitive strain in case (I,S), the next state could be recovery (R,S), death (D,D) or infected by two strains (I,I). The process to change the state considers the following rules:

- Before an infection for a sensitive strain, contact needs to occur with an infected case.
- Before an infection with a resistant strain, one of the following needs to occur: (1) contact with an infected person by a resistant strain or (2) contact with an infected person by a sensitive strain and antiviral use for treatment or prophylaxis (emergence of antiviral resistant strain).
- Before death, the infected individual goes to the hospital.
- Before recovery, the infection process ends (update natural history).

- (R,R), (D,D) are absorbing states; the remaining states are transient because a person cannot return to them after leaving.

4.1.5 Resistant Virus Emergence

For the simulation, we assume that a resistant strain may emerge in an antiviral user who has been exposed to the virus. The antiviral could be used for treatment or prophylaxis. The resistant strain is a mutation of the original virus, with the same transmissibility and severity than the original virus or less [19]. The reduction in its capacity is called fitness cost. At the end, the emergence of resistant strains could counteract the benefits of antiviral prophylaxis and treatment [12, 13, 19].

4.1.6 Objective Value Function

To measure the performance of each mitigation strategy, we defined an objective value function in terms of cost that includes two broad components: societal and economic cost [1, 55]. The economic cost (C_E) includes medical attention cost (outpatient, hospitalization, use of antiviral) and the cost for cases not medically attended. The societal cost (C_S) includes the loss of productivity and the value of lost life, measured as the value of a statistical life. The costs are differentiated by age (g) and health condition (r: high risk and no risk)[1]

$$C_E = \sum_{g,r} \left\{ n_g(I^n_{gr}) + o_{gr}(I^o_{gr}) + h_{gr}(I^h_{gr}) + c(I^a_{gr}) + m_{gr}(D_{gr}) \right\} \tag{4.7}$$

n_{gr} Unit cost of infected with age g and health risk r who do not need medical attention

I^n_{gr} Number of infected with age g and health risk r who do not need medical attention

o_{gr} Unit cost of outpatient with age g and health risk r

I^o_{gr} Number of outpatients with age g and health risk r

h_{gr} Unit cost of inpatient (hospitalized) with age g and health risk r

I^h_{gr} Number of inpatients (hospitalized) with age g and health risk r

c Unit cost of antiviral course

I^a_{gr} Number of infected with age g and health risk r who takes antiviral

m_{gr} Unit cost of pre-mortality case with age g and health risk r

D_{gr} Number of deaths with age g and health risk r

$$C_S = \sum_{g,r} d_{gr}(D_{gr}) + l \cdot L \tag{4.8}$$

d_{gr} Value of lost life with age g and health risk r

D_{gr} Number of deaths with age g and health risk r

l Value of lost productivity day

L Number of person-days lost

4.2 Testbed Design

4.2.1 Description of Testbed

To analyze the impact of our mitigation strategies and the emergence of an antiviral resistant strain, the simulation model was tested in a region similar to Hillsborough County, Florida, with a population of 1.27 million, 540 thousand households, 2,900 workplaces, 790 educational centers, and 1,060 errand locations (more information about the population is included in the Appendix A) [56]. The people move around based on schedules (adopted from [57]) in discrete time intervals of one hour (Δt = 1). The infection process and the disease dynamics also were evaluated every hour.

For the disease, the profile of infectiousness follows Equation 4.1 (or Equation 4.6 for antiviral resistant strain) with parameters δ = -72 and γ = 1.8 (mean and standard deviation of a lognormal form) [34]. The infectiousness was calibrated considering different levels of infection attach rate (IAR, number of new infected cases divided by the number of persons at risk in the population). The antiviral efficacy by sensitivity (AVE_{Si}), infectiousness (AVE_{Ij}), and pathogenicity (AVE_P) were for oseltamivir, which affects transmissibility and severity [28]. The values of age-dependent base infection probabilities (α_i in Equation 4.5) were adopted from [37].

The disease natural history (see Figure 4.4) included a latent period of 24 hours; an incubation period from 24 to 96 hours, with an average of 48; an infectiousness period from 120 to 168 hours; and a period leading to health outcome from 127 to 240 hours [4, 58].

4.2.2 Calibration and Validation Process

The simulation model was calibrated considering three levels of IAR = (20%, 35%, 50%)[4, 34] with no emergence of an antiviral resistant strain. The calibration parameter (ρ in Equation 4.2) was defined to obtain the values of IAR and mortality rate for H1N1-2009 pandemic using the interventions implemented in the testbed region [59]. Based on that information, the model reported costs that are comparable with Molinari [1]. Table 4.1 shows costs for influenza disease in a population of 1.27 million estimated by [1] and our simulation model (10 iterations).

After that, the calibrated model was updated with the emergence of an antiviral resistant virus and the simulation of dual infection (infected by sensitive, resistant, or both strains).

4.2.3 Results of an Optimal Strategy for Specific Scenario

We implemented mitigation strategies that include a mix of PHI and NPI in a specific scenario, similar to the H1N1-2009 pandemic. Table 4.2 shows the incremental levels for PHI before contact with an infected individual (post-exposure) or before that (pre-exposure). The parameters for NPI are fixed considering the CDC recommendation and previous research (see Table B.2) [18, 53].

Table 4.1: Cost comparison between Molinari [1] and simulation model.

Type of Costs	Based on Molinari (Population1.27M)		Testbed simulation			
	Cases	Total cost ($1,000)	Cases: 95% CI		Cost: 95% CI ($1,000)	
			Lower	Upper	Lower	Upper
Ill (not medically attended)	56,450	8,185	54,543	58,341	7,731	9,386
Outpatient only	43,809	28,128	42,314	48,557	26,683	28,223
Hospitalized	1,208	24,533	1,125	1,319	22,851	25,999
Death	169	49,392	157	182	45,659	51,393
Total	101,636	110,239	98,138	108,399	109,109	118,781

Table 4.2: Post-exposure chemoprophylaxis interventions.

Name		Intervention
I. < 2	I	Infected under 2 years old
+ I. > 65	II	(I) + Infected over 65 years old
All Infected	III	All infected
+ P. HH < 2	IV	(III) + Prophylaxis for household under 2 years old with at least one infected case at home
+ P. HH > 65	V	(IV) + Prophylaxis for household over 65 years old with at least one infected case at home
+ P. HH All	VI	(III) + Prophylaxis for household with at least one infected case at home
+ P. WP 25%	VII	(VI) + Prophylaxis for 25% of the members of a mixing group with at least one infected case
+ P. WP 50%	VIII	(VI) + Prophylaxis for 50% of the members of a mixing group with at least one infected case
+ P. WP 75%	IX	(VI) + Prophylaxis for 75% of the members of a mixing group with at least one infected case
+ P. WP 100%	X	(VI) + Prophylaxis for all members of a mixing group with at least one infected case

The impact of each strategy was measured using the infection attack rate (IAR) (see Figure 4.6), considering persons infected by the sensitive strain, the resistant strain, and two strain (Dual). The increasing use of antivirals reduced the number of those infected by the sensitive strain (blue bars) but increased the number of those infected by the antiviral resistant strain (red bars). We identified some cases in each strategy that were infected by two strains during the pandemic event (green bars).

Figure 4.7 shows the total cost of the pandemic using Equations 4.7 and 4.8 and the units cost determined by[1]. In this specific scenario, the minimal cost was for +P. HH < 2 (antiviral for all infected plus prophylaxis for household under 2 years old with at least one infected case at home).

The strategy to mitigate a pandemic includes various antiviral interventions and a fixed non - pharmaceutical strategy. We showed that the increasing use of antivirals reduces the number of infected by the antiviral sensitive strain, but increases the number of infected by the antiviral resistant strain. A balanced mitigation strategy that minimizes the total cost of the PI depends on the PI characteristics.

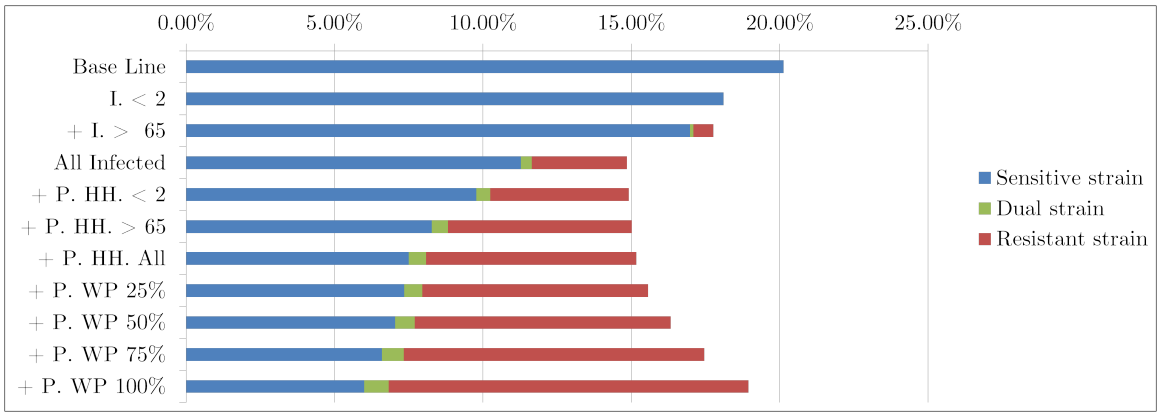


Figure 4.6: IAR per strategy and per strain that cause disease.

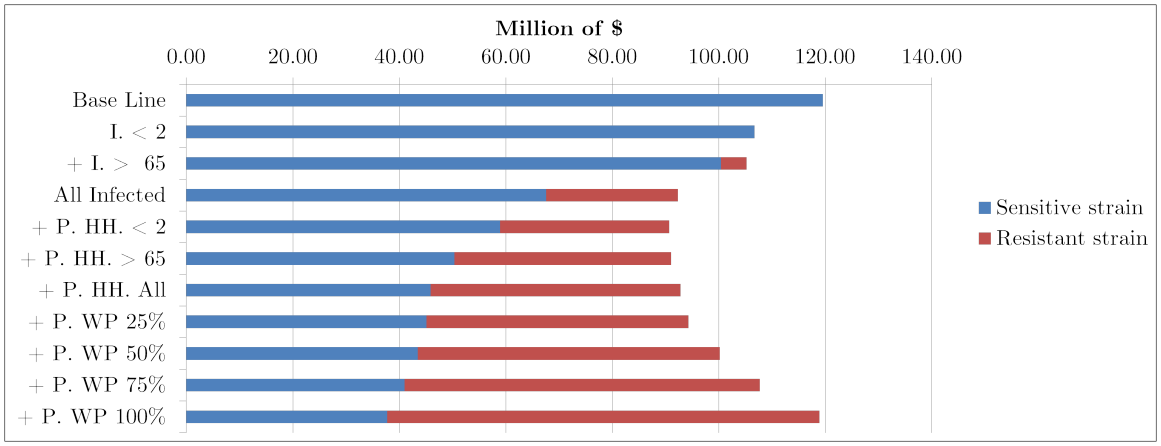


Figure 4.7: Cost per strategy and per strain that cause disease.

Chapter 5: Nonlinear Regression Models to Examine the Impact of Antiviral Treatment and Prophylaxis Strategies

5.1 Design of Experiments (DOE)

We used experiments to study the performance of mitigation strategies in different PI scenarios. The strategies were combinations of levels of controllable factors (NPI and PHI), which were tested in each scenario. The scenarios were defined as a combination of levels of uncontrollable factors (in the real world but controllable for the study) associated with the transmissibility and severity of the sensitive and resistant strains. Figure 5.1 shows how all these factors interacted in the PI simulation model to obtain the total cost of PI, including information about the society as an input.

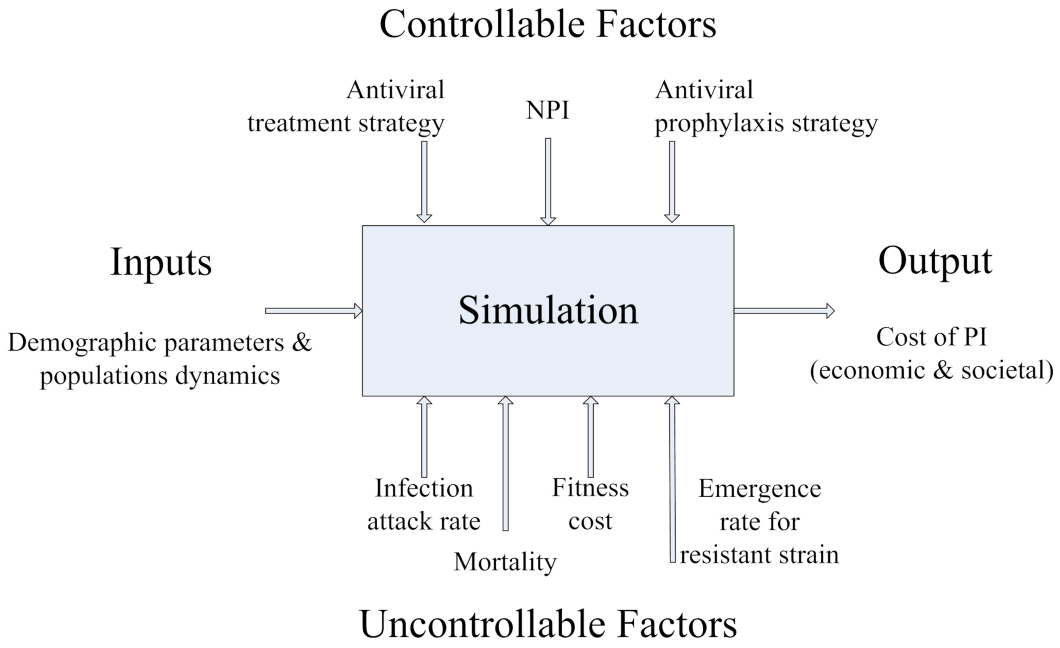


Figure 5.1: IP simulation model considered for the DOE.

