Designing Better Allocation Policies for Influenza Vaccine

by

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I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.
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ABSTRACT

Influenza has been one of the most infectious diseases for roughly 2400 years. The most effective way to prevent influenza outbreaks and eliminate their seasonal effects is vaccination. The distribution of influenza vaccine to various groups in the population becomes an important decision determining the effectiveness of vaccination for the entire population. We developed a simulation model using the Epifire C++ application program [2] to simulate influenza transmission under a given vaccination strategy. Our model can generate a network that can be configured with different degree distributions, transmission rates, number of nodes and edges, infection periods, and perform chain-binomial based simulation of SIR (Susceptible-Infectious-Recovered) disease transmission. Furthermore, we integrated NOMAD (Nonlinear Optimization by Mesh Adaptive Direct Search) for optimizing vaccine allocation to various age groups. We calibrate our model according to age specific attack rates from the 1918 pandemic. In our simulation model, we evaluate three different vaccine policies for 36 different scenarios and 1000 individuals: The policy of the Advisory Committee on Immunization Practices (ACIP), former recommendations of the Centers for Disease Control and Prevention (CDC), and new suggestions of the CDC. We derive the number of infected people at the end of each run and calculated the corresponding cost and years of life lost. As a result, we observe that optimized vaccine distribution ensures less infected people and years of life lost compared to the fore-mentioned policies in almost all cases. On the other hand, total costs for the policies are close to each other. Former CDC policy ensures slightly lower cost than other policies and our proposed in some cases.

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I would like to thank and acknowledge my mentors, and friends, who helped me through my study and work at the University of Waterloo, where I dedicate a special thanks to my supervisor Dr. Fatih Safa Erenay and my co-advisor Osman Ozaltin for their support and guidance during the program of study.

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Contents

List of Figures

List of Tables

Chapter 1

Introduction

1.1 Influenza Outbreak and Vaccination

Influenza has been one of the most infectious diseases for roughly 2400 years. Although there is no detailed historical data about influenza spread and effect before 18^{th} and 19^{th} centuries, effects of influenza can easily be seen after 20^{th} century. For instance, during Spanish Flu pandemic, which lasted from 1918 to 1919, it is estimated that 20 to 100 million people died [20]. Moreover, due to 1957 Asian Flu and 1968 Hong Kong Flu, approximately 2-3 million people died even though they were smaller outbreaks compared to Spanish Flu [20]. Furthermore, it is estimated that next possible influenza pandemic would cause 89,000 to 207,000 deaths; 314,000 to 734,000 hospitalizations; 20 to 47 million additional illness as well as 18 to 42 million outpatient visits [14]. Furthermore, the effects of influenza is not limited to deaths. An influenza outbreak costs million of dollars to governments and insurances companies since it delays or hinders daily routines such as transportation, education, health care, etc. Economic impact of a prospective outbreak would cost \$71.3 to \$166.5 billion excluding damage to society and commerce in the USA [14].

In addition to pandemics, influenza can be also seen annually, though seasonal epidemics. This sudden outbreak has significant effect on populations before it disappears. Epidemics affect especially developed countries negatively since the absence of labor result in productivity loss. In addition to labor cost, it is pre-

dicted that seasonal epidemics are responsible for 3.1 million hospitalized days, and approximately 610 life-years lost. Moreover, $10.4 billion medical cost is paid annually in the USA due to seasonal influenza epidemic [17].

The most effective way to prevent seasonal influenza outbreaks is vaccination. Unfortunately, vaccines are scarce resources and even if the most developed countries encounter problems in production, supply, distribution, and scheduling, during influenza epidemics. Moreover, vaccine strain have to be updated annually since type of circulating influenza virus changes. This is the most important factor to prevent producing large amount of flu shot at once. In this context, the distribution of influenza vaccination to the groups in the population becomes an important decision determining the effectiveness of vaccination for the entire population. The effect of influenza differ by age and risk groups including elderly, people who have chronic diseases, healthcare workers, etc. In the Literature, researchers considered the following questions:

1. How does influenza virus spread in a particular population?

2. At the end of an outbreak, how many people are infected and how many are still susceptible?

3. How should we allocate finite number of vaccine to different age groups in a population?

It is also important to determine some performance measures for influenza coverage for a given vaccine allocation policy. Purpose of influenza vaccine allocation strategies evaluated in the literature is to decrease total number of infected people in population during epidemic and pandemic, to decline total number of death, to decrease cost of hospitalization, drug, and number of vaccine applied to the population by obtaining the optimal vaccine distribution decisions.

1.2 Motivation and Contribution

Many influenza spread models exist in the literature. Specifically, we divide these studies into two general categories, mathematical and simulation models. Lack of adequate simulation methods led researchers to model and solve infectious diseases problems mathematically in the beginning. Recently, mathematical models provide more accurate and realistic results thanks to ongoing developments in computation tools and electronic data management [16]. However, deterministic models based on differential equations assume that the progression of the disease in a population follows a distinct pathway given the model parameters. This is a very strong assumption because the nature of the disease spread is stochastic, therefore, disease transmission and effect of vaccination can be modeled more accurately by using stochastic models. Some statistical and stochastic approaches are employed to formulate more accurate models reflecting random nature of the disease spread. However, the complexity of the system prevents solving these models exactly. Furthermore, assumption of homogeneous population where each individual identically interacts with every other individual, which is called "mass-action dynamic", is commonly used in mathematical models. Different contact patterns in society significantly invalidate this assumption.

Simulation models are more appropriate for both incorporating the stochastic nature of the disease progression. Particularly, network models, which enable the heterogeneous contact pattern in the simulation, are very helpful to model influenza spread in the society accurately. Thus, we develop a simulation model instead of a mathematical model to mimic influenza transmission.

Although simulation models in the literature can provide good approximations for modeling of influenza spread, they have some disadvantages. First, many of them ignore the age pattern, and assume that all people in a population have the same age characteristic [2][8][9]. However, age is a significant factor that effects contact and death rates, hospitalization, and cost. Next, a couple of vaccination strategies which include allocation of different number of vaccine to a population

are numerically tested in simulation models. However, a great number of allocation strategies are possible and evaluating all of them to find the optimal one might not even be feasible. For this purpose, we modify a C++ based application, Epifire [2], to model influenza spread considering different age groups, vaccine interventions, and heterogeneous contact pattern. In addition to this, we used NOMAD (Nonlinear Optimization by Mesh Adaptive Direct Search) simulation optimization application to minimize the number of infections in a particular population.

1.3 Thesis Outline

In chapter 2, we review existing studies about influenza spread models and vaccination strategies. In chapter 3, we describe some models for disease transmission. In chapter 4, we introduce Epifire simulation software, NOMAD optimization package, and how to associate NOMAD with Epifire for simulation optimization. In chapter 5, we present data employed in our model, such as infectious period, death rates, cost, and years of life lost as well as calibration process. In the chapter 6, we perform sensitivity analysis. We conclude with our results and discuss potential future work.

Chapter 2

Literature Review

2.1 Influenza Vaccination Strategies

Although there are many studies related to influenza transmission models, control and prevent strategies, and vaccine supplement and logistics in the literature, we only discuss vaccination strategies because of the scope of our research.

An agent-based simulation model (ABM) which includes Washington DC metropolitan region is constructed by the University of Pittsburgh Models of Infectious Disease Agent Study (MIDAS) team to help the Assistant Secretary of Public Preparedness and Response Office, Department of Health and Human Service [13]. Their main purpose is to figure out important key questions related to vaccine distribution during the 2009 H1N1 influenza pandemic. They compare the policy of inoculating children the first to vaccinating individuals who are at high risk group as recommended by the advisory Committee on Immunization Practices (ACIP). According to the simulation results, ACIP prioritization policy for the H1N1 influenza vaccine allocation should be applied when vaccine is limited. After that, children can be vaccinated to decrease serological attack rate.

Bansal et al. [9] build a contact network model based on demographic information of Vancouver. They compare two classes of recommended vaccination policies, mortality-based policy, which tries to minimize total number of deaths by covering high risk population and morbidity-based policy, which minimizes overall incidences

of influenza disease covering high prevalence population. They assess the effectiveness of these strategies for two distinct age-specific mortality distribution and high transmission rates with limited vaccine supply in a large urban population. They observe that appropriate policy depends on transmission rate of the virus critically. Morbidity-based policies are more successful than mortality-based strategies for reasonable transmission rates. On the other hand, mortality-based policies should be preferred when transmission rate of the virus is high. Moreover, mortality-based strategies outperform morbidity-based policies in the circumstance of vaccination delays and multiple introductions of disease into the society.

Ventresca et al. [11] construct agent-based network simulation model to examine targeted preventative vaccination strategies for the Greater Toronto Area of 5 million individuals. They build a weighted contact network including daily travel habits of individuals in the urban region. They find that vaccination policies perform well only if they can catch individuals who have high contact rate and those who have strong relationship with these individuals in a population.

Chao et al. [1] construct an individual-based simulation model to observe influenza spread dynamics in a large population. Social contacts, transmission rate, and infection period derived from the knowledge of natural history of influenza are assigned to individuals in the population. They show how to postpone influenza epidemic or pandemic by employing pharmaceutical interventions and social distancing measures.

Medlock et al. [3] find optimal vaccine distribution based on five criteria: deaths, infectious, years of life lost, economic cost, and contingent valuation. They observe that school children and adults age 30 to 39 years should have priority to be successful in vaccination since the highest transmission rate of influenza virus becomes among school children. Furthermore, their parents are responsible for spreading the disease to the rest of the population. Particularly, they emphasize that the major factor regarding the optimal distribution of influenza vaccine is consideration of age-specific transmission dynamics. Finally, they state that previous and new suggestions of the US Center for Disease Control and Prevention for epidemic

and pandemic influenza underperform in comparison to their optimal results in all outcome measures.

Lee et al. [8] make an agent-based simulation model including Washington DC metropolitan region to understand the possible effects of vaccinating employees. Their purpose is to find how workers are effected when vaccine coverage, compliance, timing, and prioritization vary. Simulation results imply a potential loss of approximately $112.6 million in productivity. When the attack rate rises up to 25%, possible productivity losses goes up to $193.8 million. They recommend that at least 20% of the health care and critical infrastructure workers should be vaccinated.

Chowell et al. [5] employ an age-structured transmission model to find the best vaccine strategy against pandemic influenza in Mexico by calibrating their model with local epidemiological data derived from 2009 H1N1 pandemic. They compare vaccination young children and people over 65 years of age primarily to vaccination people who have high hospitalization and death rate by using mathematical compartmental model. Consequently, they find that the adaptive vaccination strategy has superior results for death and hospitalization rates compared to seasonal vaccination strategy under a possible pandemic that effects a wide range of the country.

Tuite et al. [6] try to find the optimal vaccine distribution based on distinct risk and age groups in the population of Canada. They build a deterministic, age-structured compartmental model with data derived from in the early stage of the epidemic in Ontario. Vaccinating high risk individuals (chronic conditions and pregnancy) primarily reduces the frequency of severe outcomes in all scenarios significantly. Although prioritization of age groups that have high transmission rate results in lower population level attack rate, mortality and intensive care unit admission rise up remarkably. They suggest that high risk groups should be vaccinated at the outset, regardless of age, those with increased risk of severe outcomes should be inoculated next.

Basta et al. [7] evaluate policies for vaccinating young people in the United

States by employing a simulation model. They observe that population-level attack rate can be reduced by vaccinating children when altering the coverage level, vaccine type, number basic reproduction number(R). They find that vaccinating 70% of children effectively can prevent approximately 19 million influenza cases.

Chapter 3

Tools of Modeling Influenza Spread

We discuss three models: compartmental model (SIR model), transmission model, and network structure since Epifire employs a combination of them.

3.1 Compartmental Models

First of all, the behavior of the disease has to be known to understand its effects and resulting health outcomes. Two scientists, Kermack and McKendrick, modeled the behavior of infectious diseases [15]. Three classes, susceptible (S), infectious (I), and recovered (R) exist in a population for SIR model. After interactions with infected individuals at a rate (β), people in class S contract and move to class I. Finally, they move to class R after a certain infection period with rate r and are protected against prospective disease as demonstrated in Figure 3.1. In this model, latent period, which is called incubation period as well, and asymptomatic infectiousness, when a person takes the virus without showing its symptoms, do not exist. Another important assumption is closed population which means there is no entry to or exit from the population [10]. According to equations 3.1, 3.2, and 3.3 [10], each infected person (I) spreads the disease to a susceptible person (S) who encounters with rate β. Also r is a rate representing recovery.

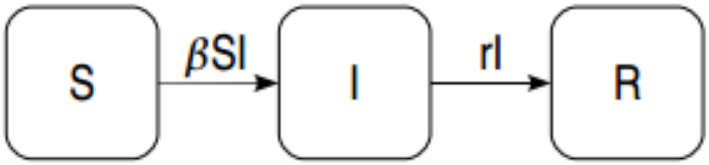

Figure 3.1: Basic compartmental model [10]

$$S' = \beta SI \tag{3.1}$$

$$I' = \beta SI - rI \tag{3.2}$$

$$R' = rI \tag{3.3}$$

Figure 3.2 includes vaccination and treatment.

