Modeling and Responding to Pandemic Influenza: Importance of Population Distributional Attributes and Non-Pharmaceutical Interventions

by

Karima Robert Nigmatulina

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Signature of Author:_____
Sloan School of Management
May 14, 2009

Certified by:_____
Richard C. Larson
Mitsui Professor of Engineering Systems Division & Civil Engineering;
Director of Center for Engineering Systems Fundamental
Thesis Advisor

Accepted by:_____
Dimitris Bertsimas
Boeing Professor of Operations Research
Codirector, Operations Research Center

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ABSTRACT

After reviewing prevalent approaches to the modeling pandemic influenza transmission, we present a simple distributional model that captures the most significant population attributes that alter the dynamics of the outbreak. We describe how diversities in activity, susceptibility and infectivity can drive or dampen the spread of infection. We expand the model to show infection spread between several linked heterogeneous communities; this multi-community model is based on analytical calculations and Monte Carlo simulations.

Focusing on mitigation strategies for a global pandemic influenza, we use our mathematical models to evaluate the implementation and timing of non-pharmaceutical intervention strategies such as travel restrictions, social distancing and improved hygiene. In addition, as we witnessed with the SARS outbreak in 2003, human behavior is likely to change during the course of a pandemic. We propose several different novel approaches to incorporating reactive social distancing and hygiene improvement and its impact on the epidemic curve. Our results indicate that while a flu pandemic could be devastating; there are non-pharmaceutical coping methods that when implemented quickly and correctly can significantly mitigate the severity of a global outbreak.

We conclude with a discussion of the implications of the modeling work in the context of university planning for a pandemic.

Thesis Supervisor: Richard C. Larson
Title: Mitsui Professor of Engineering Systems & Civil and Environmental Engineering; Director of Center for Engineering Systems Fundamentals

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CHAPTER 1:
WHY WORRY ABOUT PANDEMIC FLU?

"Pandemic influenza is like hurricanes, tsunamis, and earthquakes: It will happen."
– Michael Osterhold[1]

An outbreak of pandemic influenza has the potential to be more disastrous than a nuclear exchange between two warring nations. Historical examples, such as the 1918-19 flu which killed over 40 million people, have demonstrated how catastrophic the flu can be. Influenza pandemics have occurred intermittently over centuries, and experts agree that the next pandemic is only a matter of time. While medical advances over the past century have been significant, we still don't have a simple cure for the flu, and if a new flu virus emerges, it can spread quickly throughout the world causing a pandemic. Such a disaster would not only place extraordinary and sustained demands on the public health and medical care systems, but would also burden the providers of essential services and strain the operations of all businesses. The federal government forecasts that up to 40% of the US population may be absent from their daily routines for extended periods as a result of illness or care-giving responsibilities (IPNSPI, 2006). High rates of worker absenteeism could in turn affect critical infrastructure, including the operations of water

[1] Center for Infectious Disease Research and Policy, University of Minnesota.

treatment facilities and power plants, while efforts to slow the spread of disease could limit the availability of food. A pandemic would impact all sectors of society.

The US National Intelligence Council's 2020 Project ''Mapping the Global Future" identified a flu pandemic as the single most important threat to the global economy (Karesh, 2005). A report from the Lowy Institute for International Policy concluded that even a very mild pandemic, like the 1968–1969 version, would result in a global economic loss of $330 billion and a human loss of 1.4 million people (McKibbin, 2006). A catastrophically severe 1918 version is forecasted to wipe out $4.4 trillion of global economic output and kill more than 140 million people (McKibbin, 2006).

The potential magnitude of this disaster requires advance planning, early preparedness and rapid action triggered by the detection of a new, easily transmissible and lethal virus. During the past few years policymakers have begun to realize the severity of this threat, and preparedness plans have started to develop across many layers of government. The US Department of Health and Human Services issued guidelines in November 2005, but left it to the states to produce specific plans, indicating that states should not rely on the federal government for much help during a pandemic. States have released versions of their pandemic plans, but most states do not include personal contact-avoidance or other more non-pharmacologic containment steps (Holmberg, 2006). One authority was even quoted saying that ''short of obtaining [antiviral] drugs, there is not much we can do to prepare" for a pandemic (Weaver, 2005). To explain this omission, policymakers point to the lack of epidemiologic data proving the effectiveness of non-pharmaceutical interventions. However, evidence from the SARS outbreak

indicate that improved hygiene, use of masks and other behavioral changes decreased the spread of respiratory disease by 90% (Lo, 2005)!

There are many questions that policy makers and public health officials have been trying to answer regarding the effectiveness, timing and drawbacks of various medical and non-pharmaceutical interventions. Decision makers have been trying to gain insight into the future to try and forecast how a pandemic would spread through the global population as well as within countries, regions, cities or even individual families. Their goals include determining which interventions are best suited for which types of scenarios. The timing and magnitude of the control measures are also important. Policy makers have been trying to address all of these issues. It is unethical to run experiments of pandemic flu transmission, thus developing mathematical models is the best approach to analyzing and playing through pandemic what-if scenarios. Mathematical models provide us with a systematic method of detecting the important transmission changing factors, testing various control strategies and considering the likelihood of various outcomes.

In this thesis we will model the spread of influenza through a population and incorporate various interventions and behavioral changes to evaluate and analyze their impact. As a result we hope to provide decision makers with a systematic approach to evaluating and comparing the effectiveness of various government imposed containment strategies and voluntary behavioral changes. In addition, we will also present actionable insights from our models that have significant relevance for decision makers.

In this chapter, we will discuss the biology of influenza, talk about the transmission of the virus and its epidemiological properties as well as possible mitigation

strategies. In addition, we will discuss past pandemics and what could happen in the future if H5N1, or another influenza virus strain, mutates and initiates the next pandemic. We will also present motivation for our research of pandemic flu as well as provide some background information that will help explain the logic of our modeling approaches.

1.1 A Little Biology

There are three distinct types of influenza virus that have been identified A, B, and C. These three antigenically distinct RNA viruses comprise the Orthomyxoviridae family. Flu types A and B are responsible for epidemics associated with increased hospitalization and death rates. Type B, which mutates at a slower rate than Type A, is found only in humans and seals. Consequently, a degree of immunity to Type B is maintained by a portion of the population. Because of this slower rate of antigenic change as well as limited host range, type B influenza never results in a pandemic (Zambon, 1999). Influenza type C usually manifests itself in a very mild illness, or is completely asymptomatic and has not caused widespread outbreaks. Types B and C do not present a large magnitude of public health concern, thus we will focus on type A.

Influenza virus A can be further divided into subtypes based on differences in two surface proteins called hemagglutinin (H) and neuraminidase (N). Hemagglutinin, making up approximately 80% of the surface proteins, functions in the attachment of the virus to a host cell. The remaining 20%, the neuraminidase, is thought to facilitate the

spread of the progeny virus[2]. Antivirals function by blocking either the hemagglutinin or the neuraminidase to prevent the multiplication of the virus in the host. Both H and N are antigens to which the human body can raise antibodies. There are 16 known H and nine known N subtypes that, through various combinations, make up all the subtypes of influenza A. ***Table 1.1*** gives examples of some of the most prevalent subtypes of influenza A.

As virus cells replicate, various mutations of the surface antigens occur as a response to host immunity; this is termed "antigenic drift". These types of gradual mutations result in seasonal flu outbreaks, but do not lead to pandemics since partial immunity remains in the population. In order to deal with this gradual evolution of the virus the World Health Organization (WHO) selects and reformulates the strains of the flu virus into the annual influenza vaccine. Influenza A virus also experiences another more worrisome type of mutation called "antigenic shift". Antigenic shift is a reassortment of gene segments, and it can occur when two or more different subtypes of influenza A infect the same cell. For example, if an avian H5N1 virus and human H3N2 virus co-infect a cell, a new 'H5N2' could emerge (Webster, 2004). This new strain could have the high virulence and case fatality rate of H5N1 and the efficiency of human-to-human transmission of seasonal flu (CDC). The unusually broad range of hosts susceptible to influenza A, especially birds, pigs and humans, appears to increase the likelihood of this event. Notably, in some parts of the world, humans live in close proximity to both swine and fowl, so antigenic shift is even more likely to effect the human population. It is not possible to predict the antigenic shift mutations, thus no

[2] Neuraminidase is the target for antiviral therapy referred to as neuraminidase inhibitors. Antivirals such as Zanamavir and Oseltamavir block neuraminidase so that the release of new virus particles is inhibited and their spread is thwarted.

vaccines can be produced for these emerging strains ahead of time. This emergence of a new and unpredictable strain to which humans have no immunity or effective vaccine, can cause a global pandemic in a very short amount of time.

Subtype	Name/Location	Time Period	Cases/Deaths
H1N1	Spanish Flu, global	1918 – 1919	50 – 100 million deaths
	Endemic in humans	Annual	Seasonal
H1N2	Endemic in humans	Annual	Seasonal
H2N2	Asian Flu, global	1957 – 1958	1 – 4 million deaths
	Russian Flu[3], global	1889 – 1890	~ 1 million deaths
H3N2	Hong Kong Flu, global	1968 – 1969	~ 1 million deaths
	Endemic in humans	Annual	Seasonal
H5N1	Avian Flu, Asia-Turkey	2003 – 2009	405 cases, 254 deaths
H7N2	North America, UK	2002, 2003, 2007	6 cases
H7N3	Canada	2004	2 cases
H7N7	Netherlands	2003	89 cases, 1 death
H9N2	Hong Kong	1999, 2003, 2007	4 cases
H10N7	Egypt	2004	2 cases

Table 1.1

A non-exhaustive list of Influenza A subtypes that have infected the human population (CDC). The strains currently endemic in humans are included in the seasonal flu vaccine. The highlighted subtypes are all potential strains for a future pandemic.

Currently, the most discussed pandemic threat is caused by the H5N1 strain, which is also referred to as the "Avian Flu". This virus has infected birds in over 35 countries and has resulted in the deaths, through illness and culling, of over 200 million birds across Asia. Various control measures have been attempted, but the virus persists and is endemic in Southeast Asia where it is primarily found in long-range migratory birds and is unlikely to be eradicated soon. The H5N1 virus has been reported to have

[3] The evidence that H2N2 caused the 1889-1890 outbreak is not conclusive, but suspected based on studies in the Netherlands (Smith, 1995).

infected 405 people in 15 countries, resulting in 254 deaths (WHO, 2009). Fortunately at this time, this subtype has not shown an ability to transmit efficiently between humans; for more information on H5N1 see ***Section 1.5***. Even if the currently circulating H5N1 virus does not result in the next human pandemic, evidence suggests that a different influenza strain is likely to emerge and cause the next catastrophic pandemic. For example, H9N2 infected children in China in 1999 and 2003; H7N2 caused infections in New York and Virginia in 2002 and 2003; and H7N3 infected poultry workers in Canada in 2004 (CDC, 2005). In 2003 H7N7 infected more than 1000 people in the Netherlands, even passing from human to human (Enserink, 2004). Overall, the National Academy of Sciences, CDC and chief medical personnel across the world agree that the next influenza pandemic is only a matter of time (Gerberding, 2005; Carr-Brown, 2005; Knox, 2005). A pandemic will happen; the main source of uncertainty is when.

1.2 Flu Transmission

The transmission of influenza occurs through respiratory emissions from sick individuals when talking, sneezing or coughing. These emissions enter the environment and can either come in direct contact with a well individual or are transmitted indirectly through an inanimate object. There are two types of droplet emissions that can be produced by a sick individual: large droplets and aerosols. Large droplets are usually considered larger than 10 micrometers and are produced in the upper respiratory tract, particularly the nasopharyngeal region. Aerosol particles are formed in the lower

respiratory tract and are generally smaller than 5 micrometers. These modes of transmission are not mutually exclusive.

Large droplet transmission occurs when contagious droplets produced by the infected host are propelled a short distance, 3 to 6 feet, through coughing or sneezing and can come into contact with another person's conjunctiva, mouth or nasal mucosa. These droplets can spread directly from human to human or indirectly through contact with secretions that have settled on various surfaces. Since these droplets generally are large and do not stay suspended in the air, this mode of transmission is not affected by special air handling or control of room pressures. Several authors have argued that large droplet transmission is the predominant mode of influenza spread.

In contrast to larger droplets, aerosol or droplet nuclei can remain suspended in the air for prolonged periods and be disseminated by air currents in a room or through a facility over long distances to be inhaled by a susceptible host. When aerosols are inhaled they are deposited in the lower respiratory tract due to their small size. Aerosol transmission would be of greater concern in settings where ventilation is poor, such as in an airplane or other closed space. While this mode of transmission is highly debated, (Tellier, 2006; Bridges, 2003) there is evidence that small particles can be more infectious since they can settle deeper in the lungs. Preventing the spread of droplet nuclei requires the use of special air handling and ventilation procedures.

Indirect transmission occurs either when an infected person uses hands to contain a cough/sneeze and then touches various objects or when large droplets that are expelled from the mouth settle on a surface. In support of infection through contaminated fomites or indirect contact, there are studies that show that human influenza viruses can survive

on a variety of surfaces at a temperature of 28°C and 35-49% humidity. For example, influenza virus can survive 24-48 hours on nonporous surfaces such as plastic and steel, and 8-12 hours on porous surfaces like tissue or cloth. However, the life of any particle in the environment is affected by factors including moisture, temperature as well as size and characteristics of the virus itself. Surface disinfectants and hand hygiene should decrease this mode of transmission.

Various interventions have been proposed to decrease transmission of the flu. Improved hygiene: hand washing and using alcohol based hand sanitizer has been showed to decrease the spread of influenza in controlled environments such as day cares, schools and nursing homes.(Roberts, 2000; Luby, 2005; WHO, 2006; Falsey, 1999) While there is no conclusive data regarding the effectiveness of surgical masks, there is some evidence indicating that wearing a mask will help prevent the infected from spreading it to the well by containing and slowing the speed of droplets (HHS, Inouye, 2006). There is evidence that shows that specialized air handling, which includes ventilation, HEPA filtering and exhaust fans, are effective in reducing potential aerosol transmission of influenza (Li, 2005). In addition, ultra-violet light, specifically UV-C, has the potential to disinfect air by inactivating virus-containing aerosols (Weiss, 2007).

While it is commonly agreed that these three modes of transmission are possible, and that the above mentioned interventions may be useful, there is a great deal of debate regarding which mode of transmission is the most predominant for influenza. This implies that while these interventions have been shown to be useful, we can't easily quantify their impact. More studies are necessary to answer this important question, but it will not be addressed in this research.

1.3 Influenza Manifestation

Infection begins when a virus particle, also known as a virion, enters a host cell and begins to replicate. Initially the host has no symptoms and does not shed the virus into the environment; this is known as the latent period. After about 1-3 days of the latent period, the infectious period begins. In addition, usually about 1-2 days after the start of the infectious period the individual may start to show symptoms of the infection. These symptoms usually include sore throat, aching and fever. The time from initial infection to the start of symptoms is called the incubation period and is illustrated in ***Figure 1.1***. What makes flu complicated to contain from the public health point of view is the order in which the infectious and symptomatic periods begin. For example, during the SARS outbreak people became symptomatic before they were maximally infective. Since the sick showed symptoms avoiding infectious people was easier, and isolation and quarantine became plausible.[4] Furthermore, health care workers, rather than the general population, were more likely to be exposed. With influenza, the infectious period usually precedes symptoms by about 24 hours, giving the virus a head start in infecting people before the host even knows if he or she is sick.

In addition, especially for seasonal influenza, people can become infected with influenza and become infectious without showing any illness or only very mild and negligible symptoms. These "healthy carriers" are estimated to comprise up to 50% of the infected population in seasonal flu. This aspect makes it difficult for people to effectively isolate the sick and avoid infection when well. Fortunately, the presence of healthy

[4] Another reason that isolation and quarantine were more realistic for SARS is because of the longer timeline of the virus. The latent period was 10 to 14 days, unlike 1-3 days for the flu, giving the government more time to track infectious and potentially infected individuals.

carriers is considered very unlikely for infection with a virus completely novel to the human immune systems.

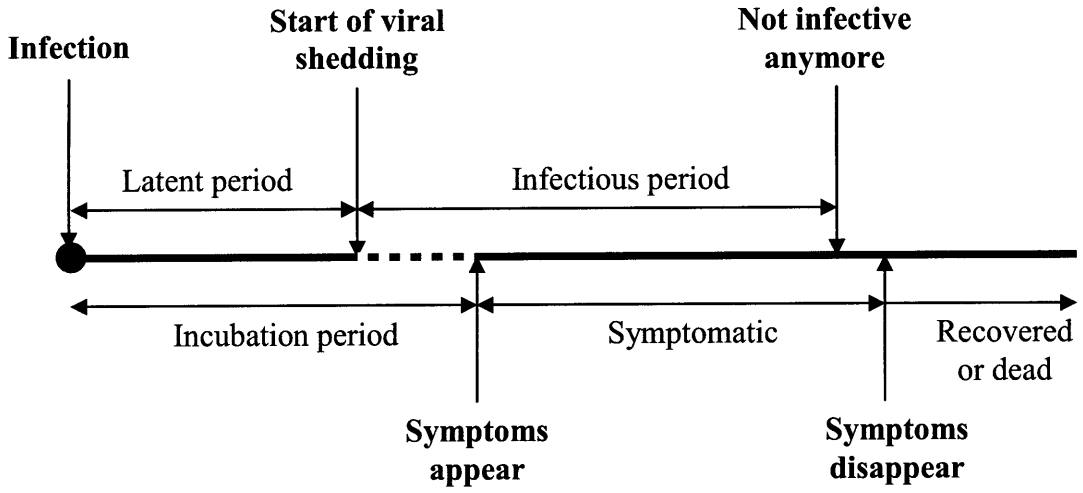


Figure 1.1

The temporal progression of the flu's symptoms and infectiousness. The highlighted dashed line segment between the start of viral shedding and appearance of symptoms is the reason that quarantine and isolation are very difficult for flu.

Individuals who become symptomatic usually experience high fever, cough, sore through, runny or stuffy nose, headache, muscle aches and extreme fatigure. Most people who get the flu recover completely in one to two weeks, but some can develop serious and potentially life-threatening medical complications such as pneumonia. It is approximated that in the United States seasonal flu is associated with about 36,000 deaths and 200,000 hospitalizations annually (WHO, 2003). On a global level, in a year's normal two flu seasons, one per hemisphere, there are between three to five million severe cases and up to 500,000 deaths (WHO, 2003). Flu-related complications can occur at any age, but for seasonal flu, the elderly and people with chronic health problems are more likely to develop serious complications. The 1918-1919 outbreak was unusual

because it caused more morbidity in the young and generally healthy 20-40 year old population. Overall, the clinical manifestation as well as the morbidity and mortality levels differ from one flu subtype to another subtype and are impossible to predict ahead of time.

1.4 Flu Treatment

No drugs can cure influenza. Recommended treatment usually consists of bed rest an increased intake of nonalcoholic fluids and some antipyretics (fever reducers) until fever and other symptoms lessen in severity. Antibiotics are ineffective, unless prescribed for a secondary infection. Certain drugs – antivirals – have been found effective in lessoning flu symptoms, but most efforts against the flu focus on prevention through vaccination that creates immunity or through improved hygiene and social distancing measures.

Antiviral medicines can relieve flu symptoms, but only if taken during the first 48 hours of symptoms. Oseltamivir (Tamiflu), in pill form, and zanamivir (Relenza), an inhalant, are neuraminidase inhibitors that are currently preferred for flu virus infections and have shown to reduce symptoms, complications and shorten illness by one to two days (Jefferson, 2006). In addition to treating infected patients, antivirals can be used for prophylactic purposes, with prevention rate from 68-89%, for highly exposed and essential service individuals (NSW, 2006). While there are studies that suggest antiviral treatment and prophylaxis have the potential to contain a pandemic if introduced immediately (Ferguson, 2005; Longini, 2005), others have indicated that this would lead

to the emergence of resistant strains that would become highly prevalent in the population (Eichner, 2009). For example, the CDC recommends that neither Amantadine (Symmetrel) nor Rimantadine (Flumadine), both in pill form, are used to prevent influenza because some flu strains have up to 91% resistance. Different strains of the flu have varying degrees of resistance against these antivirals, and it is impossible to predict what degree of resistance a future pandemic strain may have (Webster, 2006). Also, antivirals, including Oseltamivir, have FDA label warnings about behavioral changes. Furthermore, it has been estimated that in order to mitigate a pandemic we would need multiple doses of antivirals per member of the population for only eight weeks protection (Wu, 2006). This is not long enough and also currently infeasible given our stockpiles and distribution capacities. Antivirals alone are not likely to stop the next flu pandemic.

For seasonal flu, much of the illness and death can be prevented by the annual flu vaccination; however, no vaccine exists for the next unknown pandemic subtype. After a viral strain emerges and is detected, it will take anywhere between 3-9 months before the first doses become available. It is clear that relying on vaccines, especially initially, will be impossible. As for the seasonal flu vaccine, it consists of greatly weakened, killed, or fragmented viruses. Antigens in the vaccine stimulate a person's immune system to produce antibodies against the viruses. If the corresponding flu viruses invade a vaccinated person at a later time, the sensitized immune system recognizes the antigens and quickly responds to help destroy the viruses. Vaccine efficacy varies from one person to another, but studies have shown 70 - 90% effectiveness in preventing illness. Furthermore, if infected, hospitalization and death rate are also significantly decreased. Some people believe that a seasonal flu vaccine may provide some protection for or

decrease the severity of a pandemic strain. Thus while it is clear that vaccines will not be available in time to prevent a pandemic, annual flu vaccinations are still highly recommended.

1.5 The Avian Flu: H5N1

Influenza pandemics are associated with high morbidity, excess mortality as well as economic and social disruptions. Scientifically speaking, influenza pandemics arise when:

1. A "novel" influenza virus subtype, to which the general population has no pre-existing immunological protection, emerges. This also implies that no vaccine is available at the onset of the outbreak.
2. The virus infects humans and causes serious illness
3. It spreads efficiently amongst people with sustained chains of transmission (WHO, 2003).

Once such an event starts and reaches a certain level of local or regional spread, continued worldwide spread of the virus is considered inevitable especially given the highly interconnected nature of today's world.

As mentioned in ***Section 1.2***, H5N1 is a candidate pandemic viral subtype currently found in the avian reservoir. The H5N1 subtype spreads efficiently amongst birds via the intestinal tract and can be found in their feces. Unlike many other strains that infect migratory birds without causing disease, H5N1 is deadly for the avian population. Millions of birds have died as a result. Furthermore, people who have been

infected with H5N1don't always die from secondary bacterial infections, which is more common in seasonal flu. Avian influenza, without the presence of bacteria, can cause direct pulmonary damage that in turn can result in noncardiogenic pulmonary edema and pneumonia (McFee, 2007).

"If seasonal influenza is a predictable killer, the avian flu has the potential to be a true killing machine" (McFee, 2007). Despite the various control efforts of the international health community, H5N1 persists and is unlikely to be eradicated. This virus is endemic in long-range migratory birds found in Southeast Asia. Human H5N1 infection continues to occur, and the case fatality rate is high. ***Table 1.2*** shows the impact of the H5N1 virus on the human population.

Country	Cases	Deaths
Azerbaijan	8	5
Bangladesh	1	0
Cambodia	8	7
China	38	25
Djibouti	1	0
Egypt	54	23
Indonesia	141	115
Iraq	3	2
Lao People's Democratic Republic	2	2
Myanmar	1	0
Nigeria	1	1
Pakistan	3	1
Thailand	25	17
Turkey	12	4
Viet Nam	107	52
Total	**405**	**254**

Table 1.2

The total number of laboratory confirmed H5N1 cases between January 1, 2003 and February 5, 2009.

Avian flu infects people through the respiratory tract; inhaling the virus or getting it on hands and then contacting the pulmonary mucosa. Luckily, people can't get infected by eating properly cooked poultry; however, eating raw eggs, poultry blood, or undercooked bird meat could lead to an infection. Infection does require either the unusually close handling of poultry or the inappropriate cooking of poultry products, which happen to be common practices in the countries where human avian flu cases have been recorded (McFee, 2007).

H5N1 has already achieved the first two of the three attributes of a pandemic. Moreover, the data suggests that a few cases have resulted from, albeit inefficient, human-to-human transmission. Thus far we have been fortunate that the infection has stopped at the second person in the link, usually a family member. However, if the virus does mutate, history has shown us that we could be facing a very deadly and disastrous pandemic.

1.6 Past Pandemics

It is likely that influenza viruses have existed for thousands of years, even papers by Hippocrates in 412 B.C. seem to document an influenza epidemic. Pandemics in the pre-virology era are difficult to recognize definitively, but are usually characterized by periods of excess mortality that coincide with global accounts of an illness that epidemiologically and clinically resembles influenza. The first known pandemic was in 1580 and spread from Asia to Africa, Europe and the Americas. It was a particularly severe outbreak and death rates were high: 9,000 of 80,000 people died in Rome and

some Spanish cities were described as "nearly entirely depopulated" by the illness (Beveridge, 1978). Pandemics are believed to have continued to occur periodically before the isolations of the first influenza A virus, with outbreaks in 1729-1733, 1781-1782, 1830-1833, and 1889-1890, 1918-1919 (Potter, 1998). The 1889-1890 strain, never definitively identified, was called the Russian flu because it came to Europe from the East. It came in three waves, had higher morbidity and mortality than seen in decades, and was the first pandemic for which somewhat detailed records are available (Noble, 1982).

The 1918-1919 pandemic was the most destructive outbreak in recorded history killing up to 100 million people, which is more than World War I and World War II combined. As can be seen in ***Figure 1.2***, this virus decreased the average life expectancy of people by over 10 years. While it is suspected that the virus originated in the United States in Kansas, the disease became known as the Spanish flu since Spain was the first to openly admit the impact of the outbreak. The Spanish flu spread across the whole world even reaching the remote areas of the world like the Arctic and the Pacific Islands. Even in places where the death rate was low, the virus was widespread enough to bring everyday life to a halt. Saloons, theaters, vaudeville houses, schools and churches were closed in an effort to stop the infection. The number of doctors was severely lacking and nurses, medical students, veterinarians and other medical staff were put to work as doctors. The government, which was dealing with the end of WWI a this point in time, tried to keep up morale by denying and lying about influenza, but unfortunately that caused even more panic. This was a very grim period of time.

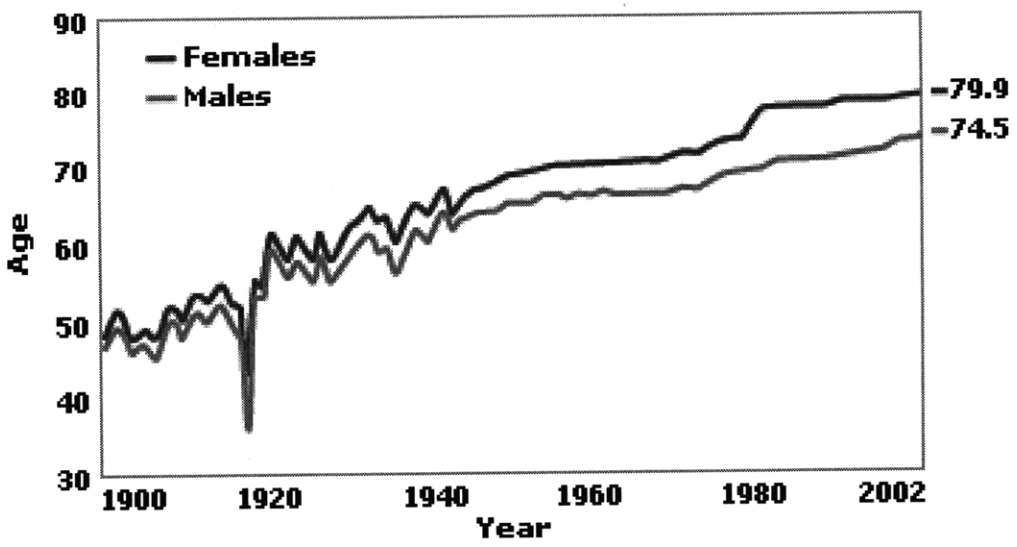


Figure 1.2

Life expectancy in the US during the 20th century. The sharp dip in life expectancy in around 1918 is the result of the Spanish Flu.

The 1918 pandemic began mostly in military camps with a relatively mild wave in the spring of 1918. This first wave was followed by two additional more severe waves in the fall and winter. The second, extremely virulent strain spread across the globe in 2 months. The average case fatality rate was about 2.5%; however, the US military experienced rates ranging from 5-10% (Barry, 2004). The unique feature of this pandemic was the disproportionately high mortality rate for healthy adults between the ages of 15 – 45 years; see ***Figure 1.3***. The mortality for pregnant women was even higher ranging somewhere between 23-71% (Barry, 2004). While in some places only a fraction of the population was infected and a small percentage died, in others, like several villages in Alaska, entire populations were wiped out.

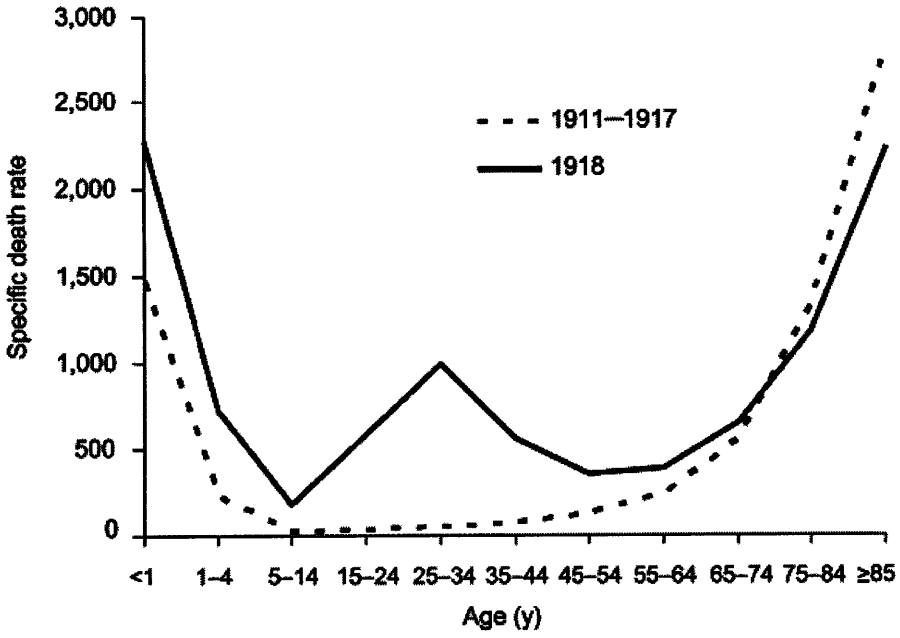


Figure 1.3

W-curve: the death rate by age for the 1918-1919 pandemic. The unique factor of this outbreak is that unlike most seasonal flu, which is deadly for solely the very young and elderly, it killed an unusually high number of people in the 20-40 years old category (Taubenberger, 1996)

The excess influenza deaths in 1918-1919 seem to be a result of either secondary bacterial pneumonia or severe acute respiratory distress-like syndrome (ARDS). It appears that the viral infection spread down the respiratory tract causing severe tissue damage and was often followed by secondary bacterial invasion (Morens, 2008). ARDS appears to have contributed about 10-15% to the overall fatality rate. Patients with ARDS experienced extremely rapid progression of the illness characterized by blue-gray facial discoloration as the patient drowned because of fluid-filled alveoli (Morens, 2007). Furthermore, investigators have postulated that an overly robust immune response, seen in the younger population, induced a "cytokine storm" that caused ARDS and may have contributed to the unusually high fatality rate. In addition, the Spanish flu had long term

effects, both economic impact in the next several years and even longer term health effects on those who were born during the pandemic (Almond, 2006). All of these factors differentiate the Spanish Flu from other pandemics of the 20th century, and make it the worst case scenario for planners who are preparing for future pandemics.

As mentioned previously there have been two other pandemics in the 20th century. In 1957, a flu outbreak occurred in a province of southwest China and within six months most areas of the world were dealing with the Asian Flu. There were two waves of the flu in the US. The first wave had the highest attack rate amongst school aged children while the second wave affected the elderly population (PanFlu, 2009). While this virus was relatively quickly identified and a limited supply of the vaccine was available, 10-35% of the world population was affected (PanFlu, 2009). The overall mortality rate was comparatively low and about 2 million people died worldwide.

The most recent and most mild pandemic of the 20th century occurred in 1968 – the Hong Kong Flu. First detected in early 1968 in Hong Kong, the virus spread worldwide during the following two winters, peaking in the winter of 1968-1969, and had a cumulative death toll of about 1 million people. Several theories explaining the lower fatality rate exist. One is that the Hong Kong strain, specifically its neuraminidase, was similar to that of the Asian flu, and thus prior infection by the Asian flu may have provided some immunity. Another suggestion is that instead of peaking in the fall, the Hong Kong flu only gained momentum near the school holidays. Children who usually contribute significantly to flu transmission stayed at home, so the rate of flu amongst schoolchildren and their families was low. The third conjecture is that medical care and antibiotics for secondary bacterial infections were available for the sick. Overall, it is

unclear whether the milder Hong Kong & Asian Flu or the severe Spanish Flu is more representative of the next flu pandemic.

1.7 Now and Then

Before using past pandemics as a way to provide us with a glimpse of the next outbreak we have to ask one important question. Given the medical and other inventions and developments over the past century, are we more or less prepared for a severe pandemic?

Even though we still do not have a simple cure for the flu, medical discoveries and creations over the past century such as vaccines and antivirals lead many to argue that the next pandemic is not going to be as traumatic. Even though vaccines for the next pandemic will take multiple months to produce and there aren't sufficient antivirals, antibiotics alone could be helpful decreasing the fatality rate. Some believe that secondary bacterial pneumonia contributed significantly to the mortality during past pandemics (Morens, 2008), thus the existence of antibiotics would make a significant difference in the future. Just the identification of the flu virus and the understanding that it spreads through respiratory contacts rather than through gases formed by decomposing bodies is a significant development. Today people understand that cutting breathing holes for the nose and mouth in a mask, as sometimes done in 1918-1919, makes the mask useless. Overall improvements in hygiene should also help decrease the transmission of the flu. At the same time we still do not know a lot about influenza transmission. We don't know which modes of transmission are the most significant and aerosol

transmission is highly controversial. Hopefully these questions can be answered before the next pandemic, so that people know how to best protect themselves against that flu.