Table 5.1: Factors and levels for DOE.[19, 61–63]

		Factor	Levels		
			Low (-1)	Intermediate (0)	High (1)
Controllable	Factors	POEP: Post-exposure chemoprophylaxis	Table 4.2 (10 levels)		
		PREP: Pre-exposure chemoprophylaxis	No antiviral		6-week course
Uncontrollable	Factors	Infection attack rate	20% (H1N1-2009)	35%	50%
		MP: Mortality probability	Lower (H1N1-2009)		Higher (Asian Flu)
		ERR: Emergence rate of resistant strain	1 / 10,000		1 / 5,000
		FC: Fitness cost of resistant strain	0	0.2	0.4

The procedure to select strategies and scenarios to be tested is called a factorial experiment, in which the levels for each factor (controllable and uncontrollable) vary together [60]. After simulating all combinations (or treatments) and obtaining the total cost for each one, it is possible to identify the effect of each factor and the effect of the interactions of factors. These effects are composed in a nonlinear regression model. Despite some factors being qualitative, this empirical model for the cost of PI allows us to identify the values that minimize the cost for quantitative factors.

The results and optimal solution shown in Figure 4.6 and Figure 4.7 are for a specific scenario (H1N1-2009 pandemic). To identify factors and how the optimal solution changes in different scenarios, we considered combinations of factors in the design of the experiment. The detail of factors and levels are shown in Table 5.1.

The combinations of levels gave us 720 treatments, for a factorial design in which the levels have been codified as -1 and +1 for two-level factors and -1, 0 and +1 for three-level factors. The factor with 10 levels also was codified with values from -1 to +1. Each treatment was simulated 10 times (replica) to result in 7,200 responses of pandemic cost. The effect of each factor and one of the most relevant interactions are

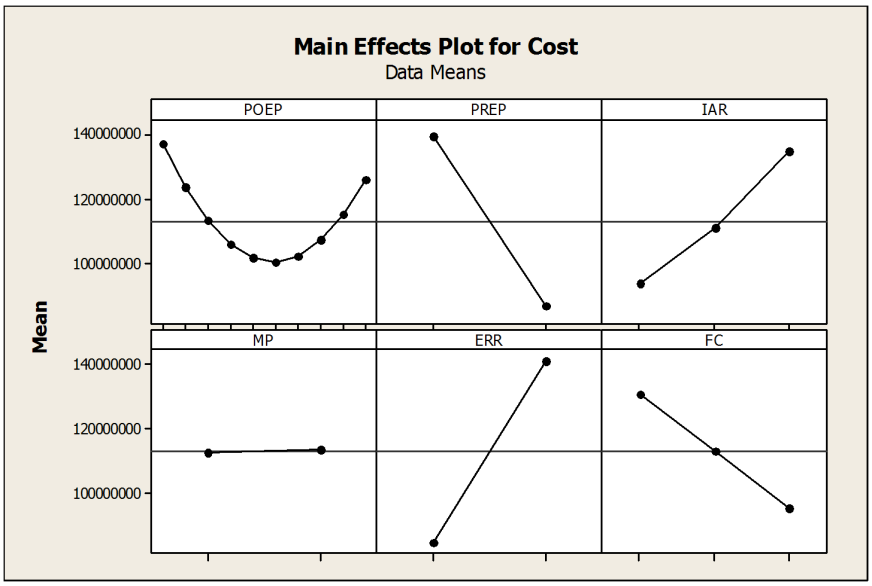


Figure 5.2: Main effect plot for total cost.

shown in Figure 5.2 and Figure 5.3, respectively. (The complete relevant interactions are in the Appendix C.)

For example, Figure 5.2 shows that if factor IAR changes from lower level (20%) to high level (50%), the average cost increases; on the other hand, if factor PREP changes from lower level (no antiviral for pre-exposure prophylaxis) to high level (six weeks of antiviral for pre-exposure prophylaxis), the average cost decreases. Changes in factor MP do not affect the cost significantly.

Figure 5.3 shows interaction between the factors. An interaction occurs when the effects of a factor in cost are different for different levels of the other factor[60]. For example, the difference in cost between levels of factor POEP at lower level of ERR is less than at higher levels.

Table 5.2: Costs per scenario and POEP factor.

	Scenario		
Factor	Mild	Moderate	Severe
IAR	20%	35%	50%
MP	Low	High	High
ERR	1/10,000	1/5,000	1/5,000
FC	0.4	0.2	0

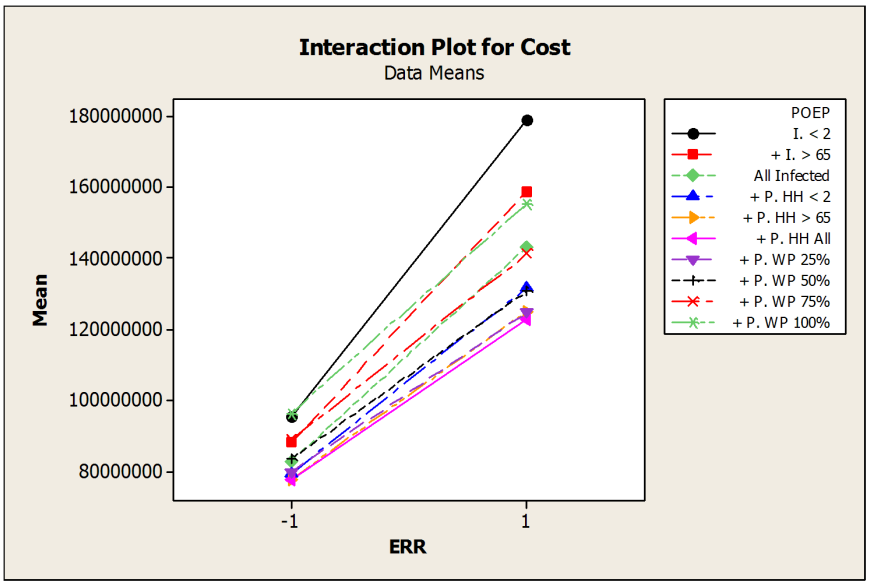


Figure 5.3: Interaction effect POEP vs ERR for total cost.

5.2 Empirical Relationship for Pandemic Cost

To identify an empirical relationship between the cost and the factors, we follow two approaches: (1) Identify equations for each combination of levels, based on the design of experiments (2) use of regression analysis.

5.2.1 Empirical Relationship Based on DOE

As a result, the effects of the main factors and interactions are reflected in an empirical set of nonlinear equations where the coefficients are specific values for each combination of factor-levels. For example, if we consider that the pandemic cost depends only on two factors with i and j levels for each one, the equation for an estimation of cost when the factor A is at level i and factor B is at level j is

$$Cost_{i,j} = \mu + \tau_i + \beta_j + (\tau\beta)_{i,j} \tag{5.1}$$

where τ_i is the effect of the ith level of factor A, β_j is the effect of the jth level of factor B and $(\tau\beta)_{ij}$ is the effect of the interaction between τ_i and β_j. Our model considers 6 factors with different number of levels

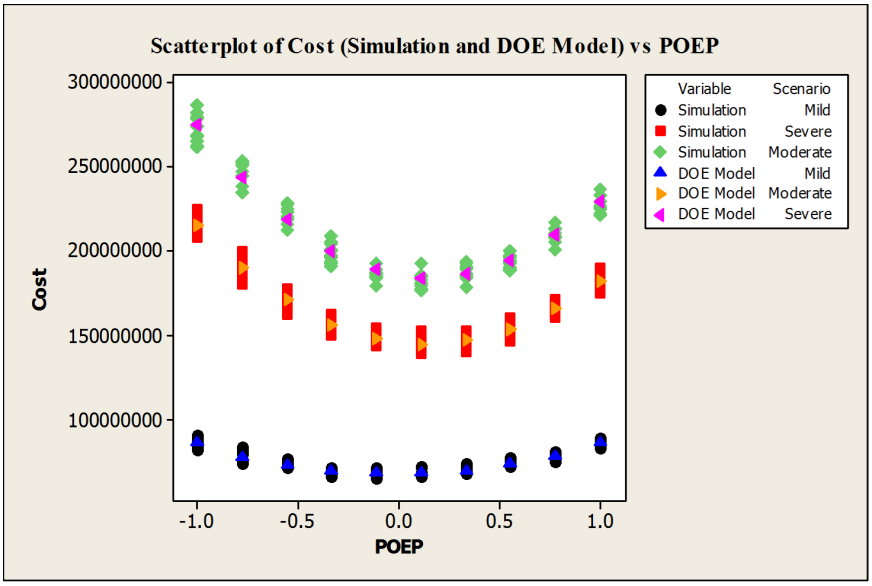


Figure 5.4: Cost of each POEP strategy for 3 PI scenarios: Effects model.

(see Table 5.1) which combine in a set of 720 equations. The complete list of effects (coefficients) are in Appendix C. This set of equations allows estimating the total cost of a PI for different factor levels. Figure 5.4 shows total cost for each POEP strategy in three scenarios, based on the simulation results and the values obtained from the set of equations.

Although 99 percent of the variability in the cost was explained by the effects model (main factors and interactions of two factors, $R^2_{adj} = 99.52\%$), managing 720 equations could be complex in some cases. That is why in the next subsection we used another method to define an empirical relationship for cost of PI.

5.2.2 Empirical Relationship Based on Regression Analysis

In this subsection we present a polynomial relationship for the cost of PI. To obtain this non-linear regression equation we consider the main factors, the interaction of two factors, squared factors and the interaction between the main factors and the squared factors. Although only the factor POEP showed a quadratic behavior, we consider other quadratic terms. To select which of these terms will be part of the model we use the stepwise regression method. This is an iterative method that consists in removing and adding predictors in the regression model to identify the useful subset of terms. The iterations of the method applied in MINITAB are in Appendix C.

Table 5.3: Coefficients of empirical relationship for pandemic cost.

Terms	Coefficients	Terms	Coefficients
Constant	98,335,238	$POEP \times FC$	1,875,643
$POEP$	-4,871,852	$IAR \times IAR$	3,153,923
$PREP$	-26,234,769	$IAR \times ERR$	1,299,270
IAR	17,441,160	$IAR \times FC$	-1,276,446
MP	520,723	$MP \times ERR$	177,343
ERR	22,936,132	$ERR \times FC$	-1,093,115
FC	-15,894,514	$POEP \times POEP \times IAR$	7,170,314
$POEP \times POEP$	31,008,516	$POEP \times POEP \times ERR$	12,757,386
$POEP \times IAR$	-3,390,393	$POEP \times POEP \times FC$	-4,147,200
$POEP \times ERR$	-5,982,268	$IAR \times IAR \times POEP$	-892,756

The stepwise method identified 19 terms significantly relevant ($p - value \approx 0$) with 98 percent of the variability explained by the model ($R^2_{adj} = 98.30\%$). Table 5.3 shows the predictors (terms) and the coefficients.

In the same way than Figure 5.4, Figure 5.5 shows total cost for each POEP strategy in three scenarios, both the simulation results as the value set by the non-linear regression model. For each scenario it is possible to identify the strategy that minimizes the total cost, showing that the largest impact of different POEP strategies is in a severe pandemic. On the other hand, choosing between POEP strategies is irrelevant if the pandemic is mild.

An important aspect to consider is the interaction of factor PREP with other factors is not relevant for the model. That means that, if we fix one level of PREP, the total cost will be affected only by its coefficient multiplied by the level selected, independently of other factors. For that reason we selected only one level of this factor (-1 gives the higher cost) to determine an optimal dynamic policy in Chapter 6.