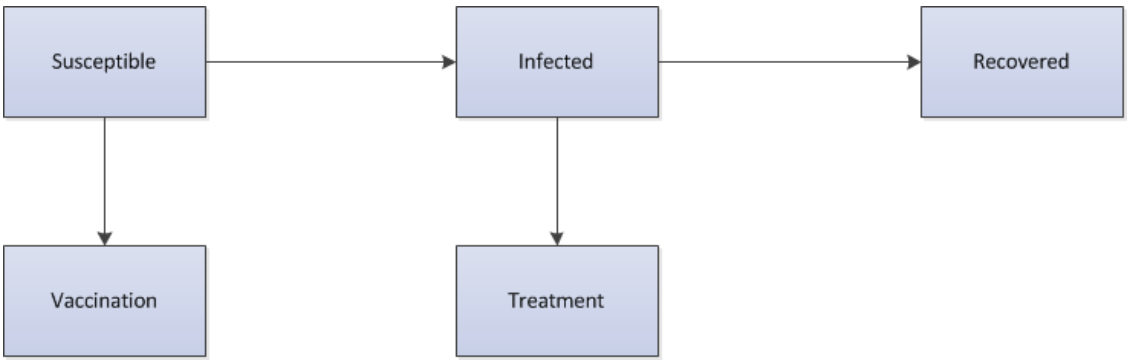

Figure 3.2: Compartmental models with vaccination and treatment

Figure 3.3 shows SEIR compartmental model included isolation and quarantine measures. For some cases, people are exposed to the virus, but they don't become ill immediately and can stay asymptomatic. Those people are represented with Exposed class in SEIR model. Susceptible individuals and asymptomatic patients move to Quarantine (S) and Quarantine (E), respectively after isolation process. If people in Quarantine (E) class start showing symptoms of the disease, they will move to Quarantine (I) [15].

Compartmental models are widely used in modeling infectious disease. In our

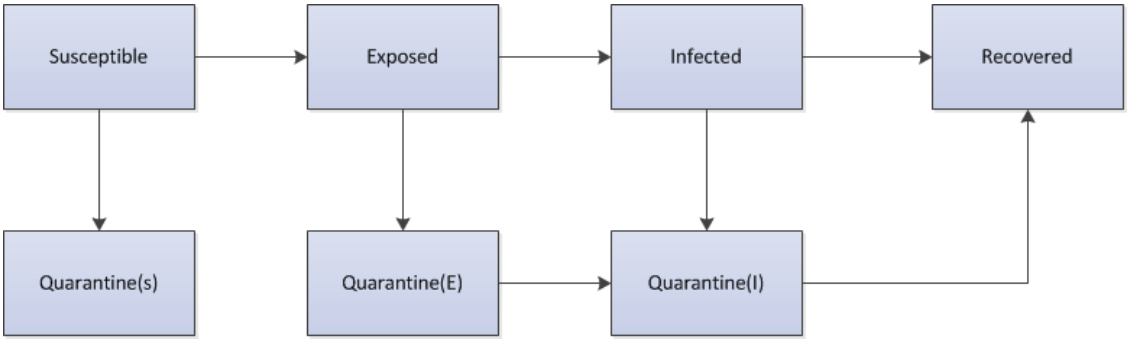

Figure 3.3: Compartmental models with quarantine and isolation

study, all nodes which represent people in a population are created as susceptible except some random nodes, which are infected due to start the disease. Each infected node spread the disease to their susceptible neighbors until they recover completely. So each node becomes in susceptible compartment in the beginning of the simulation. Next, if a node is exposed to disease, it immediately moves to infected compartment. Finally, it moves to recovered compartment when it eradicates influenza virus completely.

3.2 Network Models

Although network models are commonly employed in epidemiology, they initially appeared in social science to model spread of ideas and innovations. Similarly, spread of an infectious disease through a population has same framework; however, epidemiologists use different terms such as nodes, edges instead of actors and relations in social science [4]. In the next chapter, we explain how network models work and differ from mass-action models. We also examine commonly used network types in this chapter.

3.2.1 Random Mixed Networks

The spatial position of nodes is not relevant, and connections among nodes are assigned arbitrarily [4]. Weak clustering and homogeneity in individual level network features determine structure of the network [4] [18].

3.2.2 Lattice Networks

Nodes are assigned on a systematic grid of points in two or three dimensions, and only neighbor nodes interact with each other [4]. Initial growth of infection becomes lower in comparison to random mixed network models even though effect of disease on the population is stronger due to its high clustering structure [4].

3.2.3 Small World Networks

Small world networks were constructed to eliminate long path length problem in lattice models, and lower level clustering problem in random mixed models by Watts & Strogatz [19][4]. Infection can spread to even extreme nodes in the lattice network rapidly because of long-range connections. This can cause dramatic alteration the behavior of epidemic.

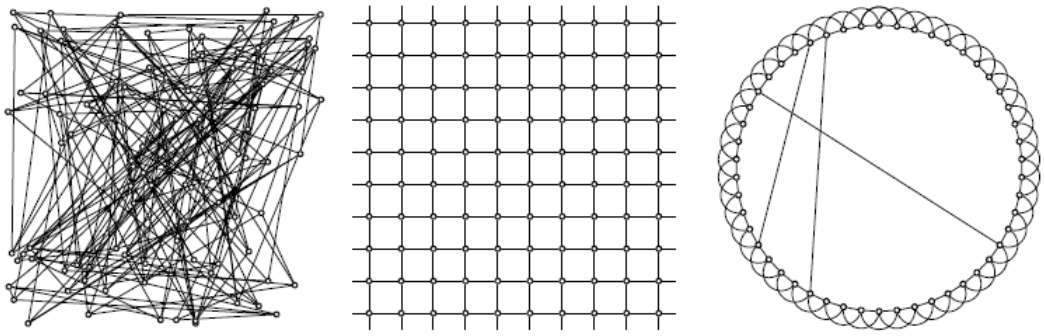

Figure 3.4: From left to right: Random mixed, lattice, and small world networks containing 100 nodes [4][18][19].

3.2.4 Spatial Networks

Spatial networks provide more flexible network construction. Nodes are set in a specific area and the relation between two nodes is established with a probability related to their separation determined by an interaction kernel. Altering the distribution of nodes or the kernel ensures to generate very different networks from small world structure to lattice type [4].

3.2.5 Scale Free Networks

Degree distribution is one of the most crucial features for a network. In a society, some individuals and groups have high contact rates while others have lower contact rates. Scale free networks can catch this heterogeneity and enable to build more realistic models [4]. Therefore, we prefer scale free network structure in our model since contact rates among individuals highly depend on their age.

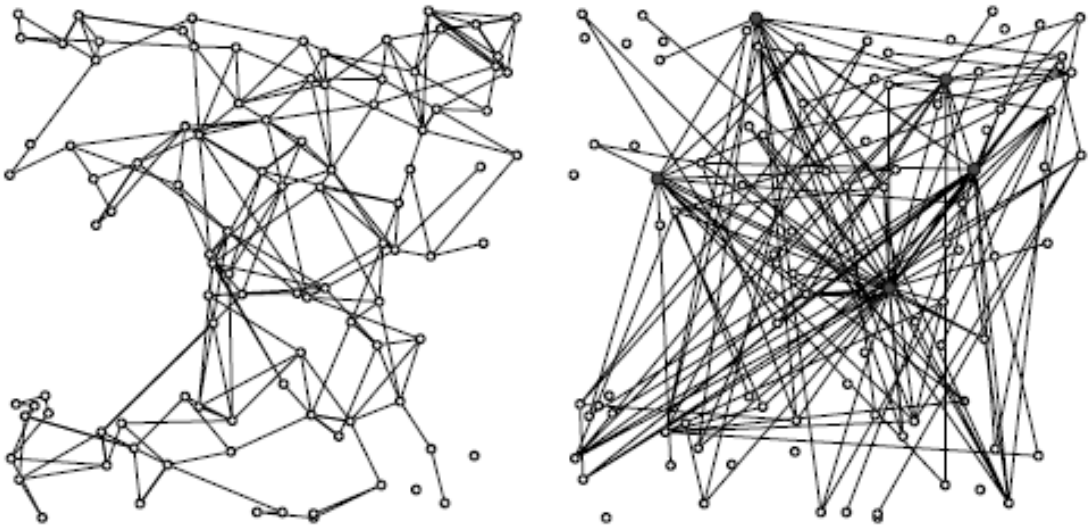

Figure 3.5: From left to right: Spatial and scale free networks containing 100 nodes [4].

3.3 Transmission Models

[1]In this section, we illustrate transmission dynamics of a disease in a host population based on Reed-Frost chain binomial model. We begin this section an introduction to the binomial model.

[1]Most of this section was prepared by referring the book, "Binomial and Stochastic Transmission Models", by M. E. Halloran, I. M. Longini, J. Struchiner.

3.3.1 Binomial Model

The binomial model is a tool for predicting the transmission probability. The general assumption in the binomial model is that each contact of an individual makes is independent. If the transmission probability is expressed as p, q, which is called the escape probability, means that the susceptible one does not take virus after interaction with infected one where $q = 1 - p$. If an individual has n contacts with sick people, the escape probability is q^n, or $(1-p)^n$. Therefore , the infection probability equals to $1 - q^n$ [24].

3.3.2 Reed-Frost Chain Binomial Model

Reed-Frost chain binomial models are dynamic systems to produce chains of infection by assuming that influenza spread occurs case by case in discrete time units.

$$N = S_t + I_t + R_t$$

where S_t represents the number of susceptible people, I_t is the number of infected people, and R_t is the number of recovered people in a population at time t [24]. N is total number of people in the population, and does not change depending on time due to the assumption of close population. Each time step S_t, I_t, R_t are calculated as below

$$Pr(I_{t+1} = i_{t+1} | S_t = s_t, I_t = i_t) = \binom{s_t}{i_{t+1}} (1 - q^{i_t})^{i_{t+1}} q^{i_t(s_t - i_{t+1})}, s_t \geqslant i_{t+1}$$

where $I_{t+1} = i_{t+1}, S_t = s_t$ [24]. Then, the number of new susceptible and immune people can be calculated as following [24]

$$S_{t+1} = S_t - I_{t+1}$$

$$R_{t+1} = R_t + I_t$$

In simulation models, whether a person is sick can be calculated by using a

random number generator. When the infection probability $1 - q^{I_t}$ at time t is less than the random number, the person escapes from the disease. Otherwise, he moves to the infected compartment [24]. Moreover, other parameters in our model such as infection duration, population distribution, contact rates are generated randomly.

Chapter 4

Proposed Methods: Epifire and NOMAD

4.1 Epifire

Epidemiological models traditionally assume that each individual in a homogeneously mixed population contacts with another person equally likely. Although mass-action models ensure good approximation in some cases, the heterogeneous contact patterns are common to model disease transmission in a population. Contact networks are used to model disease transmission in a population with heterogeneous contact patterns [2]. Each node represents a susceptible individual. Furthermore, disease spreads from an infected node to a susceptible node via edges. The number of contacts an individual is described as the degree of the corresponding node. The variety in the degree of each node is essential for a heterogeneous network structure.

The 2003 SARS pandemic in China showed that mass-action models have significant restrictions to correctly model the spread of influenza virus. The number of infected people after four months from beginning of the disease would have been between 30,000 and 10 millions based on R_0 calculated by using a homogeneous mixing model. However, only 792 SARS cases appeared during that time [21]. The most important reason is that contact patterns of entire population of China was

assumed like contact patterns of people living in overcrowded apartments in Hong Kong.

Mathematical models are commonly employed for estimating the dynamics of epidemic in a complex contact network. The epidemic process is assumed to be deterministic, that is, the progression of the disease in a population follows a distinct pathway. However, the nature of disease can be modeled more accurately by considering its stochastic nature [23]. Particularly, simulation could be an appropriate modeling tool capturing the inherent complexity of the system, and satisfying important assumptions.

We use Epifire C++ application to simulate influenza transmission under a given vaccination strategy. Epifire can perform chain-binomial simulation over a network that can be configured with different degree distribution, transmission rate, number of nodes and edges, infection period. The chain-binomial model based on Bernoulli trials that represent a susceptible person in a population at time t take the virus with probability p and becomes sick, or does not take the virus with probability 1-p and stay healthy. The Epifire functionally includes instruments to generate, manipulate, and simulate a network.

```
#include<Network.h>
int main() {
Network my_network("example network",
Network::Undirected );
my_network.populate(100);
my_network.rand_connect_poisson(5);
my_network.write_edgelist("output.csv");
return 0;
}
```

As can be seen above [2], the network generates 100 nodes which represents

individuals in a population. Each node connects to five other nodes on average with undirected edges. Basic steps of EpiFire to generate a network include:

1. The program generates a population which includes people with different characteristic.

2. Edges are created for each node.

3. The network is generated by connecting edges to each other based on contact rates.

Figure 4.1 provides an illustration of the 3 steps.

EpiFire assumes that each individual in the population is the same in terms of age characteristics. However, age of an individual affects contact rate, death rate, hospitalization, cost, etc. Therefore, we modify the current application incorporate age groups in the population. The population in our study is divided into five distinct age groups. In our model, G_0, G_1, G_2, G_3, G_4 represent people in 0-4, 5-19, 20-49, 50-64, 65+ age groups, respectively. The proportion of each age group is determined according to 2010 census data.