In addition to medical developments, other inventions and societal changes are likely to change the dynamics of a flu pandemic in the 21st century. The Spanish Flu occurred before transcontinental air travel, television or the internet. Instead many people were serving in the military and living in barracks that were breeding grounds for efficient flu spread. Better living conditions for people should help decrease transmission locally; however, air travel will very quickly spread the flu across all corners of the world. Researchers also show that air transportation increases the probability of global outbreaks in the first place (Colizza, 2007). Once a virus begins to spread, it is likely to reach the whole world very quickly. In 1918, it only took a couple of months for the Spanish Flu to circle the globe. As a result of increased travel today, it is very unlikely that geographical heterogeneities of infected and uninfected cities will last for more than one or two weeks in a country such as the US (Viboud, 2006).

Not only will the virus spread much faster, but knowledge of the virus will spread like wildfire. The internet and television provide every individual with 24/7 access to information. This immediate access to information could be very helpful if the media properly educates the public on how to behave and what to do. For instance, in 1918, Philadelphia officials denied the existence of the Spanish Flu in their city and continued to hold parades and other social gatherings that helped propagate the flu. Today this would be impossible. Alternatively, there is also a chance that the media will create a tremendous amount of panic as they show and dramatize stories of sick and dying people. In the wake of Hurricane Katrina such sensationalist reports confused, unnerved and

mislead a lot of people. Thus while it is clear that the media and internet will have a significant impact, it is unclear whether it will be beneficial or detrimental.

Other developments driven by the goal to cut costs as much as possible may be very problematic in the case of a pandemic. Our hospitals have become lean as our medical surge capacity has become very small. The seasonal flu created enough of an increase in demand to overwhelm hospitals in 1999-2000 (Mariano, 1999). While hospitals have decreased in scale, people's expectations and reliance on the medical system have increased. Today there are a lot more individuals who rely on medication and treatment. It is unclear, that in a pandemic, diabetes patients would always receive their medication or medical attention if necessary.

Cutting costs has also made us very interdependent. We depend on the products in the millions of containers that are shipped into the US annually. Very few people today are self sufficient; we buy food at the grocery store, not grow it in our back yard. Not only are we very strongly interconnected, but we also have a just-in-time mentality which requires a smooth functioning of all elements in the network. In a pandemic, as panic spreads, supply chains are likely to be disrupted. Even if the virus never enters the US, these disruptions can have cascading effects. From this perspective our society is more vulnerable than it was one century ago.

The impact of the next pandemic is very unpredictable. In addition to changes and inventions over the past century, each viral strain is different. Before the virus emerges we will not know its virulence, morbidity or mortality. What we do know is that preparation for the next pandemic is very important. Preparation and coordination

amongst all levels is crucial: the federal, state and local government, organizations, companies, families and individuals all need to have a plan for the next pandemic.

1.8 Moving Forward

Catastrophes, natural disasters and terrorist attacks have all tested people's ability to cope with and adapt to extremely grim, demanding and dangerous circumstances. Whether through social distancing, cooperating and working together or relying on the help of others, people have demonstrated that they can adjust to various difficulties; an avian flu pandemic is not going to demolish our world. However, there is evidence that during SARS the losses that resulted were fueled and magnified by panic due to lack of public information and lack of guidance. Thus in order to minimize disruption, suffering and losses the government must know how to win the trust and confidence of the population, calm the people, and organize and rally the public as a strategic partner in battling the disease.

Modern science has alerted us to the pandemic threat posed by the H5N1 avian influenza virus and provided us with forewarning that wasn't available prior to past influenza pandemics. Private businesses now have the opportunity to cooperate with governments and international financing institutions; thus if mobilized together, they could take tactical steps to prevent the spread and minimize the impact of a pandemic. In addition, recent advances in technology would allow many companies to conduct business via electronic communications, which would permit their employees to work from home. Shipping companies could maintain their operations, by letting on-line purchases offset

some of the decline in retail trade. With appropriate planning, there are ways of mitigating the effects of a global pandemic on the daily social and economic functions of our society.

From all this is it very clear that we desperately need a preplanned strategy that deals with how to cope with the avian flu pandemic. Organizations such as the WHO and CDC have presented several recommendations on policies that they believe should be implemented (WHO, 2005). Their strategies to control the risks and damages of an influenza pandemic include enhancing surveillance, using monitoring and diagnostic systems, improving public communications, establishing stockpiles of vaccines and antivirals, preparing the health care systems and facilities, and considering the implementation of control measures such as quarantines (CDC, 2004). Careful consideration of those policy recommendations makes it clear that they are too abstract and difficult to apply. For example, the CDC and HHS have provided universities with a checklist to help guide their policies. Unfortunately this checklist presents more questions than answers for university planners. There are too many gaps in our knowledge and even if we had information regarding the virulence and morbidity of the next pandemic, it would still be impossible to intuitively sense what would happen.

The best way to systematically analyze many different possibilities and scenarios is through creating mathematical models – simulations of what could happen. In these models it is possible to not only include medical and government imposed interventions, but also social distancing and hygiene behavioral changes. Moreover, not only will a flu model and implied coping strategy be constructive to the whole world, it would also have additional long-term benefits. Infectious diseases remain a leading cause of morbidity and

mortality worldwide, with HIV, tuberculosis and malaria estimated to cause 10% of all deaths each year. New pathogens continue to emerge in animal and human populations. Therefore, it is sensible to study the general implications of an infection propagation model in order to adopt broader, far reaching measures to strengthen the institutional, regulatory and technical capacity of the human health sector. An investment in researching the avian flu would have both short-term and long-term value.

In this thesis we will both provide new approaches to modeling the spread of influenza as well as discuss the impact of a pandemic on an organization. The technical contribution of this research is that we developed new modeling approaches that involve a range of tools from simple probability to dynamic programming. Using these analytical tools, we show how to model different types of human heterogeneities that are present in the population. We also created completely original models for how people change their behavior in a pandemic. The impactful and actionable contribution of this thesis is derived from the models that we have created. We are able to identify some of the most pertinent population characteristics that impact overall transmission and the probability that an individual will get sick. Additionally, we have determined what can be done to decrease the risks of infection without the use of vaccines or antivirals.

Here is a summary of how this thesis will progress. In ***Chapter 2***, we begin by reviewing the many different approaches that people have taken to modeling flu transmission. In the following chapter, we introduce the basic model that is referred to throughout this work. We show the importance of incorporating certain heterogeneities of population attributes in the models. Additionally, since people are likely to alter their daily behavior based on the information that they receive about the pandemic, we propose

several approaches to incorporating human reaction into our model in ***Chapter 4***. ***Chapter 5*** adds a spatial component to the model as well as evaluates the impact of various interventions. We change gears as we move into ***Chapter 6*** and discuss the issues that universities will have to face in a flu pandemic. Focusing on the Massachusetts Institute of Technology (MIT), we propose a few solutions to some of the problems outlined by the CDC and HHS university checklist. After examining each of the intervention factors individually, in ***Chapter 7*** we consider their combined impact and conclude that with proper planning, we can change the course of the pandemic.

Mathematical models will help us prepare our population for the next pandemic. This preparation will assist countless institutions in dealing with the cascading implications of a widespread outbreak. More importantly, advance planning will help save lives.

REFERENCES FOR CHAPTER 1

Almond, D., 2006. "Is the 1918 Influenza Pandemic Over? Long-term Effects of In Utero Influenza Exposure in the Post-1940 U.S. Population." Journal of Political Economy. vol. 114, no. 4 <http://www.journals.uchicago.edu/doi/abs/10.1086/507154>

Barry. J.M., 2004. "1918 revisited: lessons and suggestions for further inquiry. In: The threat of pandemic influenza: are we ready?" Institute of Medicine.

Beveridge W.I., 1978. "Influenza: the last great plague: an unfinished story of discovery." New York, NY: Prodist.

Bridges C.B., Kuehnert M.J., Hall, C.B., 2003. "Transmission of Influenza: Implications for Control in Health Care Settings" Healthcare Epidemiology. <http://birdflubook.com/resources/Bridges1094.pdf>

Carr-Brown, J., 2005. "Britain prepares for bird flu death toll of thousands." The Sunday Times. August 7, 2005. <http://timesonline.co.uk/article/0,2087-1724318,00.html>.

Center for Disease Control and Prevention (CDC), 2004. "Interim Recommendations for Infection Control in Health-Care Facilities Caring for Patients with Known or Suspected Avian Influenza" <http://www.cdc.gov/flu/avian/professional/infect-control.htm>.

Centers for Disease Control and Prevention (CDC), 2005. "Avian influenza infections in humans." <http://www.cdc.gov/flu/avian/gen-info/avian-fluhumans.htm>.

Colizza V., Barrat A., Barthelemy M., et al., 2007. "Modeling the Worldwide Spread of Pandemic Influenza: Baseline Case and Containment Interventions." PLoS Medicine 4(1). <http://medicine.plosjournals.org/archive/1549-1676/4/1/pdf/10.1371_journal.pmed.0040013-L.pdf>

Eichner M., Schwehm M., Duerr HP., et al., 2009. "Antiviral prophylaxis during pandemic influenza may increase drug resistance." BMC Infectious Diseases 2009, 9(4). <http://www.biomedcentral.com/content/pdf/1471-2334-9-4.pdf>

Enserink, M., 2004. Bird flu infected 1,000, Dutch researchers say. Science 306, 590.

Falsey A.R., Criddle M.M., Kolassa J.E., et al., 1999. "Evaluation of a handwashing intervention to reduce respiratory illness rates in senior day-care centers." Infection Control and Hospital Epidemiology. 20: 200-202.

Ferguson N.M., Cummings D.A., Cauchemez S., et al., 2005. "Strategies for containing an emerging influenza pandemic in Southeast Asia." Nature, 437(7056):209-214.

Gerberding, J.L., 2005. "Current status of avian influenza and pandemic threat." Institute of Medicine of the National Academies, John R. La Montagne Memorial Symposium on Pandemic Influenza Research: Meeting Proceedings, National Academies Press, Washington, DC, p. 12.

Inouye S., Matsudaira Y., Sugihara Y., 2006. "Masks for influenza patients: measurements of airflow from the mouth." Japanese Journal of Infectious Disease. 59: 179-181.

Jefferson, T., Demicheli V., Di Pietrantonj C., et al., 2006. "Neuraminidase inhibitors for preventing and treating influenza in healthy adults." Cochrane Database System Review.

Knox, N., 2005. "Europe braces for avian flu." USA Today (October 9). <http://www.usatoday.com/news/health/2005..rope-avian-flu_x.htm>.

Li Y., Leung G.M., Tang J.W. et al., 2007. "Role of ventilation in airborne transmission of infectious agents in the built environment- a multidisciplinary systematic review." Indoor air. 17: 2-18.

Longini I.M., Jr., Nizam A., Xu S., 2005. "Containing pandemic influenza at the source." Science. 309(5737):1083-1087.

Luby S.P., Agboatwalla M., Feikin D.R., et al., 2005. "Effect of handwashing on child health: a randomized controlled trial." The Lancet. 366: 225-233.

Mariano, W., Shuit, D., 1999. "Area Hospitals Are Swamped With Flu Patients." Los Angeles Times. <http://articles.latimes.com/1999/dec/18/local/me-45083>

McFee R.B., 2007. "Avian Influenza." Nuclear, Biological and Chemical Agent Exposures. CRC Press.

Morens D.M., Fauci A.S., 2007. "The 1918 influenza pandemic: insights for the 21st century. " Journal of Infectious Diseases. 195(7):1018-28. <http://www.journals.uchicago.edu/doi/pdf/10.1086/511989>

Morens D.M., Taubenberger J.K., Fauci A.S., 2008. "Predominant role of bacterial pneumonia as a cause of death in pandemic influenza: implications for pandemic influenza preparedness." Journal Infectious Diseases 198(7):962-70. <http://www.journals.uchicago.edu/doi/full/10.1086/591708?cookieSet=1>

Noble G.R., 1982. "Chapter 2: Epidemiological and clinical aspects of influenza." Beare A.S. eds. Basic and applied influenza research. Boca Raton, FL, CRC Press, 11-50.

NSW, 2006. "Use of Antivirals for Treatment and Prophylaxis of Influenza in NSW Hospitals and Residential Care Facilities." A position statement of the NSW Therapeutic Advisory Group. <http://www.ciap.health.nsw.gov.au/nswtag/publications/posstats/Antiviralsinfluenza0506.pdf>

PanFlu. 2009. "Pandemics and Pandemic Threats since 1900s." PandemicFlu.gov <http://www.pandemicflu.gov/general/historicaloverview.html>

Potter C.W., 1998. "Chapter 1: Chronicle of influenza pandemics." Nicolson K.G., Webster R.G., Hay A.J. eds. Textbook of Influenza. Malden, MA, Blackwell Sciences, 3-18.

Roberts L., Smith W., Jorm L., et al., 2000. "Effect of infection control measures on the frequency of upper respiratory infection in child care: a randomized, controlled trial." Pediatrics. 105: 738-742

Smith, F.B. 1995. Russian Influenza in the United Kingdom, 1889-1894. Social History of Medicine. 8(1):55-73.

Taubenberger J.K., Morens D.M., 1996. "1918 Influenza: the Mother of All Pandemics." Emerging Infectious Diseases, <http://www.cdc.gov/ncidod/EID/vol12no01/05-0979.htm>

Tellier R., 2006. "Review of aerosol transmission of influenza A virus." Emerging Infectious Diseases <http://www.cdc.gov/ncidod/EID/vol12no11/06-0426.htm>

Viboud C., Bjørnstad O.N., Smith D.L., et al., 2006. "Synchrony, waves, and spatial hierarchies in the spread of influenza." Science 312: 447–451. <http://www.sciencemag.org/cgi/content/abstract/1125237v1>

US Department of Health and Human Services (HHS), 2009. "Interim public health guidance for the use of facemasks and respirators in non-occupational community settings during an influenza

pandemic." U.S. Department of Health and Human Services Pandemic Influenza Website. <http://www.pandemicflu.gov/plan>

Webster, Robert G., 2006. "H5N1 Influenza — Continuing Evolution and Spread." New England Journal of Medicine. 355 (21): 2174–77. <http://content.nejm.org/cgi/content/full/355/21/2174>

Weiss M.M., Weiss P.D., Weiss D.E., Weiss J.B., 2007. "Disrupting the transmission of influenza A: face masks and ultraviolet light as control measures." American Journal of Public Health. 2007; 97: S32-S36.

World Health Organization (WHO), 2009. Cumulative number of confirmed human cases of avian influenza A/(H5N1) reported to WHO.

World Health Organization (WHO), 2003. "Influenza Fact Sheet." <http://www.who.int/mediacentre/factsheets/fs211/en/>

World Health Organization (WHO), 2005. "Responding to the avian influenza pandemic threat." Communicable Disease Surveillance and Response Global Influenza Programme. <http://www.who.int/csr/resources/publications/influenza/WHO_CDS_CSR_GIP_05_8-EN.pdf>

World Health Organization Writing Group, 2006. "Nonpharmaceutical interventions for pandemic influenza, national and community measures." Emerging Infectious Disease. 12. <http://www.cdc.gov/ncidod/EID/vol12no01/05-1371_app2.htm>

Wu J.T., Riley S., Fraser C., Leung G.M., 2006. "Reducing the Impact of the Next Influenza Pandemic Using Household-Based Public Health Interventions." PLoS Medicine. 3(9). <http://medicine.plosjournals.org/perlserv/?request=get-document&doi=10.1371/journal.pmed.0030361>

Zambon, M (November 1999). "Epidemiology and pathogenesis of influenza." Journal of Antimicrobial Chemotherapy. 44, Suppl. B: 3–9.

CHAPTER 2:
REVIEW OF PANDEMIC MODELING APPROACHES

This research uses models to examine the expected impact of various government imposed and voluntary interventions on the progression of an influenza pandemic. Past pandemics are one approach to evaluating the effect of different interventions. However, solely relying on past outbreaks is not sufficient since influenza strains continuously mutate and take on different characteristics. Also, the past provides us with a limited set of scenarios that actually occurred and does not give us any insight into would have happened if the control measures were different. Models allow us to systematically assess different scenarios as well as pandemics of varied severity. With the help of mathematical models we can consider and resolve many different "what if" questions.

The types of models that have been used to describe the spread of infection range from basic differential equations to detailed stochastic agent-based models. Compartmental models of various complexities are the most common approach to modeling influenza and will be reviewed in ***Section 2.3***. Yet as computing capabilities and memory have increased over the past decade, very complex simulations have also

become more prevalent in literature. These computationally intense approaches will be discussed in ***Sections 2.4 & 2.5***. Another widely used approach relies on one specific parameter for the description of infection spread – the basic reproductive number R_0: the average number of infections a typical infectious individual will generate in a fully susceptible population (Diekmann et al., 1990). R_0 will be further described in ***Section 2.2***.

Overall, we will discuss several types of models that have been used to offer insight into epidemics and mention the advantages and limitations of each as well as point out the circumstances in which each type of model adds the most value.

2.1 The First Steps in Epidemiology

The Greek physician Hippocrates is sometimes said to be the father of epidemiology coining the terms endemic - disease seen in some locations but not others - and epidemic – disease seen intermittently through time. Hundreds of years later, in his book *De contagione et contagiosis morbis* (1543) Girolamo Fracastoro proposed that diseases are caused by "unseeable," very small, alive particles and that personal and environmental hygiene can help prevent the disease.

A more quantitative study of epidemiology began in the 17th century and was driven by one of the most famous infectious disease epidemics – the Great Plague. John Graunt, (1620-1674) a London merchant, developed early human statistical and census methods and is known as one of the first demographers. He is also considered to be one of the first epidemiology experts because his book N*atural and Political Observations*

Made upon the Bills of Mortality (1662) was mostly focused on public health statistics. During that time London kept a bill of mortality which John Graunt analyzed to try and create a system to warn the onset and spread of the bubonic plague, see ***Figure 2.1***. While the system was never created, Gaunt was the first to use statistical analysis to study disease.

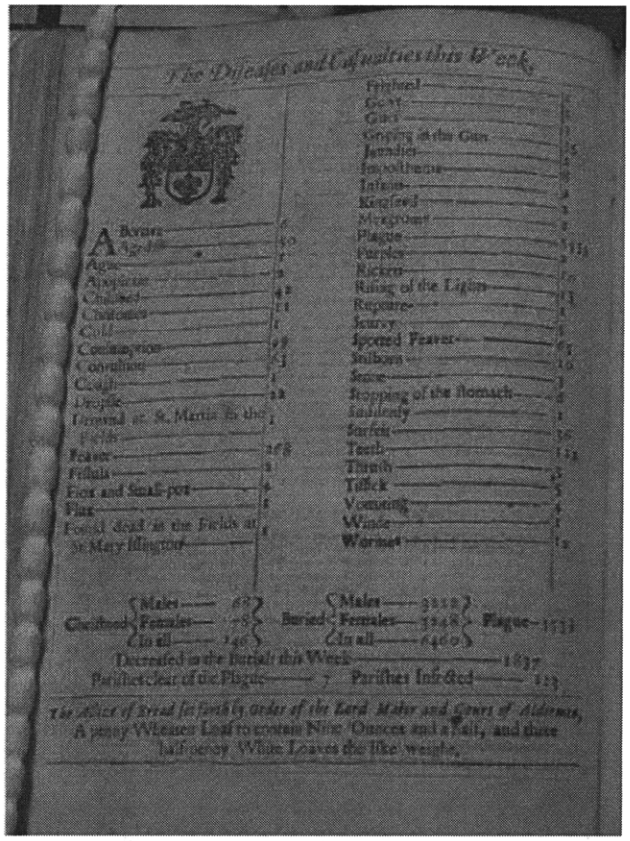


Figure 2.1
A bill of mortality for the city of London, England for the week of September 26th through October 3rd 1665.

Before the creation of the current version of compartmental models, Daniel Bernoulli developed a differential equations model to describe smallpox dynamics and the benefits of inoculating healthy individuals (Dietz, 2002). He published this work in 1776 titled as *Essai d'une nouvelle analyse de la mortalité cause par la petite vérole et*

des avantages de l'inoculation pour la prévenir. This approach was the first type of compartmental model, but is assumed that the infection rate of susceptible individuals was independent of the number of infected people in the population and thus didn't fully capture the dynamics of contagious disease transmission.

2.2 R_0 – Basic Reproductive Number

One of the most commonly referred to variables in epidemiology is R_0. The basic reproductive number – R_0, is the expected number of secondary infections produced by a typical index case in a completely susceptible population (van den Driessche, 2008). R_0, as it is now understood was established by George MacDonald in 1952, reintroduced by Klaus Dietz in the 1970s and then later canonized by Anderson and May in the early 1980s (Heesterbeek, 2003). Researchers utilize R_0 in a variety of ways; ranging from a way to calibrate their models (Ferguson, 2006), to a way to describe their model's results (Germann, 2006). A related value is the effective reproductive number. As the population of susceptibles is depleted, the generation specific reproduction number, *R(t)*, reflects how many secondary infections will result from each newly infected individual on generation t. Theoretically, *R(t)* is a monotonically decreasing function because as the number of susceptibles decreases fewer people have the potential to get infected.

Policy makers often refer to the reproductive number to guide their decision making process. It appears that one of the reasons for the popularity of R_0 is that it is somewhat intuitive. An infection can grow in a fully susceptible population if and only if $R_0 > 1$ (Hethcote, 2000). This well established statement can be somewhat misleading

because an $R_0 > 1$ does not guarantee that a disease will take off. Consider a population where half of the population – group 1 – because of behavioral and immunological reasons, can spread the virus to 4 people if infected, while the other half – group 2 – never spreads the virus. By some definitions of the reproductive number, we have an R_0 of 2. If the first person to get infected is a member of group 2 the virus dies out right away. This is an example of a case where $R_0>1$, but the disease dies out after the index case more than half of the time. To see more about the complexities of using R_0 as an input value to guide policy, refer to a study by Meyers et al. They focus their study on SARS and illustrate that for a single value of R_0, any two outbreaks, even in the same setting, may have very different epidemiological outcomes (Meyers, 2005).

The mix-up over R_0 arises partially because there is some ambiguity in its definition (Hsieh, 2003) especially where the population in question is heterogeneous (Larson, 2008). Determining who in the population is a typical index case is vague. In addition, when a disease emerges, estimates of R_0 vary significantly. With Severe Acute Respiratory Syndrome (SARS) the estimations for R_0 ranged between a little over one to values over seven (Lipsitch, 2003). While some work has been done to clarify these concepts (Wallinga, 2007), the issues are far from resolved. The matter is further complicated by the question whether control measures should or shouldn't be incorporated in calculating R_0 or $R(t)$. In the case of SARS there was a decline in the number of secondary cases that coincided with the application of control measures, including isolation of SARS cases and quarantine of their asymptomatic contacts (Lipsitch, 2003). One of the approaches to address this is to define a value R_c which is the

reproduction number with control measures in place. For a heuristic derivation of R_c see the paper by van den Driessche and Watmough (van den Driessche, 2002).

Overall, there are three types of approaches based on the basic reproduction number: models that express R_0 in terms of parameters that describe the virus' virulence and morbidity (MacDonald, 1952; Hyman, 2000), models that fit the R_0 parameter to data using branching or martingale models (Becker, 1974; Becker, 1989) and models that use endemic equilibrium data to derive R_0 (Dietz & Heesterbeek; 2002, Dietz, 1975). While using $R(t)$ or R_0 provides a computationally intuitive basis for describing disease dynamics, this approach neglects important heterogeneity and stochasticity complexities (Eubank, 2004; Larson, 2007).

2.3 Deterministic Compartmental Models

The basic compartmental models are contained within a series of three papers by W.O. Kermack and A.G. McKendrick in 1927, 1932, and 1933 (Kermack, 1927, 1932, 1933). This most prominent epidemiology modeling approach is based on dividing the host population into several compartments based on their status with respect to the disease. It also incorporates the underlying assumptions about the nature and rate of transfer amongst the compartments.

The simplest, yet applicable compartmental model, known as the SIR model divides the total population of N into three distinct groups:

1. Susceptible (S): people who have no immunity to the virus, and so have the potential to get infected

2. Infectious (I): people who are currently infected and can transmit the virus to the susceptible individuals
3. Removed/Recovered (R): people who are immune to the infection because they have recovered from the disease.

In addition to establishing these compartments the model specifies how the sizes of these groups change over time. The first case is the Kermack-McKendrick model. See ***Figure 2.2*** for a flow chart of the model.

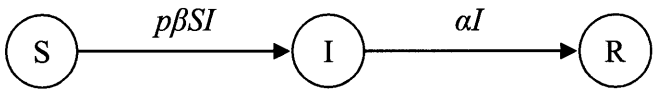


Figure 2.2
The flow chart for an SIR model.

The solution to the following set of differential equations will give size of the susceptible $S(t)$, infectious $I(t)$ and recovered $R(t)$ at time t:

$$\frac{dS}{dt} = -p\beta SI; \quad \frac{dI}{dt} = p\beta SI - \alpha I; \quad \frac{dR}{dt} = \alpha I$$

The assumptions that are embedded in this model are:

1. An average member of the population makes βN contacts per unit of time, assuming N is the total population size (mass action incidence).
2. The probability of infection spreading from an infected to a susceptible individual per contact is p.
3. Infected individuals leave the infected group at a rate of αI given I people in the infected compartment. To elaborate further, the duration of the infective period is exponentially distributed with mean $1/\alpha$.

4. There are no births or deaths from the overall model; there are no demographic effects.

The basic reproductive number, R_0 (see ***Section 2.2*** for the definition) for this model is:

$$R_0 = \frac{\beta p S(0)}{\alpha}.$$

There is a different SIR model which changes the first contact rate assumption. In this other model, the rate of contact per unit of time is constant, λ, instead of an increasing function of the population size. This approach is known as standard incidence. The reproductive number for this approach is:

$$R_0 = \frac{\lambda p}{\alpha}.$$

There are several limitations of the basic SIR model. One is that the latent and incubation periods are of equal duration and the infectious and symptomatic periods begin at the same time. Adding other compartments addressed these issues. An SEIR model adds an exposed group; after contacting the infection an individual proceeds into the exposed, but not infectious group before proceeding in the infected state.

A slightly more complex compartmental model adds two compartments to the standard SIR model. There is a group for individuals in the latent stage, L. After leaving the latent stage at rate κ, a fraction σ of the people proceed to the standard infectious group while the rest proceed to the infectious, but asymptomatic compartment, A. The individuals in the asymptomatic compartment have infectivity reduced by a factor of δ and proceed to the recovered group at a rate of η. Lastly, this model differentiates between the recovered and the dead individuals who have been removed from the

population from the infectious group f fraction of the time. Below is the set of differential equations describing this basic influenza model.

$$\frac{dS}{dt} = -p\beta S(I + \delta A); \quad \frac{dL}{dt} = p\beta S(I + \delta A) - \kappa L;$$
$$\frac{dI}{dt} = \sigma\kappa L - \alpha I; \quad \frac{dA}{dt} = (1-\sigma)\kappa L - \eta A;$$
$$\frac{dR}{dt} = f\alpha I + \eta A; \quad \frac{dN}{dt} = -(1-f)\alpha I$$

See ***Figure 2.3*** for the model flow chart.

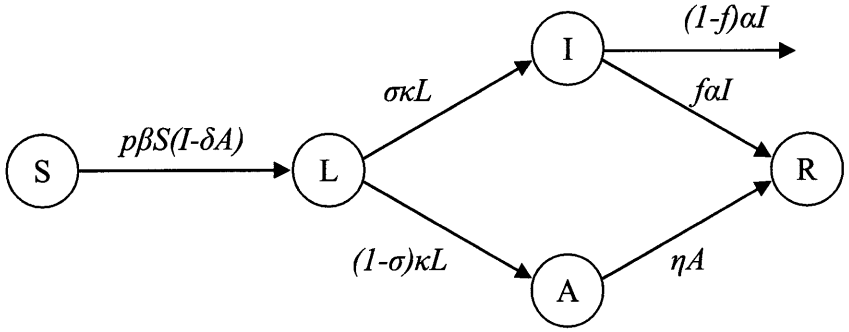


Figure 2.3
Model flow chart for influenza that incorporates the latent period and the asymptomatic people in the population.

The reproductive number for this model is:

$$R_0 = \beta pS(0)\left[\frac{\sigma}{\alpha} + \frac{\delta(1-\sigma)}{\eta}\right].$$

In order to include vaccination or antiviral treatment, more compartments can be added. See ***Appendix A*** for a few examples.

Another limitation of the simple SIR model is that it also assumes a completely homogeneous population social structure or behavioral distinctions. In many past influenza epidemics it has been observed that much of the transmission of infection can

be traced back to school children who have many very close interactions in the school environment. Some individuals are more socially active then others or some are more susceptible then others thus propagating the virus. Again, the solution proposed by modelers to add this type of heterogeneity is to add more compartments.

Consider two subpopulations of size N_1 and N_2 and a contact rate of δ_1 and δ_2 per unit of time, and that the fraction of contacts made by a member of group i with a member of group j is r_{ij}. Then

$$r_{11} + r_{12} = r_{21} + r_{22} = 1$$

and since the number of contacts made by members of group 1 with members of group 2 is equal to the number of contacts made by group 2 with group 1 we also have:

$$r_{12}\delta_1 N_1 = r_{21}\delta_2 N_2$$

At this point, the interaction level between groups one and two is still unclear. One approach is just to find values for r_{ij} , i,j=1,2 that satisfy the above three equations. The other approach is to assume that there is proportionate mixing between the groups, so the number of contacts between the groups is proportional to their activity levels (Nold, 1980). This conjecture is appropriate when contacts can be assumed to be roughly random. Under the assumption of proportionate mixing we have:

$$r_{ij} = \frac{\delta_j N_j}{\delta_1 N_1 + \delta_2 N_2}$$

and

$$r_{11} = r_{21} = \beta_1, \quad r_{12} = r_{22} = \beta_2 .$$

Assuming the same infective period for the groups as before and no deaths, the SIR model for this population is:

$$\frac{dS_1}{dt} = -\left(p\beta_1\delta_1 \frac{S_1 I_1}{N_1} + p\beta_2\delta_1 \frac{S_1 I_2}{N_2} \right);$$

$$\frac{dI_1}{dt} = \left(p\beta_1\delta_1 \frac{S_1 I_1}{N_1} + p\beta_2\delta_1 \frac{S_1 I_2}{N_2} \right) - \alpha I_1; \quad \frac{dR_1}{dt} = \alpha I_1;$$

$$\frac{dS_2}{dt} = -\left(p\beta_1\delta_2 \frac{S_2 I_1}{N_1} + p\beta_2\delta_2 \frac{S_2 I_2}{N_2} \right);$$

$$\frac{dI_1}{dt} = \left(p\beta_1\delta_2 \frac{S_2 I_1}{N_1} + p\beta_2\delta_2 \frac{S_1 I_2}{N_2} \right) - \alpha I_2; \quad \frac{dR_2}{dt} = \alpha I_2.$$

The reproductive number for this model is (van den Driessche, 2008):

$$R_0 = \frac{\delta_1\beta_1 + \delta_2\beta_2}{\alpha} = \frac{\delta_1^{\,2} N_1 + \delta_2^{\,2} N_2}{\alpha(\delta_1 N_1 + \delta_2 N_2)}.$$

Note that since all these models are deterministic, and chance does not come into play, an R_0>1 does indicate that the virus is going to spread.

By adding more compartments we can also address the problematic assumption that all people become symptomatic and spread the virus with equal intensity. Adding more compartments does give more flexibility to the model; however, this approach lacks realism because the model is not constrained to give integer values for the number of people in each of the compartments. This deterministic approach gives a good description of what would occur once the infection has taken off, but it does not capture what can occur at the initial and final stages of the virus. The early and end stages of the epidemic curve are best modeled stochastically.

We do not use compartmental models for our research because while they are a great basis for understanding transmission modeling, they are too inflexible for the purpose our research. Adding more compartments requires more input parameters and assumptions on the mixing of the population. In addition, these compartmental models

lock in people's behavior into a predetermined pattern that does not reflect the progression of the outbreak.

2.3 Stochastic Models

One of the primary uses of stochastic models is considering disease transmission in small populations, such as hospitals (Cooper, 1999). When populations are small, stochastic fluctuations may make a very big difference in the transmission dynamics. Stochastic models can also be helpful in determining disease dynamics in the initial and final stages of the illness. Additionally they give more information on the probability of the outbreak, the distributions for the final size and duration of the outbreak. The stochastic models briefly described in this section are based on SIR models. There are three different methods for formulating stochastic epidemic models:

1. Discrete time Markov chain (DTMC) model
2. Continuous time Markov chain (CTMC) model
3. Stochastic differential equation (SDE) model

We will give a brief description of the DTMC and CTMC models. Please refer to the following references for more information of the SDE model (Allen, 1999, 2003, 2008).

For the DTMS model let the number of susceptibles, infecteds and recovereds at time t be denoted as S(t), I(t), R$(t) \in \{0,1,2,...,N\}$. This model is a bivariate process $\{(S(t), I(t))\}_{t=0}^{\infty}$ with a joint probability function given by:

$$P_{(s,i)} = \boldsymbol{Pr}\{S(t) = s, I(t) = i\}$$

Also, let $t \in \{0, \Delta t, 2\Delta t, ...\}$ where Δt is small enough that at most one change in state occurs during that interval. The parameters from the SIR discrete model described in the previous section are still applied. The transition probability is then:

$$Pr\{S(t+\Delta t) = s+k, I(t+\Delta t) = i+j \mid S(t) = s, I(t) = i\} = \begin{cases} \beta pis / N\Delta t & (k,j) = (-1,1) \\ \alpha i \Delta t & (k,j) = (1,0) \\ 1 - \beta pis / N\Delta t - \alpha i \Delta t & (k,j) = (0,0) \\ 0 & otherwise \end{cases}$$

For more information on the following model please see (Allen, 2008).

The assumptions for the CTMC SIR model are similar to the DTMC model, except that $\Delta t \rightarrow 0$. The system of forward Kolmogorov differential equations is:

$$\frac{dP_{(s,i)}}{dt} = P_{(s+1,i-1)} \frac{p\beta(i-1)(s+1)}{N} + P_{(s,i+1)} \alpha(i+1) - P_{(s,i)} \left[\frac{p\beta is}{N} + \alpha i \right]$$

The complexity of stochastic models is obvious, and analytical results are very rare for realistic models. The most common usage of these models is through computer simulation.