Based on the simulation model described in Chapter 4, we developed an empirical relationship for pandemic cost including controllable factors (mitigation strategies), uncontrollable factors (scenarios of pandemic) and the emergence of a resistant strain. Using that empirical relationship, we identified and selected three PI scenarios that will be used as the testbed for the development of a dynamic programming (DP)-based methodology for dynamic antiviral treatment and prophylaxis considering antiviral resistance.

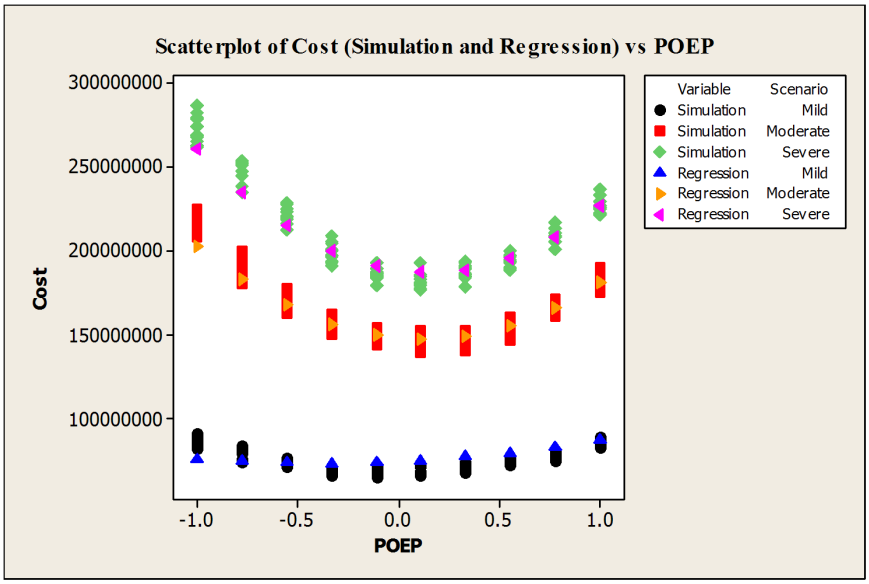


Figure 5.5: Cost of each POEP strategy for 3 PI scenarios: Regression model.

Chapter 6: Development of DP-based Methodology for Dynamic Antiviral Treatment and Prophylaxis Strategies

6.1 Dynamic Programming

Bellman introduced the term "dynamic programming"(DP) to describe the mathematical theory of a multi-stage decision process [64], also known as sequential decision making (SDM), defined as a sequence of decisions or actions taken to achieve some purpose in a finite or infinite planning horizon. DP determines the optimal solution in a multi-stage problem by simplifying a decision by decomposing it into several one-stage sub-problems using mathematical induction.

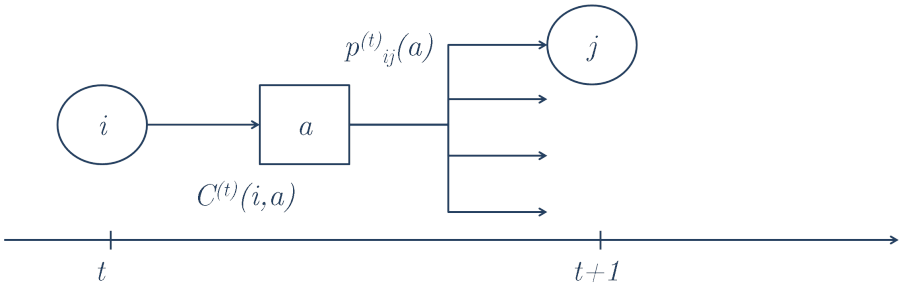


Figure 6.1: Schematic of the dynamic programming model.

During a pandemic, decisions to mitigate it will be made in several moments of time. The actual decision affects the subsequent decisions and also needs to be based on expected future decisions and results. The elements for this DP solution are:

- Stage (decision epoch) $k = 0, 1, , n$ (biweekly periods, $k = n - t$)
- State $i = 1, 2, 3, 4, 5$ (biweekly infection rate range)
- Action $a = 1, 2, , A$ (controllable factors: PHI)

Starting from $k = 1$, we need to make a decision a (which level of POEP to implement) that will affect the last stage, the end of the pandemic ($k = n - t$). This decision will cause a cost $C^{(t)}(i,a)$ and a change in the state from i to j based on a probability $p_{ij}^{(t)}(a)$. The optimal decision for the one-step problem is one that minimizes the cost. Figure 6.1 shows the concept of this explanation.

The decision process continues for earlier times $k = 2,3,,n$, working backwards, but the cost to minimize is a function $V_k(i)$ based on the one-step problem solved previously. $V_k(i)$ is a recursive equation called the Bellman equation and, for our problem, is defined as the minimum expected total pandemic cost for a k-stage (when k decisions remaining) problem if the present state is i.

$$V_k(i) = \min_a \left\{ C^{(t)}(i,a) + \sum_j p_{ij}^{(t)}(a) \cdot V_{k-1}(j) \right\} \tag{6.1}$$

where, $C^{(t)}(i,a)$ = immediate cost of strategy a when pandemic is in state i at time t and $p_{ij}^{(t)}(a)$ = probability to transit from state i to state j after implementing strategy a at time t. We assume that $V_0(i) = 0$ for all values of i.

The optimization concludes with the calculated value of $V_n(i)$, which is the optimal solution if the pandemic starts at state i. The optimal decision for the next stages (biweekly) can be determined following the results of previous calculations made for each stage and state.

This procedure guarantees that the solution is optimal based on the Principle of Optimality [64]:

> "An optimal policy has the property that whatever the initial state and initial decision are, the remaining decisions must constitute an optimal policy with regard to the state resulting from the first decision."

At this point, it is important to emphasize that the state probability is time-dependent because before the peak of the pandemic, in terms of the number of infected, the probability to move from one state to a higher one is greater before the peak. In other words, before the peak, it is more probable to go up and after the peak to go down. Figure 6.2 shows a change from $i = 1$ to $j = 5$ in biweek 3 (before the peak), and no change ($i = j = 1$) in biweek 7 (after the peak).

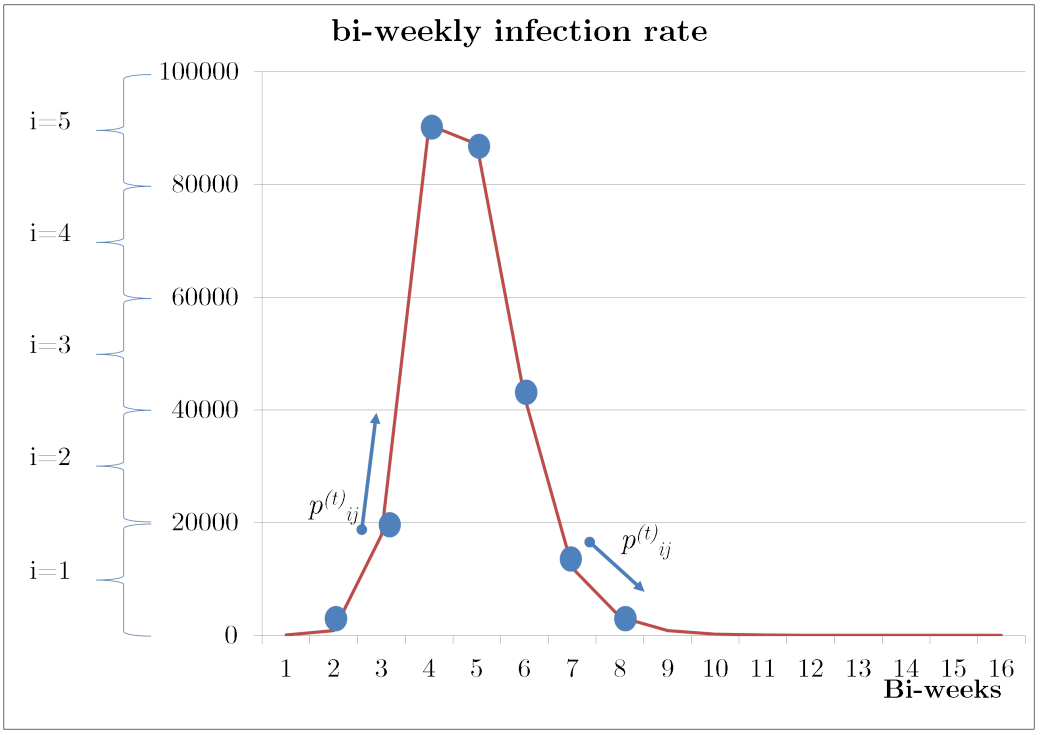


Figure 6.2: State probability and biweekly infection rate.

6.2 Procedure to Determine Dynamic Strategies

Figure 6.3 shows the sequence used to determine the optimal dynamic mitigation strategy. This process is for a selected scenario of PI (IAR, FP, ERR, FC fixed), in which we implement a specific PHI (a).

Through simulation, we identify the state of PI at time t and $t+1$ (initial state i and final state j, respectively), counting the number of infected. After several replicas of the simulation, it is possible to obtain for each t a combination of i and j and then the empirical probability $p^(t)_{ij}(a)$. For each replica, we recorded the increased cost during $[t,t+1]$, and the average is $C^(t)(i,a)$, the cost of strategy a when the pandemic is in state i at time t. When the probabilities and costs are defined for each t using specific PHI, we repeat all the procedures for another PHI, up to simulation of all sets of PHI.

Table 6.1 includes an example of costs and probabilities to change from state i to j for each PHI and time t, where t is counted every two weeks. For example, when we implement the first PHI $a = 1$ and the PI is in state $i = 3$, the probability to stay in the same state is $p^(1)_{33}(1) = 0.25$ and the cost is C.

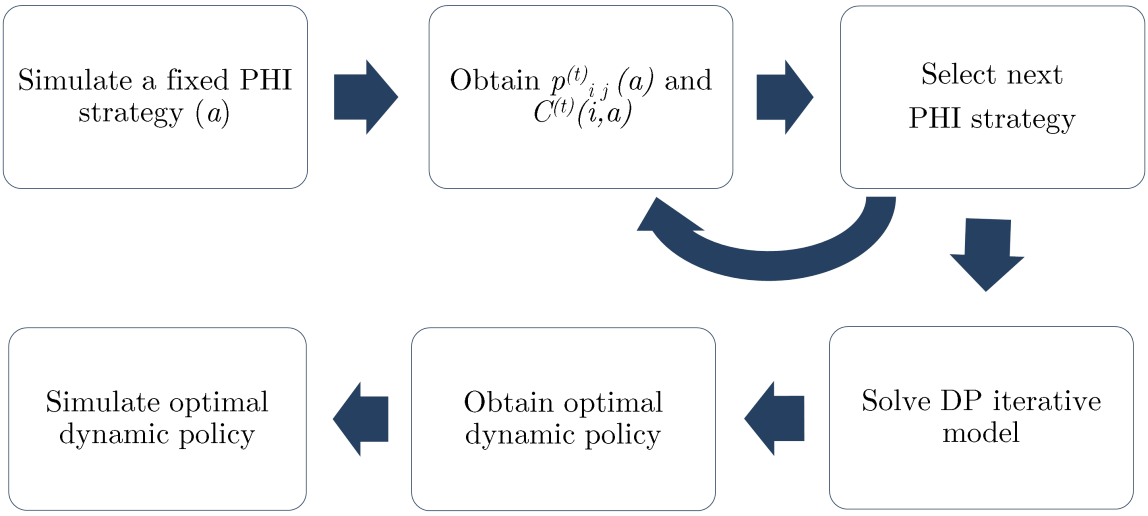


Figure 6.3: Procedure to determine dynamic strategies.

With the complete information of probabilities and costs, we implemented a dynamic programming iterative algorithm in C++ (see Appendix D). The pseudocode of the algorithm is in the Figure 6.4.

```
For each stage k
  For each initial state i
     For each final state j
          For each action a
               Determine V_k using V_k-1
          Find a for the minimum V_k
          Save V_k and a
     End
  End
End
```

Figure 6.4: Pseudocode of DP optimization.

The result is an optimal dynamic policy (rule for making a sequence of decisions) that minimizes the cost of PI. Table 6.2 shows an optimal dynamic policy, where, for example, if the pandemic is in state 2 at time t= 5, the recommendation is to implement the PHI number VI (Table 4.2).

The last step in Figure 6.1 is the simulation of the optimal dynamic policy in the corresponding PI scenario.

Table 6.1: Costs and probabilities to change from state i to j, per PHI and time t.