We use discrete distributions for each age to model the degree distributions.

```
   ////Degree Distribution Arrays for all Age Groups////
map<string, vector<double>> node_setting;
double tmp_array_0[] = {0, 0, 2, 12, 17, 15, 15, 12, 5, 12, 8, 0, 2};
node_setting["g0"] = create_dist(tmp_array_0, 13);
double tmp_array_1[] = {0, 0, 0, 0, 0, 0, 0, 1, 5, 6, 7, 10,
                        10, 11, 18, 10, 7, 6, 2, 3, 2, 2};
node_setting["g1"] = create_dist(tmp_array_1, 22);
double tmp_array_2[] = {0, 0, 0, 2, 2, 2, 10, 7, 12, 21, 14,
                       10, 8, 3, 4, 1, 1, 1, 0, 1, 0, 1};
node_setting["g2"] = create_dist(tmp_array_2, 22);
double tmp_array_3[] = {0, 0, 1, 3, 12, 11, 23, 13, 11, 5, 6,
                      10, 2, 1, 0, 1, 0, 1};
```

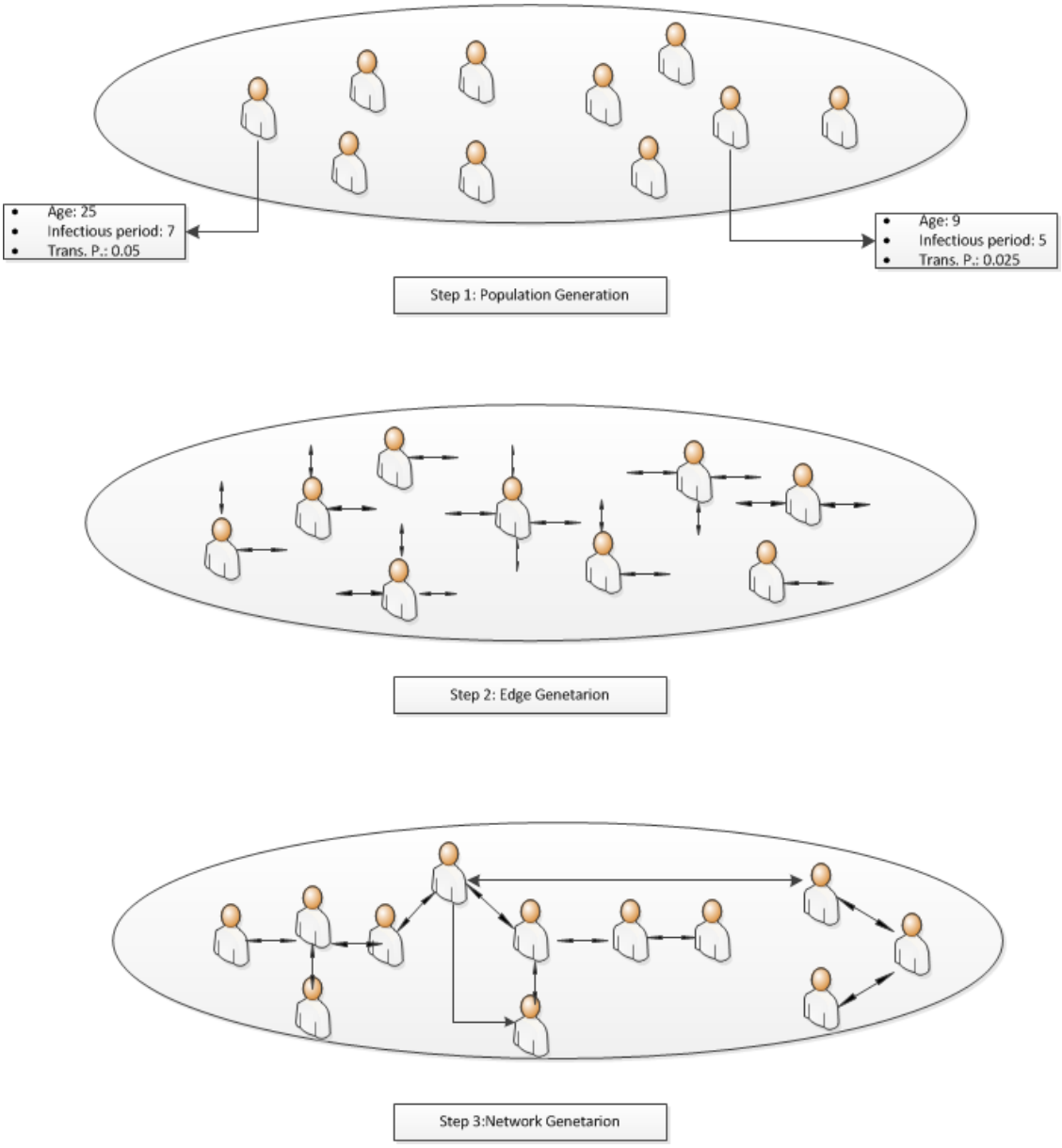

Figure 4.1: EpiFire steps

```
node_setting["g3"] = create_dist(tmp_array_3, 18);
double tmp_array_4[] = {0, 4, 8, 19, 18, 19, 14, 9, 5, 1, 1, 2};
node_setting["g4"] = create_dist(tmp_array_4, 12);
```

Each element of the degree distribution array represents the values of contacts. For instance, the first element of G_0 age group is zero. This means that the values of zero degree contacts of a person at G_0 age group is zero. On the other hand,

the values of four degree contacts of the same person is seventeen in all contacts. All contact values in arrays transform proportions with respect to their numbers via a normalization function in the model. Furthermore, assigning edges to each node in terms of its degree distribution is achieved by determining a cumulative distribution based on contact pattern of people.

Below codes show the cumulative distribution. To connect an edge of a node in one of age groups to another node, the program assigns an arbitrary number between 0 and 100.

```
      //// Cumulative Distribution////
map<string, map<string, int>> g_2_g_per;
g_2_g_per["g0"]["g0"] = 32.30;
g_2_g_per["g0"]["g1"] = 54.17;
g_2_g_per["g0"]["g2"] = 80.65;
g_2_g_per["g0"]["g3"] = 93.44;
g_2_g_per["g0"]["g4"] = 100;
g_2_g_per["g1"]["g0"] = 4.36;
g_2_g_per["g1"]["g1"] = 69.44;
g_2_g_per["g1"]["g2"] = 85.58;
g_2_g_per["g1"]["g3"] = 93.67;
g_2_g_per["g1"]["g4"] = 100;
g_2_g_per["g2"]["g0"] = 6.93;
g_2_g_per["g2"]["g1"] = 30.51;
g_2_g_per["g2"]["g2"] = 64.94;
g_2_g_per["g2"]["g3"] = 88.62;
g_2_g_per["g2"]["g4"] = 100;
g_2_g_per["g3"]["g0"] = 4.37;
g_2_g_per["g3"]["g1"] = 17.48;
g_2_g_per["g3"]["g2"] = 41.35;
g_2_g_per["g3"]["g3"] = 75.67;
g_2_g_per["g3"]["g4"] = 100;
```

```
g_2_g_per["g4"]["g0"] = 2.53;
g_2_g_per["g4"]["g1"] = 11.67;
g_2_g_per["g4"]["g2"] = 30.76;
g_2_g_per["g4"]["g3"] = 60.82;
g_2_g_per["g4"]["g4"] = 100;
```

The other improvement is to add more flexible assignment of infectious period instead of the same infection period for all age groups. One can easily configure discrete degree distribution represented infectious period of each group in the model.

```
        ///Infectious Period Arrays for all Age Groups///
map<string, vector<double>> node_infectious_period;
double inf_array_0[] = {0, 0, 0, 0, 0, 1, 1, 1, 1, 1, 4};
node_infectious_period["g0"] = create_dist(inf_array_0, 11);
double inf_array_1[] = {0, 0, 0, 0, 0, 1, 1, 1, 1, 1, 4};
node_infectious_period["g1"] = create_dist(inf_array_1, 11);
double inf_array_2[] = {0, 0, 0, 0, 0, 1, 1, 1, 1, 1, 4};
node_infectious_period["g2"] = create_dist(inf_array_2, 11);
double inf_array_3[] = {0, 0, 0, 0, 0, 1, 1, 1, 1, 1, 4};
node_infectious_period["g3"] = create_dist(inf_array_3, 11);
double inf_array_4[] = {0, 0, 0, 0, 0, 1, 1, 1, 1, 1, 4};
node_infectious_period["g4"] = create_dist(inf_array_4, 11);
```

4.2 NOMAD (Nonlinear Optimization by Mesh Adaptive Direct Search)

NOMAD is C++ based application to employ implementation of the MADS (Mesh Adaptive Direct Search) algorithm for black-box optimization under general linear or nonlinear constraints [31]. The essential purpose of the black-box system like

NOMAD is to figure out how to optimize a given problem in the absence of an algebraic model [29].

NOMAD is designed to solve single objective problems or bi-objective optimization problems.

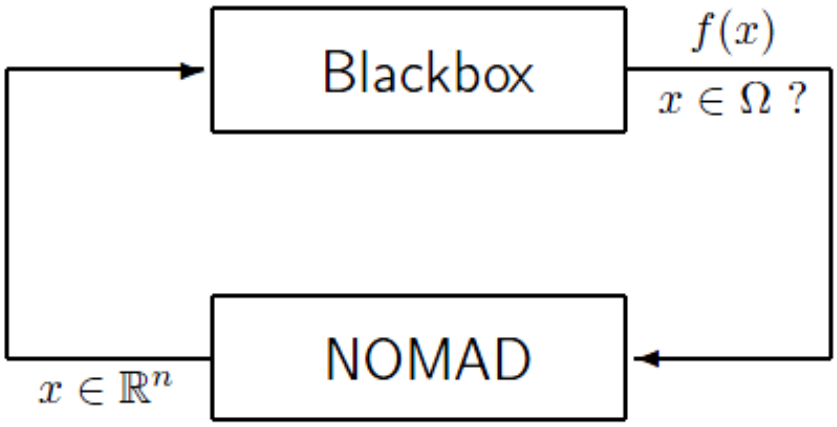

Figure 4.2: NOMAD [29]

The functions of the problem do not have exploitable features such as derivatives or their approximations. MADS algorithm, which is at the core of the NOMAD, improve the current best solution by generating a trial point on the mesh. If the trial point cannot improve the best solution, a finer mesh is generated in the next iteration. Each MADS iteration includes poll, search, and update steps.

In fact, the algorithm do not require derivatives, or estimate derivatives. It just uses the function values directly [30].

First we determine our objective function and constraints. Our objective function is

$$Min \sum_{i=0}^{4} I_i$$

where I_i shows number of infected people at age group i after the simulation is done. Our constraint is

$$\sum V_i \leq N$$

$$V_i \geq 0$$

where V_i indicates number of vaccine distributed to age group i. N is available total number of vaccine. The relationship between NOMAD and Epifire is illustrated in Figure 4.3. NOMAD starts from an initial point. For example, 100 vaccines are distributed equally to each age group. Next, NOMAD sends this information to Epifire. At the end of the simulation, Epifire collects the number of infected people in all age groups, and provides feedback to NOMAD. Total number of infected people derived after the simulation becomes a comparative point with the result of next iteration for NOMAD. It searches for a better vaccine allocation to minimize total number of infected people in the population until reaching the iteration limit.

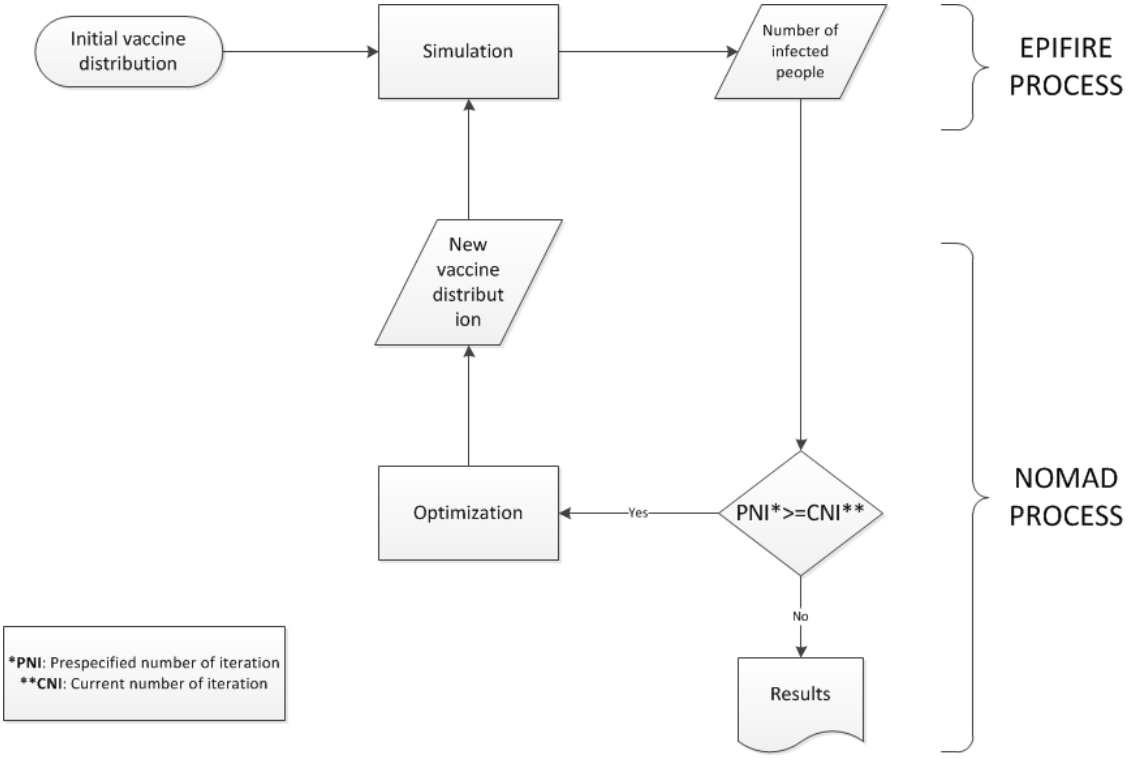

Figure 4.3: Flowchart: The relationship between NOMAD and Epifire

Chapter 5

Data Collection and Input Analysis

5.1 Demographic Information

One of the most important inputs of the model is population distribution according to age groups. We have five distinct age groups for the model: 0-4, 5-19, 20-49,50-64, 65+ in Table 5.1. This is because their contact and death rates, and infection and hospitalization cost are significantly different. 2010 USA Census data [22] are employed to calculate the population for each age group. Since simulating such a large population is computationally challenging, we calculated the proportion of population in each group as in Table 5.2 and simulated a representative population of 1000 people.