The stochastic approaches presented above are clearly a great deal more complex than their deterministic counterpart. The pertinent question here is what is more important, the extra layer of realism or a simpler model? The stochastic and deterministic approaches aim to mimic the same occurrence. The relationship between the two is that in the limit of large population size, the expected values of vectors in the stochastic models approach the vector values in the deterministic SIR model.

The other relevant question is in what circumstances is it preferable to use either stochastic models or their deterministic counterpart? As mentioned before, stochastic models are best suited for describing transmission within small populations; examples are: a family, an apartment building a small military base. The extra effort in creating a

stochastic model is also worthwhile when studying the initial and final stages of an outbreak. Before the virus has infected a sufficient number of people, there is a lot of chance determining how quickly it will take off or how long it will simmer. Stochastic models on the whole allow us to address chance occurrences. In a large outbreak within a large population unusual occurrences are lost in the mix, so deterministic models are an easier and better approach.

A limitation for both deterministic and stochastic compartmental models is that they do not reflect the dynamic relationship between human behavior and number of people getting sick from the disease. The more people get sick the more other individuals will try to decrease their daily contacts, start washing their hands more regularly and overall change their behavior to decrease their chances of getting sick. In ***Chapter 4*** we will suggest approaches to model this aspect.

2.5 Network Models

Some researchers point out that compartmental models have a flawed assumption: random mixing. Both the stochastic and deterministic models rely on the postulation that every individual is equally likely to come into contact with every other individual in the population. Realistically this is not the case. Consider the somewhat extreme scenario of modeling the whole United States; it is obvious that the likelihood of an individual from the East coast interacting with someone from the West coast is not the same as his/her probability of contacting someone from the same city on the East coast. This same logic holds true when modeling a city; people usually interact with family much more than

with strangers on the street. Infectious diseases propagate over networks of many scales: from continent to continent via the air transportation network, from neighborhood to neighborhood via subway lines and bus routes, and from person to person via social contacts. Techniques developed 30-50 years ago, including computer simulation and percolation theory have provided an approach to modeling disease transmission integrating the locality of individuals within the overall population. In the 1990's a continued interest in network science also found applications in mathematical epidemiology.

Epidemiology network models are based on social network structures and attempt to understand the impact of social mixing patterns. Interactions are modeled as a graph, where individuals are represented as nodes, while their interactions are represented as edges. For modeling disease spread using the binary, 0 or 1, approach to represent the interactions between individuals is probably not the most accurate tactic. This has led to the development of weighted edges, where each edge of the graph has a weight, usually restricted between 0 and 1.

As can be expected in these models, a node's degree determines the connectedness of a person to the overall society. The degree distribution of the overall graph is another important factor determining how quickly the illness will spread through the community. Network models can range from simple lattice and random mixing networks, to small-world graphs or incredibly detailed social networks, the latter will be discussed in ***Section 2.5***. See ***Figure 2.4*** for examples of some of these network structures. These networks provide a backbone for stochastic Monte Carlo models that simulate how an infection could spread from one source node to the rest of the

population. Percolation theory also allows researchers to study the behavior of the disease in a given graph. These studies have shown that the degree, betweenness and farness of nodes alter disease dynamics (Christley, 2005).

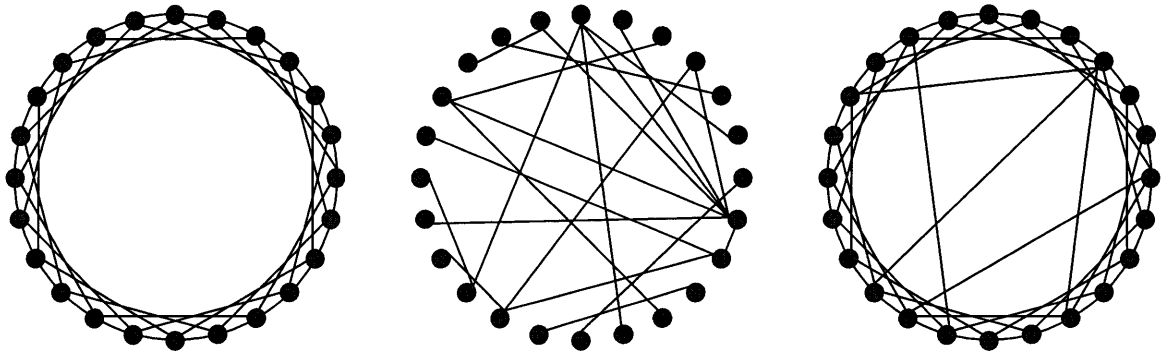


Figure 2.4
Examples of different types of networks that have been used to study infection diffusion.

2.6 Agent-based Simulation Models

As computational power has grown over the past years, microsimulation – individual based models – has increased in popularity. Microsimulation ranges from extremely detailed and reality mimicking to fairly abstracted models. The Glass et al. model is a somewhat stylized model of a society infected by the flu. They created a community where people belonged to different types of social interaction groups: household, work, school, etc. All persons within each household were linked to each other with mean link contact frequencies of 6/day. Every person also belonged to 1 multiage extended family group with a mean link contact frequency of 1/day. Furthermore, mean link contact frequencies for children in a school are 6/day. Teenager

classes, adult work, and gatherings of older adults result in 1 mean link contact per day. By incorporating these more realistic nuances the group found the importance of children mixing schools as a key driver of infection. Their dramatic finding was that children and teenagers who compose only 29% of the population are responsible for 59% of infection. This group did not rely on R_0, in fact they point out that the calculation of R_0 from small-community data such as theirs is ambiguous.

Ferguson N.M. et al. use the individual-based simulation approach to model pandemic flu transmission in the United Stated and Great Britain. This model, similarly to the Glass model, represents transmission in households, schools, workplaces and the wider community, but it also uses location specific data. Using information on transmission in each of the environments and the attack rates of past pandemics the authors calibrated their model. Afterwards they studied the speed and extent of viral spread given different interventions. Their work indicates that without significant interventions it would take about 2 months for the infection to reach its peak. As for antiviral treatment, they conclude that it could be useful for controlling transmission in both the household and the workplace, but would require many doses of the antiviral.

Two other agent-based models, similar to the one described above, were developed in an attempt to predict the scenario that could occur in Southeast Asia where the disease is expected to commence. Ferguson et al. conclude that as long as the virus is less transmissible than the 1918 flu, combining geographically and socially targeted prophylaxis and social distancing could stop a nascent pandemic (Ferguson et al., 2003). Similar in intention, the Longini et al. group has analogous findings (Longini et al., 2005). Both works highlight the importance of early diagnosis and immediate treatment,

the significance of proper timing is a shared finding that should sway policy makers' flu containment measures. Yet again, these models do not attempt to model reactive human behavior changes because it is too unpredictable.

A significant portion of current research has taken this even further making use of the advancement of computer capabilities. For example, a group at Los Alamos, with the use of their supercomputer initially created for nuclear weapons' study, models every individual within the US and studies flu spread (Germann et al., 2006). Using census data and transportation information they produced a complex program which simulated, at a very detailed level, the interaction of over 240 million ''people" over 180 days. The level of detail truly makes this model an individual-based model since each "person" is supposed to be unique. The modelers openly acknowledge that ''the spontaneous public response to news of an approaching pandemic will affect social behavior in unpredictable ways". To reflect that in their simulation they implement various social distancing behaviors that are expected given an initial pandemic curve. The problem is that human reaction should reflect the updated epidemic, but this dynamic concept is not incorporated. As a result the social intervention strategies are terminated too early to be fully effective. The researchers' conclusions are that vaccines and antiviral drugs will be the salvation to the pandemic disaster. They further assert that limiting contact between people through travel restrictions, quarantine and school closing will only buy time, perhaps enough time for vaccine production, but this strategy alone will not stop the epidemic.

Microsimulation models have provided a lot of insight, however given that there is no knowledge of the various disease parameters for the next pandemic it is unclear

whether this level of detail and computational effort is as useful as it can be for well known infections. More complex models require more inputs, and many agree that the complexity of a model should be influenced by the amount and reliability of data. Furthermore, performing sensitivity analysis and verification of these models is difficult given how detailed they are. This suggests that initially it may be appropriate to use simpler models until enough data is acquired to facilitate parameter estimation.

2.7 Modeling Pandemic Flu

Let us summarize some of the points made in this chapter that support the modeling approach that is presented in this thesis.

- The structure of interaction may be an important field of study, however given the lack of information that currently exists about the next strain of pandemic flu it may be premature to focus solely on these extremely complex models. These models may be very helpful tools for currently circulating diseases or in the future when we know more about the next pandemic flu virus. At this point, simple models for the flu pandemic are also very valuable.
- When using deterministic compartmental models or something similar, it is important to correctly define a community; it shouldn't be too large to negate the random mixing assumption, but not too small for stochastic processes to be influential.
- Modeling different types of heterogeneity is important, but is currently understudied. The lack of data is one of the complicating factors.

- Modeling behavior change as a result of the pandemic has been significantly understudied. The few existing models that include behavior changes do not dynamically connect people's reactions to the outcome of the pandemic.

The features of the model that are used to guide pre-pandemic planning and during pandemic policy must be selected with intention. It is important to know what questions we want to address before we get into the details of our models. Some of the questions that we hope to address in this thesis are:

- What characteristics that are present in our population affect the transmission of pandemic flu?
- Can we use any known population attributes to mitigate the spread of influenza?
- Should control measures be uniformly applied to all individuals or should we focus our efforts on specific member of the population?
- What kinds of control measures should we use and when should we use them?
- Can non-pharmaceutical interventions make a difference in the course of the pandemic?
- How can voluntary behavior changes alter the course of the pandemic?

With these questions in mind we have developed a multi-community transmission model. Our model accounts for population heterogeneities in many dimensions, but does not have the detail of network or simulation models. When modeling one large community we aggregate and present the expected outcomes. However, to model disease spread amongst loosely connected communities we use Monte Carlo simulation. We have

also proposed several approaches to modeling voluntary behavior changes that reflect the progression of the infection through the population.

The main modeling contributions of this thesis are in addressing two points: heterogeneity and behavior changes. ***Chapter 3*** will focus on modeling and evaluating the impact of different types of heterogeneities. ***Chapter 4*** will present several different approaches to dynamically incorporating human reaction and behavior change to the model. Understanding and evaluating the connectedness of the global interaction network would be helpful in determining how quickly the virus would spread across the world, but will not be deeply analyzed in this work. However, in ***Chapter 5*** we will present our approach to adding a spatial component to our model.

Lastly, it is important to mention that the concepts and approaches for modeling disease transmission have also been applied in studying the propagation of computer viruses, techniques of viral marketing and other areas. The concept of diffusion of infection over a network is especially important and has been heavily applied in other fields.

REFERENCES FOR CHAPTER 2

Allen E., 1999. "Stochastic differential equations and persistence time for two interacting populations." Dynamics of Continuous, Discrete and Impulsive Systems. 5: 271-281.

Allen L. J. S., 2003. "An Introduction to Stochastic Processes with Applications to Biology." Prentice Hall, Upper Sadle River, NJ).

Allen L.J.S., 2008. "An Introduction to Stochastic Epidemic Models." Mathematical Epidemiology. Springer. 81-130.

Becker N.G., 1974. "On parametric estimation for mortal branching processes." Biometrika. 61(2):393–399.

Becker N.G., 1989. "Analysis of infectious disease data." Monographs on Statistics and Applied Probability. Chapman and Hall.

Christley R.M., Pinchbeck G.L., Bowers R.G., et al., 2005. "Infection in social networks: Using network analysis to identify high-risk individuals." American Journal of Epidemiology. <http://aje.oxfordjournals.org/cgi/content/abstract/162/10/1024>.

Cooper B.S. Medley G.F. and Scott G.M., 1999. "Preliminary Analysis of the Transmission Dynamics of nosocomial infections: stochastic and management effects." Journal of Hospital Infection. 43:131-47.

Dietz K., 1975. "Transmission and Control in Arbovirus Diseases." Ludwig, D., Cooke, K.L. (Eds.), Epidemiology. Society for Industrial and Applied Mathematics, Philadelphia. 104–121. <http://igitur-archive.library.uu.nl/vet/2006-0321-200227/heesterbeek_02_daniel_bernoulli's.pdf>.

Dietz K., Heesterbeek J.A.P., 2002. "Daniel Bernoulli's epidemiological model revisited." Mathematical Biosciences. 180:1–21.

Eubank S., Guclu H., Kumar A.V.S., et al., 2004. "Modeling disease outbreaks in realistic urban social networks." Nature. 429:180–184. <http://cnls.lanl.gov/~toro/nat02541.pdf>.

Ferguson N.M., Cummings D.A.T., Fraser C., et al., 2006. "Strategies for mitigating an influenza pandemic." *Nature.*

Ferguson N.M., Mallett S., Jackson H., et al., 2003. « A population-dynamic model for evaluating the potential spread of drug-resistant influenza virus infections during community-based use of antivirals." Journal of Antimicrobial Chemotherapy. 51:977–990.

Glass R.J., Glass L.M. Beyeler W.E., Min H.J., 2006. "Targeted Social Distancing Design for Pandemic Influenza." Emerging Infectious Diseases. 12(11):1671-1681.

Heesterbeek J.A.P., 2002. "A brief history of R0 and a recipe for its calculation." Acta Biotheoretica, 50(3):189–204.

Hethcote H.W., 2000. "The mathematics of infectious diseases." Society for Industrial and Applied Mathematics. SIAM Review 42(4):599–653 <http://

www.siam.org/journals/sirev/42-4/37190.html>.

Hsieh Y-H., Chen C.W.S., 2003. "Letter to the Editor Re: Mathematical modeling of SARS: Cautious in all our movements." Journal of Epidemiology and Community Health. <http://mail.cmu.edu.tw/~hsieh/pdf/JECH-Mathematical%20modeling%20of%20SARS-03.pdf>

Hyman J.M., Li, J., 2000. "An intuitive formulation for the reproductive number for the spread of disease in heterogeneous populations." Mathematical Biosciences. 65–86 <http://math.lanl.gov/~mac/papers/bio/HL00.pdf>.

Kermack W.O., McKendrick A. G., 1927. "A Contribution to the Mathematical Theory of Epidemics." Proceeding of the Royal Society London. A(115):700-721,

Kermack W.O., McKendrick A.G., 1932. "A contribution to the mathematical theory of epidemics. The problem of Endemicity." Proceeding of the Royal Society of London. 138(834):55-83.

Kermack W.O., McKendrick A.G., 1933. "Contributions to the mathematical theory of epidemics. III. Further studies of the problem of endemicity." Proceeding of the Royal Society. 141A: 94-122.

Larson R.C., 2007. "Simple models of influenza progression within a heterogeneous population." Operations Research 55 (3), 399–412.

Larson R.C., 2008. "????" Working Paper.

Lipsitch M., Cohen T., Cooper B., et al. 2003. "Transmission Dynamics and Control of Severe Acute Respiratory Syndrome." Science 300(5627):1966-1970.

Longini Jr. I.M., Nizam A., Xu S., et al., 2005. "Containing pandemic influenza at the source." Science. 309:1083–1087.

MacDonald G., 1952. "The analysis of equilibrium in malaria." Tropical Disease Bulletin. 49:813–829.

Meyers L.A., Pourbohloul B., Newman M.E. et al. 2005. "Network theory and SARS: predicting outbreak diversity." Journal of Theoretical Biology. 232(1):71-81.

Nold A., 1980. "Heterogeneity in Disease Transmission Modeling." Mathematical Bioscience. 52:227-240.

van den Driessche P., Watmough J.,2008. "Further Notes on the Basic Reproduction Number." Mathematical Epidemiology. Springer. 159-178.

van den Driessche P., Watmough J., 2002. "Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission." Mathematical Biosciences. 180, p 29-48.

Wallinga J., Lipsitch M., 2007. "How generation intervals shape the relationship between growth rates and reproductive numbers." Proceeding of the Royal Society B. 274:599-604.

CHAPTER 3:
THE BASIC MODEL & IMPORTANCE OF HETEROGENEITY

In this chapter we will introduce the model that will be referred to and built upon throughout the remainder of this thesis. One of the main points that we will demonstrate in this chapter is the importance and impact of various types of heterogeneities that are present in our population. The model that we will use throughout this and future chapters was described by R.C. Larson in the paper titled "Simple Models of Influenza Progression Within a Heterogeneous Population" (Larson, 2007) and further elaborated on by K.R. Nigmatulina and R.C. Larson in a paper titled "Living with Influenza: Impacts of government imposed and voluntarily selected interventions" (Nigmatulina & Larson 2009).

3.1 Model Basics

The model is of one community that is divided into several groups based on their daily social activity levels (Larson, 2007). Since influenza spreads from one person to the

next through social interaction it is important to know how much people interact amongst each other. We assume that face-to-face contact is the major method of influenza transmission. We will presume that face-to-face social contacts within each community occur as a homogeneous Poisson process with rate parameters dependent on the level of social activity of the individual. Furthermore, the interaction between people in different groups is random and proportional to their activity levels (as described at the end of ***Section 2.2***). For the rest of the numerical calculations and simulations, unless otherwise noted, we will split the population of each community into three groups: high, medium and low activity persons. We will define:

λ_H - Average number of social contacts of a High activity person/day
λ_M - Average number of social contacts of a Medium activity person/day
λ_L - Average number of social contact of Low activity person/day
N_H - Initial total population of High activity persons
$N_H(t)$ - Population of High activity persons active on day t
$S_H(t)$ - Number of High activity susceptible persons on day t
$I_H(t)$ - Number of High activity infective & asymptomatic persons on day t
$R_H(t)$ - Number of High activity recovered & immune persons on day t
etc

Let us clarify that throughout this work we define one day as one generation of the infectious period of the virus. One day in the context of our model is closer to 2-3 actual 24 hour days.

We initiate the outbreak with one infectious individual who interacts normally with people on day 0. By the end of this day the initial seeder self-isolates, recovers or dies, and no longer infects any other individuals. Evidence of self-isolating behavior has been observed in practice (Zeng, 2002) and reflects peoples' departure from the

infectious category. On day one, the individuals recently infected from the index case interact normally and transmit the virus until they leave the infective group on day two. A recovered individual never reenters the susceptible population since people gain immunity if they survive the disease. This pattern continues for the rest of the outbreak.

From Larson's paper we know that for a random person on day t the probability that the next interaction will be with an infected individual is:

$$\beta(t) \equiv \frac{\lambda_H I_H(t) + \lambda_M I_M(t) + \lambda_L I_L(t)}{\lambda_H N_H(t) + \lambda_M N_M(t) + \lambda_L N_L(t)}$$

$\beta(t)$ is the fraction of all interactions of infected people over the total number of interactions in the entire active population on day t. The number of people circulating on day t is all those who have not gotten sick as well as those who have gotten sick, but also recovered and reentered the population. Assume that d is the duration of the sickness from the beginning of infection until the individual can reenter the population and that h is the fraction of people who survive the virus and can reenter the population. Then,

$$N_H(t+1) = N_H(t) - I_h(t) + hI_H(t-d)$$ [5]

Assuming homogeneous susceptibility let:

p = probability that a susceptible person becomes infected, given contact with an infectious individual.

Using the knowledge that the number of interactions is Poisson distributed, we know that the probability that a random susceptible High activity person gets infected on day t is:

$$p_H^S(t) = \sum_{i=1}^{\infty} \frac{(\lambda_H)^i}{i!} e^{-\lambda_H} \left[\sum_{j=0}^{i} \binom{i}{j} \beta(t)^j (1-\beta(t))^{i-j} \left(1 - [1-p]^j\right) \right]$$

which as shown in Larson can be simplified to (Larson, 2007):

[5] Note, for $t-d<0$, $I_j(t-d)=0$ for all j.

$$p_H^S(t) = 1 - e^{-\lambda_H \beta(t) p}$$

In ***Table 3.1***, we present the base case parameter values that we continue to use throughout this paper to present the results of our modeling analysis based on the above formulations. To see the impact of varying d – the duration of sickness, and h – the percent of people who recover and reenter the active population please refer to ***Appendix B***.

Parameter Name	Variable	Community A
Initial size of High activity group	N_H	100,000 ppl
Initial size of Medium activity group	N_M	100,000 ppl
Initial size of Low activity group	N_L	100,000 ppl
Rate of contact of High activity persons	λ_H	50 ppl/day
Rate of contact of Medium activity persons	λ_M	10 ppl/day
Rate of contact of Low activity persons	λ_L	2 ppl/day
Conditional probability of successful transmission	p	.10
Duration of sickness from day of infection	d	9 days
Percent of people who recover & reenter population	h	98%

Table 3.1

Parameters used as the base case for the research.

The average rates of contact, λ_H, λ_M, λ_L, in the different groups are based on the research done by Yang-chih Fu. Some of the best data on the frequency distribution of daily human contacts is a result of the survey conducted by Fu. He asked people in nine countries and 46 different settings: on average, about how many people do you have contact with in a typical day, including all those who you say hello, chat, talk or discuss matters with, whether you do it face-to-face, by telephone, by mail or on the Internet, and whether you personally know the person or not (Fu, 2005, 2007)? The results of the survey are shown in ***Table 3.2***.

Number of daily contacts	Number of respondents	Percent of respondents	Cumulative Percentage
0-4	410	13.67	13.67
5-9	426	14.20	27.87
10-19	685	22.83	50.70
20-49	792	26.40	77.10
50-99	349	11.63	88.73
100+	338	11.27	100
Total	3,000	100.00	

Table 3.2

The results of Yang-chih Fu's research on the distribution of the frequency of daily human contacts.

The results of this study are not perfectly suited for calibrating the activity level of people in our model because it includes human contacts that are not face-to-face such as the telephone and the Internet. While it is unclear exactly how many relevant contacts people have on a daily basis we can use the results of Fu's other study, which indicates that in Taiwan 83% of all daily contacts are face-to-face (Fu, 2005). While it is unclear if these values are best suited to describe the United States, this data is very instructive and confirms that there is a significant amount of heterogeneity in the population.

Returning to the model, the proposed approach assumes that the contact rates per day remain constant even as members of the susceptible population become sick and leave the circulating population. In the context of standard compartmental models this is known as standard incidence. Let us also consider the mass action incidence model where as the number of active people decreases, we anticipate a reduced amount of overall social activity. In this alternative approach λ, the average number of daily contacts per person, is proportional to the size of the remaining population in circulation. As shown by Larson in this case all λs become time dependent. For example, $\lambda_H(t)$ – daily rate of

social contact of a High activity person on day t. Let $N(t) = N_H(t) + N_M(t) + N_L(t)$, and then

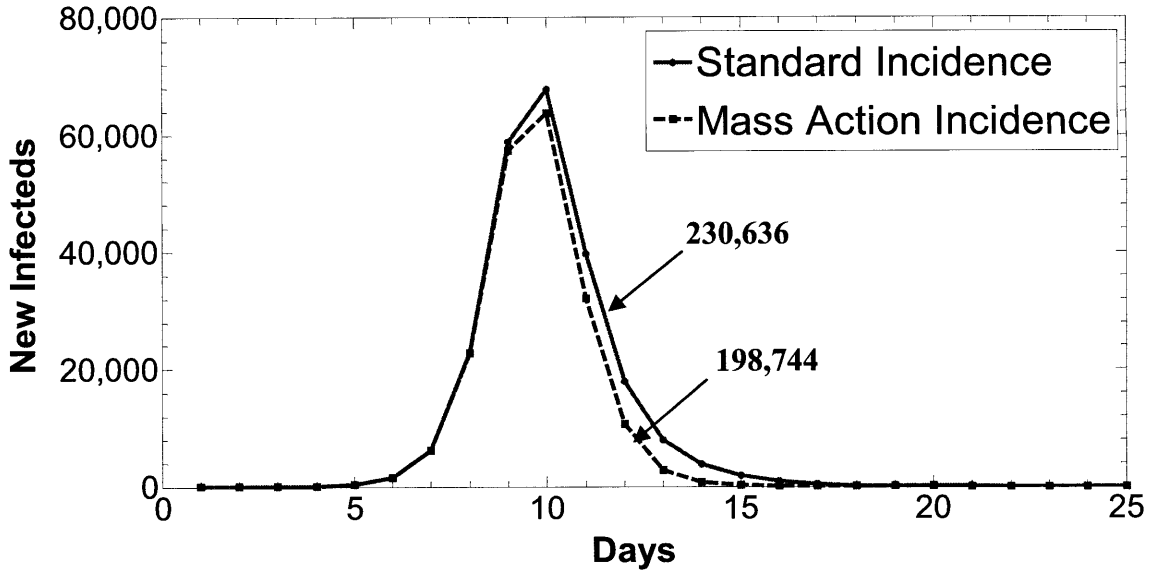
$$\lambda_H(t+1) = \frac{\lambda_H(t)N(t+1)}{N(t)} = \frac{\lambda_H(0)N(t+1)}{N(0)}.$$

Thus we have,

$$p_H^S(t) = 1 - e^{-\lambda_H(t)\beta(t)p}$$

In ***Graph 3.1*** we compare the two different approaches of standard and mass action incidence. From ***Graph 3.1*** we see that the main difference in the two approaches arises in the later half of the outbreak. As expected, the cumulative number of infected individuals, as well as the infection peak, is higher for the standard incidence model where the rate of contact stays constant regardless of the size of the circulating population. For the mass action incidence model, the biggest change in $\lambda(t)$ from $\lambda(0)$ is after the infection renders a large fraction of people sick which occurs around the peak of the outbreak.

For the remainder of this chapter we will use the mass action incidence model unless otherwise stated. It is unclear which model is better for flu modeling, but it seems that the rate of contact is somewhat dependent on the population size. If normally a salesman has an average of 50 contacts per day, when 25% of the population is out of circulation his or her number of daily contacts is likely to decrease by about 25% (Larson, 2007). ***Graph 3.1*** gives the impression that the difference between the standard incidence and mass action incidence models is not very significant, but for other cases where there is a more gradual growth of infection, the epidemic curves can differ significantly. Refer to ***Appendix C*** for a more detailed comparison of the two models and for this chapter's graphs' equivalents for the standard incidence model.



Graph 3.1

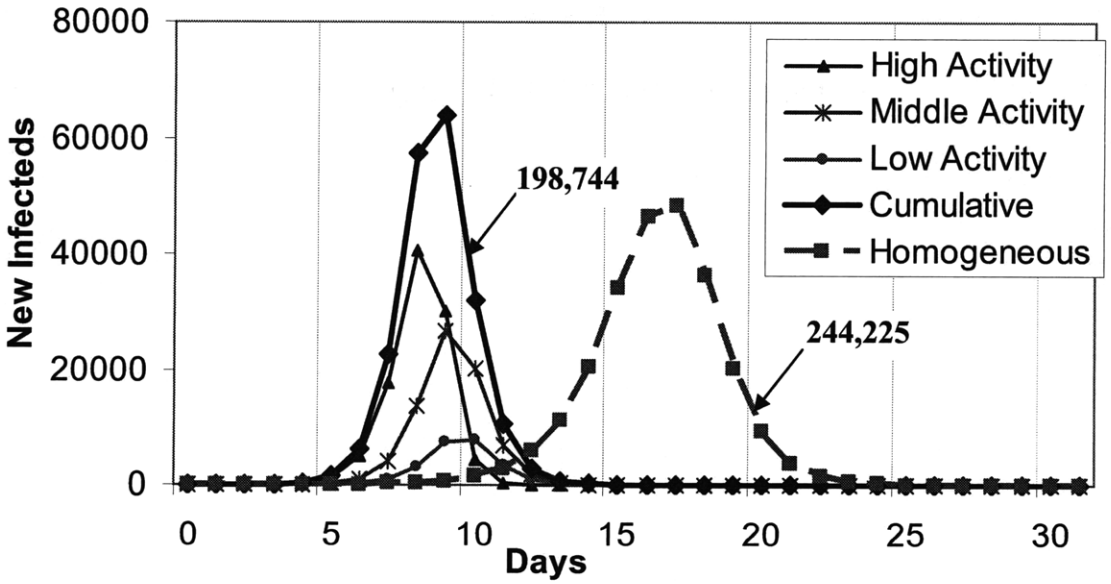
Comparison of the different approaches to modeling individuals' interaction and its impact of the epidemic curve. The standard incidence model, with a fixed rate of contact, results in higher infection rates in the second half of the outbreak.

Using the mass action incidence approach and the input values in ***Table 3.1*** we can model how the flu would transmit in the population. ***Graph 3.2***[6] is an illustration of average infection spread within a hypothetical community; notice that the virus spreads faster through a population with several activity levels when compared to a homogeneous community with an equivalent average activity level. Furthermore, it can be seen that the high activity individuals are the first to get infected. Practically all of the high activity people, 99.9% get infected while less than 25% of the low activity individuals get sick. Also, as the number of high activity people is depleted by day 9, the total number of people getting sick also starts to diminish around the same time. The high activity people are the drivers of the influenza transmission.[7]

[6] To see the equivalent graph for the standard incidence model refer to ***Appendix C, Graph C.2.***

[7] These qualitative results are supported by the findings of the real-time surveillance system at Boston's Children's Hospital. Children, compared to adults, have more contacts and increased vulnerability to be drivers of seasonal flu; particularly, preschoolers are seen as "hotbeds of infection" (Neergaard 2005).

As discussed in ***Section 2.2***, the imprecise, but widely accepted, definition of R_0 is the average number of people infected by the initial seeder in a fully susceptible population. For the heterogeneous and uniform communities, the expected number of daily contacts of a randomly selected person from either population will be the same, thus using one interpretation, without more knowledge of the activity groups' dynamics; R_0 is identical in both instances. Relying singly on R_0 would not have captured the possibility of these significantly different outcomes. R_0 is meaningless and often misleading without knowledge of the societal structure of the underlying population. ***Graph 3.2*** illustrates a fundamental flaw in the usage one averaging parameter such as R_0 (or $R(t)$) as the sole modeling factor.



Graph 3.2
Comparing spread of infection between heterogeneously and uniformly active communities of 300,000 individuals.

A central observation of this section is that the socially active individuals are not only themselves more predisposed to the flu, but are also the key spreaders of infection to the other groups.

Initially this model was represented in Microsoft Excel, but as more elements were added to the model, it was transferred to Matlab. Please see ***Appendix D*** for the code of the models presented in this chapter.

3.2 Modeling Diverse Susceptibility Levels

Diversity in human rate of contact is not the only heterogeneity that differentiates individuals; we can also include heterogeneity of people's susceptibility to infection. People who have heart conditions, asthma, chronic kidney disease or diabetes, or those who are taking medications such as steroids are thought to be more susceptible to colds and flu. Smokers are also more susceptible to upper respiratory tract infection (Cohen, 1993). Even stress can increase a person's susceptibility to the sickness (Drummond, 1997). Susceptibility to influenza also depends on the hygiene and other precautionary measures that individuals employ. As described in ***Section 1.2***, hand washing, room ventilation and other behavioral diversity that is commonly observed in our population, can all impact the likelihood of flu transmission.

In order to model that people have varying levels of susceptibility, we can split the population into groups based on their vulnerability to the disease; in this case we define different probabilities of transmission given contact with an infected individual. We can now define a single rate of contact for the total population of $\lambda(0)$=20.66 people/day[8]. We will divide the population into 3 groups, but this time it will be based on their conditional probability of infection given contact. Let us define,

[8] λ=20.66 is the average contact rate of the whole population in the basic model presented in ***Section 3.1***.

p_H - Conditional probability of infection of the Highly susceptible individuals.
p_M - Conditional probability of infection of the Medium susceptible individuals.
p_L - Conditional probability of infection of the Low susceptible individuals.
N_H - Initial total population of Highly susceptible persons.
$N_H(t)$ - Population of Highly susceptible persons active on day *t*.
$S_H(t)$ - Number of Highly susceptible, persons who have not yet been infected on day *t*.
$I_H(t)$ - Number of Highly susceptible infective & asymptomatic persons on day *t*.
$R_H(t)$ - Number of Highly susceptible recovered & immune persons on day *t*.
etc.

As a result of having one rate of contact for the whole population, calculating β is very simple; it is the ratio of the number if infected people over the total number of people circulating in the population. The probability that a random Highly susceptible person gets infected on day t is:

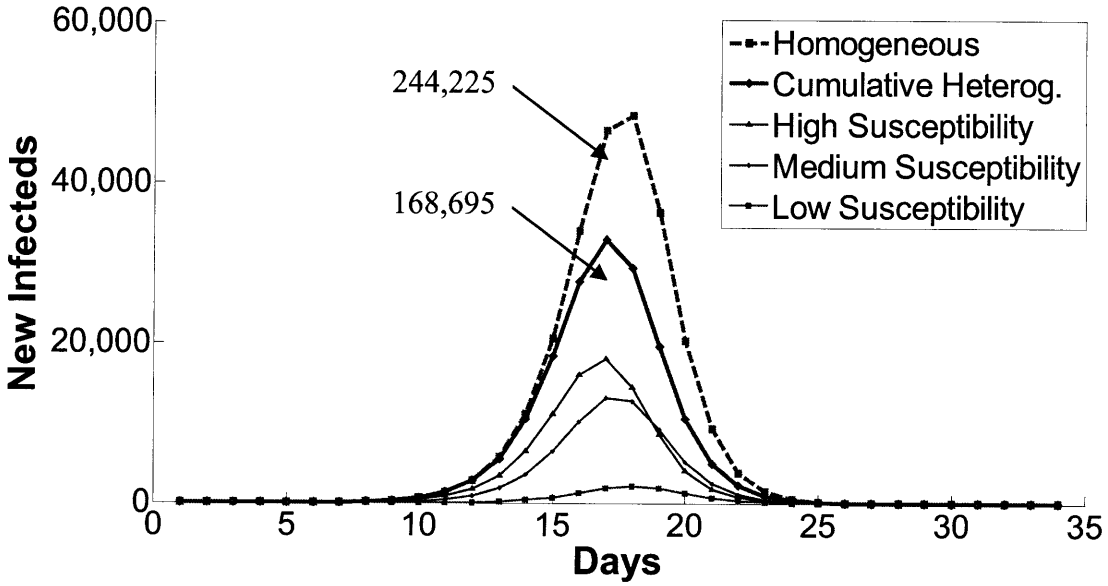
$$p_H^S(t) = 1 - e^{-\lambda(t)\beta(t)p_H}$$

Graph 3.3[9] shows how a population with varying levels of susceptibility differs from a fully homogeneous population. For the sake of fair comparison we ensure that the population's average susceptibility - the probability of infection given contact - is identical in the uniform and diverse populations. ***Table 3.3*** has the variables used for ***Graph 3.3***.