PHI (a)	Time t	State i	State j					Cost for 2 weeks ($1000)
			1	2	3	4	5	
1	1	1	0.20	0.60	0.20	0	0	756
1	1	2	0	0.10	0.50	0.40	0	854
1	1	3	0	0	0.90	0.10	0	952
1	1	4	0	0	0	0.90	0.10	977
1	1	5	0	0	0	0.0	0.0	0
1	2	1	0.10	0.70	0.20	0	0	985
...	...	...	...	...	...	...	...	...
1	2	5	0	0	0	0	0	0
...	...	...	...	...	...	...	...	...
10	1	1	0	0.2	0.5	0.25	0	857
...	...	...	...	...	...	...	...	...
10	20	5	0	0	0	0	0	0

6.3 Simulation of Optimal Dynamic Policy for Specific Scenarios

We updated the simulation model described in Chapter 4 with the optimal dynamic policy. Instead of using a static PHI, the model can select the best PHI based on the rules that the dynamic policy dictates (for example, rules in Table 6.2). A result of one instance in Table 6.3 is that it shows the states in each period (from 0 to 19) and the antiviral strategy selected from Table 6.2. Following the same example described before, in period t=5, the PI is in state 2, and the optimal dynamic policy recommended PHI VI, resulting in a cost of $805,000 for that period.

6.4 Result, Comparison and Analysis of the Optimal Dynamic Policy

The scenarios selected for these simulations were obtained from Table 5.2. Each scenario was simulated 10 times, and the average of total cost is shown in Table 6.4, including the comparison with some static policies and the mitigations strategy suggested by the CDC. The result of the comparison is a reduction up to 23 percent in the cost by implementing an optimal dynamic policy.

Table 6.2: Example of optimal dynamic policy.

t		0	1	2	3	4	5	6	…	18	19
State *i*	**1**	1	4	3	4	7	7	6	…	1	1
	2	1	6	5	8	5	6	6	…	1	1
	3	1	7	7	8	6	4	7	…	1	1
	4	1	5	6	6	5	6	6	…	1	1
	5	1	5	6	6	6	6	6	…	1	1

Table 6.3: PHI strategy selected for specific states sequence of a PI.

Period	**0**	**1**	**2**	**3**	**4**	**5**	**…**	**18**	**19**
State i	1	1	1	1	2	2	…	1	1
A/V strategy	1	4	3	4	5	6	…	6	6
Period cost ($1000)	-	$354	$310	$354	$751	$805	…	$842	$421

Considering that the antiviral stockpile for the testbed region is around 243 thousand of courses [9], this is enough if the dynamic policy is implemented in any of the scenarios.

These results suggest that the economic and societal impact of the next pandemic influenza could be reduced if decision makers implement a dynamic policy of mitigation, evaluated biweekly. This advantage is maintained in spite of the emergence of an antiviral resistant virus.

Table 6.4: Costs and antiviral requirement per strategy and scenario. Antiviral stockpile for testbed region is 243 thousand

	Total cost ($M)			Antiviral requirement (1,000 of courses)		
	Severe	Moderate	Mild	Severe	Moderate	Mild
Dynamic	**173.22**	**140.10**	**67.38**	**122**	**99**	**48**
All Infected	218.91	171.33	73.05	259	202	86
+ P. HH. All	184.37	144.47	68.41	406	318	151
+ P. WP 100%	229.91	182.40	86.96	1,113	883	421
CDC	214.54	155.39	70.90	151	110	50

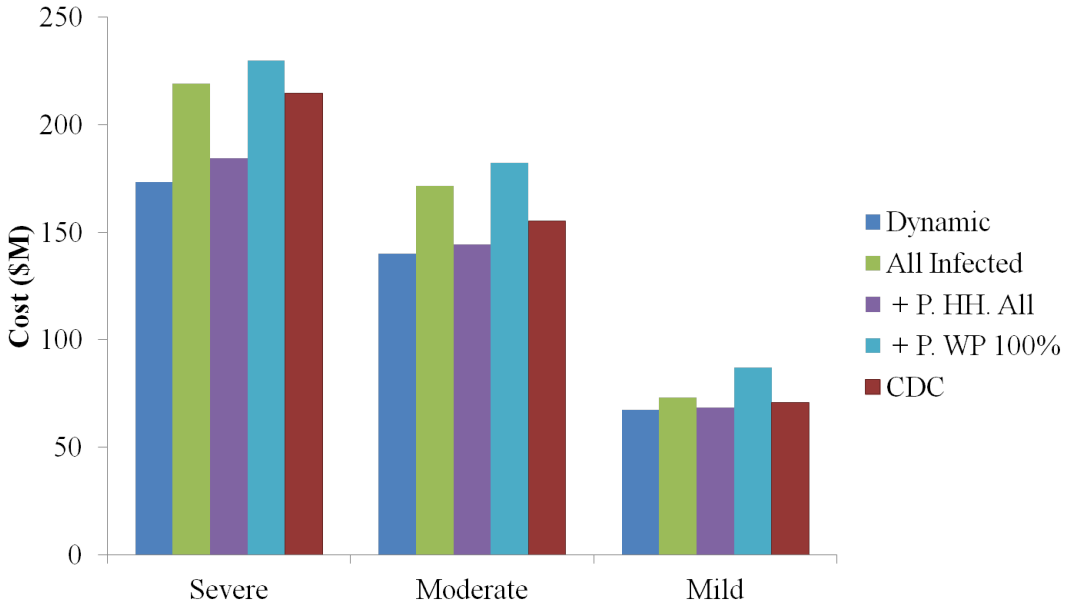


Figure 6.5: Costs per strategy and scenario.

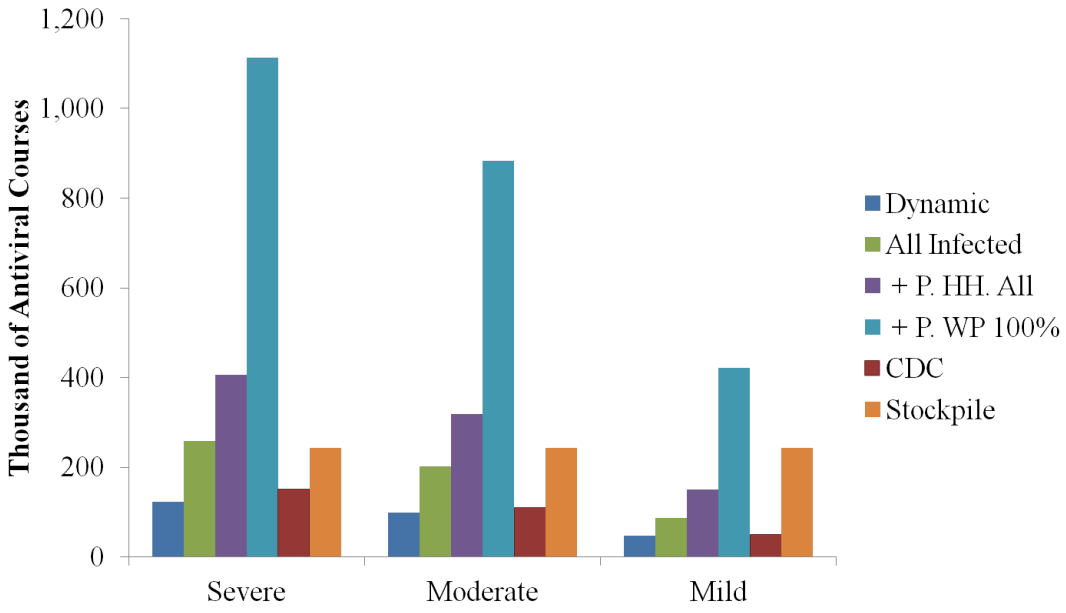


Figure 6.6: Antiviral requirement per strategy and scenario. Antiviral stockpile for testbed region is 243 thousand

Chapter 7: Summary of Main Results, Contributions and Future Research

Results from previous research have shown a reduction in the number of infected if mitigation strategies using an antiviral are implemented [27, 34, 38] and the impacts of an antiviral resistant strain in a compartmental model (SIR type)[19]. For this study, we simulated (in an agent-based simulation model) a pandemic influenza and mitigation strategies considering an antiviral sensitive strain and the emergence of an antiviral resistant strain, measuring the impact in total costs. We found the optimal mitigation strategy for different scenarios and an empirical non-linear equation for the costs using factorial design.

7.1 Main Results

The model simulated contacts in a community of 1.27 million persons in which susceptible individuals accumulate a viral load from infected contacts for the period of, at most, one day. Every hour, the model simulated the contacts, infection process, disease history, and mitigation strategy implementation.

The strategy to mitigate a pandemic includes various antiviral interventions and a fixed non pharmaceutical strategy. We showed that the increasing use of an antiviral reduces the number of infected by the antiviral sensitive strain, but increases the number of infected by the antiviral resistant strain. A balanced mitigation strategy that minimizes the total cost of the PI depends on the severity of the PI.

We simulated different scenarios of PI by a combination of non-controllable factors (see Table 5.2) using a factorial design to identify the best decision to reduce the pandemic cost. If the pandemic is severe (with high transmissibility and fatality rates and a high probability for a resistant virus emerging with no fitness cost) the total cost of PI is highly dependent on the Post-Exposure Chemoprophylaxis Interventions (POEP) strategy implemented. If the pandemic is mild, any strategy will cause the same impact.

Despite the factorial design including a non-quantitative factor, the levels have a quantitative meaning. The levels for factor POEP are related to the number antiviral courses used for the specific group of population described in each strategy. It is possible to identify an optimal strategy between two levels of use of an antiviral that minimize the cost.

After simulating the model developed in Chapter 4 for three scenarios of PI defined in Chapter 5, we obtained the transition probability and cost for each antiviral strategy, which were the input to determine an optimal dynamic policy. A simulation of this optimal policy showed an increment of 23 percent in the cost by implementing the strategy suggested by the CDC instead of our optimal dynamic policy. Less difference was identified for not-severe scenarios. These results suggest that the economic and societal impact of the next pandemic influenza could be reduced if decision makers implement a dynamic policy of mitigation, evaluated biweekly. This advantage is maintained in spite of the emergence of an antiviral resistant virus.

7.2 Contributions

The contributions of our research follow the research objectives presented in Chapter 3. In Chapter 4, we developed, to the best of our knowledge, the first large-scale simulation agent-based model for pandemic influenza that incorporates an antiviral resistant strain. The simulation model includes a complete set of PHI for treatments and pre-/post-exposure prophylaxis, as well as NPI, to mitigate the PI. An important feature, this simulates a disease that affects a community and its social interaction with two viruses: an antiviral sensitive strain and an antiviral resistant strain.

In Chapter 5, we designed an empirical nonlinear regression equation to examine the impact of using an antiviral for treatment and pre-/post-exposure prophylaxis and implemented a factorial design. The impact was measured in terms of societal and economic costs, which are functions of the parameters of mitigation as well as the parameters of the antiviral sensitive and antiviral resistant strains.

The most important contribution is in Chapter 6, in which we developed a novel DP-based methodology to select an optimal dynamic policy to mitigate a PI. We consider it an important contribution because decision makers will have a decision rule that allows for selecting the level of intervention based on current information (actual state of the pandemic) and seeking to minimize the impact or total cost of the PI.

Therefore, as a broader impact, this study will be able to support policy makers and public health decision makers in pandemic preparedness and response with mitigations strategies that include (1) antiviral treatment and prophylaxis for risk groups, (2) duration of antiviral pre-exposure prophylaxis, (3) relative role of treatment and prophylaxis in selecting resistant strains, and (4) level of antiviral stockpile.

7.3 Future Research

The dynamic policy developed in this research includes only decisions for PHI, specifically antiviral use. Including NPI in the set of strategies to implement dynamically and the interaction between PHI and NPI could bring more reductions in the cost of PI. Some issues to consider before implementing this idea are if these additional states in the DP model could seriously interfere with the solvability of the model and if the resulting optimal policy includes too much detail for actual use by decision makers.

Another direction to follow is to consider the interaction with other regions by simulating a cross-regional outbreak. This idea would augment the actual model and allow the implementation of different dynamic mitigation policies for a region, based on (1) the pandemic state internally measured in each region and (2) the interaction with the state of the PI in other regions. This also could allow to simulate several alternatives to manage the antiviral stockpile, among other resources that the regions can share.

The third idea for future work is related to the estimation of cost for each period (two weeks). We implemented a static policy to estimate the transition probability $p_{ij}^{(t)}(a)$ and cost $C^{(t)}(i,a)$, and we used that for the optimal dynamic policy. The presumption was that a period of two weeks is enough long to consider both probability and cost independent from the action taken in a previous period. Future work could search for a better procedure to estimate the parameters considering dependency.

Finally, all the information used in the simulation as parameters could be updated, refocused for another testbed, and better estimated. As more research is conducted and results are published about antiviral resistant strains, this study could be updated and adapted to help decisions makers.

References

[1] N. A. M. Molinari, I. R. Ortega-Sanchez, M. L. Messonnier, W. W. Thompson, P. M. Wortley, E. Weintraub, C. B. Bridges, The annual impact of seasonal influenza in the US: Measuring disease burden and costs, Vaccine 25 (27) (2007) 5086–5096.

[2] A. Klimov, L. Simonsen, K. Fukuda, N. Cox, Surveillance and impact of influenza in the United States, Vaccine 17 Suppl 1 (1999) S42–6.