Table 5.1: The calculation of population distribution according to age groups

Total population of USA	310,234,000 (2010)	100%
0-4 age stratum	21,100,000	6.8%
5-19 age stratum	63,051,000	20.32%
20-49 age stratum	127,470,000	41.1%
50-65 age stratum	58,384,000	18.8%
65+ age stratum	40,229,000	13%

For example, Table 5.2 shows the population distribution for a sample of 1000

people.

Table 5.2: Distribution of people in a sample population of 1000

0-4 age stratum	1000*0.068	68
5-19 age stratum	1000*0.2032	203
20-49 age stratum	1000*0.411	411
50-65 age stratum	1000*0.188	188
65+ age stratum	1000*0.13	130

5.2 Contact Parameters

Each person from a particular age group contacts the others in both the same and different age groups. Therefore, we have to determine the expected number of contacts per person to calculate how many susceptible people may be infected by this person. Mossong et al. [26] presented the daily contact rates for different age groups. Unfortunately, we can not use the results directly in our model because it includes more age groups than what we need in our model. Therefore, we converts the contact rates from Mossong et al. [26] to a form to comply with our age-group definition.

The contact matrix of all reported contacts including of the mean number of contact individuals recorded per day per survey participator can be seen in Table 5.3 and Table 5.4. We use both the USA census and the table values above to convert this information as explained the following example. Table 5.6 shows the daily number of contacts of six age groups (20-24, 25-29,30-34, 35-39, 40-44, 45-49) with the others (50-54, 55-59, 60-64). However, we need only the number of daily contacts for people in the 20-49 age group with other people in 50-64 age group. First, we calculate the sum of each row and multiply the obtained results by their population values in Table 5.5. Then, we divide the sum of the last column (multiplication of corresponding total contact rates and population value) by total population value column to find the average number of contacts.

Table 5.3: Contact rates of individuals with respect to their ages from Mossong et al. [26]

Age of Contact	0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39
0-4	1.92	0.65	0.41	0.24	0.46	0.73	0.67	0.83
5-9	0.95	6.64	1.09	0.73	0.61	0.75	0.95	1.39
10-14	0.48	1.31	6.85	1.52	0.27	0.31	0.48	0.76
15-19	0.33	0.34	1.03	6.71	1.58	0.73	0.42	0.56
20-24	0.45	0.30	0.22	0.93	2.59	1.49	0.75	0.63
25-29	0.79	0.66	0.44	0.74	1.29	1.83	0.97	0.71
30-34	0.97	1.07	0.62	0.50	0.88	1.19	1.67	0.89
35-39	1.02	0.98	1.26	1.09	0.76	0.95	1.53	1.50
40-44	0.55	1.00	1.14	0.94	0.73	0.88	0.82	1.23
45-49	0.29	0.54	0.57	0.77	0.97	0.93	0.57	0.80
50-54	0.33	0.38	0.40	0.41	0.44	0.85	0.60	0.61
55-59	0.31	0.21	0.25	0.33	0.39	0.53	0.68	0.53
60-64	0.26	0.25	0.19	0.24	0.19	0.34	0.40	0.39
65-69	0.09	0.11	0.12	0.20	0.19	0.22	0.13	0.30
70+	0.14	0.15	0.21	0.10	0.24	0.17	0.15	0.41

$$\text{Reduced Contact Rate} = 292,188,240/127,470,000 = 2.292$$

This means that a person in the 20-49 age group makes 2.292 contacts with individuals in the 50-64 age group daily. Table 5.7 shows all values after doing previous calculations for all age groups.

5.3 Other Data Requirements

5.3.1 Number of Available Vaccine Doses

According to CDC (Centers for Disease Control and Prevention)[28] data, manufacturers could ensure approximately 132 million doses for the 2011-12 influenza season. This means that 42% of the US population can be covered. However, this coverage can change during a possible pandemic since the vaccine strain must be determined according to the new type virus, and it might take a while in the beginning of the pandemic. In the sensitivity analyses, we try different policies by

Table 5.4: Contact rates of individuals with respect to their ages from Mossong et al. [26]

Age of Contact	40-44	45-49	50-54	55-59	60-64	65-69	70+
0-4	0.24	0.22	0.36	0.20	0.20	0.26	0.13
5-9	0.90	0.16	0.30	0.22	0.50	0.48	0.20
10-14	1.00	0.69	0.32	0.44	0.27	0.41	0.33
15-19	0.85	1.16	0.70	0.30	0.20	0.48	0.63
20-24	0.77	0.87	0.88	0.61	0.53	0.37	0.33
25-29	0.74	0.85	0.88	0.87	0.67	0.74	0.33
30-34	1.02	0.91	0.92	0.61	0.76	0.63	0.27
35-39	1.32	1.09	0.83	0.69	1.02	0.96	0.20
40-44	1.35	1.27	0.89	0.67	0.94	0.81	0.80
45-49	1.32	1.87	0.61	0.80	0.61	0.59	0.57
50-54	0.71	0.95	0.74	1.06	0.59	0.56	0.57
55-59	0.55	0.51	0.82	1.17	0.85	0.85	0.33
60-64	0.47	0.55	0.41	0.78	0.65	0.85	0.57
65-69	0.23	0.13	0.21	0.28	0.36	0.70	0.60
70+	0.50	0.71	0.53	0.76	0.47	0.74	1.47

Table 5.5: Population distribution according to age groups [22]

Age Groups	Population
0-4	21,100,000
5-9	20,886,000
10-14	20,395,000
15-19	21,770,000
20-24	21,779,000
25-29	21,418,000
30-34	20,400,000
35-39	20,267,000
40-44	21,010,000
45-49	22,596,000
50-54	22,109,000
55-59	19,517,000
60-64	16,758,000
65-69	12,261,000
70+	27,968,000

considering both distribution time and coverage rate of the vaccine.

Table 5.6: Contact rates of individuals with respect to their ages (20-49) from Mossong et al. [26]

Age of Contact	50-54	55-59	60-64	Row Total	Pop. Density	
20-24	0.88	0.61	0.53	2.02	21,779,000	43,993,580
25-29	0.88	0.87	0.67	2.42	21,418,000	51,831,560
30-34	0.92	0.61	0.76	2.29	20,400,000	46,716,000
35-39	0.83	0.69	1.02	2.54	20,267,000	51,478,180
40-44	0.89	0.67	0.94	2.50	21,010,000	52,525,000
45-49	0.61	0.80	0.61	2.02	22,596,000	45,643,920
				Total	127,470,000	292,188,240

Table 5.7: All contact values after reduction

Age Groups	0-4	5-19	20-49	50-64	65+
0-4	1.92	1.30	1.57	0.76	0.39
5-19	0.58	8.72	2.16	1.09	0.85
20-49	0.67	2.28	3.33	**2.29**	1.10
50-64	0.30	0.91	1.66	2.38	1.69
65+	0.12	0.45	0.94	1.48	1.93

5.3.2 Death Rates, Cost, and Years of Life Lost (YLL)

Death rates and cost for each age group are taken from a study by Medlock et al. [3] as Table 5.8 and Table 5.9. Infection costs express the average cost of absence of labor and side effects. Medical costs include average medical care costs before influenza-related deaths. We calculate years of life lost for each age group based on a 75-year-average lifetime as in Table 5.10.

Table 5.8: Death rates

Per 100 cases	0-4	5-19	20-49	50-64	65+
Death Rates	0.00221	0.00221	0.03051	0.03051	0.26644

Table 5.9: Cost

$ Per Individual	0-4	5-19	20-49	50-64	65+
Infection Cost	275.3	275.3	328.98	328.98	492.56
Medical Cost	3435	3435	7605	7605	8309

Table 5.10: Years of life lost

Age Groups	0-4	5-19	20-49	50-64	65+
YLL	73	63	40	18	5

5.4 Calibration

We calibrate our model results according to age specific attack rates from the 1918 pandemic as Table 5.11 [12].

Table 5.11: Age specific attack rates from the 1918 pandemic [12] and adjusted attack rates(rates per 100 people)

Age Groups	1918 Pandemic	Age Groups	Adjusted Attack Rates
<1	20.7	0-4	33.7
1-4	33.7	5-19	37.18
5-9	39.1	20-49	28.66
10-14	38.1	50-64	16.15
15-19	34.5	65+	11.83
20-24	32.3	Overall	26.2
25-29	33.7		
30-34	32.6		
35-39	29.6		
40-44	23.6		
45-49	20.7		
50-54	17.5		
55-59	16.2		
60-64	14.3		
65-69	13.5		
70-74	11.1		
75+	8.8		
Overall	29.4		

Attack rate means the proportion of people contracting the disease in a population. For example, if 75 people get sick in a hundred-individual population at the end of the pandemic, the attack rate equals 75. Furthermore, association of our adjusted age specific attack rates can be seen in Table 5.11. The reason of difference between actual and adjusted age specific attack rate (29.4-26.2) is that the population density of age groups in 1918 and 2010 are different than each others.

During the calibration process, transmission rates for each age group are changed

to fit attack rates of simulation to adjusted attack rates. However, it is not enough to observe approximate attack rates since the interaction between age groups that have high contact rates, such as 5-19 and 20-49 and age groups that have lower contact rates such as 50-64 and 65+, increases attack rates even though we decrease transmission rates of some groups. Therefore, we decrease the interaction among the above age groups by assuming that old people make fewer contacts with younger people due to their isolated life.

Acceptable results come at the end of the sixth simulation with transmission rates, 0.04, 0.025, 0.036, 0.03, 0.01, 0.255, for G0, G1, G2, G3, G4, overall, respectively. Table 5.12 and Table 5.13 show the first and last calibration process with a 95 % confidence interval.

Table 5.12: First calibration process(number of infected per 1000 people)

	0-4	5-19	20-49	50-64	65+	Overall
Expected Infected	22.92	75.49	117.81	30.36	15.38	262
Trans. Rates	0.03	0.03	0.03	0.03	0.03	
Results	17.19	89.78	115.81	55.15	39.12	317.05
Interval ($\alpha = 0.05$)	15.6,18.8	82.9,96.7	107.1,124.6	50.9,59.4	36.2,42.1	293.8,340.4

Table 5.13: Last calibration process(number of infected per 1000 people)

	0-4	5-19	20-49	50-64	65+	Overall
Expected Infected	22.92	75.49	117.81	30.36	15.38	262
Trans. Rates	0.04	0.025	0.036	0.03	0.01	
Results	20.42	72.5	107.9	32.9	18.8	252.6
Interval ($\alpha = 0.05$)	18.1,22.8	65.8,79.1	96.9,119.1	29.8,36.1	17.1,20.4	236.6,268.6

The above results are found numerically. We start with the same transmission rates for all age groups, and then re-calibrate the rates heuristically according to differences between actual results and expectations. Instead of depending on only confidence intervals, calibrations are evaluated by using the least square method. We calculate the sum of square of differences between expected and actual number of infected people for each age group. Table 5.14 shows results of the least square method for each age group. Overall result of calibration 6 is the lowest one. It means that the results of calibration 6 are the nearest numbers to expected results.

Table 5.14: Least square method's results (sum of squares of deviations from expected number of infected for each age group)

Number of Calibration	0-4	5-19	20-49	50-64	65+	Overall
C1	9.010	130.549	177.676	103.489	76.655	1.561.695
C2	8.665	120.396	148.465	89.134	64.756	1.376.334
C3	12.359	123.068	197.555	38.448	27.792	1.106.618
C4	12.096	103.887	206.620	28.580	13.239	501.293
C5	11.840	96.665	262.947	24.120	7.971	557.893
C6	**4.433**	**41.487**	**110.446**	**19.213**	**4.471**	**470.732**

Chapter 6

Sensitivity Analysis, Simulation, and Optimization

In this chapter, we evaluate the number of infected people, the cost, and YLL in terms of different scenarios. We emphasize that our simulation model returns the number of infected people for each scenario, as well, NOMAD optimizes the solution by minimizing the number of infected people. Cost and YLL are derived from number of sick individuals.

6.1 Scenarios

In our simulation model, three different vaccine distribution policies are evaluated. The policy of the Advisory Committee on Immunization Practices (ACIP) recommended to prioritize people aged 0 up to 24 years. The former recommendations of the Centers for Disease Control and Prevention (CDC) were to vaccinate children (0-5 age group) and adults (over 50). Finally, new suggestions of the CDC were to prioritize children (0-19 age stratum) and adults (over 50) [3]. As a result, percentages of vaccine allocated to each age group according to the above three recommendations are demonstrated in Table 6.1.

Basically, available vaccine doses are distributed based on priority and population density of each group. Percentages of vaccine allocated by NOMAD for total

Table 6.1: Percentages of vaccine allocated to each age group according to recommendations of ACIP, former, and new CDC

	0-4	5-19	20-49	50-64	65+
ACIP	11.33	33.83	18.28	18.28	18.28
Former CDC	11.33	17.83	17.83	31.33	21.67
New CDC	11.33	33.83	0.00	31.33	21.67

36 different scenarios are demonstrated in Table 6.2. In the sensitivity analysis section, you can see the explanation of all different situations.