We find that the diverse population in this case has fewer total infections. More importantly almost all the highly susceptible people get infected, at the end of the outbreak; approximately 90% of the highly susceptible people get sick. The individuals with a strong immunity, in the low susceptibility group have a little more than a 10% chance of getting infected. The minimally susceptible individuals have a small enough conditional probability of infection, that even if they interact with many infectious

[9] To see the equivalent graph for the standard incidence model refer to *Appendix C, Graph C.3.*

individuals, they rarely get sick. It is important to realize that unlike with a population of varying activity levels, the highly susceptible people do not drive the spread of infection. The reason for the significant impact of the highly active group is that the highly active people both get sick first and spread the virus to many other people. In this case, the highly susceptible people get sick first, but they are not better at spreading infection then other individuals.



Graph 3.3

Comparing the spread of infection between heterogeneously and uniformly susceptible populations of 300,000 individuals. More people get infected in the homogeneous population. The low susceptibility individuals in the heterogeneous population rarely become ill, and as a result that group stays almost completely healthy.

	Total population		Susceptibility Level	
Highly Susceptibility	N_H	100,000	p_H	.19
Medium Susceptibility	N_M	100,000	p_M	.1
Low Susceptibility	N_L	100,000	p_L	.01
Homogeneous	N	300,000	p	.1

Table 3.3

Values used to simulate immunologically diverse and homogeneous populations for ***Graph 3.3.***

3.3 Modeling Varying Levels of Infectivity

In addition to having individuals who are more susceptible to viruses, there are individuals who are more efficient at transmitting the virus to other people. Observations of some diseases have even led to the proposal of the 20/80 rule, which suggests that 20% of the most infectious individuals are responsible for 80% of the transmission (Galvani, 2005). For instance, during the SARS outbreak in Hong Kong, evidence points to the existence of superspreaders who contributed significantly to the overall spread of the virus (Shen, 2004). Superspreaders are individuals who spread the virus to eight or more people, which is unusually high for a virus such as SARS. While some of the superspreader instances can be explained by the high activity level of the individuals, some cases are better explained by the theory that certain people shed more of the virus than others (Bassetti, 2005). To see the impact of superspreaders in Singapore, refer to ***Figure 3.1***. It is very clear that while most of the population didn't contribute at all to transmission, a few people got dozens of others infected.

For other types of diseases, like *Staphylococcus aureus*, superspreading events are caused by co-infection with other respiratory viruses. For *S. aureus,* it has been demonstrated that newborns whose noses are colonized with this bacterium disperse considerable amounts of airborne *S. aureus* and become highly contagious after infection with a respiratory virus e.g. adenovirus (Eichenwald, 1960). Since the babies are literally surrounded by clouds of bacteria, they are called "cloud babies". They act like superspreaders and cause explosive *S. aureus* outbreaks in nurseries. A similar phenomenon has more recently been identified in adults (Sherertz,1996).

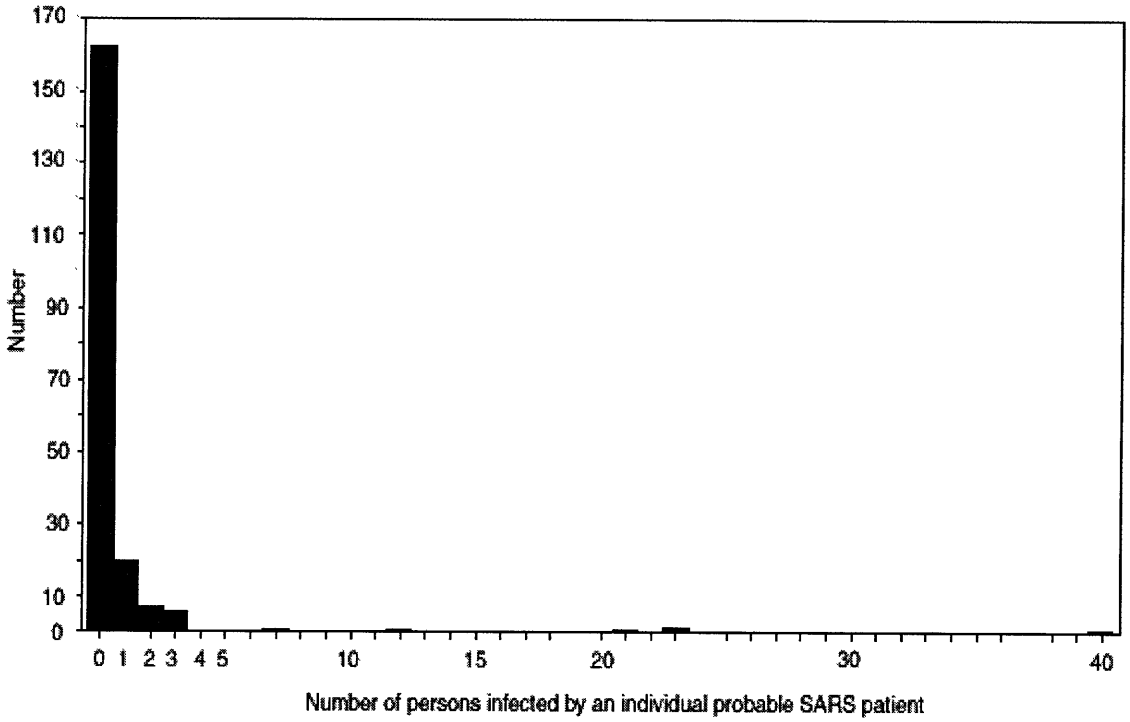


Figure 3.1

Number of direct secondary infections from probable cases of SARS in Singapore, 2003. It is clear that a few individuals contributed much more to transmission than most others. Over two thirds of the sick didn't spread the virus at all. (MMWR, 2003)

As for the flu, especially for the next pandemic strain, it is unclear if there will be varying levels of infectivity, but refer to ***Figure 3.2*** to see the heterogeneity in infectivity for other diseases. There is evidence that the quantity of virus shed is significantly correlated with severity of illness and fever score (Hall, 1979; Carrat, 2008). This suggests that the degree of clinical illness may be directly related to the transmissibility of the disease. It is reasonable to suppose that the more an infected individual coughs, sneezes, and wipes his or her runny nose, the more of the virus he or she will be transmitting. In addition, asymptomatic carriers of the flu also have decreased viral shedding (Carrat, 2008). Lastly, as a result of different behaviors exhibited by individuals, if infected they are likely to exhibit varying levels of infectivity. An

individual who sneezes into his or her hands, often touches his or her mouth, eyes or nose and rarely washes his or her hands is likely to be efficient at spreading influenza to others.

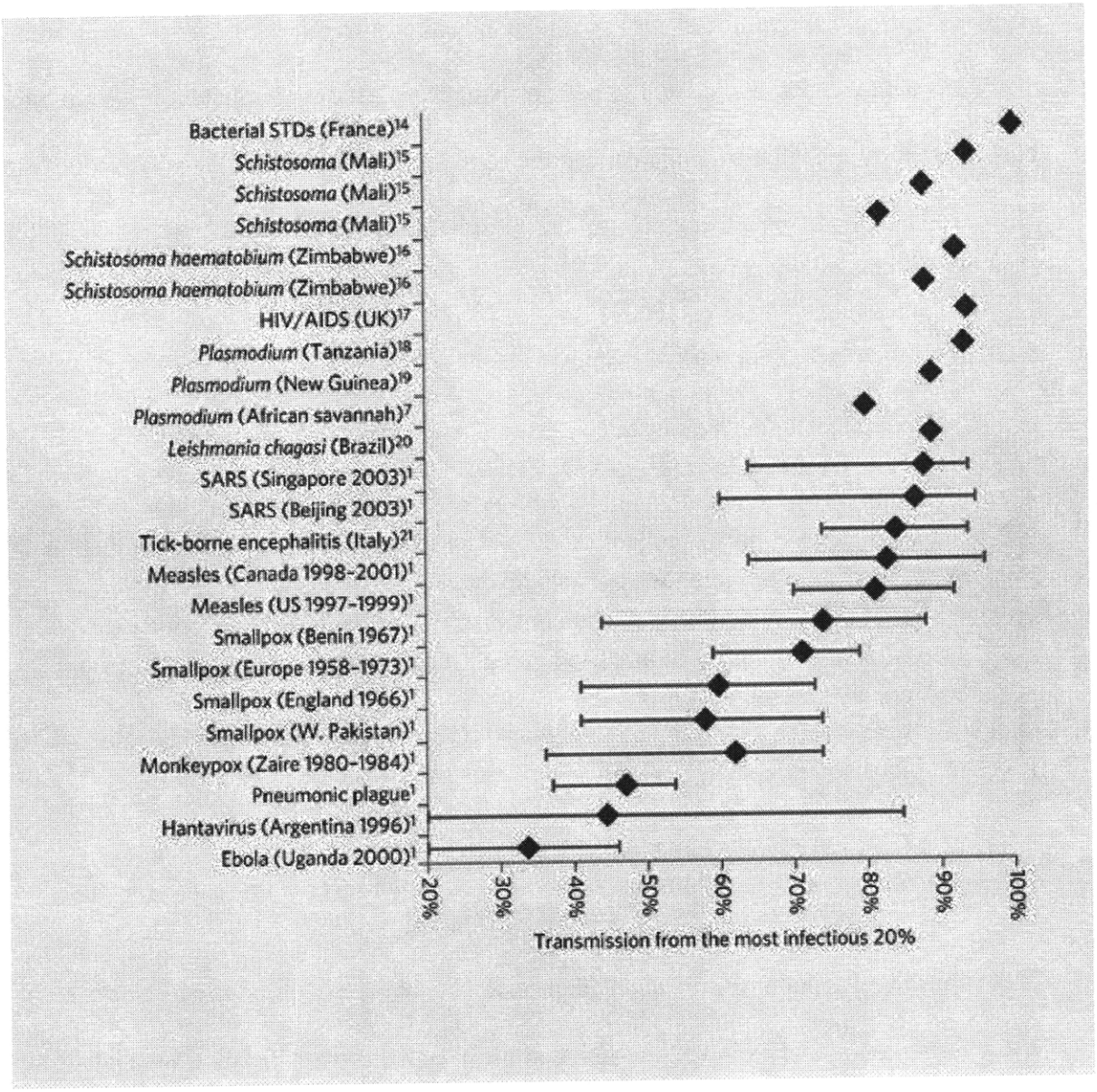


Figure 3.2

Heterogeneity in infectiousness for a range of different diseases. The measure quantifies the proportion of the transmission that results from the most infectious 20% of the population. Confidence intervals are included where available. Diagram from article by Galvani and May (Galvani, 2005)

In order to model varying levels of infectivity we are going to divide the population into 2 groups and proceed as before. We compose the first group of individuals who spread the virus very efficiently and the second of those who transmit the virus at "normal" levels. This implies that if infected, a member of group one is more likely to infect a random susceptible person than an infected individual from group two. This does not imply that individuals in group one are more susceptible to the virus. The activity level of all the individuals in the population, regardless of their potential for infectivity, is the same. Let, the contact rate for all individuals be $\lambda(0)$=20.66 people/day. Also, let us define the following variables:

p_1 - Conditional probability of infection given contact with a highly infectious individual – member of group 1.
$N_1(t)$ - Number of active people on day t who if infected are highly infectious.
$S_1(t)$ - Number of susceptible persons on day t who if infected will be highly infectious.
$I_1(t)$ - Number of highly infectious persons on day t.
$R_1(t)$ - Number of recovered/immune persons on day t who were highly infectious.
p_2 - Conditional probability of infection given contact with a minimally infectious individual – member of group 2.
$N_2(t)$ - Number of active people on day t who if infected are minimally infectious.
$S_2(t)$ - Number of susceptible persons on day t who if infected will be minimally infectious.
$I_2(t)$ - Number of minimally infectious persons on day t.
$R_2(t)$ - Number of recovered/immune persons on day t who were minimally infectious.

Let us consider a random individual. The probability that a randomly selected interaction of that individual on day t is with an infected individual from the highly infectious group is:

$$\beta_1(t) = \frac{\lambda I_1(t)}{\lambda(N_1(t) + N_2(t))} = \frac{I_1(t)}{N_1(t) + N_2(t)}$$

and the probability that a randomly selected interaction on day t is with an infected individual from the normally infectious group is:

$$\beta_2(t) = \frac{\lambda I_2(t)}{\lambda(N_1(t) + N_2(t))} = \frac{I_2(t)}{N_1(t) + N_2(t)}$$

We can now derive the probability that a random person, either a member of group one or group two, gets infected on day t. Let this probability of infection on day t be $p_1^S(t) = p_2^S(t)$. The probability of getting infected is the same for members of both groups, the individuals in the two groups only behave differently once infected. Now we will utilize the fact that the selected random individual has a Poisson number of interactions with rate λ. Assume that this number of interactions is i. Then the number of contacts with infected people of high infectiousness is j and the number of contacts with infecteds of normal infectiousness is k, and this is Multinomially distributed. Then the conditional probability that the susceptible person gets infected is one minus the probability that none of the interactions lead to infection. In equation form:

$$p_1^S(t) = \sum_{i=1}^{\infty} \frac{\lambda^i}{i!} e^{-\lambda} \left[\sum_{j=0}^{i} \sum_{k=0}^{i-j} \frac{i!}{j!\,k!\,(i-j-k)!} \beta_1(t)^j \beta_2(t)^k (1-\beta_1(t)-\beta_2(t))^{i-j-k} \left(1 - \left\{(1-p_1)^j (1-p_2)^k\right\}\right) \right]$$

We will now simplify this formula,

$$p_1^S(t) = \sum_{i=1}^{\infty} \frac{\lambda^i}{i!} e^{-\lambda} \left[\sum_{j=0}^{i} \sum_{k=0}^{i-j} \frac{i!}{j!\,k!\,(i-j-k)!} \beta_1(t)^j \beta_2(t)^k (1-\beta_1(t)-\beta_2(t))^{i-j-k} \left(1 - \left\{(1-p_1)^j (1-p_2)^k\right\}\right) \right]$$

$$= 1 - \sum_{i=1}^{\infty} \frac{\lambda^i}{i!} e^{-\lambda} \left[\sum_{j=0}^{i} \sum_{k=0}^{i-j} \frac{i!}{j!\,k!\,(i-j-k)!} \beta_1(t)^j \beta_2(t)^k (1-\beta_1(t)-\beta_2(t))^{i-j-k} \left(\left\{(1-p_1)^j (1-p_2)^k\right\}\right) \right] =$$

Let us focus on the inner double sum first, and let us define $m=i-j$.

$$\sum_{j=0}^{i}\sum_{k=0}^{i-j}\frac{i!}{j!\,k!\,(i-j-k)!}\beta_1(t)^j\,\beta_2(t)^k\,(1-\beta_1(t)-\beta_2(t))^{i-j-k}\left(\left\{(1-p_1)^j\,(1-p_2)^k\right\}\right)=$$

$$=\sum_{j=0}^{i}\frac{i!}{j!\,(i-j)!}\beta_1(t)^j\,(1-p_1)^j\sum_{k=0}^{m}\frac{m!}{k!\,(m-k)!}\beta_2(t)^k\,(1-\beta_1(t)-\beta_2(t))^{m-k}\,(1-p_2)^k=$$

$$=\sum_{j=0}^{i}\frac{i!}{j!\,(i-j)!}\beta_1(t)^j\,(1-p_1)^j\sum_{k=0}^{m}\frac{m!}{k!\,(m-k)!}(\beta_1(t)+\beta_2(t))^k\,(1-\beta_1(t)-\beta_2(t))^{m-k}\left(\frac{\beta_2(t)(1-p_2)}{\beta_1(t)+\beta_2(t)}\right)^k=$$

$$=\sum_{j=0}^{i}\frac{i!}{j!\,(i-j)!}\beta_1(t)^j\,(1-p_1)^j\,p_Z^T(z\,|\,m,\beta_1(t)+\beta_2(t),Binomial)_{z=\frac{\beta_2(t)(1-p_2)}{\beta_1(t)+\beta_2(t)}}=$$

$$=\sum_{j=0}^{i}\frac{i!}{j!\,(i-j)!}\beta_1(t)^j\,(1-p_1)^j\left[(\beta_1(t)+\beta_2(t))\left(\frac{\beta_2(t)(1-p_2)}{\beta_1(t)+\beta_2(t)}\right)+(1-(\beta_1(t)+\beta_2(t)))\right]^m=$$

$$=\sum_{j=0}^{i}\frac{i!}{j!\,(i-j)!}\beta_1(t)^j\,(1-p_1)^j\,(1-\beta_1(t)-\beta_2(t)p_2)^{i-j}=$$

$$=\sum_{j=0}^{i}\frac{i!}{j!\,(i-j)!}(\beta_1(t)+\beta_2(t)p_2)^j\,(1-\beta_1(t)-\beta_2(t)p_2)^{i-j}\left(\frac{\beta_1(t)(1-p_1)}{\beta_1(t)+\beta_2(t)p_2}\right)^j=$$

$$=p_Z^T(z\,|\,i,\beta_1(t)+\beta_2(t)p_2,Binomial)_{z=\frac{\beta_1(t)(1-p_1)}{\beta_1(t)+\beta_2(t)p_2}}$$

$$=\left[(\beta_1(t)+\beta_2(t)p_2)\left(\frac{\beta_1(t)(1-p_1)}{\beta_1(t)+\beta_2(t)p_2}\right)+(1-(\beta_1(t)+\beta_2(t)p_2))\right]^i=(1-\beta_1(t)+\beta_2(t)p_2)$$

Thus,

$$p_1^S(t)=1-\sum_{i=1}^{\infty}\frac{\lambda^i}{i!}e^{-\lambda}(1-\beta_1(t)p_1-\beta_2(t)p_2)^i=$$

$$=1-p_Z^T(z\,|\,\lambda,Poisson)_{z=1-\beta_1(t)p_1-\beta_2(t)p_2}=$$

$$=1-e^{\lambda((1-\beta_1(t)p_1-\beta_2(t)p_2)-1)}=$$

$$=1-e^{-\lambda\beta_1(t)p_1-\lambda\beta_2(t)p_2}$$

In the above notation, $p_Z^T(z\,|\,n,p,Binomial)$ is the "z-transform", or the probability generating function of the Binomial distribution with n trials and probability p of a "1". Generally, for P(N=n)≡pn, its discrete transform is defined as:

$$p_N^T\equiv\sum_{n=0}^{\infty}p_n z^n$$

and thus

$$p_Z^T(z \mid n, p, Binomial) = (pz + (1-p))^n \quad \text{and} \quad p_Z^T(z \mid \lambda, Poisson) = e^{\lambda(z-1)}.$$

For a population with multiple infectivity levels, the probability that any susceptible individual will get infected on day t using the mass action model is:

$$p^S(t) = 1 - e^{-\lambda(t)\left[\sum_i \beta_i p_i\right]}$$

where $\lambda(t)$ is defined the same as in ***Section 3.1***.

Consider a population with an average activity level of $\lambda(0)$=20.66 and three different infectiousness levels as shown in ***Table 3.4***.

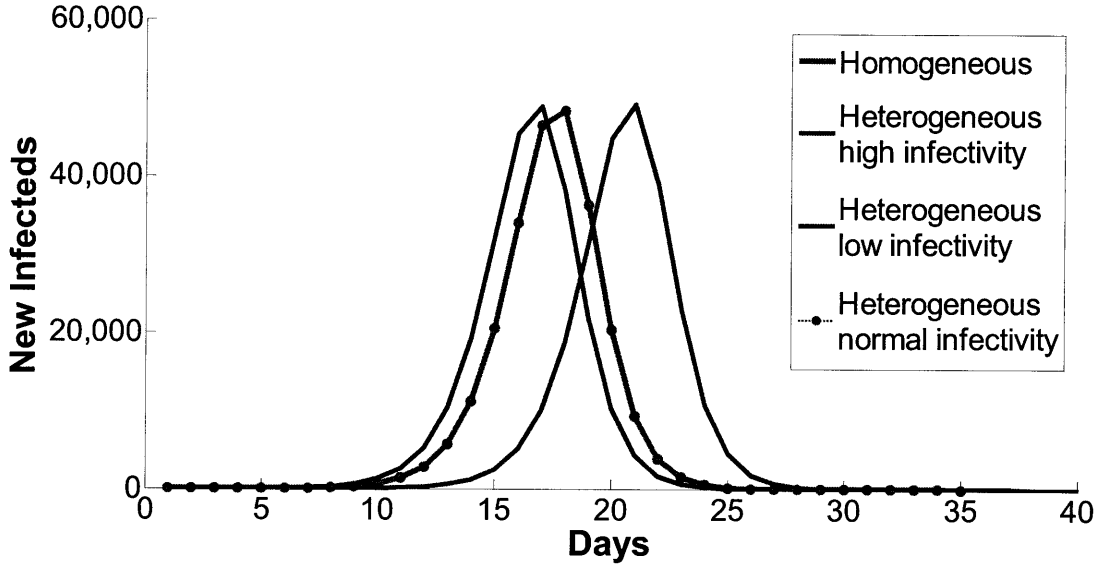
	Total population		Susceptibility Level	
Highly Infectious	N_1	100,000	p_1	.19
Moderately Infectious	N_2	100,000	p_2	.1
Minimally Infectious	N_3	100,000	p_3	.01

Table 3.4

Values used to simulate a population with varied infectivity levels for ***Graph 3.4***.

In this population of varying levels of infectiousness, it is clear that the infectiousness of the initial individual is going to impact how quickly the virus takes off. In ***Graph 3.4***[10] we show the epidemic curves dependant on whether patient zero is highly infectious, moderately infectious or minimally infectious, and compare these curves to what would occur in a fully homogeneous population.

[10] To see the equivalent graph for the standard incidence model refer to ***Appendix C, Graph C.4***.



Graph 3.4

Importance of the initial infected person in the timing of the epidemic curve in a population with varied infectivity levels. When patient zero is highly infective the initial transmission is fastest.

As expected, if the first infective is highly efficient at transmitting the virus, the initial spread is fast. When the initial patient is only moderately infective the virus takes a little longer time to take off. When the initial patient is of moderate infectivity, which is also the infectivity of the homogeneous population, the timing of the curves coincides. The results shown on ***Graph 3.4*** are expected values, but they do not indicate the amount of stochasticity that will be very important in this population with diverse infectivity groups. If the first person to get sick is minimally infective, it is highly likely that the virus will never transmit to any other individual. Before a sizeable portion of the population is infected the presence of minimally infectious people increases the probability that the virus will never take off.[11]

[11] It is likely that the virus may take of at another point in time. In a pandemic the flu will be reintroduced to fully susceptible communities. For more on this see ***Chapter 5***.

Notice, the cumulative number of people infected stays the same for all curves. The reason is because every individual regardless of their infectiousness has the same susceptibility conditional on which infective they encounter. That implies that the number of new infections in each group is the same. On any day t, the highly infectious individuals spread the disease and "make up" for the limited amount of transmission by the minimally infectious.

The number of infecteds on day t, is evenly split between the three different types of infectivity levels which implies that $\beta_1(t) = \beta_2(t) = \beta_3(t)$. Let

$$\beta_1(t) + \beta_2(t) + \beta_3(t) = \beta(t)$$

where $\beta(t)$ is the probability that on day t, a random contact of a selected person is with an infected individual. Then,

$$p_1^S(t) = p_2^S(t) = 1 - e^{-\lambda(t)(\beta_1(t)p_1 + \beta_2(t)p_2 + \beta_3(t)p_3)} = 1 - e^{-\lambda(t)\beta(t)\left(\frac{p_1+p_2+p_3}{3}\right)}$$

So the heterogeneous group infects the same number as the homogeneous group of the same size and activity level. However, if we had a second type of heterogeneity in the model, such as varied susceptibility levels, the curves would no longer coincide. In ***Section 3.5*** we will provide examples of combinations of these heterogeneities to show how together their effects amplify the changes on the epidemic curve.

3.4 Another Type of Heterogeneity: Inconsistent Behavior

Another aspect of human behavior which has never been considered in literature, but impacts the transmission of influenza, is that people change their behavior day-to-day. For example, in a survey study conducted by Yang-Chih Fu and Yi-Jr Lin, the

results indicated that people's average number of contacts varied based on the weather; on rainy days individuals have fewer face-to-face contacts then during any other type of weather (Fu, 2005). Furthermore, individuals who have significant control over the number of daily contacts, such stay-at-home women and students, have a significantly different number of contacts based on their mood. Those who are in a "very good mood" when they wake up in the morning, have more daily contacts on that day (Fu, 2005). These research findings further support the theory that people's behavior is inconsistent from day to day. Lastly, this work points out that people who work during the normal work week have significantly fewer contacts on Saturdays and Sundays (Fu, 2005).

There is another research approach that supports the above conclusions and does not involve surveys. The work done at the Reality Mining lab at the Massachusetts Institute of Technology, involves the collection of machine-sensed environmental data pertaining to human social behavior. Using 100 Bluetooth-enabled mobile telephones the group has measured the interaction and activity levels of the phone owners over a period of 9 months (Eagle, 2005). They were able to identify that some individuals have much more randomness – entropy – in their behavior and activity level, while others rarely changed their behavior (Eagle, 2005). Their results also indicate that people have significantly different activity levels on weekends. Most of the subjects who had the phone were students, and it was noticed that they increased their activity levels during finals (Eagle, 2005). They even noticed that people significantly changed their activity levels right before a conference that most of the subjects attended (Eagle, 2005). All of this supports the notion that people do not maintain consistent levels of activity.

We propose that a fraction of people in our model will change their activity from day to day. For example, someone who is highly active seeing lots of colleagues at work on Friday can become an individual of moderate activity only seeing his or her family on Saturday. Similarly, an individual working from home could be moderately active on Friday and could have many contacts on Saturday when he or she runs errands and spends time with friends and family. In the model that we are going to present in this section, we have people change their behavior from one generation of the flu to the next generation of the flu. So instead of using 24 hour days to alter individuals' behavior we use flu generation days that are about 2-3 24 hour days. To clarify, it would be possible to create a model where people alter their behavior every 24 hours, but this would require splitting up one generation of the flu into 2 or 3 days and then appropriately keeping track of the infecteds and susceptibles. Instead of pursuing the more complex approach we believe that we gain significant insight from our simplified generation of flu based model. As a result, in the remainder of this section, whenever we refer to a day, we mean a generation of the flu.

In our model, while the number of people in each activity group stays constant, the individuals who compose each activity group can change. We define a transition matrix Q, where q_{ij} indicates the fraction of people who will go from activity level i to j at the end of a day. Note, that Q is a stochastic matrix and must satisfy certain properties to ensure that all the activity groups maintain their size. If the initial size of each of the activity groups is the same, then Q has to be a doubly stochastic matrix.

Let us continue and use some of the notation defined in ***Section 3.1*** with the addition of the following variables:

$S_H'(t)$ –Number of highly active susceptible people at the end of day t after all the infections that occurred through the day, but before people have changed their activity level.

$I_H'(t)$ – Number of highly active people who got infected during day t , but have not yet changed their activity level.

$R_H'(t)$ –Number of highly active immune people at the end of day t before they have changed their activity level.

Here is how we define the transition between the different activity levels and keep track of the number of infective individuals:

$$I_H'(t) = p_H^S(t) S_H(t)$$
$$S_H'(t) = S_H(t) - I_H'(t)$$
$$I_H(t+1) = q_{HH} I_H'(t) + q_{HM} I_M'(t) + q_{HL} I_L'(t)$$
$$S_H(t+1) = q_{HH} S_H'(t) + q_{HM} S_M'(t) + q_{HL} S_L'(t)$$

We define $p_H^S(t) = 1 - e^{-\lambda_H(t)\beta(t)p}$ as before.

Transmission is slowed down by the presence of such inconsistencies in individual behavior. Consider a population with three activity groups as described in ***Section 3.1***. In one extreme case, opposite of consistent behavior, all individuals completely change their activity levels at the end of the day. For example, consider:

$$Q = \begin{bmatrix} 0 & 1 & 0 \\ 0 & 0 & 1 \\ 1 & 0 & 0 \end{bmatrix}$$

As we showed in ***Section 3.1***, most of the people who get infected on any given day t would be highly active. Thus, at the end of day t most of the infected people would change their behavior to the moderate activity level. On the other hand, there are significantly fewer people who get infected while in the low activity state, thus we would have very few infected highly active individuals on day $t+1$. The fact that most of the infectious individuals would be in the moderate and low activity groups is sufficient to

completely stop the transmission of the virus. In this extreme case, there would not be a pandemic.

Another extreme, but illustrative case is when each member of the population reselects his or her activity level for the next day independent of his or her current activity level. In this case $q_{ij}=1/3$ for all i,j. This case where each individual chooses the activity level randomly is represented as the "Random Activity" case in ***Graph 3.5***.

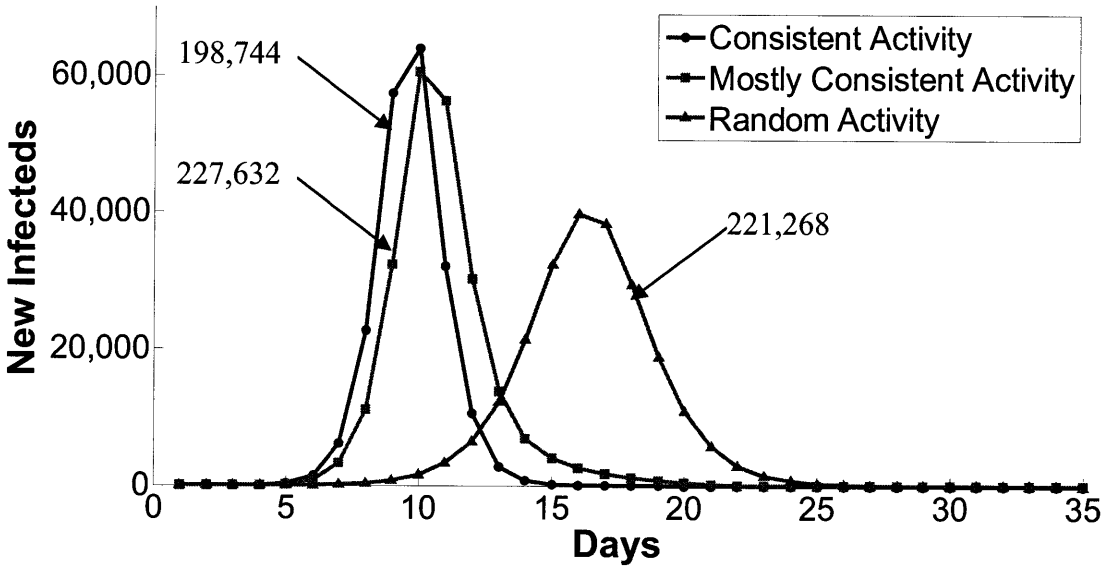
Neither of the above extreme cases is likely to be representative of our actual population; however, a population where a small fraction of the people changes their activity level from day to day is more likely. Consider population with mostly consistent behavior, where

$$Q=\begin{bmatrix} 17/20 & 1/10 & 1/20 \\ 3/40 & 17/20 & 3/40 \\ 1/20 & 1/10 & 17/20 \end{bmatrix}.$$

The "mostly consistent activity" and "random activity" cases are compared to the base case, where Q is the identity matrix, in ***Graph 3.5***[12]. As a result of individuals changing their activity levels from day to day, the virus spreads slower through the population. The timing of the virus, however, is not indicative of the cumulative burden of the infection.

It is very difficult to find input data for this type of heterogeneity. At the same time there is sufficient evidence that peoples' day to day activity levels change. We have proposed a way of including this and have shown that this often ignored aspect of human behavior can have a significant impact on the transmission of pandemic flu.

[12] To see the equivalent graph for the standard incidence model refer to ***Appendix C, Graph C.5***.



Graph 3.5

The impact of inconsistent behavior in the population on the epidemic curve. If people can change their activity levels the speed of transmission is decreased.

3.5 Combinations of all Heterogeneities

As hinted at before, the different heterogeneities analyzed separately in the above four sections, are all present simultaneously in our population. For instance, children are often considered to be highly active individuals, who are highly susceptible to flu and are known to have high infectivity levels and longer durations of infectiousness. On the other hand, we have the elderly, who are often considered to have fewer contacts, but are still thought to be highly susceptible, but maybe not as infectious. In this section we will show several cases of how these heterogeneities interact amongst each other.

It has been observed that infectivity and susceptibility are often coupled, so let us consider a population with three groups that have the same activity level of $\lambda(0)$=20.66 people/day, but have varied susceptibility and infectivity levels. Let group

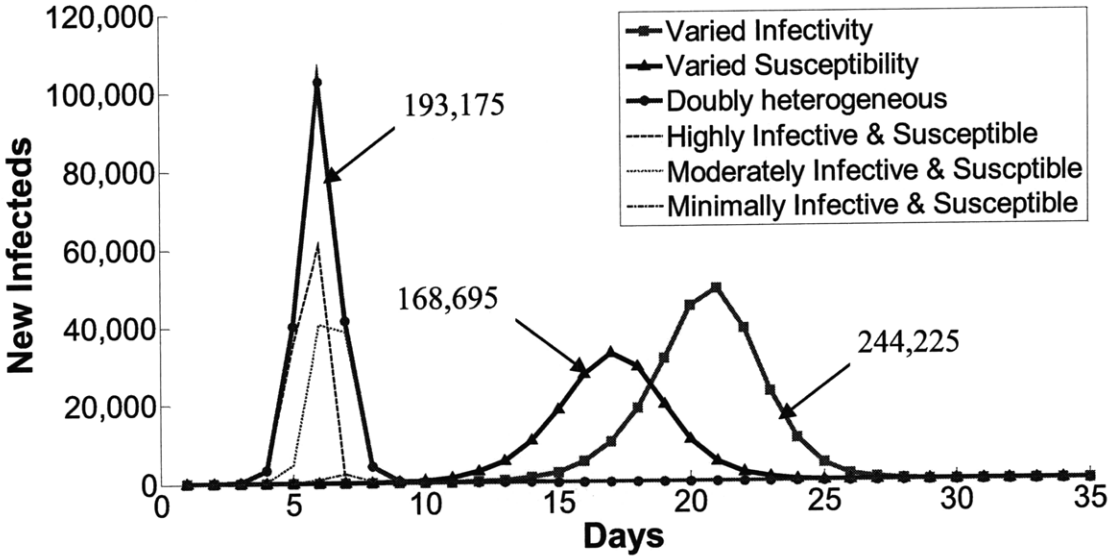
one be the most susceptible and infective, so that they are 1.9 times as susceptible and 1.9 times as infectious as the average individual. Let group two be average susceptibility and infectivity. Group three will then be the least susceptible and least infectious; 10 times less susceptible and 10 times less infectious than the average. We define the conditional probability of infection of an individual in group i given contact with someone in group j as p_{ij}. Now consider a population with the following matrix of conditional probabilities, P:

$$P = \begin{bmatrix} .361 & .19 & .019 \\ .19 & .1 & .01 \\ .019 & .01 & .001 \end{bmatrix}$$

which averages out to a conditional probability of infection of $p = 0.1$. The average susceptibility of the groups can be averaged out to give the case presented in ***Section 3.2***. The average infectivity of the groups can be averaged out to give the case presented in ***Section 3.3***. In ***Graph 3.6***[13] we see how the doubly heterogeneous population compares to the populations with one dimensional heterogeneity. It is clear that the simultaneous presence of the two types of heterogeneities has a very significant impact on transmission. The group of individuals who are both highly susceptible and highly infective speeds up and drives the transmission of the virus. When infectiousness and susceptibility are coupled the group acts a lot like the highly active people in a population with varied activity levels. Members of this first group are not only the first to get infected, but are also the ones who get many others infected when they are sick. In this case, all of the highly susceptible and infective individuals get sick, a little under 90% of

[13] To see the equivalent graph for the standard incidence model refer to ***Appendix C, Graph C.6***.

the moderately susceptible and infective individuals get sick and less than 5% of the minimally susceptible and infectious people get sick.