[3] F. S. Dawood, A. D. Iuliano, C. Reed, M. I. Meltzer, D. K. Shay, P.-Y. Cheng, D. Bandaranayake, R. F. Breiman, W. A. Brooks, P. Buchy, D. R. Feikin, K. B. Fowler, A. Gordon, N. T. Hien, P. Horby, Q. S. Huang, M. A. Katz, A. Krishnan, R. Lal, J. M. Montgomery, K. MÃČÂÿlbak, R. Pebody, A. M. Presanis, H. Razuri, A. Steens, Y. O. Tinoco, J. Wallinga, H. Yu, S. Vong, J. Bresee, M. A. Widdowson, Estimated global mortality associated with the first 12 months of 2009 pandemic influenza A H1N1 virus circulation: a modelling study, The Lancet Infectious Diseases 12 (9) (2012) 687–695.

[4] Centers for Disease Control and Prevention, CDC Estimates of 2009 H1N1 Influenza Cases, Hospitalizations and Deaths in the United States, April-November 14, 2009 | Flu.gov, URL http://flu.gov/individualfamily/about/h1n1/estimates_2009_h1n1.html, last accesed on 09/23/11, 2010.

[5] Roche Laboratories Inc., Tamiflu package insert, http://www.cdc.gov/h1n1flu/eua/pdf/tamiflu_packageinsert.pdf, last accessed on 04/11/2010, 2008.

[6] T. Klaiman, J. Kraemer, M. Stoto, Variability in school closure decisions in response to 2009 H1N1: a qualitative systems improvement analysis, BMC Public Health 11 (1) (2011) 73.

[7] D. M. Bell, Public health interventions and SARS spread, 2003, Emerging infectious diseases (Print) 10 (2004) 1900–1906.

[8] Centers for Disease Control and Prevention, FluVaxView 2009-2010 Report, http://www.cdc.gov/flu/professionals/vaccination/reporti0910/reporti0910/, last access 09/04/13, 2006.

[9] Centers for Disease Control and Prevention., Antivirals - State Allocations, http://www.flu.gov/planning-preparedness/states/antivirals.html#, 2010.

[10] D. Reddy, Responding to pandemic (H1N1) 2009 influenza: the role of oseltamivir, Journal of Antimicrobial Chemotherapy 65 (suppl 2) (2010) ii35–ii40.

[11] P. Kramarz, D. Monnet, A. Nicoll, C. Yilmaz, B. Ciancio, Use of oseltamivir in 12 European countries between 2002 and 2007–lack of association with the appearance of oseltamivir-resistant influenza A(H1N1) viruses, Euro surveillance : European communicable disease bulletin 14 (5) (2009) 19112.

[12] D. A. Boltz, J. R. A. Jr, R. G. Webster, E. A. Govorkova, Drugs in development for influenza, Drugs 70 (11) (2010) 1349–1362.

[13] A. Moscona, Global transmission of oseltamivir-resistant influenza, The New England journal of medicine 360 (10) (2009) 953–956.

[14] W. McKibben, A. Sidorenko, Global macroeconomic consequences of pandemic influenza, Lowy Institute for International Policy, Sydney, Australia, 2006.

[15] B. Sander, A. Nizam, L. P. G. Jr, M. J. Postma, M. E. Halloran, I. M. L. Jr, Economic evaluation of influenza pandemic mitigation strategies in the United States using a stochastic microsimulation transmission model, Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research 12 (2) (2009) 226–233.

[16] National Center for Biotechnology Information., Scheme of Influenza A virus replication, http://www.ncbi.nlm.nih.gov/genomes/GenomesHome.cgi?taxid=10239&hopt=scheme, last accesed on 09/23/13, 2006.

[17] N. M. Bouvier, P. Palese, The biology of influenza viruses, Vaccine 26 Suppl 4 (2008) D49–53.

[18] Centers for Disease Control and Prevention, Antiviral Agents for the Treatment and Chemoprophylaxis of Influenza, MMWR 60 (1), URL http://www.cdc.gov/mmwr/pdf/rr/rr6001.pdf, last accessed on 10/04/2011.

[19] M. Lipsitch, T. Cohen, M. Murray, B. Levin, Antiviral resistance and the control of pandemic influenza, PLoS Medicine 4 (1) (2007) 111–115.

[20] Centers for Disease Control and Prevention, Antiviral Medications: Summary for Clinicians, URL http://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm, last accessed on 12/15/2011, 2011.

[21] A. Uribe-Sanchez, A. Savachkin, A. Santana, D. Prieto-Santa, T. Das, A predictive decision-aid methodology for dynamic mitigation of influenza pandemics, OR Spectrum 33 (3) (2011) 751–786.

[22] A. Santana, Decision Aid Models for Resource Sharing Strategies During Global Influenza Pandemics, URL http://scholarcommons.usf.edu/etd/3331, last accesed on 09/15/13, 2011.

[23] F. Carrat, E. Ferguson, N. Ferguson, M. Lemaitre, S. Cauchemez, S. Leach, Timelines of infection and disease in human influenza: A review of volunteer challenge studies, Am J Epidemiol 167 (2008) 775–785.

[24] N. Becker, D. Starczak, Optimal vaccination Strategies for a Community of Households, Mathematical Biosciences 139 (1997) 117–132.

[25] S. Cauchemez, F. Carrat, C. Viboud, A. J. Valleron, P. Y. A. Boelle, Bayesian MCMC approach to study transmission of influenza: application to household longitudinal data, Statistics in medicine 23 (2004) 3469–3487.

[26] Y. Yang, J. Sugimoto, M. Halloran, N. Basta, D. Chao, L. Matrajt, G. Potter, E. Kenah, I. Longini Jr, The transmissibility and control of pandemic influenza A (H1N1) virus, Science 326 (5953) (2009) 729–733.

[27] I. M. Longini, A. Nizam, S. Xu, K. Ungchusak, W. Hanshaoworakul, D. A. T. Cummings, M. E. Halloran, Containing Pandemic Influenza at the Source, Science 309 (5737) (2005) 1083–1087.

[28] M. E. Halloran, N. M. Ferguson, S. Eubank, I. Longini, Modeling targeted layered containment of an influenza pandemic in the United States, PNAS 105 (12) (2008) 4639–4644.

[29] R. M. Anderson, R. M. May, Infectious Diseases of Humans; Dynamics and Control, tY: GEN, 1991.

[30] J. Arino, F. Brauer, P. Van Den Driessche, J. Watmough, J. Wu, Simple models for containment of a pandemic, Journal of the Royal Society Interface 3 (8) (2006) 453–457.

[31] M. P. Atkinson, L. M. Wein, Quantifying the Routes of Transmission for Pandemic Influenza, Bulletin of Mathematical Biology 70 (3) (2008) 820–867.

[32] J. D. Mathews, C. T. McCaw, J. McVernon, E. S. McBryde, J. M. McCaw, A Biological Model for Influenza Transmission: Pandemic Planning Implications of Asymptomatic Infection and Immunity, PLoS ONE 2 (11) (2007) e1220.

[33] I. M. Longini, M. E. Halloran, A. Nizam, Y. Yang, Containing pandemic influenza with antiviral agents, American Journal of Epidemiology 159 (7) (2004) 623–633.

[34] N. M. Ferguson, D. A. Cummings, S. Cauchemez, C. Fraser, S. Riley, A. Meeyai, S. Iamsirithaworn, D. S. Burke, Strategies for containing an emerging influenza pandemic in Southeast Asia, Nature 437 (7056) (2005) 209–214.

[35] Oak Ridge National Laboratory, LandScan, http://www.ornl.gov/sci/landscan/index.html, last accessed on 03/27/2011, 2011.

[36] N. M. Ferguson, D. A. Cummings, C. Fraser, J. C. Cajka, P. C. Cooley, D. S. Burke, Strategies for mitigating an influenza pandemic, Nature 442 (7101) (2006) 448–452.

[37] T. Germann, K. Kadau, I. M. Longini, C. Macken, Mitigation strategies for pandemic influenza in the United States, PNAS 103 (2006) 5935–5940.

[38] S. Eubank, H. Guclu, V. S. Kumar, M. V. Marathe, A. Srinivasan, Z. Toroczkai, N. Wang, Modelling disease outbreaks in realistic urban social networks, Nature 429 (6988) (2004) 180–184.

[39] J. T. Wu, G. M. Leung, M. Lipsitch, B. S. Cooper, S. Riley, Hedging against Antiviral Resistance during the Next Influenza Pandemic Using Small Stockpiles of an Alternative Chemotherapy, PLoS Med 6 (5) (2009) e1000085.

[40] V. Colizza, A. Barrat, M. Barthélemy, A. Vespignani, The role of the airline transportation network in the prediction and predictability of global epidemics, Proceedings of the National Academy of Sciences of the United States of America 103 (7) (2006) 2015–2020.

[41] A. Savachkin, A. Uribe, Dynamic redistribution of mitigation resources during influenza pandemics, Socio-Economic Planning Sciences 46 (1) (2011) 33–45.

[42] M. Kiso, K. Mitamura, Y. Sakai-Tagawa, K. Shiraishi, C. Kawakami, K. Kimura, F. G. Hayden, N. Sugaya, Y. Kawaoka, Resistant influenza A viruses in children treated with oseltamivir: descriptive study, Lancet 364 (9436) (2004) 759–765.

[43] S. Hatakeyama, N. Sugaya, M. Ito, M. Yamazaki, M. Ichikawa, K. Kimura, M. Kiso, H. Shimizu, C. Kawakami, K. Koike, K. Mitamura, Y. Kawaoka, Emergence of influenza B viruses with reduced sensitivity to neuraminidase inhibitors, JAMA : the journal of the American Medical Association 297 (13) (2007) 1435–1442.

[44] A. Meijer, A. Lackenby, O. Hungnes, B. Lina, S. van-der Werf, B. Schweiger, M. Opp, J. Paget, J. van-de Kassteele, A. Hay, M. Zambon, E. I. S. Scheme, Oseltamivir-resistant influenza virus A (H1N1), Europe, 2007-08 season, Emerging infectious diseases 15 (4) (2009) 552–560.

[45] Q. M. Le, H. F. Wertheim, N. D. Tran, H. R. van Doorn, T. H. Nguyen, P. Horby, V. H. I. Team, A community cluster of oseltamivir-resistant cases of 2009 H1N1 influenza, The New England journal of medicine 362 (1) (2010) 86–87.

[46] M. Baz, Y. Abed, J. Papenburg, X. Bouhy, M. E. Hamelin, G. Boivin, Emergence of oseltamivir-resistant pandemic H1N1 virus during prophylaxis, The New England journal of medicine 361 (23) (2009) 2296–2297.

[47] I. Stephenson, J. Democratis, A. Lackenby, T. McNally, J. Smith, M. Pareek, J. Ellis, A. Bermingham, K. Nicholson, M. Zambon, Neuraminidase Inhibitor Resistance after Oseltamivir Treatment of Acute Influenza A and B in Children, Clinical Infectious Diseases 48 (4) (2009) 389–396.

[48] A. Handel, I. Longini, R. Antia, Towards a quantitative understanding of the within-host dynamics of influenza A infections, Epidemics 1 (3) (2009) 185–195.

[49] S. M. Moghadas, Management of drug resistance in the population: influenza as a case study, Proceedings of the Royal Society B: Biological Sciences 275 (1639) (2008) 1163–1169.

[50] E. Hansen, T. Day, Optimal antiviral treatment strategies and the effects of resistance, Proceedings of the Royal Society B: Biological Sciences 278 (1708) (2011) 1082–1089.

[51] S. M. Moghadas, C. S. Bowman, G. RÃűst, J. Wu, Population-Wide Emergence of Antiviral Resistance during Pandemic Influenza, PLoS ONE 3 (3) (2008) e1839.

[52] M. Jaberi-Douraki, S. Moghadas, Optimality of a time-dependent treatment profile during an epidemic, J Biol Dyn 7 (1) (2013) 133–147.

[53] D. L. Martinez, Non-pharmaceutical Intervention Strategies for Pandemic Influenza Outbreaks [electronic resource], 2012, URL http://scholarcommons.usf.edu/etd/4146, last accessed on 09/15/2012, 2012.

[54] Centers for Disease Control and Prevention, Preparing for Pandemic Influenza, http://www.cdc.gov/flu/pandemic/preparedness.htm, last accessed on 04/27/2009, 2007.

[55] M. I. Meltzer, N. J. Cox, K. Fukuda, The economic impact of pandemic influenza in the United States: priorities for intervention, Emerg Infect Dis 5 (5) (1999) 659–671.

[56] United States Census Bureau, Census 2010, http://www.census.gov, 2010.

[57] T. K. Das, A. A. Savachkin, Y. Zhu, A large-scale simulation model of pandemic influenza outbreaks for development of dynamic mitigation strategies, IIE Transactions 40 (9) (2008) 893–905.