A sharp correlation depending on distribution time, infection periods, or contact rates among outcomes of NOMAD does not exist. However, the vaccine distributions tend to cluster around the 5-19 and 20-49 age groups when infectious days and contact rates are increasing. For lower disease periods and contact rates, more steady allocations are observed. Particularly, these differences can be observed between results for a 5-day-disease period with degree 1.25 and a 3-day-disease period with degree 0.75.

6.2 Sensitivity Analysis

A total of 36 different situations are examined. Table 6.2 shows all sensitivity analyses.

6.2.1 Vaccine Coverage

Instead of allocating all vaccine in the beginning of a pandemic, the simulation model distributes different amounts during the pandemic. A total of 600 vaccine doses are allocated in two ways: 300-200-100 and 100-300-200. This means that 300 doses are given to the population primarily, then 200 doses are distributed at a later time, finally, the remaining 100 doses are released at the late stage of pandemic. Coverage levels are illustrated on the graphics with cumulative percentages as below:

Table 6.2: Percentages of vaccine allocated to each age group after optimizations of NOMAD for all cases

	CoverageLevel	DistributionTime	Degree	InfectiousDays	0-4	5-19	20-49	50-64	65+
1	30-50-60	10-20-35	0.75	3	18	36	32	11	0
2	30-50-60	10-20-35	0.75	4	12	58	23	5	0
3	30-50-60	10-20-35	0.75	5	19	48	21	11	0
4	30-50-60	10-20-35	1	3	30	20	30	20	0
5	30-50-60	10-20-35	1	4	30	18	21	20	11
6	30-50-60	10-20-35	1	5	15	25	45	15	0
7	30-50-60	10-20-35	1.25	3	18	46	34	0	0
8	30-50-60	10-20-35	1.25	4	18	32	39	9	0
9	30-50-60	10-20-35	1.25	5	20	30	50	0	0
10	30-50-60	14-28-42	0.75	3	20	25	20	20	0
11	30-50-60	14-28-42	0.75	4	9	26	51	1	0
12	30-50-60	14-28-42	0.75	5	19	48	31	1	0
13	30-50-60	14-28-42	1	3	45	21	21	8	5
14	30-50-60	14-28-42	1	4	18	53	22	8	0
15	30-50-60	14-28-42	1	5	20	32	40	8	0
16	30-50-60	14-28-42	1.25	3	18	53	20	8	0
17	30-50-60	14-28-42	1.25	4	20	50	20	10	0
18	30-50-60	14-28-42	1.25	5	15	27	48	10	0
19	10-40-60	10-20-35	0.75	3	24	19	20	30	7
20	10-40-60	10-20-35	0.75	4	10	48	22	13	7
21	10-40-60	10-20-35	0.75	5	37	35	22	5	1
22	10-40-60	10-20-35	1	3	41	41	2	14	2
23	10-40-60	10-20-35	1	4	41	28	22	9	0
24	10-40-60	10-20-35	1	5	10	10	79	0	1
25	10-40-60	10-20-35	1.25	3	48	20	19	11	2
26	10-40-60	10-20-35	1.25	4	2	26	67	2	3
27	10-40-60	10-20-35	1.25	5	5	24	66	0	5
28	10-40-60	14-28-42	0.75	3	30	20	20	20	10
29	10-40-60	14-28-42	0.75	4	30	21	41	0	8
30	10-40-60	14-28-42	0.75	5	20	29	36	9	6
31	10-40-60	14-28-42	1	3	20	20	20	20	20
32	10-40-60	14-28-42	1	4	10	40	25	10	15
33	10-40-60	14-28-42	1	5	30	42	21	7	0
34	10-40-60	14-28-42	1.25	3	26	38	16	18	2
35	10-40-60	14-28-42	1.25	4	30	40	10	20	0
36	10-40-60	14-28-42	1.25	5	10	30	40	20	0

$$300 - 200 - 100 \Rightarrow 30\% - 50\% - 60\%$$

$$100 - 300 - 200 \Rightarrow 10\% - 40\% - 60\%$$

The most important reason to distribute the vaccine in a variety of amounts is that manufacturing all shots before the beginning of pandemic is a strong assumption.

6.2.2 Vaccine Distribution Time

We have two distribution times for each coverage level. Vaccine can be allocated on the 10^{th}, 20^{th}, and 35^{th} days of the pandemic or 14^{th}, 28^{th}, and 42^{nd} days of the pandemic.

6.2.3 Infection Period

This refers to the time frame when a sick person transmits disease to susceptible people before totally recovered. Initial average infection period in our model is 4 days [13]. However, we observe effects of $-/+25\%$ alteration on the results by trying 3 and 5 day infectious periods.

6.2.4 Contact Degree

As mentioned in the previous chapter, we use contact rates derived from study by Mossong et al. [26] to determine the number of interactions among individuals in the model. However, it is imperative to observe alteration of the results when contact rates are changing. Therefore, we add 25% increase and decrease to the contact rates in sensitivity analysis. Degree 0.75 expresses contact rates decreased by 25%. Similarly, degree 1.25 shows contact rates increased by 25%.

6.3 Results

Each scenario is simulated 30 times, and then average results are recorded for each age group. NOMAD iterates 200 times for each iteration to find optimum results. Finally, we calculate cost and YLL by using the results of diseased individuals and corresponding cost and YLL rates.

6.3.1 Number of Infected People

Table 6.3 shows the number of infected people for each age group and total numbers for each scenario and NOMAD. As can be seen, NOMAD gives the least total

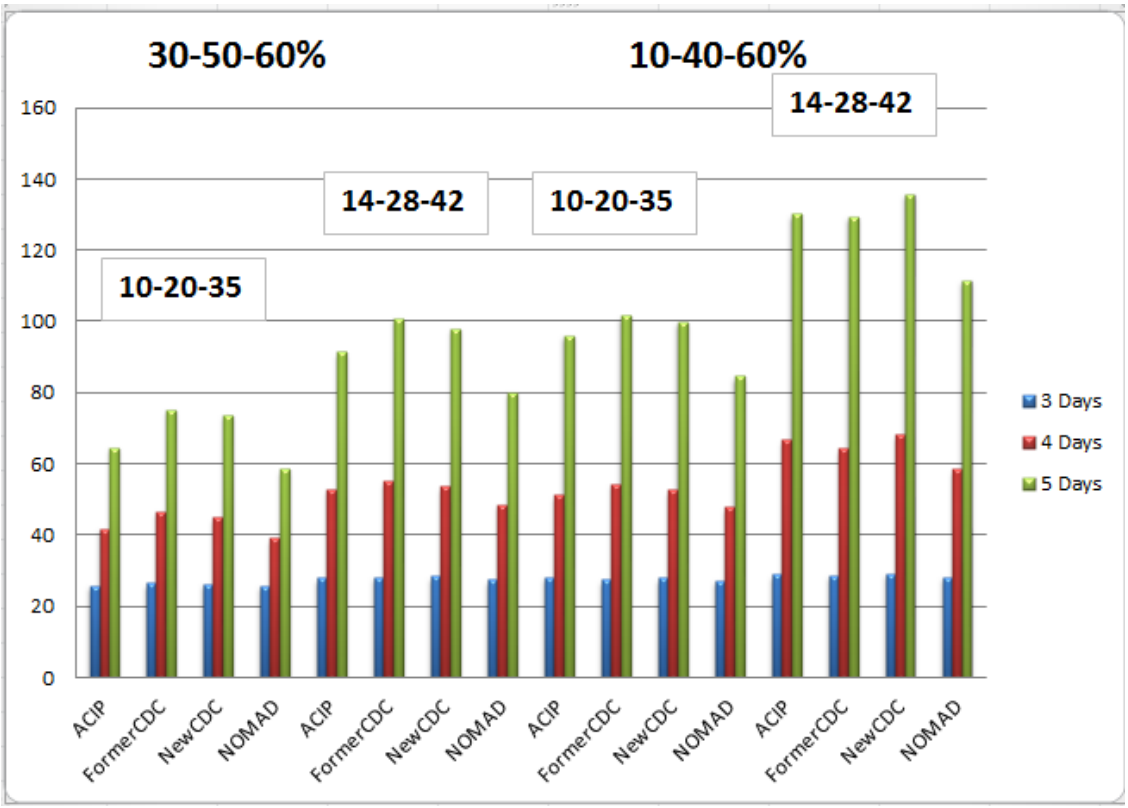

Figure 6.1: Number of infected people with degree 0.75

number of infected people even though results for sick individuals aged 50 and over are slightly higher than other policies. On the other hand, ACIP recommendations provide superior results compared to former and new CDC suggestions. For more detailed information about all sensitivity analysis results, please refer to the appendix.

Table 6.3: Number of infected people (30-50-60% coverage level, 14-28-42 distribution time, 4 days infectious duration, degree 1)

	Total Infected	0-4	5-19	20-49	50-64	65+
ACIP	86.10	6.47	24.07	39.50	7.77	8.30
Former CDC	94.20	6.63	29.10	43.57	6.97	7.93
New CDC	91.90	6.53	24.40	46.23	6.63	8.10
NOMAD	75.63	5.00	20.10	33.87	7.77	8.90

Figure 6.1 shows the number of infected people for all scenarios and NOMAD in all coverage levels, distribution times, and infectious periods with degree 0.75. It is clear that NOMAD significantly reduces the number of diseased individuals at all

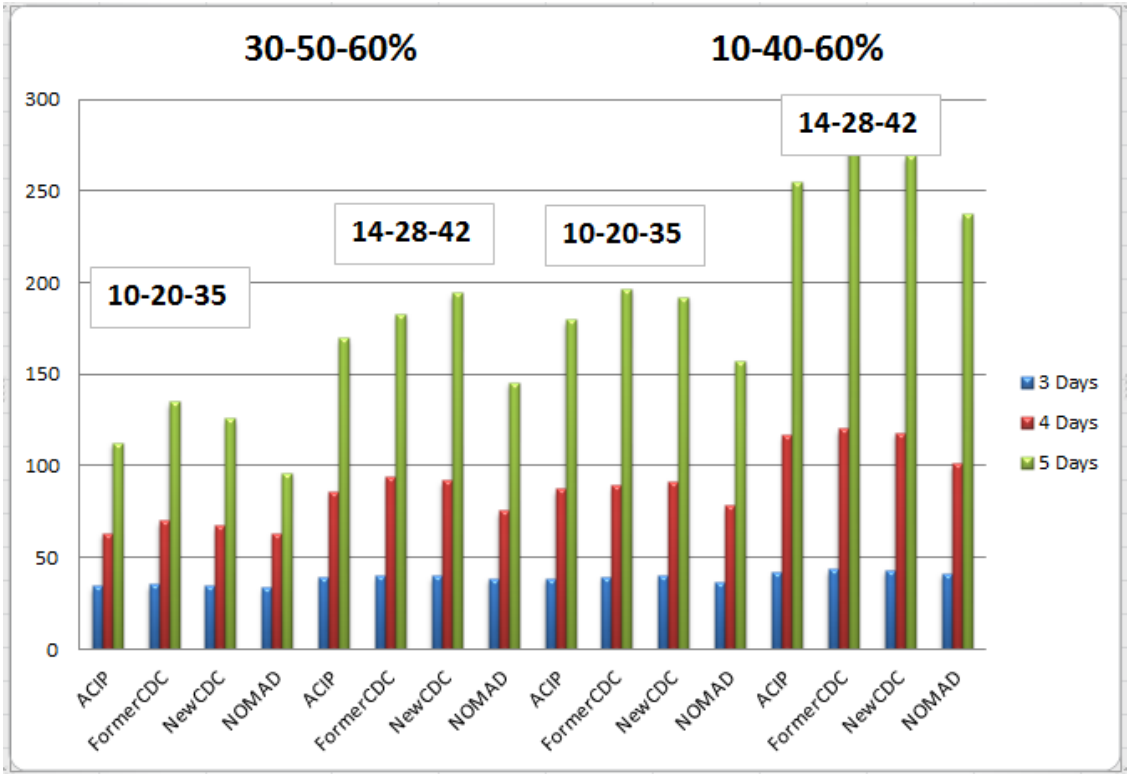

Figure 6.2: Number of infected people with degree 1

coverage levels, distribution times, and infection days. On the other hand, ACIP policy provides less infected people than others for all situations except the former CDC policy which is better at 10-40-60 % coverage level and 14-28-42 distribution time.

Overall, allocating the vaccine as early as possible decreases total amount of infected people in the population for all scenarios. Finally, the results slightly change for a 3-day-infection period. However, the results are sharply different from each other when the infectious period are 4 and 5 days.