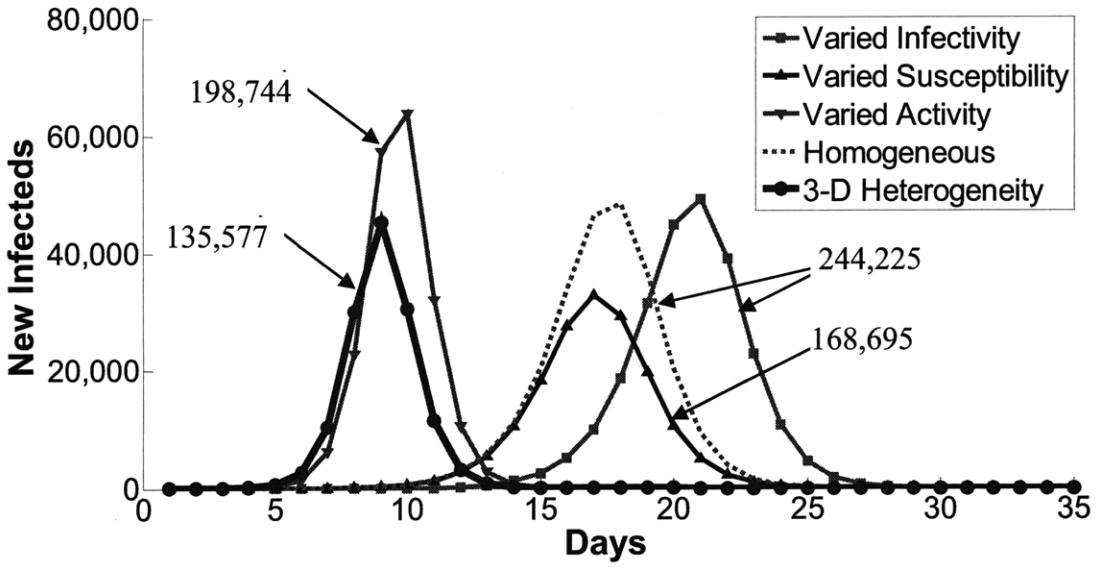
Graph 3.6

Heterogeneity in two dimensions: susceptibility and infectivity. The simultaneous presence of both high susceptibility and high infectivity results in an explosive outbreak that is driven by this doubly dangerous group.

Realistically, heterogeneity is present at all levels and susceptibility is not always correlated with infectivity. Thus we will now present the model with heterogeneity in three dimensions: activity, susceptibility and infectivity. We will consider the case where there are three levels of heterogeneity in each dimension, so there will be a total of 27 groups present in the population and all combinations of high, moderate and low activity, susceptibility and infectivity will be equally present in the population. In ***Graph 3.7***[14] we present how the triply heterogeneous population compares to the homogeneous case and the populations with heterogeneity in one of the three dimensions. The triply

[14] To see the equivalent graph for the standard incidence model refer to ***Appendix C, Graph C.7.***

heterogeneous population experiences a rapid growth of the epidemic curve that is driven by the highly active individuals as well as the people who are both highly susceptible and infectious. However, not as many people get infected because a large portion of the population has very low susceptibility and rarely gets sick. In addition, the minimally infective and minimally active individuals act like absorbers of transmission. When one of these people gets infected they pass on the virus to very few other individuals.



Graph 3.7

Heterogeneity in all dimensions: activity level, susceptibility and infectivity. The highly active, highly susceptible and highly infective individuals are the drivers of infection spread. The low activity, low susceptibility and low infectivity individuals decrease the cumulative impact of the outbreak on the population.

The presence of heterogeneity in many dimensions is clearly very important when modeling the spread of infection. In this chapter we present cases where all heterogeneous groups are equally present in the population. It is likely that when modeling varied activity levels, it could be important to add a group that is about 1% of the population, but hose members have over 100 contacts/day. Similarly, the number of

extremely susceptible or extremely infective people is likely to be only a small fraction of the population. However, since there is little to no data on what values we should use, we have presented cases where each heterogeneity level is equally prominent. We are not arguing that this is representative of reality, but feel that this approach best allows us to make our point.

3.6 Other Types of Heterogeneities

Our social order is very complex and this chapter does not model all the different types of heterogeneities that exist in our population. The most commonly discussed aspect of society that has been discussed at length in the literature is the existence of structure within our population that contradicts random mixing. One approach to remedy this predicament has been to create age based mixing groups since there is evidence that people of the same age are much more likely to interact (Mossong, 2008). In addition, not only are contacts between certain people more likely, but contacts between certain individuals, like family members, are more intimate and longer in duration and thus more conducive to infection transmission. To capture this level of detain and complexity we refer the reader to network models and microsimulation briefly described in ***Sections 2.4 & 2.5***.

Another type of heterogeneity is the duration of the infectious period for different people. Flu virus transmission on average is less than a week, but sometimes it can last over 2 weeks (Carrat, 2008). The duration of the incubation period also varies amongst individuals. People can be asymptomatic spreaders for varying amounts of time. Another

type of heterogeneity is the length of time it will take for the individual to recover and reenter the population at his or her prior levels of activity. The survival rate is also likely to vary amongst different groups. In 1918-1919 the young adult population was hard hit, and they are usually one of the more active groups and are the drivers of the economy. Also, the death rate amongst pregnant women was incredibly high ranging between 20-70% compared to the 2-2.5% mortality in other groups. There may be many other types of heterogeneities, and we encourage people to study and incorporate them into their modeling work.

3.7 Summary

In this chapter we have outlined some of the most noteworthy heterogeneities and have shown that they have a significant impact on the epidemic curve and must be included when modeling pandemic flu. Let us now summarize some of the main findings in this chapter.

We have been able to determine that *activity level is the most important type of heterogeneity*; highly active people are the biggest drivers of infection spread. One dimensional *heterogeneity in susceptibility alters the fraction of the population who becomes infected.* One dimensional *heterogeneity in infectivity alters the timing* of the curve. Similarly changing activity levels doesn't play as significant a role as contact rate. The population attribute that is *another driver of infection is coupled heterogeneity in both susceptibility and infectivity.* Individuals who are both highly susceptible and highly

infective drive transmission like the highly active individuals. Here is a little more detail on these findings:

- Contact rate heterogeneity is a major component that speeds up transmission. The presence of highly active individuals is doubly dangerous because they are both likely to get sick early on and they are likely to infect many people if they get sick.
- The presence of multiple levels of susceptibility does not change the speed of transmission, but can change the cumulative burden of the virus. The individuals with really low susceptibility rarely get sick, so that group of the population remains mostly uninfected. On the other hand, the highly susceptible group is almost guaranteed to get the infection.
- Heterogeneity in infectivity levels does not impact the cumulative number of infecteds, but can be very important in the initial stages of the outbreak. If patient zero is not efficient at transmitting the virus to others, the disease could die out with that initial patient.[15]
- Inconsistency in activity levels helps decrease the spread of infection, but is not likely to make as large an impact as other types of heterogeneities.
- If high susceptibility is coupled with high infectivity in one group, then those individuals are also likely to get infected early and get many others infected. This group will drive the transmission of the flu much like the highly active individuals.

The implications of these findings are that, it is important for us to identify the highly active individuals as well as those who are both highly susceptible and highly infective. Both of these types of people are drivers of the flu. In order to mitigate the

[15] It is likely that the virus may be reintroduced into the population and restarts again, see ***Chapter 5***.

pandemic we will have to either change these individuals' behavior or treat them with the limited stockpile of antivirals or the pre-pandemic partially effective vaccine. Unfortunately, neither of these attributes is completely obvious, so the relevant groups are difficult to identify.

Identifying the highly active individuals is somewhat realistic because people usually know approximately how many people they interact with on a daily basis even though that number is likely to fluctuate from one day to the next. However, in a pandemic it would be highly unlikely that decision makers would announce "If you interact with more than 50 people a day, get rid of half of your daily interactions." Identifying the type of people who usually have many daily contacts as a result of their social standing or occupation would make more sense.

We know that school children interact very closely with many other school children; thus school children are one group that falls in the highly active category. Furthermore, university students especially those residing on campus are also likely to be highly active because they attend lectures and live in dorms with dozens and even hundreds of other students. As a result one pandemic management approach could be to temporarily close the organizations that have a high concentration of these high active individuals; closing down schools is probably the best approach to reducing children's contact rates. Stopping classes in universities could also be helpful, if students don't replace class time with other social interaction[16].

Furthermore, certain types of professions: grocery store clerks, servers, salesmen, doctors, nurses, ministers etc require more social interaction. Another approach would be to try and identify these high risk individuals before the pandemic. In the case of a

[16] For more on planning for a pandemic in a University setting see ***Chapter 6***.

pandemic, these individuals could be educated about their high risk status and given specifically tailored recommendations on how they could decrease their risks. During a pandemic there will not be enough time to conduct such detailed studies and develop customized messages. Classifying a given individual as highly active is not very difficult because most people could know how many people they see on a daily basis. We need to take advantage of this and identify the high activity professions and craft the tailored messages before the pandemic hits.

Identifying the susceptibility and infectivity level of individuals is a much more complex matter because it is not easily observable. There is some correlation between infectivity and susceptibility with age. Usually children are considered to be more susceptible to flu because they have less or no immunity from prior influenza infections. In addition, children are also known to shed the virus efficiently and for a longer period of time which makes them more infectious than adults. Another factor that is thought to impact the susceptibility of an individual to the flu is the overall health of a person. People with asthma, heart disease, diabetes, AIDS and other underlying medical conditions are also potentially more susceptible for infection. Coincidentally, both children and individuals with medical conditions usually have higher than normal complication rates[17]. This additional factor supports the importance of trying to ensure that members of this group do not get infected. Vaccinating these highly susceptible and infectious individuals with an unmatched vaccine may help boost their immune systems so that they do not get infected. Prophylactic use of antivirals could be another approach, if sufficient stockpiles of antivirals are available.

[17] This was not the case during the 1918-1919 pandemic where the healthiest age group 15-45 was hit very hard, see ***Figure 1.3***.

Overall, stressing the importance of non-pharmaceutical interventions ranging from hand washing and wearing masks to decreased social contact is the most realistic and potentially powerful strategy for protecting at risk individual and drivers of the outbreak. In ***Chapter 4*** we will focus on these voluntary non-pharmaceutical interventions and the benefits that they have in slowing down or even stopping the spread of pandemic influenza.

REFERENCES FOR CHAPTER 3

Bassetti S., Bischoff W.E., Sherertz R.J., 2005. "Are SARS superspreaders cloud adults [letter]?" Emerging Infectious Diseases. <http://www.cdc.gov/ncidod/EID/vol11no04/04-0639.htm>

Carrat F., Vergu E., Ferguson N.M., et al., 2008. "Time Lines of Infection and Disease in Human Influenza: A Review of Volunteer Challenge Studies." American Journal of Epidemiology. 167:775-785. <http://aje.oxfordjournals.org/cgi/reprint/167/7/775>

Cohen S., Tyrrell D.A., Russell M.A., et al., 1993. "Smoking, alcohol consumption, and susceptibility to the common cold." American Journal of Public Health, 83: 1277-1283.

Drummond P.D., Hewson-Bower B, 1997. "Increased psychosocial stress and decrease mucosal immunity in children with recurrent upper respiratory tract infections." Journal of Psychosomatic Research. 43(3): 271-8.

Eagle N., Pentland A., 2006. "Reality Mining: Sensing Complex Social Systems." Personal and Ubiquitous Computing. 10(4), 255-268. <http://reality.media.mit.edu/pdfs/realitymining.pdf>

Eichenwald H.F., Kotsevalov O., Fasso L.A., 1960. "The "cloud baby": an example of bacterial-viral interaction." American Journal of Diseases of Children. 100:161–73.

Fu Y.-C., 2005. "Measuring personal networks with daily contacts: A single-item survey question and the contact diary." Social Networks. 27:169–186.

Fu Y.-C., 2007. "Contact diaries: Building archives of actual and comprehensive personal networks." Field Methods. 19(2):194–217.

Fu Y.-C., Lin Y.-J., 2005. "Consistency and Accuracy in the Measurement of Daily Contacts: Surveys and Contact Diaries Compared." Survey Research: Method and Application. 17.

Galvani A.P., May R.M., 2005. "Epidemiology: Dimensions of superspreading." Nature. 438:293-295. <http://www.nature.com/nature/journal/v438/n7066/full/438293a.html>

Hall C.B., Douglas R.G., Geigman J.M., Meagher M.P., 1979. "Viral shedding patterns of children with influenza B infection." The Journal of Infectious Diseases. 140(4):610-613.

Larson R.C., 2007. "Simple models of influenza progression within a heterogeneous population." Operations Research. 55(3):399–412.

Morbidity and Mortality Weekly Report (MMWR), 2003. "Severe Acute Respiratory Syndrome – Singapore, 2003." Center for Disease Control and Prevention. 52(18):405-411.

Nigmatulina K.R., Larson R.C., 2009. "Living with Influenza: Impacts of government imposed and voluntarily selected interventions." European Journal of Operational Research. 195:613-627.

Mossong J., Hens N., Jit M., et al. 2008. "Social Contacts and Mixing Patterns Relevant to the Spread of Infectious Diseases." PLoS Medicine. 5(3):381-391. <http://medicine.plosjournals.org/archive/1549-1676/5/3/pdf/10.1371_journal.pmed.0050074-L.pdf>

Shen Z., Ning F., Zhou W., et al., 2004. "Superspreading SARS events, Beijing, 2003." Emerging Infectious Diseases. <http://www.cdc.gov/ncidod/EID/vol10no2/03-0732.htm>.

Sherertz R.J., Reagan D.R., Hampton K.D., et al., 1996. "A Cloud Adult: The Staphylococcus aureus-Virus Interaction Revisited." Annals of Internal Medicine. 124 (6): 539-547.

Zeng X., Wagner, M., 2002. "Modeling the effects of epidemics on routinely collected data." Journal of the American Medical Informatics Association. 9(6). <http://www.jamia.org/cgi/content/abstract/9/6_suppl_1/S17>.

CHAPTER 4:
MODELING BEHAVIOR CHANGES AND THEIR IMPACT ON FLU TRANSMISSION

The range of possible influenza pandemic management strategies can be separated into medical responses: vaccines[18], antivirals, and non-pharmaceutical interventions (NPIs): closures, social distancing, self-isolation, masks, etc. Today in the Western World, NPIs are manifested through voluntary behavior changes exhibited by the population. Some people have a fatalistic view that nothing short of a vaccine will stop the flu once it becomes easily transmissible and all other efforts will only slightly slow down the virus. Unfortunately, no country in the world will have sufficient vaccine stockpiles while antiviral effectiveness and usage is controversial. There is currently a dearth of strong evidence illustrating the efficacy of social containment strategies in decreasing the cumulative burden of infection, which is particularly troublesome given that many of these interventions will carry significant economic, social, ethical, and logistical consequences. The World Health Organization (WHO) recommends non-pharmaceutical public health interventions as a means of containing the infection,

[18] Refer to ***Chapter 5*** for models of vaccination strategies.

delaying its spread and otherwise reducing the impact of the disease (WHO, 2004). Our results indicate that these voluntary behavior altering strategies could be more effective than expected and must be included in modeling efforts.

It is unlikely that society will implement measures from 1918-1919 making it "unlawful to cough and sneeze" punishing violators with up to a year in jail (Hudson, 1999). Making it a crime to shake hands and throwing people in jail for not wearing masks is an extreme measure that would only perpetuate panic and protest. It is expected that even without forceful implementation people will try to decrease their likelihoods of getting ill by improving hygiene related behaviors. Most people will not maintain their daily routines if they discover that there is a deadly disease attacking within their city, state, country or the world. Based on the information portrayed in the media, individuals are likely to both limit their daily contacts and decrease the closeness of the remaining contacts. History has provided us with multiple examples of people responding to news of a disease by altering their daily behavior.

Recent statistical studies of the 1918 influenza pandemic in US cities have supported the hypothesis that early implementation of multiple non-pharmaceutical interventions could reduce transmission rates by 30-50% and lower the peak death rates by about 50% (Bootsma, 2007; Hatchett, 2007). The timing and force of these interventions have been attributed as some of the main reasons for the variation of different cities' experiences (Bootsma, 2007). The array of outcomes ranges from the Philadelphia one hump epidemic curve lasting a month and a half with a peak excess death rate of over 250/100,000 population, to the St. Louis two wave four month experience with a peak excess death rate of less than 75/100,000 population (Hatchett,

2007). The findings of these studies suggest that these interventions within cities helped save lives during the 1918-1919 pandemic, and may help save future lives.

Those who still doubt the relevance of behavior changes, should consider the recent example of the social behavior changes that occurred during SARS. One survey indicates that during the SARS outbreak in Hong Kong 78% of the population covered their mouths while sneezing or coughing, 76% of individuals wore masks, 65% washed their hands after contact with possibly contaminated objects (Lo, 2005). Economic factor studies in Hong Kong, Beijing, Singapore and Toronto indicate that there was a sharp drop in interactive social activities as restaurants and entertainment centers suffered sharp drops in clientele (Fan, 2003). Specifically in Hong Kong, tourism was crippled in March when the WHO issued a rare warning for travelers to avoid Hong Kong and the Guangdong Province. As a result of weakening demand, airlines slashed more than a third of flights and hotels in Hong Kong reportedly were up to 90% empty (Wiseman, 2003). In Singapore sales were down about 30% as people avoided stores and malls, some stores suffered up to 75% declines in sales (Wiseman, 2003). It is clear that voluntary activities like tourism were strongly affected by fear of the disease. The resulting adverse economic impact in parts of East Asia was comparable with the 1998 financial market crisis (Schoen, 2003; MSNBC News Service, 2003 a,b). It is apparent that a lot of people took precautionary measures as a result, and the outcome in Hong Kong was the 90% decrease in the spread of other respiratory diseases (Lo, 2005)!

Similarly, in a more Western city of Toronto, during the SARS outbreak there was a reported drop of up to 71.5% in revenue per available hotel room for downtown Toronto. This translates into hotel occupancy rates in the range of 30% to 40%, instead of

the seasonal 70% average (Rosszell, 2003). At least five major citywide conventions were called off, contributing a loss of over 20,000 attendees, and this doesn't include the vast amount of individual-hotel convention businesses that were also cancelled (Rosszell, 2003). The long list of voluntary behavior changes in Toronto due to SARS includes over 800 bus tours, music concerts, corporate travel, and school field trips (Rosszell, 2003). All these examples are strong evidence that people will not maintain their daily actions. We know that the effect of these "soft" and self-imposed interventions was significant (Tang, 2003). There are significant gaps in our knowledge of these behavior changes, but overlooking these behavior changes is indefensible.

In this section, we provide examples of behavior changes in several different scenarios. Since there isn't an overwhelming amount of evidence for any one approach to creating behavior models, we also propose several approaches to modeling behavior changes that are driven by the presence of the disease in the population. We explain the differences and motivations behind the approaches in the four models that we presented. We conclude by extracting the insights from our models and by describing what kind of non-medical policies and behavior changes have the potential to stop or reduce influenza transmission.

4.1 Importance of Behavior Changes

Before we delve into how we propose to incorporate behavior changes into our model, let us explore further why behavior changes are important and relevant. In order to support the approach of the models that will be presented later on in this chapter we

need to illustrate two points. First, knowledge of increased risk for a disease causes people to change their behavior. Second the changes in behavior in turn impact the probability that people will get the disease.

Let us elaborate on a few examples that show people altering their behavior as a result of information that indicates that they are at risk of disease. Every couple of years we hear that schools have shut down in response to a staph or meningitis outbreak, and we read about the various hygiene improvement campaigns that take place as a result (McClure, 2009; MSNBC, 2007; Zezima, 2007). Another example is people who alter their behavior when they learn that they have a chronic disease or are genetically predisposed for a serious illness. It has been shown that such diagnosis prompts many people into action as they start to watch their diet, quit smoking and increase the amount of physical activity (Boyle, 1998; MMWR, 1998). It is very natural to expect that when they feel threatened, people will do as much as possible to decrease their risks of illness or death.

4.1.1 STD Driven Behavior Changes & Their Impact

The best studied cases of disease driven behavior changes are sexually transmitted diseases (STDs), and especially the Acquired Immune Deficiency Syndrome (AIDS) caused by the Human Immunodeficiency Virus (HIV). AIDS was first identified by US clinicians in 1981, and throughout 1982-1985 were years of "intense discovery" as people learned more about the virus. The population group in the West that was considered the most at risk in the 1980's was the homosexual and bisexual male

population. Multiple studies have shown how members of this population altered their behavior as they learned more about the virus.

There were multiple studies of the homosexual male populations in different cities in the United States; San Francisco was one of the most studied cities. The San Francisco Men's Health Study focuses on the years 1984-1986 and finds that the prevalence of men who have more than 10 sexual partners in a six month period declined by more than 60% (Winkelstein, 1987). Another study identified that the number of monogamous relationships increased and the fraction of receptive anal intercourse (RAI) without a condom decreased in 1983 (McKusick, 1985). In this study, the determinant and source of these behavior changes was seeing a victim with advanced AIDS (McKusick, 1985). Visualizing the deterioration that results from the virus led people to learn more about the preventative measures and to become less risky in their actions. In New York, the median number of sexual partners per year decreased from 36 in the pre-AIDS time frame, to 8 in 1985 (Martin, 1987). Throughout the 1980s, homosexual men all over the country were taking various measures that decreased their risk of becoming sick (MMWR, 1991).

Over 80% of the AIDS cases in England and Wales have occurred in homosexual men (Johnson, 1989). In a cohort study of 100 homosexual men in London over 1984-1986, the researchers found that the median number of partners per month fell from three to one. The proportion of respondents practicing RAI, with more than two partners a year, fell from 41% to 16% (Carne, 1987). Individuals all over the world were changing their behavior to avoid AIDS. These marked changes in sexual behavior as a result of the emergence of AIDS prove our first point: people do take precautionary measures when their health is endangered.

While it is difficult to identify how these behavioral changes impacted the prevalence of AIDS, it is clear that these behavior changes decreased the transmission of other STDs. In the years 1985-86 there was a marked reduction in rates of Gonorrhea, syphilis and acute hepatitis B in homosexual men (Johnson, 1989). This demonstrates our second point: behavior changes make a difference in the overall health of the population and decrease disease transmission.

Heterosexual members of the population have also significantly altered their behaviors as a result of HIV and STDs. In a study of female prostitutes in New York, 92% of the informants indicated that they started using condoms as a response to concerns of herpes and other STDs (DesJarlais, 1987). More recently, the decline in HIV in Eastern Zimbabwe between 1998-2003 is attributed to the decreased number of sexual partners in both the male and female populations (Gregson, 2006). In the case of STDs, there is consensus that people alter their behavior to avoid getting infected and these actions do lead to reductions in the prevalence of STDs in the overall population (Becker, 1988).

4.1.2 SARS driven Behavior Changes & Their Impact

Possibly the best recent illustration of reactive behavior in the population is SARS in 2003. SARS was first identified in China's southern province of Guangdong in November 2002. By February 26, 2003 Hong Kong officials reported their first case of SARS and no later than March 14, 2003 the virus reached Canada. Overall the virus spread to some 37 countries all over the world, with 8,096 known infection cases and 774 deaths. During the initial several months of disease transmission in southern China, the

government tried to deny the existence of the illness. However, in early April there seems to have been a change in official policy when SARS started to receive much greater prominence in the official media. Possibly this can be attributed to the death of an American or the emergence of accusations regarding the undercounting of cases in Beijing military hospitals. Regardless of the motivation, at that point in time people started to realize the impact and risks associated with SARS which inspired changes to their behaviors in order to protect themselves from infection.

Let us elaborate on the response to SARS within Hong Kong. A large number of SARS cases in Hong Kong were first reported on March 10th in the Prince of Wales Hospital and continued until June 2nd (Lau, 2004). On March 26th a second large scale outbreak occurred in Amoy Gardens (Lau, 2004). As a reaction, on March 29th all classes were suspended (Lau, 2003). On March 31st a large number of Amoy Gardens' residents were quarantined. On April 2nd the WHO issued a travel advisory warning for Hong Kong. Afterwards, the situation started to improve. Classes resumed in universities on April 14th and while secondary schools reopened in later April, primary schools stayed closed till May 12th or 19th. At the end of the outbreak a total of 1,755 SARS cases were recorded.

During that time phone surveys were conducted by several different research groups and all groups found that public health measures, such as wearing masks, frequent hand washing, avoidance of crowded places, disinfection of the living quarters, etc had been practiced by most of the Hong Kong population (Lo, 2005; Lau, 2003; Lau 2004). In one of these studies, the progression of the voluntary interventions throughout the outbreak were recorded. Through ten sequential telephone surveys 1397 adult Hong

Kong residents were asked about their knowledge and perceptions of the disease, its risks and fatality as well as their susceptibility and practice of various interventions. In ***Table 4.1*** one can find the results of this survey that are relevant to this research.

	Initial phase						Second phase				
Date of interview	**3/21**	**3/22**	**3/23**	**3/24**	**3/28**	**4/1**	**4/8**	**4/11**	**4/24**	**5/12**	**All**
New SARS cases on previous day	20	32	20	25	51	80	41	28	24	4	
Perceived chance of infection (% very large/large)	3.9	9.2	8.8	11.1	14.3	12.4	7.0	7.1	7.3	4.7	8.7
Improved Hygiene											
Wearing a mask	11.5	16.7	7.7	16.7	66.9	84.3	87.3	87.7	93.9	85.4	64.3
Hand hygiene	61.5	66.7	63.7	80.3	94.1	95.1	93.7	94.2	94.5	95.9	86.9
Disinfecting home	-	-	-	36.4	56.8	69.4	72.2	80.0	83.5	73.1	70.1
Behavior											
Avoid going outside	28.2	28.2	31.9	36.4	50.0	57.1	62.4	58.7	47.3	36.3	45.8
Avoid crowded places	59.0	67.7	54.9	68.2	76.3	85.4	81.0	89.0	81.2	69.6	75.5
Avoid visiting hospitals	59.7	63.5	52.7	62.1	73.4	75.0	76.4	86.5	79.9	68.6	71.8
Avoid using public transportation	14.1	15.4	16.5	24.2	26.6	36.2	27.8	31.0	25.0	17.1	24.4
Avoid going to work	-	2.6	2.2	4.5	6.1	8.1	7.7	7.3	5.5	1.2	4.9
Not allow kids to go to school	-	-	-	12.5	35.7	38.1	31.0	36.7	39.6	16.3	31.6

Table 4.1

Results of a telephone survey monitoring community knowledge, perceptions and practices during the SARS outbreak in Hong Kong in 2003. (Lau, 2003).

It is clear that the perceived chance of infection fluctuated with the number of people that became infected on the previous day. Furthermore, the various hygiene and behavioral measures implemented by the population are correlated to the number of new cases. In this study, the researchers found that the correlation between the number of cases and the fraction of the population participating in the intervention was highly

correlated[19] for the initial, escalating phase of the outbreak that lasted through April 1st (Lau, 2003). As the perceived chance of infection increased, more people started altering their behavior to reduce the likelihood of illness. From the experience of Hong Kong that is captured in this study, it is clear that people not only alter their behavior in the case of a disease outbreak, but the worse the outbreak, the more the population will react. The importance of timely, accurate, comprehensive information about the disease becomes vital in this scenario. The researchers conclude that "perceptions are important in determining preventative behaviors," and that policy makers should be aware of the importance of the public' reactions. Further in this chapter we will propose several approaches to including these human behaviors into our model.

Beijing experiences the world's largest outbreak of SARS which began on March 5th and was resolved within six weeks of its peak in late April. In Beijing there were multiple government imposed control measures as well as individual driven behavior changes, but the response seems to have been slower than in Hong Kong. The timeline of the epidemic curve and the resulting interventions for the Beijing SARS oubreak can be found in ***Appendix E***. It took till April 20th for the Ministry of Health (MOH) to publicaly announce the severity of the outbreak. Once people finally recognized the significance of the outbreak, they educated themselves about the disease. The time lag between symptoms onset and hospitalization decreased significantly during the outbreak from a median of 5 to 6 days before April 20th, to 2 days afterwards (Pang, 2003). This increased knowledge also made people more cautious. An example of resulting voluntary interventions is the significantly reduced patronage of restaurants during the peak of the outbreak, while restaurants were never ordered to close (Pang, 2003). Furthermore, in

[19] r* is in the range of.85- .97 for the different interventions.

early May, the streets of Beijing were noted to be virtually empty because people were trying to avoid getting sick (Pang, 2003).

The first three cases of SARS in Singapore were confirmed on March 6th and by May 11th a total of 205 cases were confirmed. The reactions to SARS in Singapore were also researched through a telephone survey conducted during the time of the outbreak. The interventions practiced in Singapore were similar to other cities with the exception that very few – 4% of the survey respondents – wore masks (Quah, 2004). The researchers also found that those who believed they were more likely to get the disease reported slightly more anxiety which in turn appeared to motivate preventative behaviors (Quah, 2004). Thus in Singapore, like in Hong Kong and Beijing, people voluntarily altered their behavior to improve their chances of staying healthy through the outbreak.

While we see that as a result of the government response, the timing of people's reactions varied for different cities, but in all cases behavioral changes were observed. In the next several sections we will present how to incorporate behavior changes such as improved hygiene and decreased social contact into our model. We will now present several appraoches that capture the different elements in behavior that have been mentioned in this section.

4.2 Model 1: Human Concern Factor

As we have shown in the case of SARS in Hong Kong, people will react to the news of infection spread by altering their daily routines depending on the severity of the

news. Furthermore, the survey study of Singapore found that people who were more anxious about becoming sick, practiced more precautionary measures (Quah, 2004).

There are several social behavior models that predict that people will alter their behavior given knowledge of a deadly infection. Coping responses affect human functions to moderate and decrease the negative impacts and stressors in life's circumstances (Pearlin, 1981). Protection motivation theory, the transactional model of stress and coping, the health belief model (HBM) and behavior intention model (BIM) all indicate that individuals will attempt to assess their perceived risk or attitude towards the threat based on factors like threat severity and their vulnerability (TCW, 2004). Combining threat assessment with perceived response efficacy and level of confidence in one's ability to react appropriately, individuals determine their intended and actual behavior (TCW, 2004).

A comparative study of the HBM and BIM in predicting human intentions regarding the swine flu vaccination program undertaken in October 1976 found that while the BIM is a better predictor, practitioners can apply the concepts of either model to the decision making process (Oliver, 1979). Motivated by social science risk perception and health behavior models, a survey study of 5 European and 3 Asian regions revealed that in a hypothetical pandemic precautionary measures would be taken across all regions, the measures included avoidance of public transportation, entertainment venues and partial isolation within the home (Sadique, 2007). If vaccines and antivirals will be unavailable, the concern level will increase throughout the epidemic and individuals' coping options will be to limit their daily contacts and/or decrease the probability of transmission given

contact. Before delving into these manifestations of altered behavior we explain our approach in evaluating the overall perceived level of community concern.

It is difficult to predict which kind of information people will use to assess their "perceived threat". Logical choices for evaluating susceptibility will be the virus' proximity to home and its virulence, while mortality and morbidity rates are likely to determine perceived severity. Since we do not specify the death rate for the disease the number of infected individuals is the best gauge that reflects both community members' vulnerability to the disease and the severity of the threat. We apply the concepts of the various behavior models and use this factor to gauge human reaction. While our approach may seem primitive, there has been little progress in the field of quantitative health behavior modeling (Weinstein, 2004). In this section we suggest one method for incorporating behavior changes into our model and it is supported by Sadique's questionnaire study results. In the next sections we will propose three more approaches to modeling behavior.

In order to incorporate behavior change into our model we use $\pi_X(t)$ as a feedback parameter that indicates the "concern level" within Community X on day t. If $\pi_X(t)=1$ then there is no anxiety or behavior change within the community, for $\pi_X(t)=0$ the community practically shuts down. We describe three possible data sets that the population could use to gauge their risk levels, to define their $\pi_X(t)$ and consequently alter their behavior. Please note, that when we use the term "day" throughout this chapter, we are referring to one generation of the flu, which corresponds to 2-3 actual days. Since there is no evidence suggesting one level of time granularity for tracking behavior over

another, we use the most analytically logical time step: one generation of the flu. This model was implemented in Microsoft Excel.

1. The first communities that experience the virus will not be able to use the lessons learned by their neighbors. Early on, the only information people will have will be the experience of their own community. People may use the number of yesterday's new infections ignoring everything that happened before yesterday. We quantify this memoryless approach of evaluating the risk factor as $\pi^1_X(t, C_1)$:

$$\pi^1_X(t, C_1) = \left(1 - \frac{\text{Number of infected people in Community X from day } t-1}{\text{The total population in Community X}}\right)^{C_1}$$

C_1 an input that represents the importance of yesterday's information to the people. For $C_1 = 1$ the number of infected individuals is linearly correlated to the risk level. As C_1 grows, the relevance and impact of yesterday's news grows exponentially.[20]

2. The media is likely to present the cumulative number of infections within the community, this is another possible data set that people may use to estimate their risk levels. The related concern parameter is $\pi^2_X(t)$:

$$\pi^2_X(t, C_2) = \left(1 - \frac{\text{Number of infecteds in Community X up to and including day } t-1}{\text{The total population in Community X}}\right)^{C_2}$$

[20] The authors have not been able to find the application of the behavior forecasting models to predict general behavior changes in the case of pandemic flu, but we have found numerous examples of HBM used to estimate altered human interactions to reduce their risk for HIV infection. Studies in this area indicate that there may be non-linear relationships between the factors and the dependent variable, thus we allowed for this variability through the addition of the C parameters (Stiles, 2004).