[58] World Health Organization (WHO), Cumulative number of confirmed human cases of Avian Influenza A(H5N1) reported to WHO, http://www.who.int/csr/disease/avian_influenza/country/cases_table_2010_08_31/en/index.html, last accessed on 10/14/2010, 2010.

[59] Centers for Disease Control and Prevention, Emergency preparedness and response, http://www.bt.cdc.gov/episurv/, last accessed on 04/06/2011, 2011.

[60] D. C. Montgomery, Design and analysis of experiments, John Wiley and Sons, NJ, 2005.

[61] N. Khazeni, D. M. Bravata, J. E. Holty, T. M. Uyeki, C. D. Stave, M. K. Gould, Systematic review: safety and efficacy of extended-duration antiviral chemoprophylaxis against pandemic and seasonal influenza, Annals of Internal Medicine 151 (7) (2009) 464–473.

[62] J. K. Louie, S. Yang, M. Acosta, C. Yen, M. C. Samuel, R. Schechter, H. Guevara, T. M. Uyeki, Treatment With Neuraminidase Inhibitors for Critically Ill Patients With Influenza A (H1N1)pdm09, Clinical Infectious Diseases 55 (9) (2012) 1198–1204.

[63] Centers for Disease Control and Prevention, Interim pre-pandemic planning guidance: Community strategy for pandemic influenza mitigation in the United States, http://www.pandemicflu.gov/plan/community/community_mitigation.pdf, last accessed on 04/01/2010, 2007.

[64] R. Bellman, Dynamic Programming, Dover, NY, 2003.

Appendices

Appendix A: Demographic Data for Testbed

Table A.1: Age distribution and household composition.

Age Distribution			Household Composition		
Age Range		Probability	Adults	Child	Probability
0	5	0.0384	1	0	0.279
5	9	0.0368	1	1	0.04
9	14	0.0400	2	0	0.309
14	17	0.0208	1	2	0.043
17	22	0.0240	2	1	0.129
29	64	0.6700	1	3	0.012
64	99	0.1700	2	2	0.127
			1	4	0.005
			2	3	0.056

Table A.2: Number of business, per type, in the testbed region.

Type of Business		Number of Business
1	Factory	613
2	Office	2266
3	Pre-school	224
4	Elementary school	66
5	Middle school	134
6	High school	59
7	University	46
8	Afterschool center	256
9	Grocery store	390
10	Restaurant	223
11	Entertainment	360
12	Church	86

Appendix A: (continued)

Table A.3: Contact probability based for type of business and age of infected/susceptible case.

Business Type	Infected age L	Infected age H	Susceptible age L	Susceptible age H	Hourly contact probability
0	0	18	0	18	0.07352
0	0	18	19	99	0.02929
0	19	99	0	18	0.02929
0	19	99	19	99	0.04168
1	0	99	0	99	0.00492
2	0	99	0	99	0.00492
3	0	99	0	99	0.03526
4	0	99	0	99	0.0037
5	0	99	0	99	0.00318
6	0	99	0	99	0.00266
7	0	99	0	99	0.00266
8	0	99	0	99	0.0037
9	0	99	65	99	0.00007
9	0	99	19	64	0.00005
9	0	99	5	18	0.00002
9	0	99	0	4	0.00001
10	0	99	65	99	0.00007
10	0	99	19	64	0.00005
10	0	99	5	18	0.00002
10	0	99	0	4	0.00001
11	0	99	65	99	0.00007
11	0	99	19	64	0.00005
11	0	99	5	18	0.00002
11	0	99	0	4	0.00001
12	0	99	65	99	0.00007
12	0	99	19	64	0.00005
12	0	99	5	18	0.00002
12	0	99	0	4	0.00001

Appendix B: Disease, Antiviral and NPI Data

Table B.1: Infection and fatality: H1N1-2009.

Hospitalized and fatal cases

		0-17 years		>=18 years	
	All Cases	Fatal	Nonfatal	Fatal	Nonfatal
Male	532	3	203	56	270
Female	556	5	133	54	364
Total	1088	8	336	110	634
Mortality male		1.46%		17.18%	
Mortality female		3.62%		12.92%	
Mortality total		2.33%		14.78%	

Antiviral Treatment

		0-17 years		>=18 years	
	All Cases	Fatal	Nonfatal	Fatal	Nonfatal
Antiviral	701	5	205	65	426
No	183	3	62	24	94
Total	884	8	267	89	520
Mortality A/V		2.38%		13.24%	
Mortality NO A/V		4.62%		20.34%	

Received <=48h after symptom onset

		0-17 years		>=18 years	
	All Cases	Fatal	Nonfatal	Fatal	Nonfatal
Antiviral	357	1	117	17	222
More than 48h	344	4	88	48	204
Total	701	5	205	65	426
Mortality A/V		0.85%		7.11%	
Mortality NO A/V		4.35%		19.05%	

Chronic comorbid illness associate with severe influenza

		0-17 years		>=18 years	
	All Cases	Fatal	Nonfatal	Fatal	Nonfatal
Chronic	741	6	199	83	453
No chronic	347	2	137	27	181
Total	1088	8	336	110	634
Mortality chronic		2.93%		15.49%	
Mortality NO chronic		1.44%		12.98%	

Appendix B: (continued)

Table B.2: NPI fix interventions.

Non pharmaceutical Intervention Parameters	Value
Infected cases to activate policies	10
Delay days quarantine	3
Isolation delay	1
Isolation period	7
Isolation compliance workers	0.75
Isolation compliance non workers	0.84
Household quarantine delay	1
Household quarantine period	7
Household compliance workers	0.75
Household compliance non workers	0.84
Cases quarantine mixing groups schools	4
Mg to close schools	5
Mixing group quarantine period schools	10
Cases quarantine mixing groups workplaces	6
Percentage mg quarantine workplaces	0.6
Mixing group quarantine period workplaces	10

Appendix C: DOE Analysis

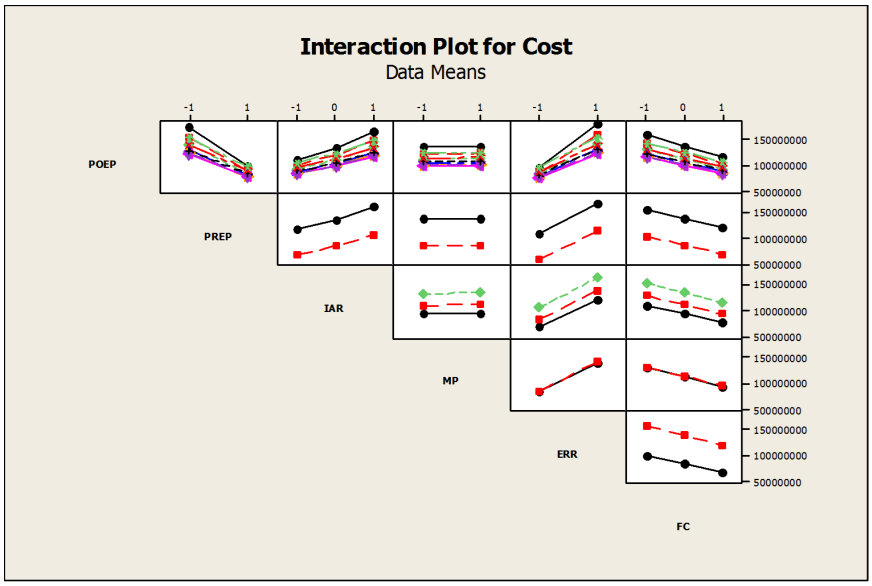


Figure C.1: Interaction effect for total cost.

Appendix C: (continued)

The MINITAB report below shows the analysis of factorial design.

General Linear Model: Cost versus POEP, PREP, IAR, MP, ERR, FC

```
Factor  Type   Levels  Values
POEP    fixed      10  -1.00000, -0.77778, -0.55556, -0.33333, -0.11111,
                       0.11111, 0.33333, 0.55556, 0.77778, 1.00000
PREP    fixed       2  -1, 1
IAR     fixed       3  -1, 0, 1
MP      fixed       2  -1, 1
ERR     fixed       2  -1, 1
FC      fixed       3  -1, 0, 1


Analysis of Variance for Cost, using Adjusted SS for Tests

Source       DF       Seq SS       Adj SS       Adj MS          F      P
POEP          9  9.79152E+17  9.79152E+17  1.08795E+17   10368.50  0.000
PREP          1  4.95549E+18  4.95549E+18  4.95549E+18  472275.04  0.000
IAR           2  2.00613E+18  2.00613E+18  1.00306E+18   95595.34  0.000
MP            1  1.95230E+15  1.95230E+15  1.95230E+15     186.06  0.000
ERR           1  5.69880E+18  5.69880E+18  5.69880E+18  543114.20  0.000
FC            2  1.48417E+18  1.48417E+18  7.42083E+17   70723.02  0.000
POEP*PREP     9  1.77782E+17  1.77782E+17  1.97536E+16    1882.58  0.000
POEP*IAR     18  5.56713E+16  5.56713E+16  3.09285E+15     294.76  0.000
POEP*MP       9  2.22687E+14  2.22687E+14  2.47430E+13       2.36  0.012
POEP*ERR      9  2.56010E+17  2.56010E+17  2.84455E+16    2710.95  0.000
POEP*FC      18  1.76330E+16  1.76330E+16  9.79609E+14      93.36  0.000
PREP*IAR      2  7.18305E+15  7.18305E+15  3.59152E+15     342.28  0.000
PREP*MP       1  2.39545E+14  2.39545E+14  2.39545E+14      22.83  0.000
PREP*ERR      1  5.85134E+15  5.85134E+15  5.85134E+15     557.65  0.000
PREP*FC       2  3.53983E+13  3.53983E+13  1.76991E+13       1.69  0.185
IAR*MP        2  5.43326E+13  5.43326E+13  2.71663E+13       2.59  0.075
IAR*ERR       2  8.10344E+15  8.10344E+15  4.05172E+15     386.14  0.000
IAR*FC        4  5.21649E+15  5.21649E+15  1.30412E+15     124.29  0.000
MP*ERR        1  2.26445E+14  2.26445E+14  2.26445E+14      21.58  0.000
MP*FC         2  6.29642E+13  6.29642E+13  3.14821E+13       3.00  0.050
ERR*FC        2  5.75354E+15  5.75354E+15  2.87677E+15     274.17  0.000
Error      7101  7.45095E+16  7.45095E+16  1.04928E+13
Total      7199  1.57402E+19


S = 3239261   R-Sq = 99.53%   R-Sq(adj) = 99.52%


Term              Coef  SE Coef        T      P
Constant     113070989    38175  2961.91  0.000
POEP
-1.00000      23944019   114525   209.07  0.000
-0.77778      10374588   114525    90.59  0.000
-0.55556       -117982   114525    -1.03  0.303
-0.33333      -7477463   114525   -65.29  0.000
-0.11111     -11674233   114525  -101.94  0.000
 0.11111     -12896478   114525  -112.61  0.000
 0.33333     -10850445   114525   -94.74  0.000
 0.55556      -5985725   114525   -52.27  0.000
 0.77778       1906529   114525    16.65  0.000
PREP
-1            26234769    38175   687.22  0.000
IAR
-1           -19311100    53988  -357.69  0.000
```