Figure 6.2 and 6.3 show total number of infected people with degree 1 and 1.25. In comparison to the results with degree 0.75, the number of infected people for all scenarios are almost twice as much. Outcomes with degree 1 and 1.25 usually have a similar pattern with the results with degree 0.75, which means NOMAD and ACIP policies provide preferable results, but a couple of exceptions exist. First, as you can see in Figure 6.2, changing the infectious duration from 3 to 5 days

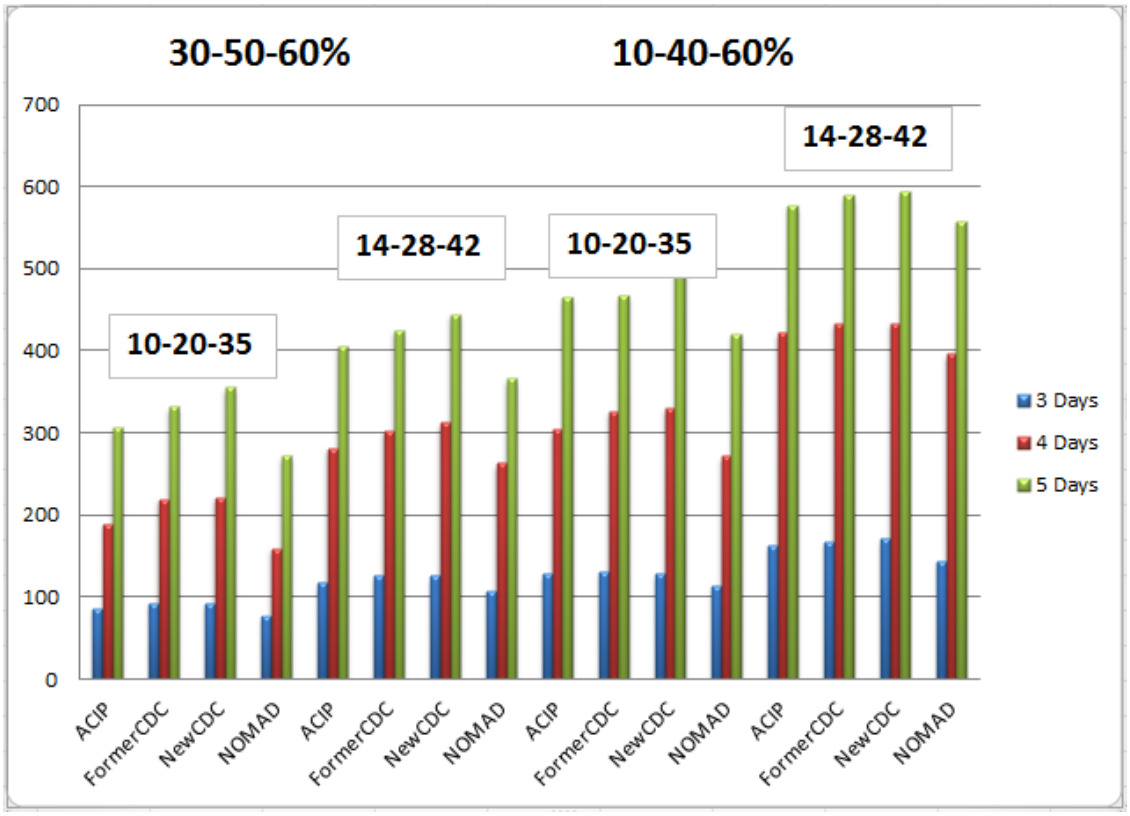

Figure 6.3: Number of infected people with degree 1.25

increases the results with regular contact rates (degree 1) more than other degrees. Furthermore, the former CDC policy gives superior results with degree 1 and 1.25 while new CDC decreases amount of the infected people with degree 0.75 more than former CDC.

6.3.2 Cost

Table 6.4 shows the cost of disease and hospitalization for each age group and total cost for each policy. It is clear that the two highest proportions in total cost belong to 20-49 and 65 over age groups. On one hand, the proportion of people aged between 20 and 49 in the population is 0.41, and this causes more infected people in the 20-49 age group. On the other hand, higher death and hospitalization rates for the older people increases cost even though their proportions in the population is lower than the others'. NOMAD reasonably provides lower cost for 0-4, 5-19,

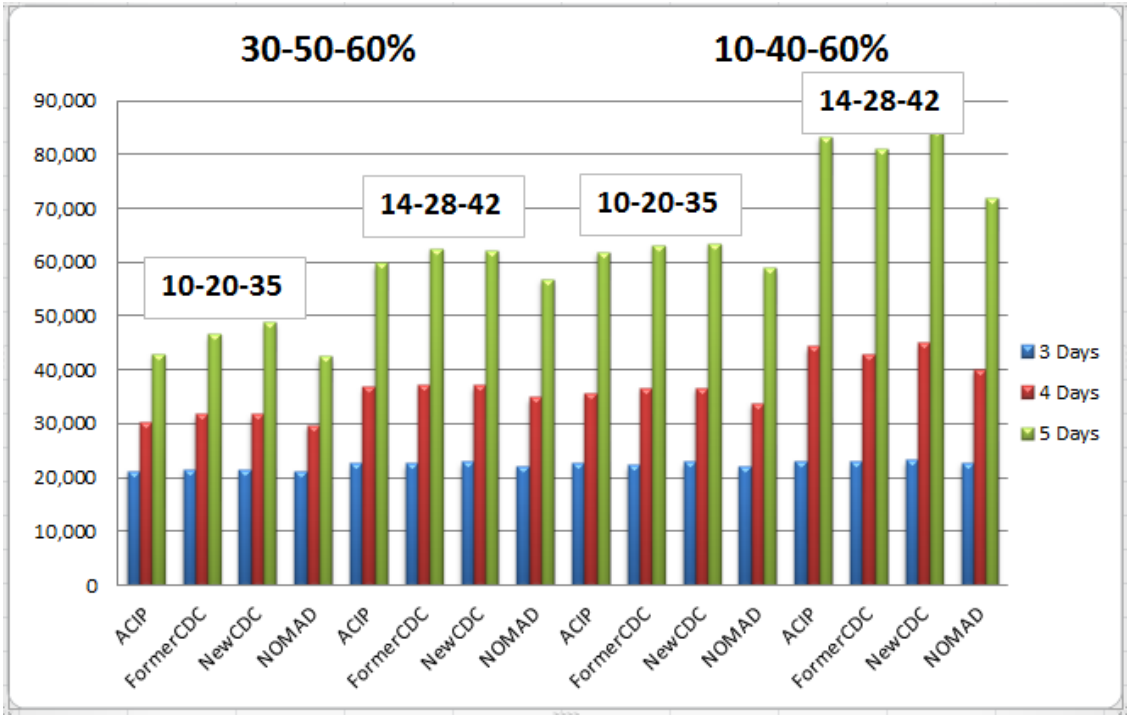

Figure 6.4: Cost($) with degree 0.75

20-49 age groups while other policies have superior results for people 50 over aged.

Table 6.4: Cost (30-50-60% coverage level, 14-28-42 distribution time, 4 days infectious duration, degree 1)

	0-4	5-19	20-49	50-64	65+	Total Cost
ACIP	1,829	6,808	22,160	4,357	22,463	57,618
Former CDC	1,877	8,232	24,441	3,908	21,471	59,929
New CDC	1,848	6,903	25,937	3,721	21,922	60,331
NOMAD	1,414	5,686	19,001	4,359	24,087	54,548

As can be seen, NOMAD generally gives lower cost compared to other scenarios. However, the amount of cost with degree 0.75 and 1, and 3-4 infectious days are closer to each other. One reason is that NOMAD tries to optimize the number of infected people by distributing available vaccine to especially 5-19 and 20-49 age groups since their proportion in the population and interaction with others in both their group and other groups are higher than other groups. Therefore, the number of diseased individuals 50 and over aged reasonably goes up. Because the average cost of medical care is more expensive for this age group, total cost in NOMAD is

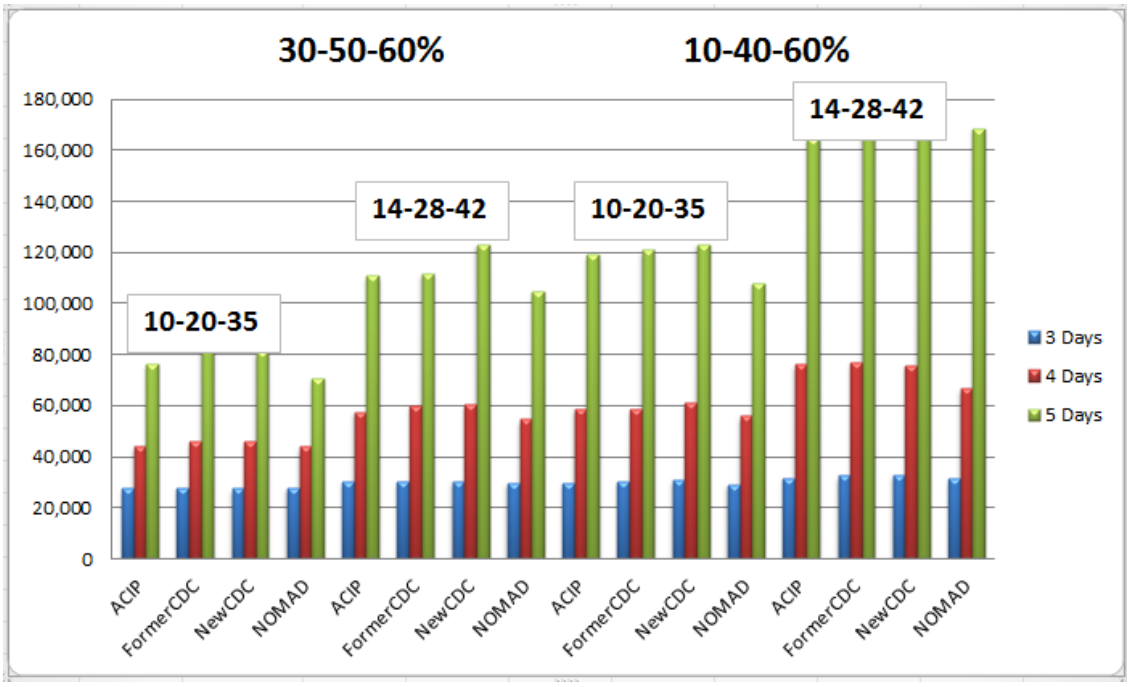

Figure 6.5: Cost($) with degree 1

not significantly lower than other policies while we take better results for the total amount of sick individuals.

Particularly, increasing contact degree from 1 to 1.25 has a significant effect on cost. Former CDC policy ensures slightly lower cost than other policies and NOMAD.

6.3.3 Years of Life Lost (YLL)

Table 6.5: YLL (30-50-60% coverage level, 14-28-42 distribution time, 4 days infectious duration, degree 1)

	0-4	5-19	20-49	50-64	65+	Total YLL
ACIP	1.04	3.35	48.21	4.27	11.06	67.92
Former CDC	1.07	4.05	53.17	3.83	10.57	72.69
New CDC	1.05	3.40	56.42	3.64	10.79	75.31
NOMAD	0.81	2.80	41.33	4.27	11.86	61.06

Table 6.5 demonstrates YLL for each age group and total YLL for each scenario and NOMAD. In common with cost, YLL for people aged from 20 to 49, and 65

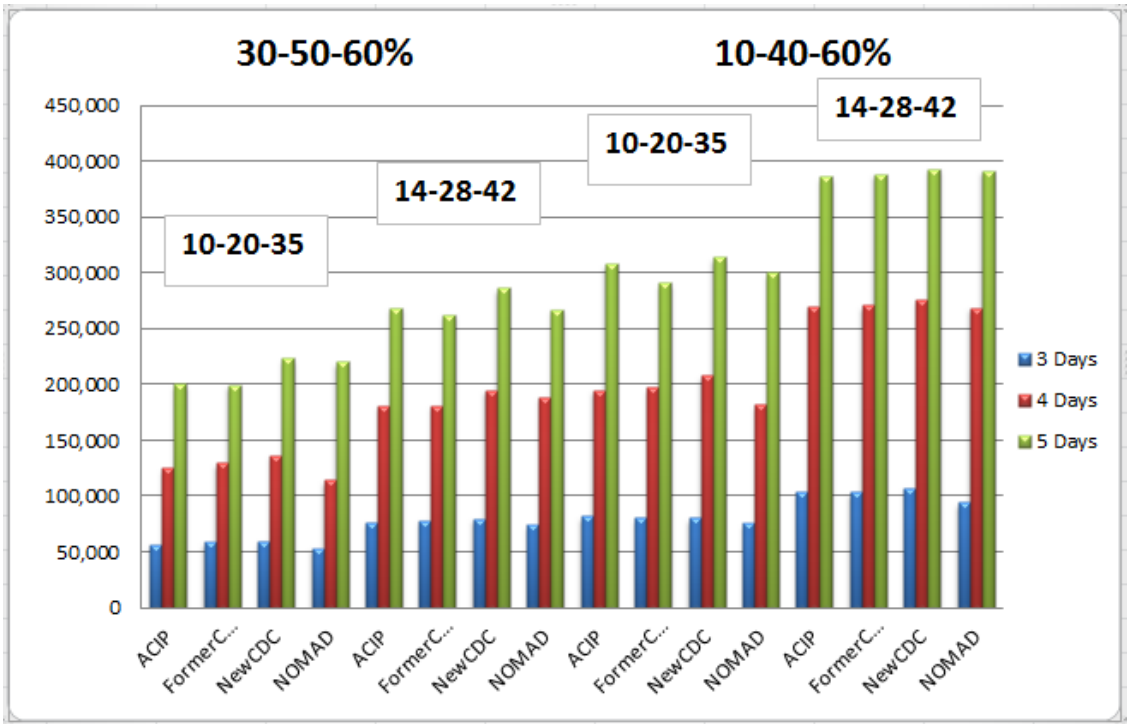

Figure 6.6: Cost($) with degree 1.25

and over are higher than others. However, YLL for 65 over are significantly lower even though death rates of this age group are almost ten times as much as 20-49 age group (Table 5.8). The explanation is that YLL per person aged 65 over is 5 while this is 40 for the 20-49 age group (Table 5.10).

In comparison to cost, NOMAD reasonably gives superior results for YLL in all cases. On the other hand, ACIP policy has more preferable outcomes compared to other policies in most cases while former CDC ensures slightly lower YLL than ACIP for degree 1.25.