C_2 is another input which represents the strength of impact of this cumulative information. We acknowledge that C_1 will have a smaller impact than C_2 of the exact same value. [21]

3. It is also clear that if a city's adjacent communities all get infected the level of concern within the city will be heightened to reflect the suffering of neighboring cities. In one study of SARS in 2003 discovered that while people respond to the events in their own city, they also become more cautious when they see that other communities nearby are suffering (Shi, 2003).[22] This presents us with another factor in evaluating the behavior change feedback parameter, $\pi^3_X(t)$:

$$\pi^3_X(t, C_3) = \left(1 - \frac{\text{Number of infecteds in all Communities up to and including day } t-1}{\text{The total population in all Communities that have been infected}}\right)^{C_3}$$

Again C_3 is an input representing the impact of this information. Notice the denominator is the population of only the infected communities, so this reflects a human informational bias that focuses on only the infected communities.

In reality each individual is likely to change their behavior using a combination of all three described approaches. Yesterdays' information is likely to be the most prevalent in the mind of the community, but they are also likely to remember the events of the past several weeks and be aware of the experiences of their neighbors. In our model we can uniformly alter the actions of people within each group using

$$\pi_X(t, C_1, C_2, C_3) = \pi^1_X(t, C_1) * \pi^2_X(t, C_2) * \pi^3_X(t, C_3)$$

as the feedback parameter for behavior change.

---

[21] Studies in this area indicate that there may be non-linear relationships between the factors and the dependent variable, thus we allowed for this variability through the addition of the C parameters.

[22] To see the application of this approach where the events in neighboring communities have an impact on the concern factor refer to ***Chapter 5***.

The two parameters that will incorporate πX(t, C1, C2, C3) to reflect changing behavior due to awareness and alarm over the infection are λ and p.

One other option to determining the concern parameter is an intermediate between individuals fully remembering all events up to and including yesterday equally or just focusing on yesterday. This intermediate approach to evaluating the concern parameter is by having an exponential decay of the memory of events. In this case the number of cases who got sick yesterday is the most prominent memory, but the day before yesterday is also remembered, just not as well, etc. For this exponential decay case we would calculate the concern factor accordingly:

$$\pi_X(t,C,\alpha)=\prod_{i=0}\left(1-\frac{\text{Number of infected people in Community X on day } t\text{-}1\text{-}i}{\text{The total population in Community X}}\right)^{\frac{C}{\alpha^i}}$$

The parameter C as in previous cases is an input parameter that indicates how important historical information is to the population. The parameter α is another input parameter that determines how quickly people forget the information; the bigger the α, the faster people forget. Note, that we will not present the results of the exponential decay model in the following section. However, to see the graphical representation of the manifestation of this type of behavior, refer to ***Appendix F***.

4.2.1 Limited Contact

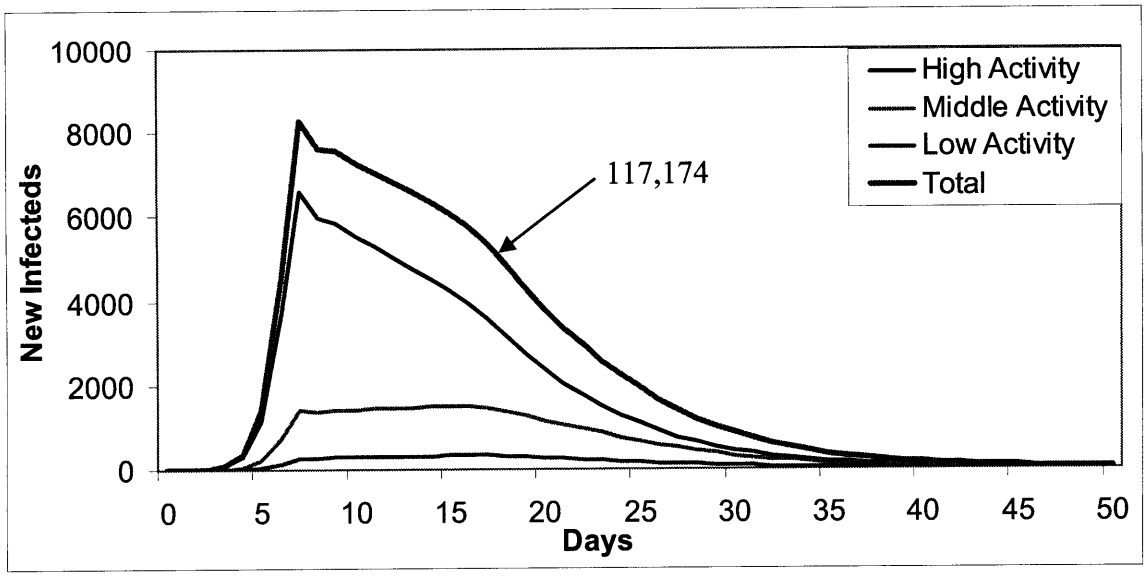
People in all activity levels are likely to decrease the number of contacts that they have on a daily level. It is highly probable that children will be kept at home, public transportation will be avoided, entertainment activities such as shopping or going to the

movies will be temporarily suspended, even the number of contacts within the office may decrease as conference calls replace face-to-face contacts (Sadique, 2007). All these behavior changes were observed during the SARS outbreak (Wiseman, 2003). We model the manifestations of altered behavior by updating the average number of contacts per generation of the flu, λ^j, by multiplying it by, $\pi_X(t, C_1, C_2, C_3)$, the appropriate level of impact. So,

$$\lambda^j(t) = \lambda^j \pi_X(t, C_1, C_2, C_3)$$

As can be seen from ***Graph 4.1***, relying on yesterday's information as the indicator for the concern level results in a lowered peak of the epidemic but a much slower decline of the disease. The cumulative number of infections is decreased, but the virus maintains its presence within the community for a long period of time requiring sustained vigilance. However, people are likely to use more than just yesterday's information to define their behavior. The community can "remember" the number of people who were infected prior to yesterday, then the prevalence of the virus declines much faster. ***Graph 4.2*** illustrates the potential success of social distancing in decreasing the cumulative number of infecteds to a significantly smaller fraction of the total population.[23] The main difference in people's reactions presented in the two graphs is the intensity of the interventions in the declining half of the outbreak. In ***Graph 4.2*** the interventions are maintained at a high level until the infection is completely depleted, so we use the second approach to find the concern factor based on all information up to and including yesterday. For ***Graph 4.1*** the intensity of the interventions decreases in the later half of the outbreak; the first approach of calculating the concern factor is applied.

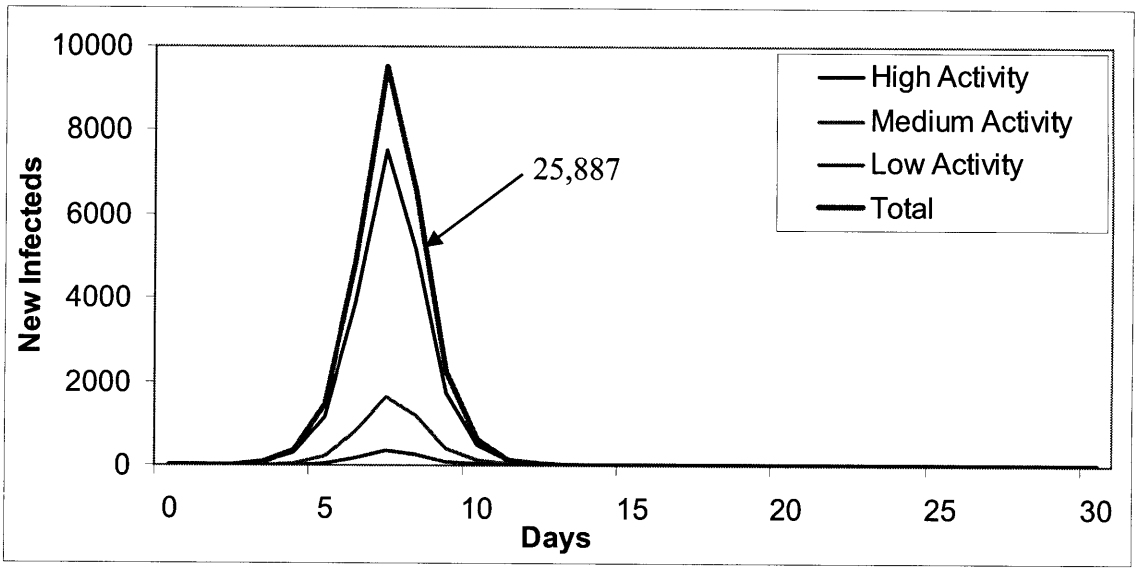
[23] Refer to ***Chapter 5*** to see the importance of decreasing the number of infections for the other communities.



Graph 4.1:

Infection spread within a community that reacts, by proportional scaling back the average number of contacts for all its members, to previous day's news only.

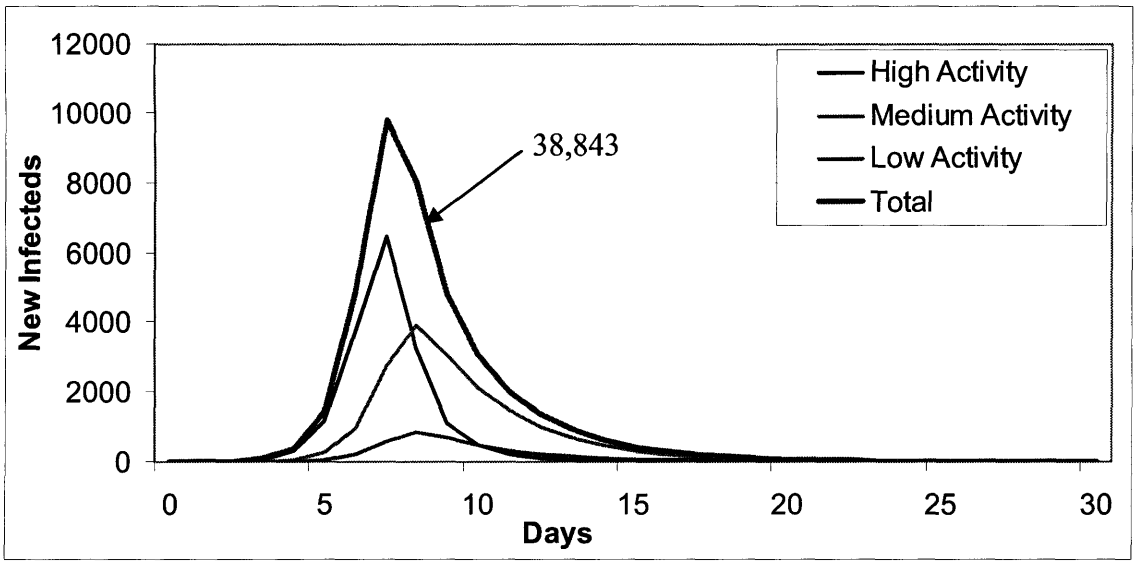
The average number of interactions is likely to decrease, but it is unlikely that the λ 's are going to change to the same degree for each activity level. Highly active people will be able to decrease their number of interactions drastically, but less active people may be unable to sever their few, but vital ties to the community. For example, a politician may decide to cancel his/her campaign rally, stay at home and contact his office through telecommunication. On the other extreme, a retired handicapped grandmother whose only daily contact is with her grandson who brings her daily groceries, is not likely to change her pattern at all.



Graph 4.2

Infection spread within a community that reacts, by social distancing, to news cumulative over all previous days.

This leads us to consider the scenario where only the highly active individuals, with many voluntary contacts, limit their daily contacts. The results are presented in ***Graph 4.3***. Just changing the behavior of the highly active individuals has a similar impact as decreasing the behavior of the entire community. If highly active individuals decrease their number of daily contacts by about 90% during the riskiest time, then a massive communitywide outbreak could be prevented. This result has multiple policy implications. It underlines the importance of closing schools since children have a high number of non-vital daily contacts within a school setting. All individuals who act as social focal points should decrease their average number of contacts, especially if this can be done without disrupting the community.



Graph 4.3
Infection spread within a community that reacts by social distancing only in the highly active group, to news over all previous days.

4.2.2 Decreased Probability of Transmission

Reduced closeness of contact and improved hygiene are coping mechanisms that will decrease the probability of transmission given contact between an infected and susceptible individual. In order to reflect this phenomenon we update the probability of transmission given contact on a flu generation basis by multiplying p^j by the appropriate, $\pi_X(t, C_1, C_2, C_3)$, level of impact. So,

$$p^j(t) = p^j \pi_X(t, C_1, C_2, C_3)$$

In our model the impact of decreased susceptibility is the same as the impact of decreased contact. Since our model provides us with the expected number of infecteds, we incorporate decreased probability of transmission by integrating a multiple of the risk factor in the exponent. As before, if people start taking precautions based solely on yesterday's information, they will lower the peak and extend the length of the epidemic

curve, as seen in ***Graph 4.1***. If the probability of transmission is dependent on all information up to and including yesterday then the length of the epidemic is shorter; see ***Graph 4.2***. Also, we can combine the two protective approaches and decrease the average number of contacts and limit the probability of transmission. For example, to significantly curb the impact of the outbreak, highly active individuals need to decrease their number of average daily contacts to 6 and their transmission parameter to about 3%; the result is presented in ***Graph 4.3***. It is also important to point out that highly active individuals who cannot limit their contact rate will have to rely tremendously on these improved hygiene measures, if the want to stay well. To make up for their incredibly high level of interaction, the high actives will have to use hand sanitizer, avoid shaking hands, start wearing masks and implement other protective measures.

The timing of the reaction is one of the most important factors in determining the overall impact of the disease. The benefit of these behavioral effects can be amplified if the community reacts preemptively before the virus enters their population. For information on infection spread in a multi community model refer to ***Chapter 5***.

4.3 Model 2: Balancing Tradeoffs

We are now going to shift gears by proposing a different approach to modeling reactionary behavior. This method considers why people change their behavior and what drives their actions on any given day. An individual who learns about the presence of a highly infective and potentially deadly virus spreading through the population will face the tradeoff between:

- Maintaining a socially active lifestyle and thus an increased probability of getting sick.
- The inconvenience or even impossibility of limiting their social interactions, but also decreasing their probability of getting sick.

In this section we will present a model in which people select their behavior level based on this tradeoff. In this approach we will not assume that all people alter their behavior, but only a fraction of the population changes its actions.

For this model we are going to simplify the structure of our population. Let us consider a uniform population with 300,000 individuals all with the same rate of social contacts $\lambda=30$ contacts/day and a conditional probability of infection $p=0.05$. A fraction of this population will recognize that there is an outbreak of infection and will therefore alter their behavior. We will call this the "reactive group". Let the fraction of the population initially in the reactive group be known as y. Let us define the following variables:

$N_N(t)$ - Number of active individuals who are Non-reactive on day t.
$S_N(t)$ - Number of susceptible Non-reactive persons on day t.
$I_N(t)$ - Number of infective & asymptomatic Non-reactive persons on day t.
$N_R(t)$ - Number of active individuals who are in the Reactive group on day t.
$S_R(t)$ - Number of susceptible persons in the Reactive group on day t.
$I_R(t)$ - Number of infective & asymptomatic persons in the Reactive group on day t.

On every single new generation of the flu, members of the reactive group will be able to select their activity level between a set of A possible activity level options. For the rest of this section when we refer to a day we imply a generation of the flu which is equivalent to approximately 2-3 actual 24 hour days. These activity level options will all be equal to or less than the rate of social contact in a non-pandemic scenario. While

several individuals may have more contacts as a result of the pandemic, only decreases in activity are logical and will be observed at the overall population level. Consider the case where the reactive group will be selecting their activity out of the following set of contact rates:

$$\Lambda = \{30,20,15,10,5\}$$

We will use the following notation: $\Lambda_1 = 30, \ldots, \Lambda_5 = 5$. Also, if the activity level selected is $j \in J$, then we will use Λ_j as the selected contact rate.

The reason that we do not create a behavior level where 0 contacts are made on a daily basis is because this type of behavior would be almost impossible for most individuals. Most people live in homes with their families or roommates. Those who live alone usually live in apartment buildings. These living situations would make it almost impossible to avoid all contact unless the government stepped in and isolated people in separate facilities.

From our Λ options we can define, $p_j^R(t)$ the probability that an individual will get infected on day t if they select activity level j. We assume that all individuals in the reactive group will be selecting the same behavior. From prior calculations we know that:

$$p_j^R(t) = 1 - e^{-\Lambda_j \beta_j(t) p}$$

where,

$$\beta_j(t) \equiv \frac{\Lambda_j I_R(t) + \lambda I_N(t)}{\Lambda_j N_R(t) + \lambda N_N(t)}$$

Now that we have determined the probability of infection associated with each behavior option, we need to identify the actual benefits and drawbacks of each type of behavior.

First, let us define the function $u(x)$ which is the benefit, or utility that an individual from the reactive group receives on a given day[24] when their daily rate of contact is x. The benefit function, $u(x)$ is likely to be either a linear or a concave function because each additional contact is likely to have marginally decreasing benefit. We will first assume that $u(x)$ is a linear function and then change this assumption to evaluate its impact. This type of function would be accurate for a salesman who receives a fixed commission for each sale that he or she makes; the more people the salesman sees, the bigger the commission he expects to receive. Initially let $u(x) = x$ utils.[25]

If an individual becomes sick, he or she will experience several losses. First, the person will not be active for the duration of their illness. As in ***Chapter 3*** we define d as the duration of the sickness. For the sake of numerical examples, let d= 2 days. In addition to the loss of social contacts during the illness, there is a general loss to a sick individual. Not only is the flu an unpleasant experience, it can be deadly. So we define Δ – the balloon cost of becoming sick. Note, the units for the benefit function and for the balloon cost should be the same. Let us define Δ=1000 utils.

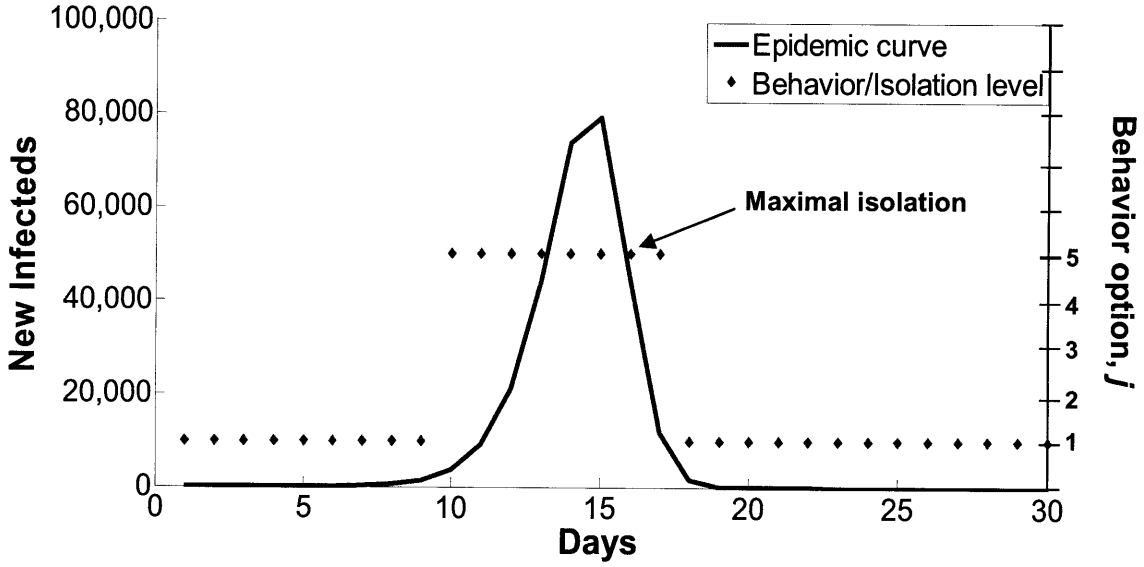
In this case, the objective of the reactive group on a daily[6] basis becomes to select the activity level j such that:

$$\max_{j \in J} \left\{ u(\Lambda_j) + p_j^R(t) \left(u(\overline{\Lambda}) d + \Delta \right) \right\}$$

where $\overline{\Lambda}$ is the average of all possible contact rates. For a given epidemic curve we can determine $p_j^R(t)$, the probability of infection on a daily basis. As a result, for a given curve we can determine the behavior that will be chosen by the reactive group. In ***Graph***

[24] Day refers to one generation of the flu, equivalent to approximately 2-3 24 hour days.
[25] We define a benefit unit – util. Utils are used in economic studies. In future work $ units could be used to replace utils.

4.4 you can see the epidemic curve and behavior selection of the reactive group for that specific curve.

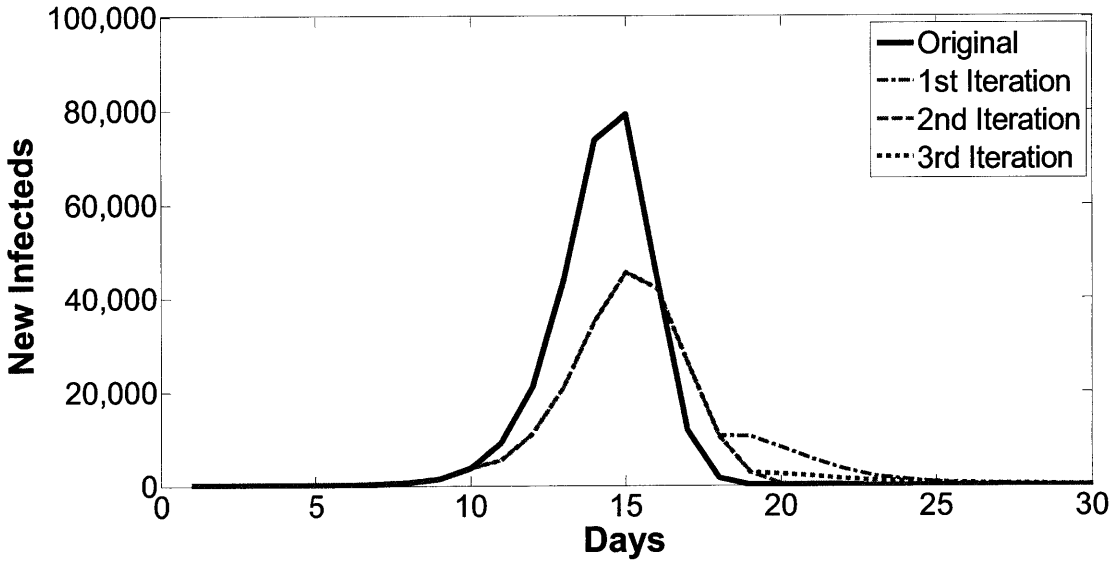


Graph 4.4
The behavior of the reactive group over the course of the outbreak.

You may notice that in this case the behavior of the reactive group is either maximally isolated or completely normal – a "Bang-Bang" behavior. The reason for this extreme selection is the linearity of the benefit function, $u(x)$. We will provide an example of how this changes when the benefit function is concave later on in this section.

If the reactive group is a significant enough portion of the population and if these individuals change their behavior according to the above predicted approach, then the epidemic curve is going to change. Therefore, the next step is to recalculate our epidemic curve assuming that the non-reactive group maintains their behavior and the reactive members change their daily contact levels according to the pattern predicted by the original epidemic curve. A new epidemic curve in turn means that the behavior of the reactive group may be different than for the original outbreak. The next step is to find the

appropriate behavior pattern for the new epidemic curve, and so we reiterate the process. For a reactive group that makes up 50% of the total population, the epidemic curve converges after 2-4 iterations as can be seen in ***Graph 4.5***. Unless the size of the reactive group is big enough to completely stop the spread of the virus, the number of iterations till conversion increases with the size of the group. The smaller sized reactive groups require only 1-2 iterations.



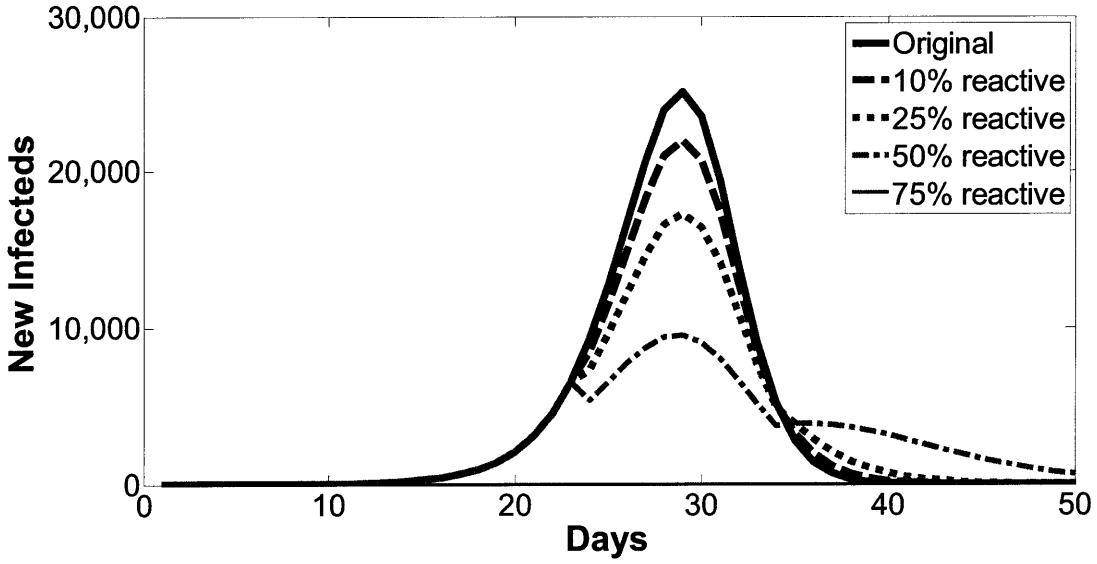
Graph 4.5
For a reactive group that makes up 50% of the overall population the epidemic curve converges after 3 iterations.

The size of the reactive group is a crucial factor in determining the actual epidemic curve. As we saw with SARS, it is unlikely that everyone in the population will alter their behavior. Studies of peoples' perception of avian flu also indicate that peoples' attitudes and perceptions of risk differ from country to country (Zwart, 2007). Also, depending on the timing of the community outbreak within the scope of the global outbreak the size of the reactive group is likely to vary. In the 1918-1919 pandemic, the

cities that experienced the outbreak at a later period, had more people reactively changing their behavior (Markel, 2007). One thing is clear: a certain fraction of the population will change their behavior. As can be seen in ***Graph 4.6*** even for a reactive group which is only 25% of the overall population, the cumulative infection rate is decreased, and the peak of epidemic curve is lowered. If the reactive group is 75% of the population, the transmission of the influenza never takes off; a large enough fraction of people limit their interactions early enough in the outbreak. While the overall infection rate decreases, it is important to notice that the duration of the outbreak increases for a larger reactive group. As long as the susceptible pool is big enough, the virus will persist.[26]

By altering their behavior during the risky, high-transmission days of the outbreak the reactive group significantly improves their own chances of never becoming infected, thus their actions are justified. Furthermore, the change in behavior of the reactive individuals has some marginal benefit on the infection rate of the non-reactive group. This is somewhat similar to the concept of herd immunity, which specifies that in order to stop transmission only a certain fraction of the population needs to be vaccinated. Similarly in the case of behavior change, as long as a large enough fraction of population is decreasing overall transmission, those who don't change their behavior still benefit. To see the infection rates in the reactive and non-reactive groups refer to ***Table 4.2.***

[26] The size of the susceptible pool necessary to maintain transmission is different for each of the scenarios.



Graph 4.6

The impact of varying sized reactive groups on the epidemic curve. The larger the reactive group the less the burden of the infection. However, unless the virus dies out like in the case of 75% reactive group, a larger reactive group leads to a longer outbreak.

	Infection rate for Non-Reactive group (%)	Infection rate for Reactive group (%)	Cumulative Infection rate (%)
0% reactive	68.8	26.1 *	68.8
10% reactive	67.4	26.3	63.3
25% reactive	65.0	27.1	55.5
50% reactive	61.1	33.6	47.4
75% reactive	~0	~0	~0

Table 4.2

The infection rate in the different groups based on the overall size of the reactive population.

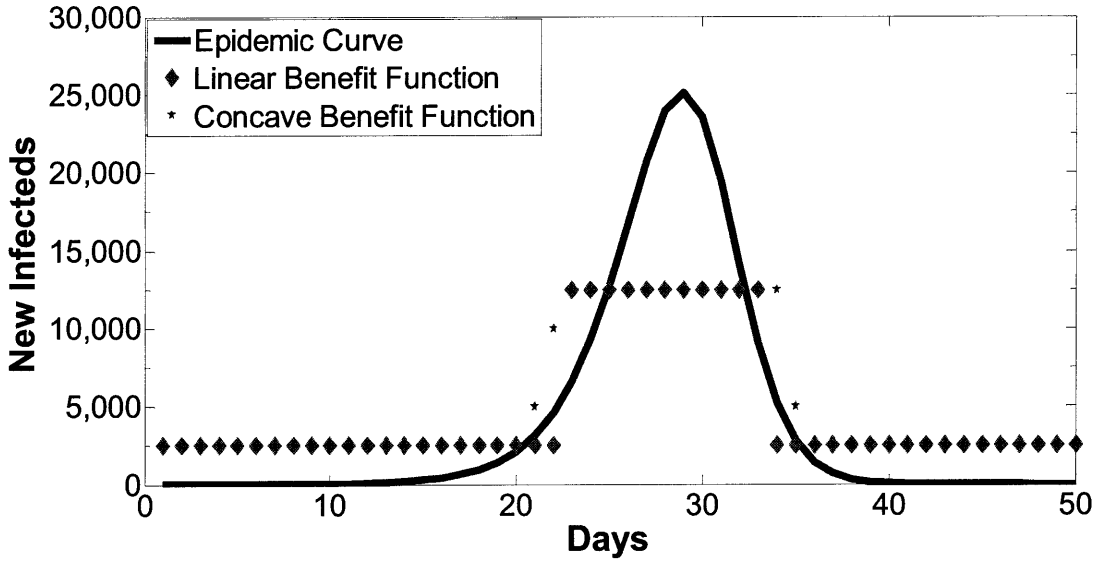
** If 1 individual changes his or her behavior, the probability of infection for that individual will be 26.1%*

Notably, as can be seen in ***Table 4.2*** as the size of the reactive group increases the benefit experienced by the reactive group decreases. The probability of becoming infected for a member of the reactive group that is 50% of the population is 33.6%. While if only one individual thought to change his or her behavior, that person would have a

26.1% chance of infection. It occurs because a larger reactive group leads to a longer outbreak and the increase in duration makes up for the decreased daily infection rate. This type of decreasing benefit pattern is not consistent for all populations. Refer to ***Appendix G*** for another example where this is not the case. However, this phenomenon may imply that future studies can consider some game theory applications.

As we mentioned before, the type of benefit function used to determine the importance of contacts determines whether non-extreme behaviors are ever selected. Consider the case where the daily[27] benefit is the concave function $u(x) = 5\sqrt{x}$.[28] Such a concave benefit function is a very reasonable assumption because for most people seeing their direct family members is very valuable, while contact with the 30th coworker doesn't bring them much benefit. In this case, as seen in ***Graph 4.7***, the members of the reactive group decrease their contacts to a level of maximum isolation more gradually and ramps down the isolations in two steps. Refer to ***Table 4.3*** to see the impact of a concave benefit function on the infection rate within the different groups.

[27] Day refers to one generation of the flu, equivalent to approximately 2-3 24 hour days.
[28] The multiplicative of 5 is to ensure that the scales of the linear and concave functions are comparable; the two function intersect at 25 contacts.



Graph 4.7

Comparing the behaviors of the reactive groups with linear and concave benefit functions. A nonlinear benefit function allows for non-extreme behavior choices.

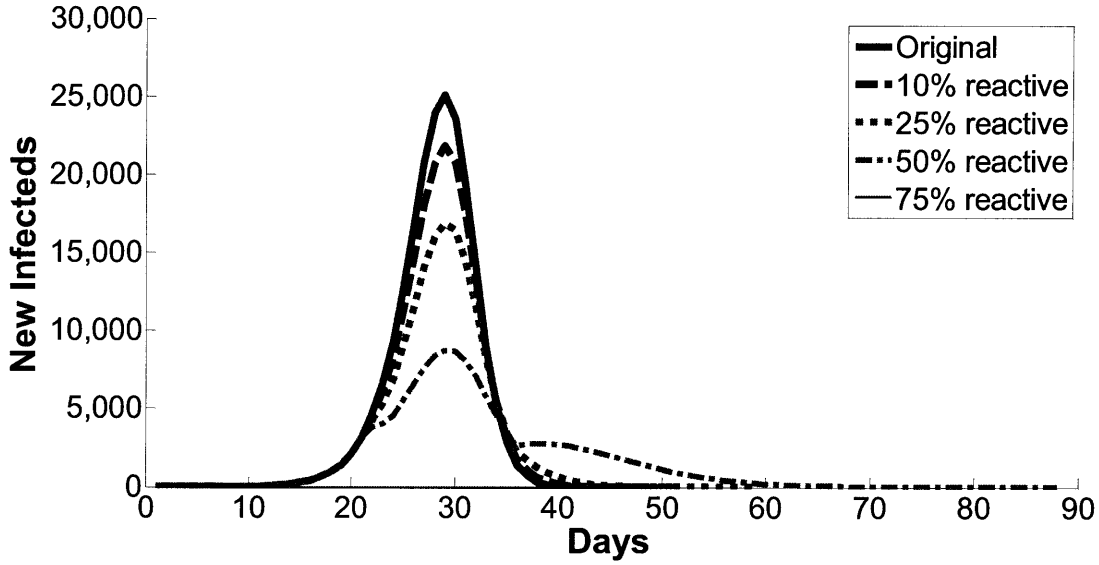
	Infection rate for Non-Reactive group (%)	Infection rate for Reactive group (%)	Cumulative Infection rate (%)
0% reactive	68.8	22.3*	68.8
10% reactive	67.2	22.2	62.7
25% reactive	64.2	22.2	53.7
50% reactive	59.9	30.3	45.1
75% reactive	~0	~0	~0

Table 4.3

The infection rate in different groups based on the size of the reactive population.
** If 1 individual changes his or her behavior, the probability of infection for that individual will be 22.3%*

In the case of the $u(x)=5\sqrt{x}$ benefit function, the behavior choices of the individuals are earlier and last longer and thus fewer people become infected. This is not always the case, and sometimes a concave function can lead to slightly slower reactions. In either case, the rate of infection and the epidemic curves in ***Graph 4.8*** are comparable for either type of benefit function. There is very little data that indicates which benefit

function would be appropriate for the reactive group. While it is likely that a concave function may be more appropriate for each particular individual, it is unclear if this would hold for the whole reactive group. We suggest that using a linear benefit function may be easier for initial studies.