Appendix C: (continued)

```
 0            -2102615    53988   -38.95  0.000
MP
-1             -520723    38175   -13.64  0.000
ERR
-1           -28133601    38175  -736.96  0.000
FC
-1            17575902    53988   325.55  0.000
 0               16433    53988     0.30  0.761
POEP*PREP
-1.00000 -1   11502273   114525   100.43  0.000
-0.77778 -1    5753205   114525    50.24  0.000
-0.55556 -1    1761955   114525    15.38  0.000
-0.33333 -1   -1638731   114525   -14.31  0.000
-0.11111 -1   -3628372   114525   -31.68  0.000
 0.11111 -1   -4654898   114525   -40.65  0.000
 0.33333 -1   -4728867   114525   -41.29  0.000
 0.55556 -1   -3676476   114525   -32.10  0.000
 0.77778 -1   -1890766   114525   -16.51  0.000
POEP*IAR
-1.00000 -1   -6826940   161963   -42.15  0.000
-1.00000  0   -1476719   161963    -9.12  0.000
-0.77778 -1   -3927111   161963   -24.25  0.000
-0.77778  0    -647686   161963    -4.00  0.000
-0.55556 -1   -1004543   161963    -6.20  0.000
-0.55556  0    -119473   161963    -0.74  0.461
-0.33333 -1     937906   161963     5.79  0.000
-0.33333  0     181820   161963     1.12  0.262
-0.11111 -1    2278224   161963    14.07  0.000
-0.11111  0     364575   161963     2.25  0.024
 0.11111 -1    2917217   161963    18.01  0.000
 0.11111  0     642609   161963     3.97  0.000
 0.33333 -1    2837949   161963    17.52  0.000
 0.33333  0     667272   161963     4.12  0.000
 0.55556 -1    2463962   161963    15.21  0.000
 0.55556  0     342418   161963     2.11  0.035
 0.77778 -1    1060404   161963     6.55  0.000
 0.77778  0     225908   161963     1.39  0.163
POEP*MP
-1.00000 -1     -88778   114525    -0.78  0.438
-0.77778 -1      -8691   114525    -0.08  0.940
-0.55556 -1    -163744   114525    -1.43  0.153
-0.33333 -1     143363   114525     1.25  0.211
-0.11111 -1    -167812   114525    -1.47  0.143
 0.11111 -1     173150   114525     1.51  0.131
 0.33333 -1     -48898   114525    -0.43  0.669
 0.55556 -1     301590   114525     2.63  0.008
 0.77778 -1    -285323   114525    -2.49  0.013
POEP*ERR
-1.00000 -1  -13587705   114525  -118.64  0.000
-0.77778 -1   -7254676   114525   -63.35  0.000
-0.55556 -1   -2068517   114525   -18.06  0.000
-0.33333 -1    1981856   114525    17.30  0.000
-0.11111 -1    4537226   114525    39.62  0.000
 0.11111 -1    5720853   114525    49.95  0.000
 0.33333 -1    5622607   114525    49.09  0.000
 0.55556 -1    4415133   114525    38.55  0.000
 0.77778 -1    1972544   114525    17.22  0.000
POEP*FC
-1.00000 -1    4170122   161963    25.75  0.000
-1.00000  0    -115118   161963    -0.71  0.477
-0.77778 -1    2604668   161963    16.08  0.000
-0.77778  0    -126028   161963    -0.78  0.437
-0.55556 -1     671064   161963     4.14  0.000
```

Appendix C: (continued)

```
-0.55556  0     187066   161963     1.15  0.248
-0.33333 -1    -636752   161963    -3.93  0.000
-0.33333  0     -48078   161963    -0.30  0.767
-0.11111 -1   -1486420   161963    -9.18  0.000
-0.11111  0     -84041   161963    -0.52  0.604
 0.11111 -1   -1863340   161963   -11.50  0.000
 0.11111  0    -122835   161963    -0.76  0.448
 0.33333 -1   -1843832   161963   -11.38  0.000
 0.33333  0      92128   161963     0.57  0.569
 0.55556 -1   -1572752   161963    -9.71  0.000
 0.55556  0     100590   161963     0.62  0.535
 0.77778 -1    -619018   161963    -3.82  0.000
 0.77778  0     103112   161963     0.64  0.524
PREP*IAR
-1   -1       -1245022    53988   -23.06  0.000
-1    0          44663    53988     0.83  0.408
PREP*MP
-1   -1        -182401    38175    -4.78  0.000
PREP*ERR
-1   -1        -901491    38175   -23.61  0.000
PREP*FC
-1   -1          89535    53988     1.66  0.097
-1    0          -7859    53988    -0.15  0.884
IAR*MP
-1  -1           120906    53988     2.24  0.025
 0  -1           -41596    53988    -0.77  0.441
IAR*ERR
-1  -1          1305492    53988    24.18  0.000
 0  -1           -12445    53988    -0.23  0.818
IAR*FC
-1  -1         -1262975    76350   -16.54  0.000
-1   0           -36840    76350    -0.48  0.629
 0  -1             -448    76350    -0.01  0.995
 0   0           20692    76350     0.27  0.786
MP*ERR
-1 -1            177343    38175     4.65  0.000
MP*FC
-1 -1            -52671    53988    -0.98  0.329
-1  0            -78721    53988    -1.46  0.145
ERR*FC
-1  -1         -1057744    53988   -19.59  0.000
-1   0           -70742    53988    -1.31  0.190
```

Appendix C: (continued)

The MINITAB report below shows the stepwise regression.

Stepwise Regression: Cost versus POEP, PREP, ...

Alpha-to-Enter: 0.15 Alpha-to-Remove: 0.15

Response is Cost on 45 predictors, with N = 7200

Step	1	2	3	4	5	6
Constant	113070989	100437853	100437853	100437853	100437853	100437853
POEP	-5467022	-5467022	-5467022	-5467022	-5467022	-5467022
T-Value	-20.36	-31.62	-36.25	-41.02	-42.87	-44.35
P-Value	0.000	0.000	0.000	0.000	0.000	0.000
PREP	-26234769	-26234769	-26234769	-26234769	-26234769	-26234769
T-Value	-153.04	-237.75	-272.57	-308.38	-322.32	-333.42
P-Value	0.000	0.000	0.000	0.000	0.000	0.000
IAR	20362408	20362408	20362408	20362408	17441160	17441160
T-Value	96.98	150.67	172.74	195.43	115.64	119.62
P-Value	0.000	0.000	0.000	0.000	0.000	0.000
MP	520723	520723	520723	520723	520723	520723
T-Value	3.04	4.72	5.41	6.12	6.40	6.62
P-Value	0.002	0.000	0.000	0.000	0.000	0.000
ERR	28133601	28133601	22936132	22936132	22936132	22936132
T-Value	164.11	254.95	157.50	178.19	186.25	192.66
P-Value	0.000	0.000	0.000	0.000	0.000	0.000
FC	-17584119	-17584119	-17584119	-17584119	-17584119	-17584119
T-Value	-83.75	-130.11	-149.17	-168.76	-176.40	-182.47
P-Value	0.000	0.000	0.000	0.000	0.000	0.000
POEP*POEP		31008516	31008516	31008516	31008516	31008516
T-Value		100.83	115.60	130.79	136.71	141.41
P-Value		0.000	0.000	0.000	0.000	0.000
POEP*POEP*ERR			12757386	12757386	12757386	12757386
T-Value			47.56	53.81	56.24	58.18
P-Value			0.000	0.000	0.000	0.000
POEP*ERR				-5982268	-5982268	-5982268
T-Value				-44.88	-46.91	-48.53
P-Value				0.000	0.000	0.000
POEP*POEP*IAR					7170314	7170314
T-Value					25.81	26.70
P-Value					0.000	0.000
POEP*IAR						-3390393
T-Value						-22.46
P-Value						0.000
S	14546059	9363332	8167126	7218781	6906368	6676624
R-Sq	90.33	95.99	96.95	97.62	97.82	97.96
R-Sq(adj)	90.32	95.99	96.95	97.62	97.82	97.96

Appendix C: (continued)

Step	7	8	9	10	11	12
Constant	98335238	98335238	98335238	98335238	98335238	98335238
POEP	-5467022	-5467022	-5467022	-5467022	-5467022	-5467022
T-Value	-45.49	-46.30	-46.95	-47.52	-48.02	-48.48
P-Value	0.000	0.000	0.000	0.000	0.000	0.000
PREP	-26234769	-26234769	-26234769	-26234769	-26234769	-26234769
T-Value	-341.99	-348.10	-352.98	-357.28	-360.99	-364.46
P-Value	0.000	0.000	0.000	0.000	0.000	0.000
IAR	17441160	17441160	17441160	17441160	17441160	17441160
T-Value	122.70	124.89	126.64	128.18	129.51	130.76
P-Value	0.000	0.000	0.000	0.000	0.000	0.000
MP	520723	520723	520723	520723	520723	520723
T-Value	6.79	6.91	7.01	7.09	7.17	7.23
P-Value	0.000	0.000	0.000	0.000	0.000	0.000
ERR	22936132	22936132	22936132	22936132	22936132	22936132
T-Value	197.62	201.15	203.97	206.45	208.59	210.60
P-Value	0.000	0.000	0.000	0.000	0.000	0.000
FC	-17584119	-15894514	-15894514	-15894514	-15894514	-15894514
T-Value	-187.16	-113.82	-115.41	-116.82	-118.03	-119.16
P-Value	0.000	0.000	0.000	0.000	0.000	0.000
POEP*POEP	31008516	31008516	31008516	31008516	31008516	31008516
T-Value	145.05	147.64	149.71	151.53	153.10	154.58
P-Value	0.000	0.000	0.000	0.000	0.000	0.000
POEP*POEP*ERR	12757386	12757386	12757386	12757386	12757386	12757386
T-Value	59.68	60.74	61.59	62.34	62.99	63.59
P-Value	0.000	0.000	0.000	0.000	0.000	0.000
POEP*ERR	-5982268	-5982268	-5982268	-5982268	-5982268	-5982268
T-Value	-49.78	-50.67	-51.37	-52.00	-52.54	-53.05
P-Value	0.000	0.000	0.000	0.000	0.000	0.000
POEP*POEP*IAR	7170314	7170314	7170314	7170314	7170314	7170314
T-Value	27.39	27.87	28.27	28.61	28.91	29.18
P-Value	0.000	0.000	0.000	0.000	0.000	0.000
POEP*IAR	-3390393	-3390393	-3390393	-3390393	-3390393	-3390393
T-Value	-23.03	-23.44	-23.77	-24.06	-24.31	-24.55
P-Value	0.000	0.000	0.000	0.000	0.000	0.000
IAR*IAR	3153923	3153923	3153923	3153923	3153923	3153923
T-Value	19.38	19.73	20.00	20.25	20.46	20.65
P-Value	0.000	0.000	0.000	0.000	0.000	0.000
POEP*POEP*FC		-4147200	-4147200	-4147200	-4147200	-4147200
T-Value		-16.12	-16.35	-16.55	-16.72	-16.88
P-Value		0.000	0.000	0.000	0.000	0.000
IAR*ERR			1299270	1299270	1299270	1299270
T-Value			14.27	14.45	14.60	14.74
P-Value			0.000	0.000	0.000	0.000
POEP*FC				1875643	1875643	1875643
T-Value				13.31	13.45	13.58
P-Value				0.000	0.000	0.000

Appendix C: (continued)

ERR*FC					-1093115	-1093115
T-Value					-12.28	-12.40
P-Value					0.000	0.000
IAR*FC						-1276446
T-Value						-11.82
P-Value						0.000
S	6509148	6394969	6306629	6230687	6166716	6108005
R-Sq	98.07	98.13	98.18	98.23	98.26	98.30
R-Sq(adj)	98.06	98.13	98.18	98.22	98.26	98.29

Step	13	14
Constant	98335238	98335238
POEP	-4871852	-4871852
T-Value	-24.96	-24.97
P-Value	0.000	0.000
PREP	-26234769	-26234769
T-Value	-364.78	-364.91
P-Value	0.000	0.000
IAR	17441160	17441160
T-Value	130.88	130.92
P-Value	0.000	0.000
MP	520723	520723
T-Value	7.24	7.24
P-Value	0.000	0.000
ERR	22936132	22936132
T-Value	210.79	210.86
P-Value	0.000	0.000
FC	-15894514	-15894514
T-Value	-119.27	-119.31
P-Value	0.000	0.000
POEP*POEP	31008516	31008516
T-Value	154.71	154.77
P-Value	0.000	0.000
POEP*POEP*ERR	12757386	12757386
T-Value	63.65	63.67
P-Value	0.000	0.000
POEP*ERR	-5982268	-5982268
T-Value	-53.09	-53.11
P-Value	0.000	0.000
POEP*POEP*IAR	7170314	7170314
T-Value	29.21	29.22
P-Value	0.000	0.000
POEP*IAR	-3390393	-3390393
T-Value	-24.57	-24.58
P-Value	0.000	0.000
IAR*IAR	3153923	3153923
T-Value	20.67	20.68

Appendix C: (continued)

P-Value	0.000	0.000
POEP*POEP*FC	-4147200	-4147200
T-Value	-16.90	-16.90
P-Value	0.000	0.000
IAR*ERR	1299270	1299270
T-Value	14.75	14.76
P-Value	0.000	0.000
POEP*FC	1875643	1875643
T-Value	13.59	13.60
P-Value	0.000	0.000
ERR*FC	-1093115	-1093115
T-Value	-12.41	-12.41
P-Value	0.000	0.000
IAR*FC	-1276446	-1276446
T-Value	-11.83	-11.84
P-Value	0.000	0.000
IAR*IAR*POEP	-892756	-892756
T-Value	-3.74	-3.74
P-Value	0.000	0.000
MP*ERR		177343
T-Value		2.47
P-Value		0.014
S	6102505	6100346
R-Sq	98.30	98.30
R-Sq(adj)	98.30	98.30

Appendix C: (continued)

General Regression Analysis: Cost versus POEP, PREP, IAR, MP, ERR, FC

Regression Equation

Cost = 9.83352e+007 - 4.87185e+006 POEP - 2.62348e+007 PREP + 1.74412e+007 IAR + 520723 MP + 2.29361e+007 ERR - 1.58945e+007 FC + 3.10085e+007 POEP*POEP - 3.39039e+006 POEP*IAR - 5.98227e+006 POEP*ERR + 1.87564e+006 POEP*FC + 3.15392e+006 IAR*IAR + 1.29927e+006 IAR*ERR - 1.27645e+006 IAR*FC + 177343 MP*ERR - 1.09312e+006 ERR*FC + 7.17031e+006 POEP*POEP*IAR + 1.27574e+007 POEP*POEP*ERR - 4.1472e+006 POEP*POEP*FC - 892756 IAR*IAR*POEP