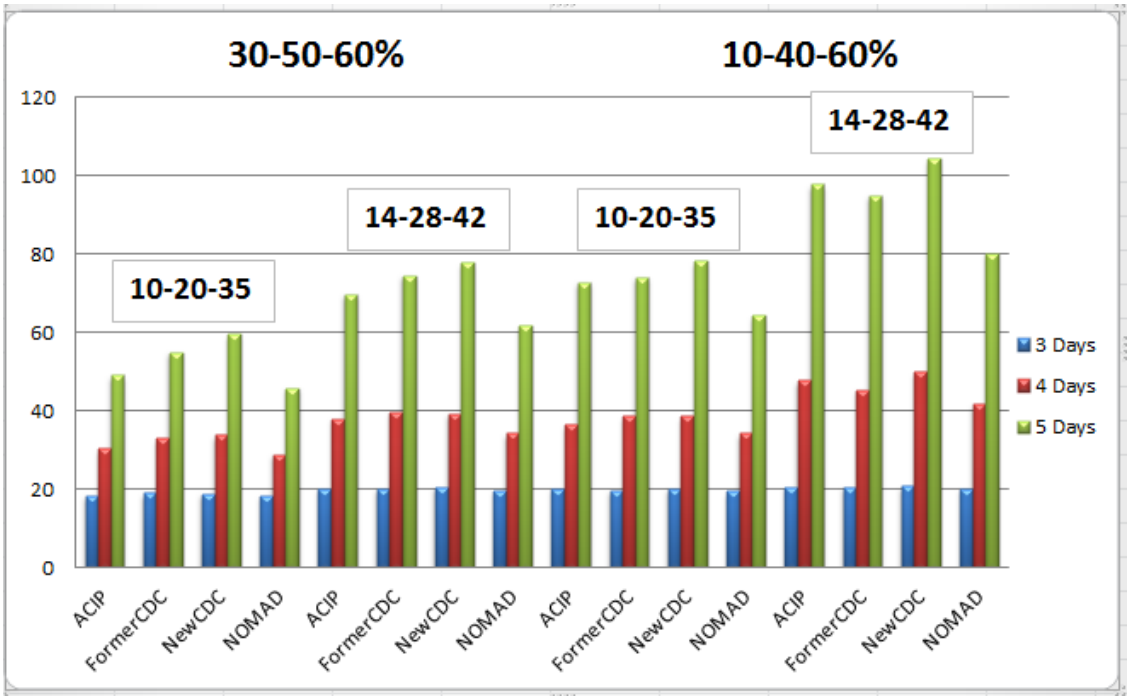

Figure 6.7: YLL with degree 0.75

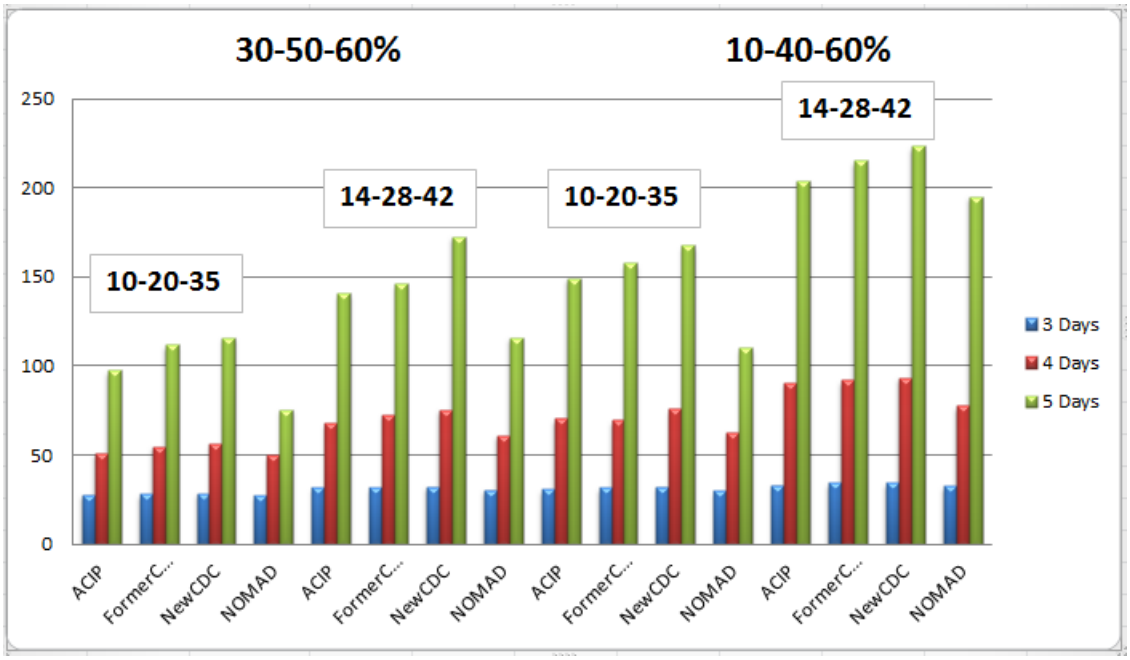

Figure 6.8: YLL with degree 1

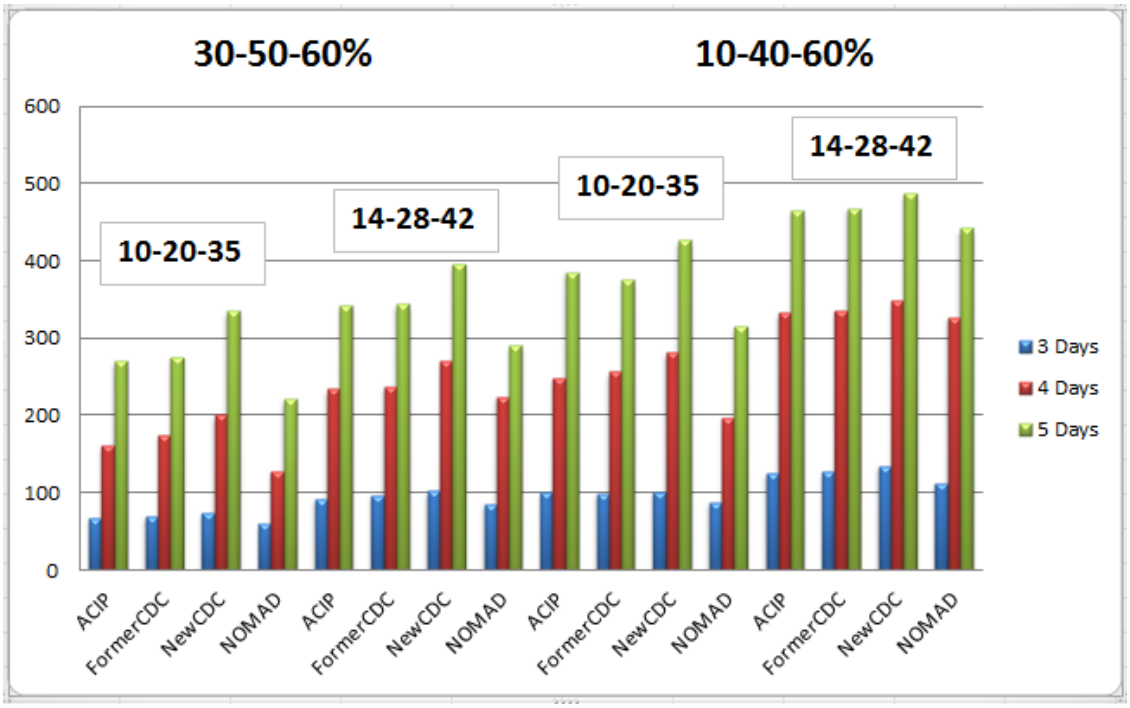

Figure 6.9: YLL with degree 1.25

Chapter 7

Conclusions and Future Work

7.1 Conclusions

In Chapter 1, we have given general information about influenza epidemics and pandemics, their negative effects on the society, and vaccination, which is the most common and strongest prevention method. Moreover, we have mentioned which factors motivate us to formulate our model , and how to contribute to the literature by employing this model.

In Chapter 2, studies on influenza vaccine allocation in the literature are reviewed. Three different models, compartmental model (SIR model), transmission model, and network structure, which we have employed in the simulation, are introduced in Chapter 3.

In Chapter 4, we introduced EpiFire simulation application, NOMAD optimization tool, and how to associate NOMAD with EpiFire for the simulation optimization process.

We have demonstrated necessary data such as demographic information, contact parameters, death rates, cost, and years of life lost for both simulation and optimization in Chapter 5. Finally, we show and discuss simulation and optimization outcomes by presenting our scenarios and sensitivity analysis in Chapter 6.

We observe that optimized vaccine distribution ensures less infected people and years of life lost compared to the fore-mentioned policies in almost all cases. On the

other hand, total costs for the policies are close to each other. Former CDC policy ensures slightly lower cost than other policies and our proposed in some cases. A sharp correlation depending on distribution time, infection periods, or contact rates among outcomes of NOMAD doesn't exist. However, the vaccine distributions tend to cluster around the 5-19 and 20-49 age groups when infectious days and contact rates are increasing. For lower disease periods and contact rates, more steady allocations are observed. Particularly, these differences can be observed between results for a 5-day-disease period with degree 1.25 and a 3-day-disease period with degree 0.75.

7.2 Future Work

There are several points of research arising from this work which should be pursued. First, we made simulations and optimizations for a population size of one thousand because of computational limitations. However, a larger sample size can provide more accurate outcomes since the number of people who are affected from disease can be millions in real life. Furthermore, population size can affect the accuracy of creating and connecting of edges and nodes to each other in terms of contact patterns of age groups in simulation.

On the other hand, we tried to minimize the number of infected people and calculate corresponding cost and YLL. In the future research, we plan to redesign the simulation model and NOMAD to provide minimum cost and YLL. We believe that the comparison of optimal vaccine allocations for the number of infected people, cost, and YLL will lead decision makers to more accurate conclusions.

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Number of infected people (30-50-60% Coverage Level, 10-20-35 Distribution Time, Degree 0.75, 3 Days Infection Duration

	Total Infected	0-4	5-19	20-49	50-64	65+
ACIP	25.77	2.50	9.17	8.13	1.30	4.67
Former CDC	26.40	2.50	9.43	8.53	1.23	4.70
New CDC	26.17	2.50	9.17	8.53	1.33	4.63
NOMAD	25.67	2.50	9.10	8.17	1.23	4.67

Number of infected people (30-50-60% Coverage Level, 10-20-35 Distribution Time, Degree 0.75, 4 Days Infection Duration

	Total Infected	0-4	5-19	20-49	50-64	65+
ACIP	41.63	3.50	14.30	15.63	2.63	5.57
Former CDC	46.67	3.70	17.47	17.70	2.43	5.37
New CDC	44.87	3.53	14.77	18.43	2.70	5.43
NOMAD	39.10	3.23	13.17	14.33	2.63	5.73

Number of infected people (30-50-60% Coverage Level, 10-20-35 Distribution Time, Degree 0.75, 5 Days Infection Duration

	Total Infected	0-4	5-19	20-49	50-64	65+
ACIP	64.47	4.90	20.27	28.07	4.83	6.40
Former CDC	75.17	5.23	27.23	32.77	3.63	6.30
New CDC	73.73	5.10	21.10	36.27	4.43	6.83
NOMAD	58.47	3.87	17.50	24.83	4.97	7.30

Number of infected people (30-50-60% Coverage Level, 10-20-35 Distribution Time, Degree 1, 3 Days Infection Duration

	Total Infected	0-4	5-19	20-49	50-64	65+
ACIP	34.33	2.77	9.53	14.60	2.03	5.40
Former CDC	35.37	2.93	10.30	14.83	1.87	5.43
New CDC	34.67	2.80	9.43	15.17	1.93	5.33
NOMAD	33.70	2.63	9.43	13.87	2.07	5.70

Number of infected people (30-50-60% Coverage Level, 10-20-35 Distribution Time, Degree 1, 4 Days Infection Duration

	Total Infected	0-4	5-19	20-49	50-64	65+
ACIP	63.03	4.33	17.20	29.47	5.27	6.77
Former CDC	69.93	4.43	22.10	32.97	3.90	6.53
New CDC	67.10	4.57	17.17	34.77	4.00	6.60
NOMAD	63.23	3.37	19.67	28.43	4.77	7.00

Number of infected people (30-50-60% Coverage Level, 10-20-35 Distribution Time, Degree 1, 5 Days Infection Duration

	Total Infected	0-4	5-19	20-49	50-64	65+
ACIP	112.43	6.10	24.40	60.03	11.80	10.10
Former CDC	134.87	6.57	38.57	73.03	7.57	9.13
New CDC	125.80	6.20	24.87	78.07	7.63	9.03
NOMAD	96.00	5.43	28.30	39.80	10.33	12.13

Number of infected people (30-50-60% Coverage Level, 10-20-35 Distribution Time, Degree 1.25, 3 Days Infection Duration

	Total Infected	0-4	5-19	20-49	50-64	65+
ACIP	86.40	5.77	26.03	40.03	6.50	8.07
Former CDC	92.67	6.00	31.87	41.17	5.67	7.97
New CDC	92.43	6.00	26.50	45.80	6.13	8.00
NOMAD	76.27	4.70	22.33	32.70	8.13	8.40

Number of infected people (30-50-60% Coverage Level, 10-20-35 Distribution Time, Degree 1.25, 4 Days Infection Duration

	Total Infected	0-4	5-19	20-49	50-64	65+
ACIP	189.63	9.37	45.47	98.93	20.13	15.73
Former CDC	219.13	10.37	68.70	113.57	13.00	13.50
New CDC	221.30	10.10	46.87	136.80	14.27	13.27
NOMAD	158.77	6.40	43.77	69.13	21.27	18.20