Graph 4.8

The epidemic curve for different sized reactive groups with concave benefit functions. The epidemic curves are very similar to those resulting from a linear benefit function.

The main insight from this approach to modeling behavior change is that by altering their contact levels, people can change transmission dynamics. While the duration of the outbreak is lengthened, the cumulative burden of infection as well as the peak rate of infection are significantly decreased. There is even the potential to stop the outbreak completely.

The models and graphs presented in this section were created in Matlab, refer to ***Appendix H*** for the coding of this model.

4.4 Model 3: Behavior Constraints and their Impact

As we have reiterated throughout this chapter, behavior changes will occur in an influenza pandemic. In the two models that we presented earlier, we argue that people will alter their behavior and isolate during the "high risk" days of the pandemic. The question that quickly comes up is: realistically, can people actually isolate for a long period of time? Is it accurate to assume that those who alter their behavior will do so consistently during the whole time? As we have seen with the two previous models, the more forcefully the community responds and changes its behavior, the longer the outbreak will persist in the community. This idea is also supported by some of the instances in 1918-1919 pandemic, where cities that were very effective at managing the infection experienced outbreaks that were twice as long or even longer (Markel, 2007). As a result the "high risk" days may last for multiple weeks.

Lack of essential items such as food, water and medication reduces the length of time that people could stay at home in isolation, and increases the burden and urgency with which the government would need to deliver supplies (Williams, 2005). In Toronto during the SARS outbreak of 2003 there were large scale quarantines. Through interviews as well as telephone polling one study focused on the issues that affected the population's willingness to comply with quarantine (DiGiovanni, 2004). They identified that sometimes workers had to leave their homes and break quarantine to go to work and that the continuation of their wages, salaries and other forms of income while they were not working were important factors in their willingness to comply (DiGiovanni, 2004). People were also concerned about how they would be supplied with groceries and other services for daily living (DiGiovanni, 2004). Another study of a mumps outbreak that

occurred in 2006 on a Kansas college campus found that the longer students were asked to stay in isolation, the less likely they were to fully comply with the quarantine (Soud, 2009). In addition, a study of London's citizens indicated that less than half of the population has the emergency supplies necessary for an emergency (Page, 2008). All this indicates that peoples' behavior would not be consistently isolationist in a pandemic.

In order to incorporate this aspect we develop another approach to modeling peoples' behavior. As in the model described in ***Section 4.3*** we will have a fraction of the population – y, be reactive and alter their behavior in order to minimize their risks of infection. Instead of balancing tradeoffs as before, this reactive group will be attempting to minimize their risk of infection subject to the constraints that they have on their behavior. Constraints may be that the individual needs to attend work and go to the grocery store every couple of days. We will represent that as a constraint on the minimal number of contacts that the individual will have to make throughout several days, but other types of constrains could also be modeled using a similar tactic.

We define our model with the same variables as before:

$N_N(t)$ - Number of active individuals who are Non-reactive on day t
$S_N(t)$ - Number of susceptible Non-reactive persons on day t
$I_N(t)$ - Number of infective & asymptomatic Non-reactive persons on day t
$N_R(t)$ - Number of active individuals who are in the Reactive group on day t
$S_R(t)$ - Number of susceptible persons in the Reactive group on day t
$I_R(t)$ - Number of infective & asymptomatic persons in the Reactive group on day t

On every new generation of the flu, members of the reactive group will select their activity level between a set of Λ_j possible activity level options. As before whenever we refer to a day in this section, we imply one generation of the flu, which is approximately

2-3 actual 24 hour days. For the purpose of numerical examples consider the following contact rate options:

$$\Lambda = \{30, 20, 10\}$$

Again, we will use the following notation: $\Lambda_1 = 30, \ldots, \Lambda_3 = 10$. If the activity level selected is $j \in J$, then we will use Λ_j as the selected contact rate. As before, we do not create a behavior level where 0 contacts are made on a daily basis. We assume all individuals in the reactive group will be selecting the same behavior. Yet again, for a given epidemic curve we can define, $p_j^R(t)$ the probability that an individual will get infected on day t if they select activity level j:

$$p_j^R(t) = 1 - e^{-\Lambda_j \beta_j(t) p}$$

where,

$$\beta_j(t) \equiv \frac{\Lambda_j I_R(t) + \lambda I_N(t)}{\Lambda_j N_R(t) + \lambda N_N(t)}$$

Unlike before, members of the reactive group have a constraint on their behavior. We can model different types of constraints in this format, but for the sake of simplicity, consider the case where the number of contacts that an individual needs to make in 4 days[29] has to be greater than or equal to X contacts. The objective of the reactive group is to minimize the likelihood of becoming infected, or maximize the probability of staying healthy, over the entire outbreak while following the above mentioned constraint.

This can be formulated as a dynamic program (DP). Let us define:

$F(t, S(t))$ – the probability of staying healthy from day t till the end of the outbreak given that the state on day t is $S(t)$.

[29] Four days in the context of our model is 4 generations of the flu or 1-1.5 weeks of actual 24 hour days.

The state on day t is defined based on the constraints that the reactive group has imposed on their behavior. In the case of our example the state $S(t)$ has 4 components – the behavior selections over the past 4 days including day t. Thus, $S(t) = \{i, j, k, l\}$ –indicates that the behavior choice on day t is l, on day $t-1$ it is k, on $t-2$ it is j and on day $t-3$ it is i. We will use the $F(t,\{i,j,k,l\})$ and the $F(t,S(t))$ notation in our calculations. Lastly, let us define the set A of combinations $\{i,j,k,l\}$ such that the contact rate over the four days is greater than or equal to X. So, $\{i,j,k,l\} \in A$ if $\Lambda_i + \Lambda_j + \Lambda_k + \Lambda_l \geq X$.

Let us call the last day of the outbreak day T, then we know that,

$$F(T,\{i,j,k,l\}) = 1 - p_I^R(T)$$

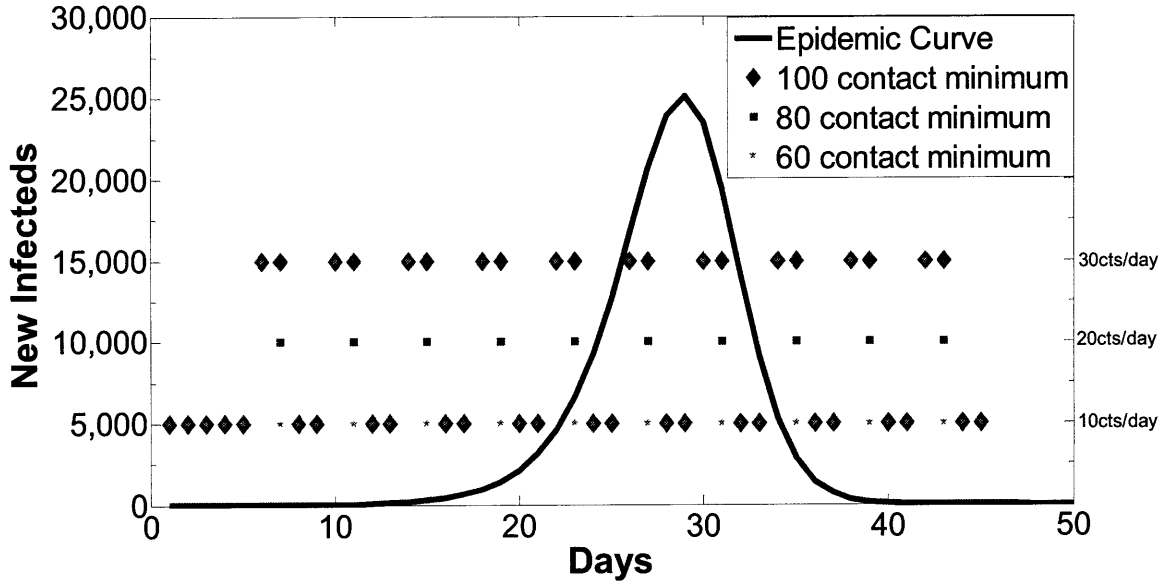
and

$$F(t-1,\{i,j,k,l\}) = \max_{m,\text{s.t.}\{i,j,k,m\}\in A} \left[F(t,\{j,k,l,m\}) * \left(1 - p_m^R(t)\right)\right]$$

Using this approach we can find the objective function value $max\ F(0,S(0))$ and the behavior pattern necessary to achieve maximal probability of staying healthy. In ***Graph 4.9*** we show what the behavior pattern would look like for values of $X = 80, 90, 100$. Notice that when the constraint is a minimum of 80 contacts over 4 days, the better behavior is to isolate maximally to 10 contacts per day on two days and to be normally active on the other two days instead of maintaining a constant 20 contacts per day.[30] The "Bang-Bang" approach is better for minimizing the cumulative risk of infection. In this case the only times that the intermediate behavior is exhibited is when the individual has to observe a specific constraint and thus cannot isolate maximally. For example, to satisfy a 90 contact minimum, the behavior pattern is one day of maximal isolation, one of intermediate isolation and two of normal behavior.

[30] Day refers to one generation of the flu, the equivalent of approximately 2-3 24 hour days.

As before, if the reactive group makes up a significant portion of the population and its members alter their behavior following the above behavior pattern, then the epidemic curve is going to change. Thus, we iterate the process of determining the epidemic curve and the behavior pattern until it converges.

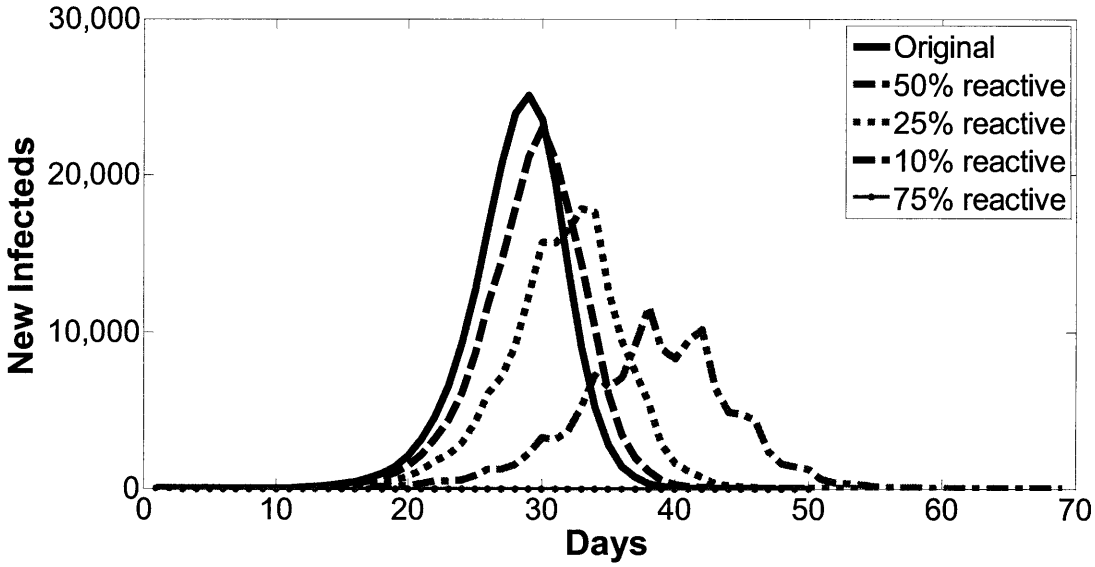


Graph 4.9

Behavior patterns that are selected to maximize the probability of staying healthy throughout the entire outbreak while satisfying the minimal contact rate.

Let us now see the impact of this type of on and off isolationist behavior on the epidemic curve. Consider the scenario where the minimal number of contacts in 4 days, $X = 80$, so the behavior is two days of maximal isolation followed by two days of maximally social behavior [31]. Depending on the size of the reactive group within the overall population the epidemic curve is going to vary significantly as can be seen in ***Graph 4.10***. The corresponding cumulative infection rates for the different sized reaction groups are presented in ***Table 4.4***.

[31] Day refers to one generation of the flu, the equivalent of approximately 2-3 24 hour days.



Graph 4.10

The epidemic curve for different sized reactive groups that throughout the outbreak follow the 2 days of maximal isolation followed by two days of active behavior pattern.

	Infection rate for Non-Reactive group (%)	Infection rate for Reactive group (%)	Cumulative Infection rate (%)
0% reactive	68.8	53.9*	68.8
10% reactive	66.5	51.4	65.0
25% reactive	62.3	47.0	58.4
50% reactive	51.8	37.0	44.4
75% reactive	~0	~0	~0

Table 4.4

The Infection rate for different groups based on the size of the reactive group.

** If 1 individual changes his or her behavior, the probability of infection for that individual will be 53.9%*

An important assumption in our model is that all the individuals in the reactive group isolate and interact in synch. Not only do all the people in reactive group have the same behavior pattern, but they isolate and interact on the same days as everyone else. This assumption is the reason that there are oscillations in the epidemic curve, especially for the case where the reactive group is large. For example when the reactive group is 50% of the total population, the epidemic curve is jagged. This occurs because on certain

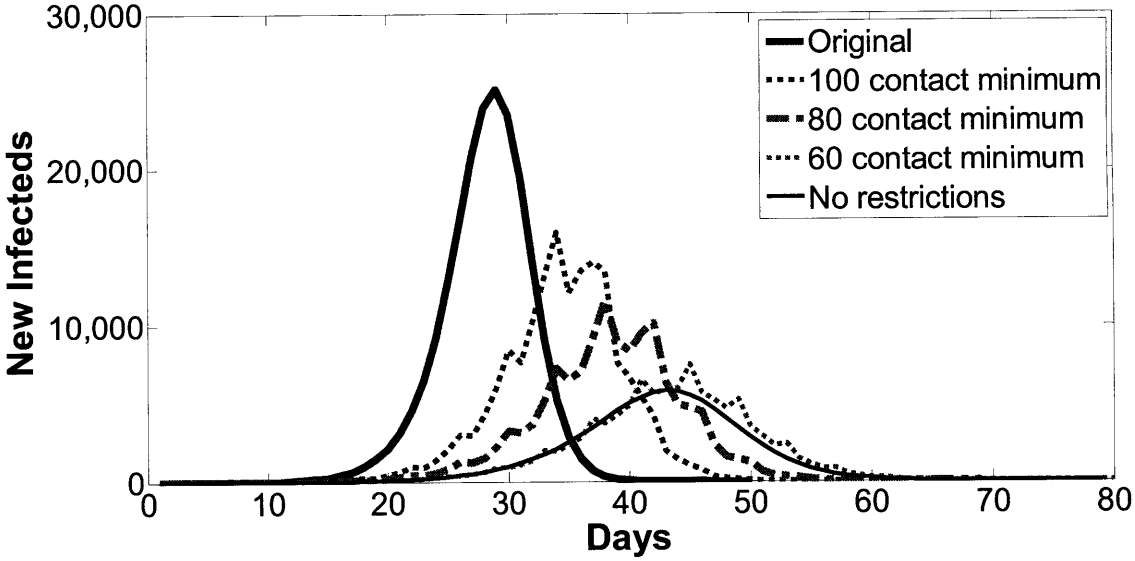
days half of the population isolates simultaneously and this causes the temporary drop in transmission. When as a result of their behavioral constrain everyone in the reactive group returns to their normal behavior the transmission rebound to a higher level, thus creating the jagged pattern in the curve.

Realistically, while there may be some overlap, people will not perfectly coordinate their isolation behavior. This is somewhat reminiscent of the heterogeneity presented in ***Section 3.4***. While a fraction of the reactive group will be isolating, different individuals will be staying at home on different days. If people react and isolate out of synch, then the epidemic curve will be smoothed out as different individuals stay at home on different days.

The infection rate is lower in the reactive group, but the difference in the infection rates for the two groups is not as significant as for model 2. The reason is that even one day of not following precautions can result in infection. This is especially true for the cases where the reactive group is small and at the peak of the outbreak the number of infecteds is very high and any activity during the peak days is very likely to cause infection. However, the benefit of the reactive group is still significant and translates to a marginal benefit for the non-reactive group as well. Moreover, if the fraction of individuals altering their behavior is high enough, in this case 75%, the infection dies out without infecting a substantial fraction of the population. Lastly, the larger the reactive group the longer the outbreak persists in the population.

The next question is: what is the impact of the behavioral constraint on the epidemic? What if the population is prepared with stockpiles of food and other essential items and can stay at home for a somewhat longer period of time? Let us focus on the

case where the reactive group makes up 50% of the overall population. The impact of the constraint on the epidemic curve can be seen in ***Graph 4.11*** and the corresponding infection rates in ***Table 4.5***; we vary X from 40 contacts to 100 contacts. When the individuals need only 40 contacts in any four day segment, they maximally isolate, so we call that the "No restrictions" case.



Graph 4.11

Impact of different behavior constrains on the epidemic curve when 50% of the population is in the reactive group.

	Infection rate for Non-Reactive group (%)	Infection rate for Reactive group (%)	Cumulative Infection rate (%)
100 min	58.0	50.4*	54.2
80 min	51.8	37.0	44.4
60 min	43.9	24.1	34.1
No restriction	44.3	17.7	31.0

Table 4.5

The infection rates for different types of behavioral constraints, for a population where 50% are in the reactive group.

** If 1 individual changes his or her behavior, the probability of infection for that individual will be 50.4%*

There are several important observations. Consider the most demanding constraint of 100 contacts; it allows the reactive individuals to maximally isolate only one day out of four. This one day of isolation not only decreases the peak infection rate by almost a factor of two, but also decreases the cumulative infection rate from 68.8% down to 54.2%. Also, by requiring people to be active one out of four days, the case of 60 contacts, the cumulative infection rate is 34.1% which is not much worse than the case where there are no restrictions and the resulting infection rate is 31%. When the size of the reactive group is small the benefits are significantly diminished. For example even if 25% of the population maximally isolates throughout the entire outbreak, the cumulative infection rate is still 49%.

What this model reveals is that even inconsistent behavior changes can decrease the infection burden significantly as long as a sufficient number of people are altering their behavior. Even if people can't maximally isolate throughout the entire outbreak, it is very important that as many people as possible attempt to alter their behavior as much as they can. The implication for the policy perspective is that it is important to focus resources on educating as many people as possible and encouraging them to change their behavior. Changing the behavior of the mass is more important than focusing resources on a few individuals and putting them into maximally restrictive quarantine[32].

The numerical calculations and graphs presented in this section were developed in Matlab. Refer to ***Appendix I*** for the coding of this approach.

[32] Note, in this section we do not have highly active individuals. In the case of highly active individuals who contribute a disproportionally high fraction to the infection rate, focusing resources may be helpful.

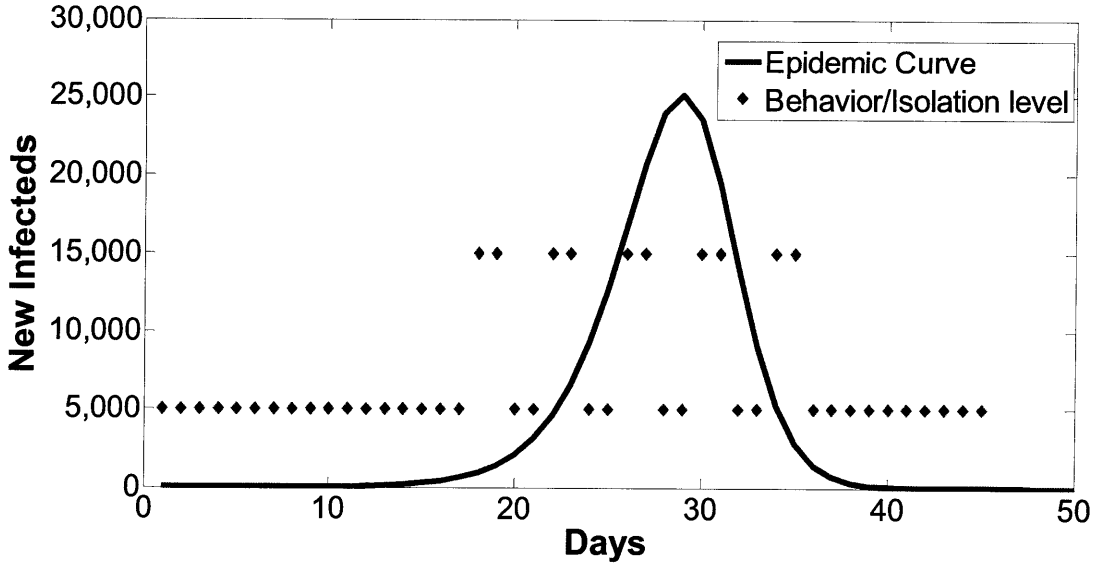
4.5 Combination of Models 2 & 3: Balancing Tradeoffs while Following Constraints

Before we summarize the insights from our different approaches to modeling behavior changes in the population, there is one more model that we would like to propose. This method is simply the combination of the two models presented in ***Sections 4.3 & 4.4***: because in reality people both consider the tradeoffs of isolation and interaction and are not able to isolate indefinitely.

We model this by first determining the behavior pattern according to the dynamic programming approach described in ***Section 4.4***. Second, for each day that the reactive individuals consider isolation they also perform the tradeoff analysis presented in ***Section 4.3***. For the days that the individual can't isolate because of their prior isolationist behavior, the tradeoff analysis is not performed because the constraint on behavior overrides the tradeoff analysis. In ***Graph 4.12*** you can see the behavior isolation level that is selected by the reactive group for the epidemic curve shown.

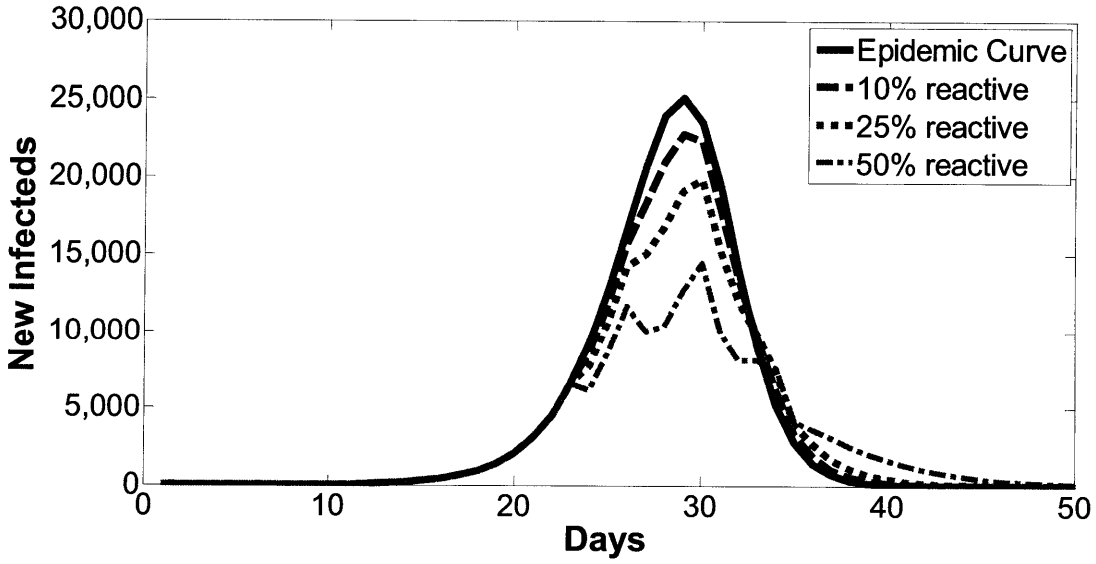
The resulting epidemic curve given this type of behavior pattern for different sized reactive groups can be seen in ***Graph 4.13***. The corresponding infection rates for the reactive and non-reactive groups are shown in ***Table 4.6***.

As before, we assume that all the individuals in the reactive group isolate and interact in synch. Again this assumption causes the oscillations in the epidemic curve that can be seen for larger sized reactive groups. Realistically, individuals are not likely to coordinate their behavior strategies, thus the more appropriate epidemic curve will be smoothed out to a certain degree.



Graph 4.12

The behavior selection that both balances the tradeoff and follows behavioral constraints for the shown epidemic curve. The parameters used in this graph are $\Lambda = \{30,20,10\}$, p=0.05, X=80, u(x)=x, $\Delta = 1000$, d=2.



Graph 4.13

The epidemic curve for the case where the reactive group both considers the tradeoffs of their activity level and satisfies the constraints that they have on their behavior. For this graph, the reactive groups isolated for a total of 6 days (flu generations).

	Infection rate for Non-Reactive group (%)	Infection rate for Reactive group (%)	Cumulative Infection rate (%)
0% reactive	68.8	56.5*	68.8
10% reactive	66.7	53.6	65.4
25% reactive	63.2	50.4	60.0
50% reactive	56.2	44.8	50.5
75% reactive	0	0	0

Table 4.6

The infection rates for the different groups that both evaluate the tradeoffs of their activity level and satisfy all behavioral constraints.

** If 1 individual changes his or her behavior, the probability of infection for that individual will be 56.5%*

For the epidemic curves and infection rates presented in this model, the reactive group only isolates for a total of 6 days[33] out of about 50 days. Even this limited amount of isolation, significantly decreases the peak and cumulative rates of infection, as long as the size of the reactive group is large enough. This further supports our previous statement that it is important to encourage a large number people to alter their behavior. Furthermore, it is important to coordinate the behavior change so that it coincides with the peak of the epidemic curve. An early response is great, however it may be dangerous if it causes people to lower their guards during the peak times of the outbreak.

The model presented in section was implemented in Matlab; refer to ***Appendix J*** for the code.

4.6 The Reproductive Number and Behavior Changes

One of the reasons that the basic reproductive number – R_0 is not the best approach to guide policy is because it doesn't take into account the fact that people are

[33] 6 flu generation days, which corresponds to 10-18 normal 24 hour days.

likely to change their behavior during the pandemic. The effective reproductive number – *R(t)* is the average number of secondary cases from a typical infective on day *t*. When it comes to modeling pandemic flu, there are practically no instances of including the behavioral response in evaluating R(t). In our case we can determine *R(t)* for the models that include behavior changes. The approximation of *R(t)* for our model is just:

$$R(t) = \frac{\sum_j I_j(t+1)}{\sum_j I_j(t)}$$

which is just the number of people who end up infected tomorrow over the number of people who are infected today.

Using this approach the reader can calculate the reproductive number for all the models present in this chapter. One of the findings is that *R(t)* will not be monotonically decreasing for these models of behavior change. Since peoples' reaction will not be constant throughout the outbreak, and may even oscillate between maximal isolation and relatively social behavior, like in ***Section 4.4***, the effective number in certain cases will also go up and down.

4.7 Other Factors That Will Change Peoples' Behavior

There are several factors that have not been explicitly mentioned in the above models, but will clearly influence how people will react in the case of an influenza pandemic. One of the most important assumptions that we made in the above models is that people will react rationally: decrease their contact rates and improve their hygiene practices. Actions of this type imply that the population will understand how influenza

transmits, know how to avoid the infection and respond to the information regarding the presence of the infection.

An important factor in the Behavior Intention Model (BIM) is the perceived behavioral control – the ability to perform the behavior (TCW, 2004). If individuals believe that they can easily fulfill the necessary requirements they are much more likely to act accordingly (TCW, 2004).This implies that the relevant institutions should be prepared to implement appropriate leave-of-absence laws and help citizens maintain high levels of hygiene during the pandemic. BIM also emphasizes the importance of subjective norms – humans' actions reflect what others believe is the right thing to do (TCW, 2004). In the course of a pandemic, public figures from local and federal governments could influence their constituents by explaining the importance of control measures to the public. The transaction model of stress and coping indicates that in a stressful situation individuals will demonstrate "information seeking behavior", implying that the media must portray information in a constructive manner (TCW, 2004). Educating the public can ensure the cooperation of individuals; when people don't understand the risks they do not act (Hong, 2006). The main conclusion we draw from these behavior feedback models is that the information people receive, both about the extent of the epidemic and our ability to manage the situation, will help determine peoples' reactions and thus directly impact the course of the pandemic.

As of today, people do not have a very good understanding of pandemic influenza, how it differs from seasonal flu and what can be done to protect oneself from it (Janssen, 2006). Educating the public about the modes of influenza transmission should encourage people to decrease their activity levels. Furthermore, people will need to learn

the importance of hand and cough hygiene. Knowledge and understanding of the disease is not sufficient, people must also be capable of changing their behavior. Improved hygiene measures imply that soap, hand sanitizer and other protective measure supplies will be available to the public. Limiting social contact assumes that some people will have the ability to telecommute to work – that the internet and other communication lines will be up. While we hope that these conjectures will hold in a pandemic, no one can guarantee that their local WalMart will have a sufficient stockpile of hand sanitizer, or that our electricity and communication lines will be functional.

In addition to knowledge, understanding and capability to implement the behavior changes, the public needs to hear a unified and timely message from different sources informing them about the outbreak. In 1918-1919 Philadelphia city officials denied the presence of the Spanish Flu while simultaneously people were dying from the virus that was ravaging their city. While the government's intent was to try and calm the public, the result was the complete opposite as panic broke out, doctors and nurses were kidnapped from hospitals and bodies piled up on the streets. On the other hand, during the SARS outbreak in 2003, the public health officials in Hong Kong very quickly and efficiently informed the population about the seriousness and extent of the disease. As a result the population of Hong Kong was motivated to alter their daily actions to avoid becoming infected.

The results of one study indicate that people will rely on the information provided by the CDC, information found through the Google search engine as well as general media (Janssen, 2006). If people focus on the information seen in the media there is a danger that there may be miscommunication and somewhat conflicting messages

amongst different sources. Sometimes the news provided by the media can be sensationalist; this type of approach may cause panic instead of a controlled response. Today there are many media outlets, and an individual living in New York can very easily access the Boston news sources to learn about the events in other cities. If people access different sources for information and find conflicting messages, the results could be very problematic. If one school district closes its schools, while the neighboring school district does not, the result could be of confusion and frustration about the discrepancy. It has also been observed that some individuals are somewhat distrustful of the government in this type of scenario (Janssen, 2006). People will turn to their physicians and other sources for information. Quickly and accurately educating healthcare workers will help reinforce the message presented to the general public. It is important that all people hear a unified message and coordinated response plan in the case of a pandemic.

Another issue that is important to take into account and that uniquely applies to the United States is that this is a country that brings together many cultures. Because of language barriers and cultural perceptions there are people in the US who do not turn to American news sources for information. According to the 2000 US census 18% of US citizens do not speak English in their homes. Approximately 17 million Americans, who by their own acknowledgement cannot speak English very well, could at worst miss the entire informational announcement or at best have difficulty understanding the informational content. Moreover, in certain states like California where 2 out of 5 people do not speak English in their homes the concentration of non-English speakers is very high. In a pandemic those individuals are just as susceptible to infection, and it becomes

important to instruct and inform these people in a way that they will understand. This means producing the educational materials in different languages. Language is not the only important factor, sensitivity to cultural and religious differences will also be important. For example, in the UK there have been instances where Muslim healthcare workers refused to use hand sanitizer because of its alcohol content (MacAllen, 2007). In a pandemic, cultural and religious differences are bound to surface and should be anticipated.

Another issue that could become prominent in determining people's behavior in a pandemic is the socioeconomic status of individuals. In a pandemic the financially well established individuals have more control over their work schedules and usually have an easier time negotiating working remotely or even taking some time off with their employers (Blain, 1993). This means that reducing contact levels may be very difficult for certain portions of the population. It has also been pointed out that closing schools would not burden the middle and upper class, but would create significant burden on the population in the lower economic levels. Not only will these parents struggle trying to stay home with the kids while not losing their jobs, but they would also lose the school lunches that their children receive. Sensitivity to the socioeconomic diversities and understanding of their impact will also be important in crafting the message to the public.

Another important aspect revealed by a study of the response to the SARS outbreak is that people respond differently based on the way that the information about the disease is presented to them. Presenting negative information about the impact of the disease: the number of cases and deaths, causes people to worry and potentially panic unnecessarily (Shi, 2003). Presenting positive information like the number of recoveries

and other success stories in battling the infection helps reinforce positive action in the population (Shi, 2003). To the extent possible, it is important to pair positive actions that the public can take to protect themselves and their families with the descriptions of pandemic influenza and its consequences. A study by Janssen et al. determined that the usage of extremely negative terms in fact sheets should be used sparsely or edited out and balanced with positive elements to encourage peoples' cooperation (Janssen, 2006).

Influenza does not see borders, differentiate by ethnicity or socioeconomic level, thus if we want to successfully mitigate the impact of the flu, the education of and communication with all of these different groups should create a unified response.

4.8 Implications of Behavior Models

The behavior models presented in this section have multiple implications in the policy arena. While we presented different models, we were able to make several overarching observations. Let us recap these different insights.

From the first model that we presented, we saw the importance of the highly active individuals in the population. Simply by altering the behavior of these very socially interactive individuals we could significantly alter the course of the outbreak and decrease the overall infection rate. School children are one example of individuals with a high level of activity; by shutting down schools and keeping kids at home the overall infection rate will diminish. Those who have to stay highly active throughout the outbreak will have to alter their actions in other ways to stay healthy. Doctors and nurses

but also grocery clerks and other similarly active people will need to rely on hand sanitizers, masks and other protective hygiene measures.

From all of the models that we have presented in this chapter we have seen that the timing of the behavior changes is very important in determining their effectiveness. The results of the first model have indicated that early behavior changes can be incredibly effective, but only if the measures are maintained throughout the entire outbreak. The timing of the end of behavior changes is just as important as the timing of their beginning. If people do not maintain their precautions, a second wave of the outbreak is likely to occur.