Coefficients

Term	Coef	SE Coef	T	P
Constant	98335238	148891	660.449	0.000
POEP	-4871852	195089	-24.972	0.000
PREP	-26234769	71893	-364.913	0.000
IAR	17441160	133218	130.922	0.000
MP	520723	71893	7.243	0.000
ERR	22936132	108772	210.864	0.000
FC	-15894514	133218	-119.312	0.000
POEP*POEP	31008516	200353	154.769	0.000
POEP*IAR	-3390393	137949	-24.577	0.000
POEP*ERR	-5982268	112635	-53.112	0.000
POEP*FC	1875643	137949	13.597	0.000
IAR*IAR	3153923	152509	20.680	0.000
IAR*ERR	1299270	88051	14.756	0.000
IAR*FC	-1276446	107840	-11.836	0.000
MP*ERR	177343	71893	2.467	0.014
ERR*FC	-1093115	88051	-12.415	0.000
POEP*POEP*IAR	7170314	245381	29.221	0.000
POEP*POEP*ERR	12757386	200353	63.675	0.000
POEP*POEP*FC	-4147200	245381	-16.901	0.000
IAR*IAR*POEP	-892756	238935	-3.736	0.000

Summary of Model

S = 6100346 R-Sq = 98.30% R-Sq(adj) = 98.30%

Appendix C: (continued)

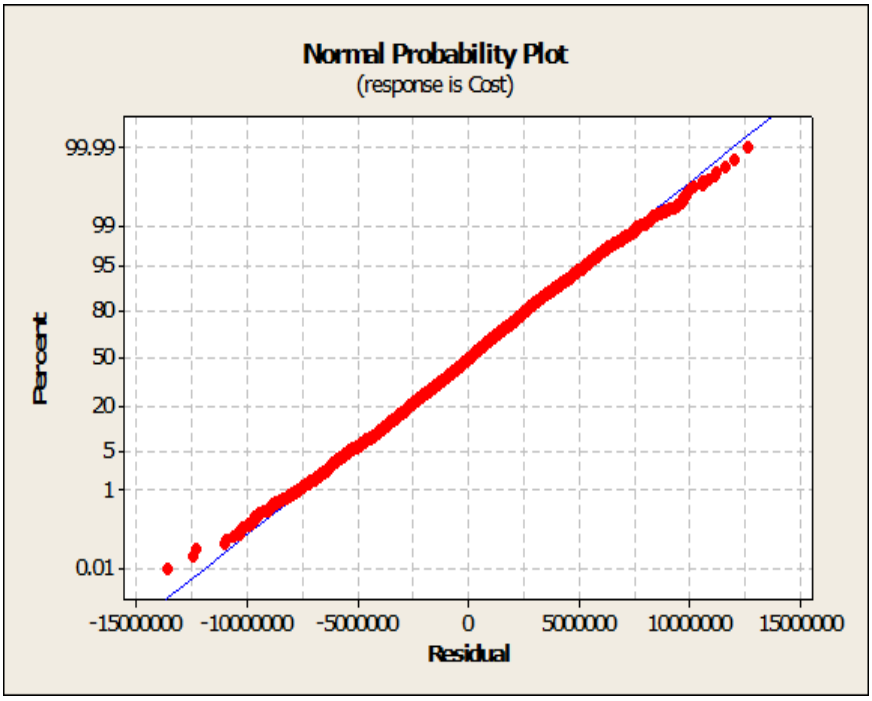


Figure C.2: Normal plot for residuals: Effects model.

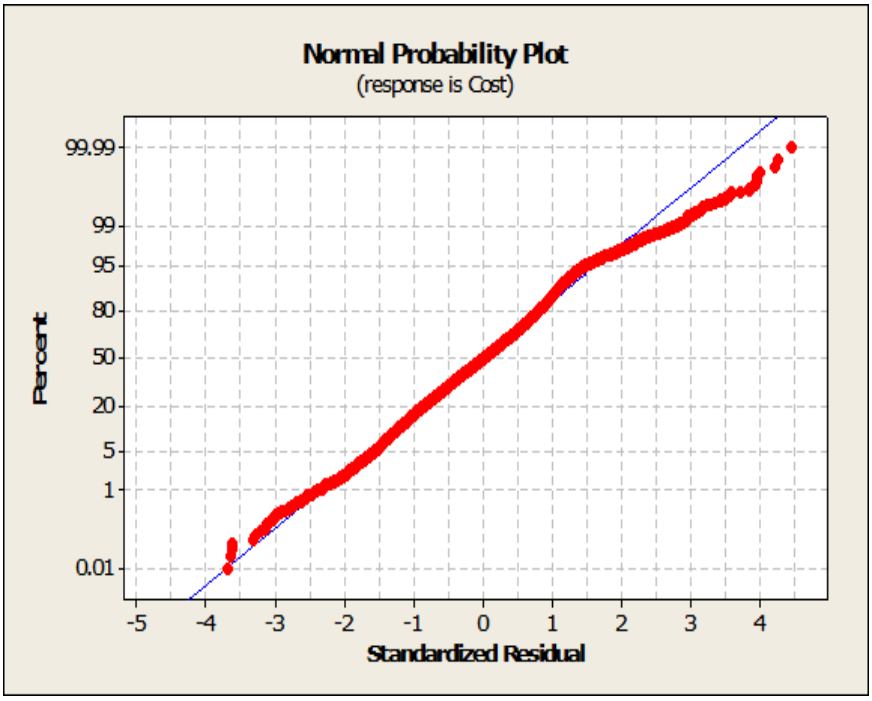
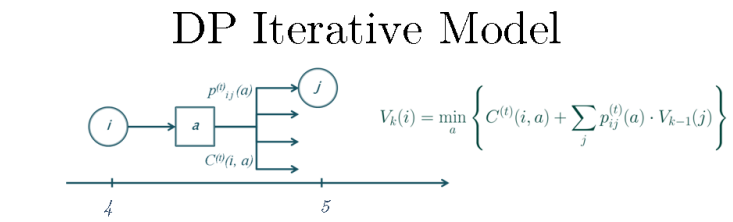


Figure C.3: Normal plot for residuals: Regression model.

Appendix D: Dynamic Programming

Below is a schematic of the DP iterative model.



1	I. < 2
2	+ I. > 65
3	All Infected
4	+ P. HH < 2
5	+ P. HH > 65
6	+ P. HH All
7	+ P. WP 25%
8	+ P. WP 50%
9	+ P. WP 75%
10	+ P. WP 100%

Period *t*		**0**	**1**	**2**	**3**	**4**	**5**	**6**	**…**	**18**	**19**
State *i*	**1**	1	4	3	4	7	7	6	…	1	1
	2	1	6	5	8	5	6	6	…	1	1
	3	1	7	7	8	6	4	7	…	1	1
	4	1	5	6	6	5	6	6	…	1	1
	5	1	5	6	6	6	6	6	…	1	1

Set of optimal policy

Illustration of Optimal Dynamic Policy

Period *t*	**0**	**1**	**2**	**3**	**4**	**5**	**…**	**18**	**19**
State *i*	1	1	1	1	2	2	…	1	1
A/V strategy	1	4	3	4	5	6	…	6	6

+ P. HH All

Set of optimal policy

Period *t*		**0**	**1**	**2**	**3**	**4**	**5**	**6**	**…**	**18**	**19**
State *i*	**1**	1	4	3	4	7	7	6	…	1	1
	2	1	6	5	8	5	6	6	…	1	1
	3	1	7	7	8	6	4	7	…	1	1
	4	1	5	6	6	5	6	6	…	1	1
	5	1	5	6	6	6	6	6	…	1	1

Figure D.1: Iterative model and ilustration of optimal dynamic policy.

Appendix D: (continued)

Below is the dynamic programming code.

```
#include <iostream>

using namespace std;

void initialize(void);
void readdata(void);
void savedata(void);

float cost[6][11][21];
float p[6][6][11][21];
float v[21][6];
float u[21][6][11];
int poli[21][6];

FILE *probfile, *costfile, *vfile, *polifile, *statfile;

int main()
{
	printf("1\n");
	initialize();
	readdata();

	for(int k=1;k<=20;k++)
		for(int i=1;i<=5;i++)
			for(int a=1;a<=10;a++)
			{
				float SD=0;
				float SS=0;
				for(int j=1;j<=5;j++)
				{
					SD=p[i][j][a][20-k]*v[k-1][j]+SD;
					SS=p[i][j][a][20-k]*u[k-1][j][a]+SS;
					if(k>=18)
					{
						printf("k=%d a=%d i=%d j=%d p=%f v=%f SD=%f\n
SS=%f\n",k,a,i,j,p[i][j][a][20-k],v[k-1][j],SD,SS);
					}
				}
				u[k][i][a]=cost[i][a][21-k]+SS;
				if(cost[i][a][21-k]+SD < v[k][i])
				{
					poli[20-k][i]=a;
					printf("k-1=%d i=%d V=%f\n",k-1,i,v[k-1][i]);
					v[k][i]=cost[i][a][21-k]+SD;
					printf("k=%d i=%d cost=%f V=%f
a=%d\n",k,i,cost[i][a][21-k],v[k][i],poli[20-k][i]);
				}
			}
	savedata();

}

void initialize(void)
{
```

Appendix D: (continued)

```
	for(int k=0;k<=20;k++)
		for(int i=1;i<=5;i++)
			v[k][i]=100000000000000;
	for(int i=1;i<=5;i++)
		v[0][i]=0;
}

void readdata(void)
{

	costfile=fopen("cost.txt","r");
	if(costfile!=(FILE*)NULL)
		for(int t=1;t<=20;t++)
			for(int a=1;a<=10;a++)
				for(int i=1;i<=5;i++)
					fscanf(costfile,"%f",&cost[i][a][t]);
	else
		printf("Could not open input file\n");


	probfile=fopen("probabilities.txt","r");
	if(probfile!=(FILE*)NULL)
		for(int t=0;t<=19;t++)
			for(int a=1;a<=10;a++)
				for(int i=1;i<=5;i++)
				{
					for(int j=1;j<=5;j++)
					{
						fscanf(probfile,"%f",&p[i][j][a][t]);
						printf("%f",p[i][j][a][t]);
					}
					printf("\n");

	}
	else
		printf("Could not open input file\n");
	printf("%f",p[5][5][1][12]);
	printf("\n");
}

void savedata(void)
{
	char name[255];
	sprintf(name,"objfunc.txt");
	vfile=fopen(name,"w");
	fprintf(vfile,"k 1 2 3 4 5");
	sprintf(name,"policies.txt");
	polifile=fopen(name,"w");
	fprintf(polifile,"t 1 2 3 4 5");
	sprintf(name,"statobjfunc.txt");
	statfile=fopen(name,"w");
	fprintf(statfile,"a k 1 2 3 4 5");

	for(int t=0;t<=20;t++)
	{
		fprintf(vfile,"\n%d ",20-t);
		fprintf(polifile,"\n%d ",t);
		for(int i=1;i<=5;i++)
```

Appendix D: (continued)

```
                {
                        fprintf(vfile,"%f ",v[20-t][i]);
                        fprintf(polifile,"%d ",poli[t][i]);
                }
        }
        for(int a=1;a<=10;a++)
                for(int t=0;t<=20;t++)
                {
                        fprintf(statfile,"\n%d %d ",a, 20-t);
                        for(int i=1;i<=5;i++)
                                fprintf(statfile,"%f ",u[20-t][i][a]);
                }

        fclose(vfile);      fclose(polifile); fclose(statfile);
}
```

About the Author

Sandro Paz earned his B.S in industrial engineering from Pontificia Universidad Catolica del Peru (PUCP) and M.S in industrial and systems engineering from the University of Puerto Rico at Mayaguez. In 2009, he began his Ph.D. at University of South Florida after being Associate Professor at PUCP. He has taught courses in quality, operations research, applied probability and statistics. His research focuses on simulation, optimization theory and applications, in particular in the areas of dynamic decisions for public health.

He has broad consulting experience solving problems related to statistical process control, simulation and operations research. He was evaluator of the Peruvian National Quality Award, which is based on the Malcolm Baldrige National Quality Award. He is an expert in accreditation processes of engineering programs based on ABET and CEAB (Canada) models.

In 2009-2011, Sandro Paz was awarded the Florida-Georgia Louis Stokes Alliance for Minority Participation (FGLSAMP) Bridge to the Doctorate Fellow Award. In addition, he was awarded the USF Graduate School Diverse Student Success Fellowship (2009-2011).