Number of infected people (30-50-60% Coverage Level, 10-20-35 Distribution Time, Degree 1.25, 5 Days Infection Duration

	Total Infected	0-4	5-19	20-49	50-64	65+
ACIP	306.23	13.70	61.87	170.17	37.40	23.10
Former CDC	332.03	15.03	94.63	180.83	21.33	20.20
New CDC	355.60	15.20	64.57	231.23	23.33	21.27
NOMAD	272.17	7.77	61.80	101.00	61.27	40.33

Number of infected people (30-50-60% Coverage Level, 14-28-42 Distribution Time, Degree 0.75, 3 Days Infection Duration

	Total Infected	0-4	5-19	20-49	50-64	65+
ACIP	28.03	2.60	9.80	9.23	1.60	4.80
Former CDC	28.20	2.63	10.00	9.20	1.53	4.83
New CDC	28.43	2.63	9.87	9.43	1.67	4.83
NOMAD	27.43	2.57	9.80	8.80	1.50	4.77

Number of infected people (30-50-60% Coverage Level, 14-28-42 Distribution Time, Degree 0.75, 4 Days Infection Duration

	Total Infected	0-4	5-19	20-49	50-64	65+
ACIP	52.87	4.43	18.40	19.97	3.80	6.27
Former CDC	55.13	4.63	19.50	21.57	3.33	6.10
New CDC	53.63	4.37	18.37	21.30	3.37	6.23
NOMAD	48.60	3.73	17.60	17.07	3.87	6.33

Number of infected people (30-50-60% Coverage Level, 14-28-42 Distribution Time, Degree 0.75, 5 Days Infection Duration

	Total Infected	0-4	5-19	20-49	50-64	65+
ACIP	91.33	6.60	28.40	40.40	7.40	8.53
Former CDC	100.93	6.97	34.97	44.47	6.37	8.17
New CDC	97.83	6.63	29.03	48.13	5.97	8.07
NOMAD	80.03	5.00	23.87	33.20	8.67	9.30

Number of infected people (30-50-60% Coverage Level, 14-28-42 Distribution Time, Degree 1, 3 Days Infection Duration

	Total Infected	0-4	5-19	20-49	50-64	65+
ACIP	39.37	3.00	11.23	17.00	2.57	5.57
Former CDC	40.10	3.03	11.90	17.07	2.43	5.67
New CDC	39.90	3.03	11.27	17.50	2.47	5.63
NOMAD	38.63	2.90	11.40	15.97	2.73	5.63

Number of infected people (30-50-60% Coverage Level, 14-28-42 Distribution Time, Degree 1, 4 Days Infection Duration

	Total Infected	0-4	5-19	20-49	50-64	65+
ACIP	86.10	6.47	24.07	39.50	7.77	8.30
Former CDC	94.20	6.63	29.10	43.57	6.97	7.93
New CDC	91.90	6.53	24.40	46.23	6.63	8.10
NOMAD	75.63	5.00	20.10	33.87	7.77	8.90

Number of infected people (30-50-60% Coverage Level, 14-28-42 Distribution Time, Degree 1, 5 Days Infection Duration

	Total Infected	0-4	5-19	20-49	50-64	65+
ACIP	169.57	11.00	40.60	85.43	18.47	14.07
Former CDC	182.77	10.53	54.27	92.17	13.07	12.73
New CDC	194.47	10.97	41.57	114.00	14.53	13.40
NOMAD	145.37	7.50	38.80	61.87	20.40	16.80

Number of infected people (30-50-60% Coverage Level, 14-28-42 Distribution Time, Degree 1.25, 3 Days Infection Duration

	Total Infected	0-4	5-19	20-49	50-64	65+
ACIP	117.10	8.10	33.60	53.93	11.17	10.30
Former CDC	125.57	8.43	40.03	58.23	8.97	9.90
New CDC	126.03	8.30	34.83	63.00	10.07	9.83
NOMAD	108.13	7.07	30.23	48.70	11.07	11.07

Number of infected people (30-50-60% Coverage Level, 14-28-42 Distribution Time, Degree 1.25, 4 Days Infection Duration

	Total Infected	0-4	5-19	20-49	50-64	65+
ACIP	281.67	16.20	67.83	143.20	32.83	21.60
Former CDC	303.10	16.83	92.63	148.97	25.53	19.13
New CDC	312.17	16.63	71.57	176.20	27.03	20.73
NOMAD	262.73	12.70	56.63	127.87	37.37	28.17

Number of infected people (30-50-60% Coverage Level, 14-28-42 Distribution Time, Degree 1.25, 5 Days Infection Duration

	Total Infected	0-4	5-19	20-49	50-64	65+
ACIP	405.50	21.77	89.40	206.77	53.90	33.67
Former CDC	424.83	22.23	118.67	215.87	38.60	29.47
New CDC	444.27	22.07	91.90	256.70	41.63	31.97
NOMAD	365.63	18.23	95.30	151.10	57.27	43.73

Number of infected people (10-40-60% Coverage Level, 10-20-35 Distribution Time, Degree 0.75, 3 Days Infection Duration

	Total Infected	0-4	5-19	20-49	50-64	65+
ACIP	28.07	2.67	9.73	8.97	1.80	4.90
Former CDC	27.43	2.63	9.67	8.77	1.57	4.80
New CDC	28.03	2.67	9.80	8.90	1.73	4.93
NOMAD	27.20	2.57	9.77	8.73	1.43	4.70

Number of infected people (10-40-60% Coverage Level, 10-20-35 Distribution Time, Degree 0.75, 4 Days Infection Duration

	Total Infected	0-4	5-19	20-49	50-64	65+
ACIP	51.27	4.23	18.30	18.97	3.60	6.17
Former CDC	54.27	4.07	20.17	20.90	3.10	6.03
New CDC	52.60	4.23	17.77	20.77	3.63	6.20
NOMAD	47.87	3.97	16.97	17.90	3.10	5.93

Number of infected people (10-40-60% Coverage Level, 10-20-35 Distribution Time, Degree 0.75, 5 Days Infection Duration

	Total Infected	0-4	5-19	20-49	50-64	65+
ACIP	96.00	7.20	29.83	42.43	7.97	8.57
Former CDC	101.63	7.27	35.73	43.37	6.83	8.43
New CDC	99.90	6.87	30.20	47.63	6.93	8.27
NOMAD	84.67	4.70	27.43	34.90	8.17	9.47

Number of infected people (10-40-60% Coverage Level, 10-20-35 Distribution Time, Degree 1, 3 Days Infection Duration

	Total Infected	0-4	5-19	20-49	50-64	65+
ACIP	38.73	3.23	11.03	16.20	2.63	5.63
Former CDC	39.57	3.07	11.37	17.10	2.40	5.63
New CDC	40.13	3.17	11.40	17.20	2.57	5.80
NOMAD	36.63	2.73	10.33	15.60	2.27	5.70

Number of infected people (10-40-60% Coverage Level, 10-20-35 Distribution Time, Degree 1, 4 Days Infection Duration

	Total Infected	0-4	5-19	20-49	50-64	65+
ACIP	87.60	6.43	23.40	41.27	8.13	8.37
Former CDC	89.43	6.13	27.57	41.03	6.43	8.27
New CDC	91.53	6.47	23.23	46.30	7.03	8.50
NOMAD	78.40	4.13	22.07	34.53	8.70	8.97

Number of infected people (10-40-60% Coverage Level, 10-20-35 Distribution Time, Degree 1, 5 Days Infection Duration

	Total Infected	0-4	5-19	20-49	50-64	65+
ACIP	179.93	11.27	42.87	89.57	20.83	15.40
Former CDC	196.60	11.90	56.77	99.23	14.90	13.80
New CDC	191.87	11.57	42.43	108.50	15.20	14.17
NOMAD	157.23	10.87	52.67	53.67	22.60	17.43

Number of infected people (10-40-60% Coverage Level, 10-20-35 Distribution Time, Degree 1.25, 3 Days Infection Duration

	Total Infected	0-4	5-19	20-49	50-64	65+
ACIP	128.27	8.47	37.90	59.87	11.43	10.60
Former CDC	131.00	9.50	42.30	58.87	10.40	9.93
New CDC	128.03	8.80	37.03	61.83	10.37	10.00
NOMAD	113.57	5.13	36.67	49.67	11.13	10.97

Number of infected people (10-40-60% Coverage Level, 10-20-35 Distribution Time, Degree 1.25, 4 Days Infection Duration

	Total Infected	0-4	5-19	20-49	50-64	65+
ACIP	303.67	18.00	75.83	148.67	37.50	23.67
Former CDC	326.30	19.10	97.33	160.33	27.97	21.57
New CDC	330.87	18.97	78.10	180.23	30.63	22.93
NOMAD	271.80	23.73	78.63	101.83	40.67	26.93

Number of infected people (10-40-60% Coverage Level, 10-20-35 Distribution Time, Degree 1.25, 5 Days Infection Duration

	Total Infected	0-4	5-19	20-49	50-64	65+
ACIP	465.23	27.13	107.80	228.53	62.50	39.27
Former CDC	466.70	27.63	127.93	231.13	46.37	33.63
New CDC	494.80	28.50	109.53	273.17	48.83	34.77
NOMAD	420.37	30.50	112.00	153.67	75.97	48.23

Number of infected people (10-40-60% Coverage Level, 14-28-42 Distribution Time, Degree 0.75, 3 Days Infection Duration

	Total Infected	0-4	5-19	20-49	50-64	65+
ACIP	28.90	2.63	10.23	9.40	1.80	4.83
Former CDC	28.67	2.63	10.23	9.30	1.67	4.83
New CDC	29.13	2.70	10.27	9.50	1.80	4.87
NOMAD	28.07	2.57	10.03	8.93	1.67	4.87

Number of infected people (10-40-60% Coverage Level, 14-28-42 Distribution Time, Degree 0.75, 4 Days Infection Duration

	Total Infected	0-4	5-19	20-49	50-64	65+
ACIP	66.67	5.37	23.07	25.677 5.63	6.93	
Former CDC	64.20	5.43	22.87	24.37	4.67	6.87
New CDC	68.07	5.63	22.97	27.97	4.63	6.87
NOMAD	58.50	4.47	20.77	21.67	4.93	6.67

Number of infected people (10-40-60% Coverage Level, 14-28-42 Distribution Time, Degree 0.75, 5 Days Infection Duration

	Total Infected	0-4	5-19	20-49	50-64	65+
ACIP	130.23	9.67	40.37	56.33	12.60	11.27
Former CDC	129.30	9.43	43.77	55.27	9.97	10.87
New CDC	135.60	9.87	41.47	63.33	10.33	10.60
NOMAD	111.40	7.77	38.20	44.07	11.00	10.37

Number of infected people (10-40-60% Coverage Level, 14-28-42 Distribution Time, Degree 1, 3 Days Infection Duration

	Total Infected	0-4	5-19	20-49	50-64	65+
ACIP	42.07	3.40	12.07	17.90	2.97	5.73
Former CDC	43.77	3.43	12.83	18.63	2.97	5.90
New CDC	43.27	3.47	12.27	18.60	2.90	6.03
NOMAD	41.43	3.17	12.27	17.33	2.87	5.80

Number of infected people (10-40-60% Coverage Level, 14-28-42 Distribution Time, Degree 1, 4 Days Infection Duration

	Total Infected	0-4	5-19	20-49	50-64	65+
ACIP	116.67	8.73	32.87	52.87	11.87	10.33
Former CDC	120.50	8.87	37.03	54.27	10.10	10.23
New CDC	117.80	8.30	33.50	56.10	9.90	10.00
NOMAD	101.23	8.10	28.90	43.93	10.87	9.43

Number of infected people (10-40-60% Coverage Level, 14-28-42 Distribution Time, Degree 1, 5 Days Infection Duration

	Total Infected	0-4	5-19	20-49	50-64	65+
ACIP	254.90	17.33	64.63	120.97	31.23	20.73
Former CDC	274.10	18.47	78.30	132.17	25.67	19.50
New CDC	269.23	17.93	64.93	139.17	27.23	19.97
NOMAD	237.50	11.67	56.47	108.00	36.13	25.23

Number of infected people (10-40-60% Coverage Level, 14-28-42 Distribution Time, Degree 1.25, 3 Days Infection Duration

	Total Infected	0-4	5-19	20-49	50-64	65+
ACIP	163.10	11.23	48.43	73.70	16.57	13.17
Former CDC	167.63	12.07	52.60	75.40	14.93	12.63
New CDC	170.73	11.83	48.50	81.27	15.83	13.30
NOMAD	143.83	9.27	42.07	64.57	14.97	12.97

Number of infected people (10-40-60% Coverage Level, 14-28-42 Distribution Time, Degree 1.25, 4 Days Infection Duration

	Total Infected	0-4	5-19	20-49	50-64	65+
ACIP	421.77	27.33	112.27	194.93	53.70	33.53
Former CDC	433.47	28.30	125.73	199.83	46.77	32.83
New CDC	433.87	28.40	114.00	210.70	47.13	33.63
NOMAD	395.63	19.00	99.13	191.37	49.03	37.10

Number of infected people (10-40-60% Coverage Level, 14-28-42 Distribution Time, Degree 1.25, 5 Days Infection Duration

	Total Infected	0-4	5-19	20-49	50-64	65+
ACIP	576.33	37.83	139.53	266.00	80.60	52.37
Former CDC	588.90	39.20	155.93	271.27	70.03	52.47
New CDC	594.03	38.87	142.33	288.47	73.03	51.33
NOMAD	558.37	38.20	142.73	241.60	75.87	59.97