For individuals who cannot self isolate for the entire duration of the epidemic, the best approach is to isolate during the peak infection period of the outbreak. While in the context of our model we can easily say which days are the best for isolation, in real life it is difficult for individuals to identify when the outbreak is about to reach its peak. People have various responsibilities – work, groceries, other errands – that will require that they leave their home. Our recommendation is to minimize the risk of infection by staying and isolating at home for as many days as possible and running all errands during as few days as possible. Also, the each individual should strive to time his or her outing on the day with the fewest number of infected people. This strategy of maximal isolation is not guaranteed to keep the individual healthy, but it does reduce the transmission within the overall population.

It is important for public health officials to be aware that behavioral changes will increase the length of the epidemic. While there is a large enough pool of susceptibles left in the population, influenza can still persist within the community. This is why the timing

of the return to normal behavior is important. If behavior changes are maintained then the peak of the epidemic curve is lowered and the cumulative rate of infection is significantly diminished. Some researchers argue that behavior changes simply "flatten" the epidemic curve without decreasing the total burden of the infection, but we have shown that this is not the case. Hopefully, the extra time we gain as a result of these voluntary interventions will help us buy some time until we have the vaccine for those who have not yet gotten sick. On the other hand, as a result of this longer outbreak the economic impacts may be increased.

We have also found that in an outbreak it is important to get as many people to implement at least minor behavior changes as possible; in this case it is about quantity rather than quality. From a public health standpoint this means that it is very important to reach and educate as many people as possible about the disease. The whole population does not have to turn into qualified doctors overnight. Simply knowing how easily the flu transmits and how it can be prevented should compel most people to change their behavior in minor ways and make a difference on a large scale. If the majority of the population started avoiding crowded public areas, using hand sanitizer and switching to virtual interaction such as telephone and internet whenever possible, the outcome of the outbreak could be significantly reduced.

An interesting finding is that the benefit of changing behavior impacts the entire population. This is somewhat reminiscent of herd immunity. As long as a sufficiently large number of people alter their behavior the risks of infection for the rest are also reduced. It is clear that by becoming more cautious, people are less likely to get sick, but

as a result of never becoming sick they also never have the potential to infect anyone else. Thus the rate of infection is diminished for everyone in the population.

The most important point that we would like to make in this chapter is that behavior changes such as limited social contact and improved hygiene must be included in future pandemic flu models. Behavior is considered to be a decisive factor in modeling sexually transmitted disease, but has been neglected in the context of other infections. We have focused on developing ways of relating how people change their behavior in relation to the epidemic curve. Unfortunately, there is very limited data that we can use to calibrate and validate our model. While there is a lot of evidence of people altering their behavior in various outbreaks there exist very few studies that quantify and relate the changes in behavior to the progression of the disease. Hopefully sociologists, epidemiologists and other interdisciplinary researchers will record these observations in the future, and we can improve the accuracy and validity of our models.

REFERENCES FOR CHAPTER 4

Becker M.H., Joseph J.G., 1988. "AIDS and Behavioral Change to Reduce Risk: A Review." American Journal of Public Health. 78(4):394-408.

Blain J., 1993. "I Can't Come in Today, the Baby Has Chickenpox! Gender and Class Processes in How Parents in the Labour Force Deal with the Problem of Sick Children." Canadian Journal of Sociology. 18(4):405-429.

Bootsma M.C.J., Ferguson N.M., 2007. "The Effect of Public Health Measures on the 1918 Influenza Pandemic in U.S. cities." Proceedings of the National Academy of Sciences of the United States. <http://www.pnas.org/cgi/content/abstract/0611071104v1>

Boyle R.G., O'Connor P.J., Pronk N.P., Tan A., 1998. "Behavior Change : Stages of Change for Physical Activity, Diet, and Smoking Among HMO Members with Chronic Conditions." American Journal of Health Promotion. 12(3):170-175.

Carne C.A., Weller I.V.D., Johnson A.M., et al., 1987. "Prevalence of antibodies of human immunodeficiency virus, gonorrhea rates and changing sexual behavior in homosexual men in London." Lancet. 656-658.

Des Jarlais D.C., Wish E., Friedman S.R., et al., 1987. « Intravenous drug use and the heterosexual transmission of the human immunodeficiency virus : current trends in New York City." New York State Medical Journal. 20:283-286.

DiGiovanni C., Conley J., Chiu D., et al., 2004. « Factors Influencing Compliance with Quarantine in Toronto During the 2003 SARS Outbreak." Biosecurity and Bioterrorism. 2(4):265-272.

Fan E.X., 2003. "SARS: Economic Impacts and Implications. ERD Policy Brief. Economics and Research Department." Asian Development Bank. <http://www.adb.org/Documents/EDRC/Policy_Briefs/PB015.pdf>

Gregson S., Garnett G.P., Nymukapa C.A., et al., 2006. "HIV Decline Associated with Behavior Change in Eastern Zimbabwe." Science. 311:664-666.

Hatchett R.J., Mecher C.E., Lipsitch M., 2007. "Public Health Interventions and Epidemic Intensity During the 1918 Influenza Pandemic." Proceedings of the National Academy of Sciences of the United States. <http://www.pnas.org/cgi/content/abstract/0610941104v1>

Hong S., Collins A., 2006. "Societal Responses to Familiar Versus Unfamiliar Risk: Comparisons of Influenza and SARS in Korea." Risk Analysis. 26(5): 1247-1257. <http://www.blackwell-synergy.com/doi/pdf/10.1111/j.1539-6924.2006.00812.x>

Hudson C., 1999. "Something in the air." Daily Mail, August 21, 30-31.

Janssen A.O., Tardif R.P., Landry S.R., Warner J.E., 2006. "'Why Tell Me Now?' The Public Healthcare Providers Weigh in on Pandemic Influenza Messages." Journal of Public Health Management Practices 12(4):388-394.

Johnson A.M., Gill O.N., 1989. "Evidence for Recent Changes In Sexual Behavior in Homosexual Men in England and Wales." Philosophical Transactions of the Royal Society of London Series B. 325:153-161.

Lau J.T.F., Tsui H., Kim J.H., 2003. "Monitoring community responses to the ARS epidemic in Hong Kong: from day 10 to day 62." Journal of Epidemiology and Community Health. 57:864-870.

Lau J.T.F., Tsui H., Lau M., Yang X., 2004. "SARS Transmission, Risk Factors, and Prevention in Hong Kong." Emerging Infectious Diseases. 10(4):587-592.

Lo J.Y.C., Thomas H.F., Tsang Y.H.L., et al., 2005. "Respiratory Infections during SARS Outbreak, Hong Kong, 2003." Emerging Infectious Diseases. 11(111):1738-1741.

MacAllen S., 2007. "Islamic Superstition Endangers Healthcare System in the West." Islam Watch. <http://www.islam-watch.org/Mac/Islam_Superstition_Health_issues.htm>

Markel H., Lipman H.B., Navarro J.A., et al., 2007. "Nonpharmaceutical Interventions Implemented by US Cities During the 1918-1919 Influenza Pandemic." Journal of the American Medical Association. 298:644-654.

Martin J.L., 1987. "The impact of AIDS on gay male sexual behavior patterns in New York City." American Journal of Public Health. 77:578-581.

McClure R., 2009. "Killer Bug: Staph Outbreaks Prompt More Precautions." About.com: Child Care. <http://childcare.about.com/od/caregonewrong/qt/staph.htm>

McKusick L., Hortsman W., Coates T.J., 1985. "AIDS and sexual behavior reported by gay men in San Francisco." American Journal of Public Health. 75:493-496.

Morbidity and Mortality Weekly Report (MMWR), 1991. "Patterns of Sexual Behavior Change Among Homosexual/Bisexual Men – Selected U.S. Sites 1987-1990." Center for Disease Control. 40(46):792-794.

Morbidity and Mortality Weekly Report (MMWR), 1998. "Cardiovascular Disease Risk Factors and Prevention Practices Among Adults – United States, 1994 A Behavioral Risk Factor Atlas." Center for Disease Control. 47(SS-5):35-69.

MSNBC News Service. 2003a. "Record SARS deaths in Hong Kong." 15th April. <http://www.msnbc.com/news/885653.asp>.

MSNBC News Service. 2003b. "SARS hits airlines, Qantas cuts jobs." 9th April. <http://www.msnbc.com/news/897719.asp>.

MSNBC News Service. 2007. "21 Schools shut after teen dies of staph, Virginia student contracted drug-resistance strain of infection." 16th October. <http://www.msnbc.msn.com/id/21324612/>.

Oliver R., Berger, P., 1979. "A Path Analysis of Preventive Health Care Decision Models." Journal of Consumer Research. 6:113-121.

Page L. Rubin J., Amlôt R., et al., 2008. « Are Londoners Prepared for an Emergency ? A Longitudinal Study Following the London Bombings." Biosecurity and Bioterrorism. 6(4):309-320

Pang X., Zhu Z., Xu F., et al., 2003. "Evaluation of Control Measures Implemented in the Severe Acute Respiratory Syndrome Outbreak in Beijing, 2003." Journal of the American Medical Association. 290(24):3215-3221.

Pearlin L.I., Menaghan E.G., Lieberman M.A., Mullan J.T., 1981. "The Stress Process." Journal of Health and Social Behavior. 22:337-56.

Quah S.R., Hing-Peng L., 2004. "Crisis Prevention and Management during SARS Outbreak, Singapore." Emerging Infectious Diseases. 10(2):364-368.

Rosszell M., 2003. "SARS and Its Impact on Tourism in Toronto." Canadian Lodging Outlook and HVS International. Toronto.
<http://www.hotelonline.com/News/PR2003_2nd/May03_CanadianReview.html>.

Sadique M.Z., Edmuns W.J., Smith R.D. et al., 2007. "Precautionary Behavior in Response to Perceived Threat of Pandemic Influenza." Emerging Infectious Diseases.
<http://www.cdc.gov/EID/content/13/9/1307.htm>.

Schoen J.W., 2003. "SARS business impact spreading." MSNBC News Service, 2nd April.

Shi K., Lu J., Fan H., et al., 2003. "Rationality of 17 cities' public perception of SARS and predictive model of psychological behavior." Chinese Science Bulletin. 48(13):1297-1303.

Soud F.A., Cortese M.M., Curns A.T., et al., 2009. "Isolation compliance among university students during a mumps outbreak, Kansas 2006." Epidemiology and Infection. 137(01).
<http://journals.cambridge.org/download.php?file=%2FHYG%2FHYG137_01%2FS0950268808000629a.pdf&code=b0143b791f19c1e2ef0a6e06d5ccf9fa>.

Stiles B., Kaplan, H., 2004. "Factors influencing change behavior: Risk reduction for HIV infection." Social Behavior and Personality.
<http://findarticles.com/p/articles/mi_qa3852/is_200401/ai_n9437692>.

Tang C., Wong C., 2003. "An Outbreak of the Severe Acute Respiratory Syndrome: Predictors of Health Behaviors and Effect of Community Prevention Measures in Hong Kong, China." American Journal of Public Health. 93(11): 1887–1888.
<http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1448068>.

TCW., 2004. "Health Communication." University of Twente. Netherlands.

Weinstein N.D., Rothman A.J., 2005. "Commentary: Revitalizing research on health behavior theories." Health Education Research. 20(3):294-297.
<http://her.oxfordjournals.org/cgi/content/full/20/3/294>.

Williams M., Saathoff G., Guterbock T., et al., 2005. "Community Shielding in the National Capitol Region: A Survey of Citizen Response to Potential Critical Incidents." Charlottesville: University of Virginia.

Winkelsetin W., Samuel M., Padian N.S., et al.,1987. "The San Francisco Men's Health Study: III Reduction in human immunodeficiency virus transmission in homosexual/bisexual men, 1982-1986." American Journal of Public Health. 77:685-689.

Wiseman P., 2003. "SARS in Hong Kong behavior changes: Panic over illness has bigger impact than SARS itself." USA Today. <http://www.usatoday.com/money/economy/2003-04-13-sars-asia_x.htm>.

World Health Organization., 2004. "WHO consultation on priority public health interventions before and during an influenza pandemic." Department of Communicable Disease Surveillance and Response. Geneva, Switzerland. <http://www.who.int/csr/disease/avian_influenza/final.pdf>.

Zezima K.. 2007. "More Rhode Island Schools Closed in Disease Outbreak." New York Times. <http://www.nytimes.com/2007/01/05/us/05warwick.html>.

Zwart O., Veldhuijzen I.K., Elam G., et al., 2007. "Avian Influenza Risk Perception, Europe and Asia." Emerging Infectious Diseases. 13(2):290-293.

CHAPTER 5:
MULTICOMMUNITY MODEL & OTHER INTERVENTIONS

In this chapter we will present several features that can be added on to our basic model: spatial spread and vaccination. Geographical spread of the virus allows us to estimate the usefulness of travel restrictions. In addition, we can model behavioral changes that are more gradual and only become more prominent as the virus transmits to its neighboring communities and becomes a globally recognized threat. We will show how these strengthening behavioral responses can eventually slow down or stop the outbreak.

We will also present an approach to modeling vaccination of individuals, to show the importance of vaccination timing.

Both spatial spread and vaccination have been studied previously in the context of standard compartmental models. Our findings regarding travel restrictions and vaccination strategies are in line with work done by other researchers.

5.1 Multiple Layered Interventions

In the case of an influenza pandemic, it is highly unlikely that any single intervention will be sufficient to stop the outbreak, but a combination of several measures may have the chance of halting the spread of infection. Hand hygiene measures are effective at slowing down transmission, but if the virus is highly virulent and has a reproductive number, $R_0 \approx 2$ or higher, hygiene improvements may be insufficient unless people also socially distance themselves. Many interventions that can be implemented within a community are not mutually exclusive, and need to be assessed and implemented together. In fact, the CDC has put out a document titled "Interim Pre-pandemic Planning Guidance: Community Strategy for Pandemic Influenza Mitigation in the United States. Early, Targeted, Layered Use of Nonpharmaceutical Interventions" discussing the importance of implementing multiple NPIs early on in the outbreak. We believe that this can be taken a step further; NPIs, as well as pre-pandemic low efficacy vaccines, antivirals, and other measures should all be considered and evaluated by modelers as bundles of interventions.

While we do not evaluate the interplay of these different interventions in this thesis, we do look at many of the interventions separately, and suggest an approach to presenting their combined efficacy. It is important to note that the effectiveness of the interventions will not be additive. For example, using alcohol based hand sanitizer is not going to be as incrementally beneficial to someone who already washes his or her hands, but is still likely to be somewhat useful. Each additional measure will decrease the reproductive number until eventually R_0 is below the pandemic causing threshold of 1. We propose creating a multidimensional boundary defining "tent" that illustrates what

bundles of interventions are sufficient to lower the reproductive number to below 1. The effectiveness of various interventions will be on the different axes. All the points below the boundary tent will be combinations of interventions that are unable to stop transmission, and the points above are all the bundles of measures that will lead to disease extinction.

Consider the following simple, two dimensional example. First, we know from ***Chapter 2*** that the reproductive number, $R_0 = \lambda p$, where λ is the average rate of contact and p is the conditional probability of infection. Both of these parameters are not disease specific constant and can be altered through various hygienic, social distancing or even medical measures. In order to avoid an outbreak, the reproductive number needs to become less than 1, so the objective is to get to a scenario where as a result of all interventions $\lambda p<1$. In ***Figure 5.1*** one can see the two dimensional threshold tent. It is the thick red line where R_0=1, and any points in the gray area under that tent would cause a disease to die out in the population. Consider a flu strain that is comparable in virulence to the 1918-1919 pandemic[34] and, without any interventions, has an R_0 = 2.0. Thus without any interventions, the scenario can be described by a point on the green dashed line in ***Figure 5.1***. In order to stop the transmission, the combination of NPIs and medical interventions needs to decrease either λ or p or both to the gray area, where R_0<1 and the virus will die out.

Our crude example can be extended to multiple dimensions, where each dimension represents a specific type of intervention rather than the aggregate. If developed, this type of tool would be tremendously helpful for decision makers who

[34] The reproductive number for the 1918-1919 pandemic was estimated to be somewhere in the range of 1.8 to 3 (Mills, 2004).

could test out their multiple intervention policies. We encourage future research in this area.

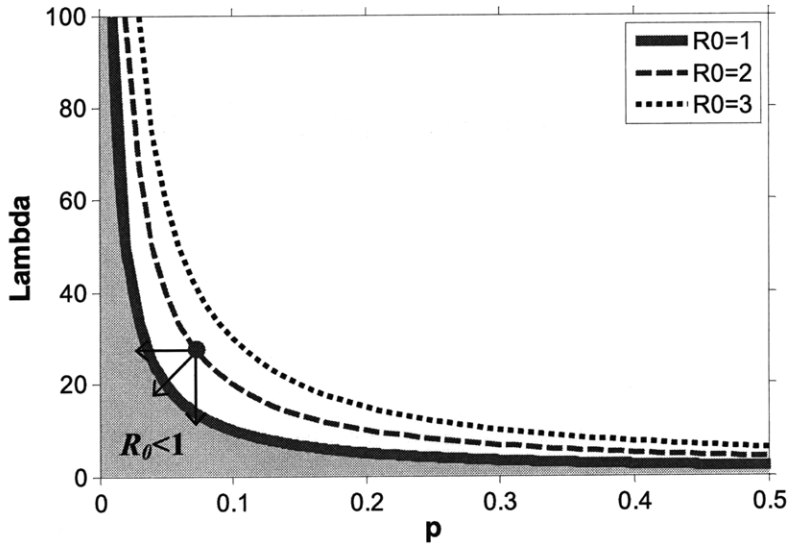


Figure 5.1

The two dimensional tent where $R_0<1$. In order to stop a pandemic, the set of interventions must decrease either λ or p or both to the gray area under the tent.

5.2 Spatial Spread in Past Pandemics

Historical examples show that one infected traveler is enough to infect a whole population. During the 1918-1919 flu, many Alaskan villages were completely devastated by influenza because the man who brought the villagers their mail also brought the flu (Underwood, 2005). In China's remote Shanxi province, the spread of the 1918 pandemic was traced to a single woodcutter, tramping from village to village (Greger, 2006). In Canada, the virus wore the uniform of a stubborn Canadian Pacific Railways official who flouted quarantine, dropping off infected repatriate soldiers from Quebec all the way west to Vancouver (Greger, 2006). Some of the only places to escape unscathed

during the 1918 pandemic were 3 small islands completely shut off from the outside world; they even refused mail delivery (Herda, 1995). On the mainland one successful case was a resort town in New Zealand, which went to the extreme of cutting itself off from the world by using a "rotating roster of shotgun-wielding vigilantes" (Greger, 2006).

There are more recent examples of one traveler sparking a large outbreak; a pilgrim returning from Mecca was the source of a large smallpox outbreak in Yugoslavia in the early 1970s. The outbreak resulted in 174 cases and 35 deaths in Yugoslavia (WHO, 1972). The pilgrim contracted the infection in Baghdad while visiting a religious site, but because his symptoms were mild, he was never confined to bed and was able to continue his travels, return home and start an outbreak.

Finally, in the case of SARS, studies indicate that thermal screening and health declarations of travelers didn't significantly stop the flow of determined travelers or the spread of SARS (Bell, 2004). Within a matter of weeks in early 2003, SARS spread from the Guangdong province of China to rapidly infect individuals in some 37 countries around the world (Smith, 2006).

While travel restrictions appear to be a somewhat intuitive response to stopping the spread of infection, the examples above indicate that they may not be sufficiently strict and generally ineffective. The above described scenarios suggest that it would be useful to develop a model that captures geographical dispersion of infection resulting from traveling infected people.

5.3 Fully Connected Multi-Community Model

5.3.1 Two Communities Model.

We are going to add another layer of realism to the basic model presented in ***Section 3.1***; and that layer is spatial complexity. We developed a loosely connected multi-community structure using Monte Carlo simulation to model disease spread between cities. In a two community model each community – Community A and Community B – has its own demographic and epidemiological composition. In our case we will construct two communities with identical compositions: 100,000 people in the high activity, medium activity and low activity groups in each 300,000 people community. The populations are loosely connected by very few random daily travelers. A certain number of randomly selected people from each activity level j, T_{AB}^{j}, travel overnight from A to stay exactly one day in B before returning home the next night. In the base case $T_{AB}^{j} = T_{BA}^{j} = 2$, giving us a total of 12 travelers going back and forth between two communities. During a visitor's one-day stay in the adjacent community his interaction level is unchanged from what it was within his/her home community.

We initiate the outbreak with an infectious seed in Community A, and the disease propagates to other individuals within this community (***Graph 3.2***). Since travelers continue their movement between communities, eventually it is likely that one of the travelers becomes infected, thus he becomes the passageway for the transition of the infection from one community to another. Let us emphasize that there are 2 ways that Community B can get the infection:

1. An infected individual residing in A travels from A to B and infects people in Community B which instigates the outbreak in B (even though the traveler returns to A at the end of the day)
2. A susceptible individual residing in B travels from B to A and gets infected while visiting Community A. The newly infected individual returns home to Community B and becomes the initial spreader within his community.

We have two processes competing to bring the pandemic to Community B. After the pandemic is in both populations, we assume that the few individuals traveling back and forth, with or without the infection, will not change the disease dynamics in either of the communities.

This structure allows us to apply large population-based averaging techniques to model the infection spread within the community. At the same time, we use Monte Carlo simulation to model the stochastic person-to-person transmission of infection to reflect the intra community spread of infection. Using this structure, we address the question: if the initial case occurs on day 0 within Community A, on average how quickly will it spread to an adjacent community?

The probability of the virus spreading to a new community changes with every generation of the flu. Whenever we refer to a day in the remainder of this chapter we imply one generation of the flu which is equivalent to approximately 2-3 actual 24 hour days. In order to find the probability that on day t at least one infectious individual from activity level j visits Community B, we can "identify" this random individual and find the probability that this traveler gets infected during day t-1. The probability that exactly k

infected individuals of activity level j travel from A to B and bring in the virus on day t is:

$$p_j^{AB}(k,t) = \binom{T_{AB}^j}{k}\left(1-e^{-\lambda_j{}^A\beta^A(t-1)p}\right)^k\left(e^{-\lambda_j{}^A\beta^A(t-1)p}\right)^{T_{AB}^j-k}$$

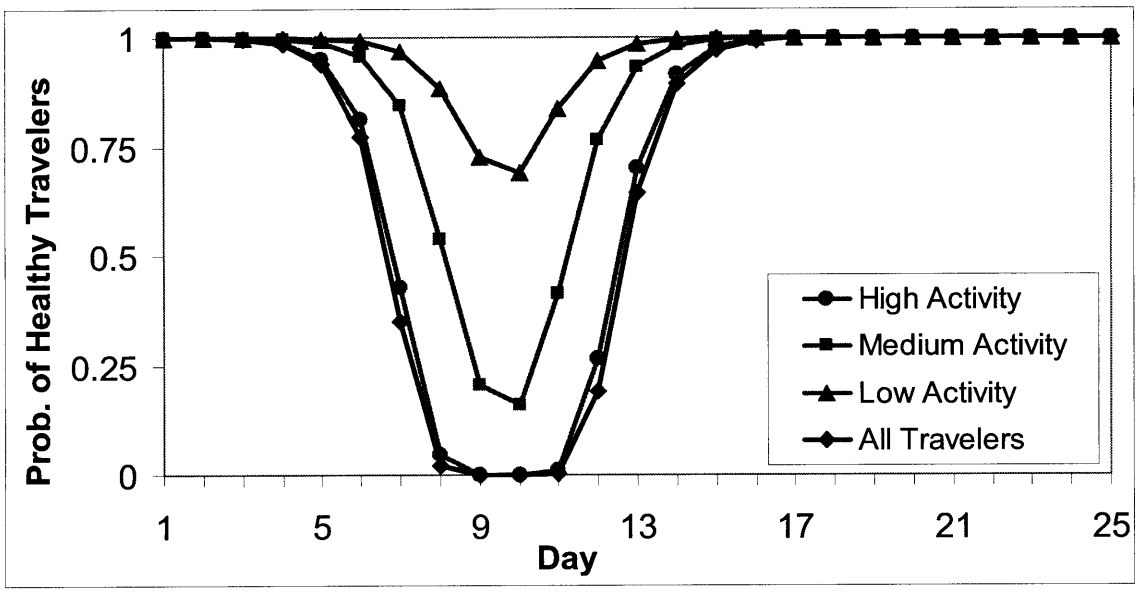
Thus the probability that none of day t's travelers from A to B are infectious is:

$$\prod_j p_j^{AB}(0,t) = \prod_j\left(e^{-\lambda_j{}^A\beta^A(t-1)p}\right)^{T_{AB}^j}$$

Symmetrically, as long as $T_{AB}{}^j = T_{BA}{}^j$ for all j, the probability that a traveler from Community B gets infected and brings back home the infection on day t is the same. So $p_j^{AB}(k,t) = p_j^{BA}(k,t)$. Lastly the probability of having the infection enter for the first time on day i is:

$$P(i \text{ is the 1st day of infection in B}) = \prod_{t=0}^{i-1}\prod_j p_j^{AB}(0,t)p_j^{BA}(0,t) * \left(1 - p_j^{AB}(0,i)p_j^{BA}(0,i)\right)$$

Notice that the probability of never infecting a neighboring community is greater than 0, thus the expected time till the next community gets contaminated is infinity. As a result we can't rely on expected value, instead it is helpful to know the probability that day t is the first day of infection entering into the neighboring community. From ***Graph 5.1*** we see the probability of infection spread is almost certain if the twelve travelers maintain their trips and if the virus is relatively transmissible amongst individuals. This occurs because the high activity travelers are very likely to be infected during the peak times of the community outbreak.



Graph 5.1

Probability of having all healthy travelers between the infection source and the neighboring community on day *t*.

Performing sensitivity analysis on the transmissibility parameter, we find that if p is low enough, not only will the infection die out quickly within Community A, but the probability of spreading to Community B also decreases. As long as the virus does not achieve epidemic status within the initial community, it is not likely to transfer to neighboring towns, but heterogeneous communities make the infection more persistent. If the initial seed community had a homogeneous population where all individuals had a contact rate of 20.67 contacts per day, a conditional probability of transmission $p<0.0484$ should be sufficient to stop the pandemic. Given a heterogeneous population such as the one presented in this section, the conditional probability of infection has to be $p<0.03$ for the infection to die out. The presence of highly active individuals not only drives the spread within the initial Community A, but also the highly active travelers end up driving the infection spread to other communities.

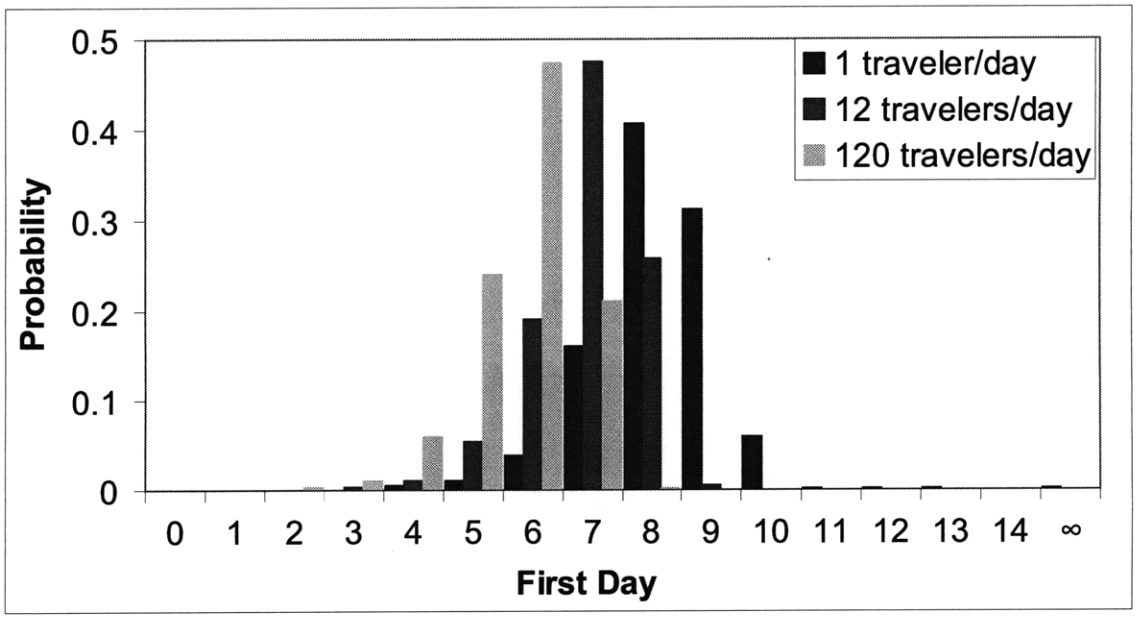
5.3.2 Travel Restrictions

During SARS, some governments forced travel restrictions, and even simple travel advisories decreased the number of voluntary travelers to SARS infected communities (Bell, 2004). This suggests that travel patterns will change in the case of flu, so it is interesting to further consider the potential effect of travel restrictions. We varied the number of travelers between the cities from our baseline number of 12 daily[35] travelers to between 1 and 120 daily travelers. In the case of one daily traveler, the person is a highly active individual. Realistically, highly active individuals are more likely to travel outside of their community than the recluses. Notice that the direction of the traveler, whether it's A to B, or B to A, is not important.

Our results for a varied number of travelers are summarized in ***Graph 5.2***. As the number of travelers increases, the infection becomes more likely to reach the adjacent community earlier. This suggests that Japan's plan to fly home all of its citizens in the event of a pandemic (Shimbun, 2009) may cause it to be one of the earlier countries to become infected. The startling finding is that even with one daily highly-active traveler between the two communities, the disease still spreads to the adjacent community with an incredibly high probability. This indicates that travel restrictions, unless 100% effective, will fail to stop infection spread. During the outbreak, the number of sick grows exponentially while the restriction only decreases travel by a fixed factor. As a result, incomplete travel controls only delay the spread by one or two days, until the exponentially growing number of sick becomes high enough and any traveler is highly likely to become sick.

[35] Day refers to one generation of the flu, equivalent to approximately 2-3 24 hour days.

In order to stop the disease from moving into a neighboring city, all travel must be stopped and the intervention must be initiated early on (~Day 5) and sustained beyond the peak of the epidemic (~Day 15) until the threat of the transition is small (***Graph 5.1***). Since travel restrictions need to last during the peak of the epidemic, the more virulent strains of the virus, which flame out faster, would require earlier, but shorter travel restrictions. Travel restrictions would be more burdensome when used in combination with other interventions and behavior changes that spread out the virus over a longer period. Lastly, once a travel restriction fails and an infected individual enters a fully susceptible town, the travel restriction becomes totally useless because it does not change the dynamics of the disease within the newly infected town. Overall, travel restrictions are expensive, almost impossible to implement and are often ineffective.



Graph 5.2

A histogram of the first day of infection spread in Community B which is adjacent to the source community. Even if the number of travelers is decreased from 120 to 1 person a day, influenza is still highly likely to spread.

5.3.3 Three Communities Model

Consider a fully interconnected three community model with one initially infected community and two neighboring susceptible communities; this is shown in ***Figure 5.2***. This model was also implemented in Microsoft Excel.

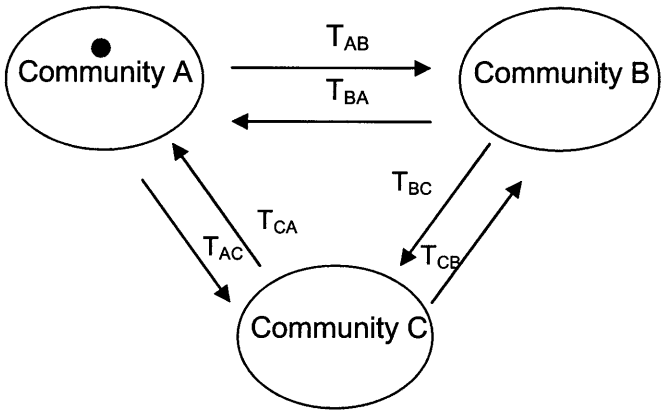
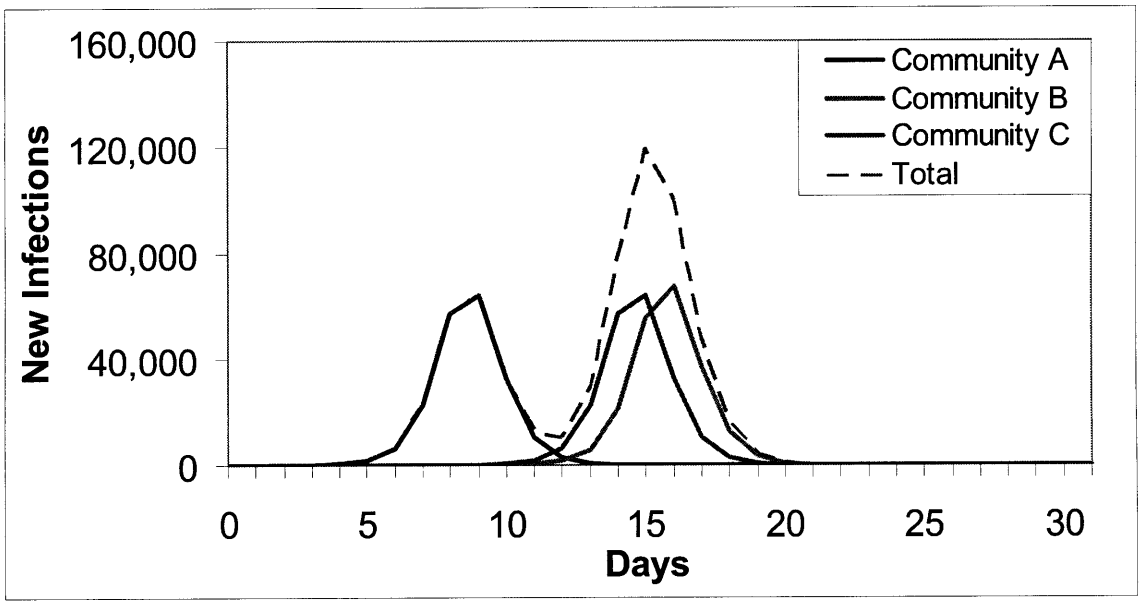


Figure 5.2
The fully interconnected three community model

As can be seen from ***Graph 5.3***, in this case the disease spreads almost concurrently to all of its adjacent communities. In the scenario where susceptible cities are connected to multiple sources of infection, the community experiencing a more severe outbreak will dominate infecting new cities. Today the number of commuters between nearby cities is high; management consultants are an example of people who are likely to criss-cross the world in the course of a week. Given the highly connected nature of our society, unless preventative measures are put in place, the virus will spread very rapidly attacking many cities in a very short time. This could be a catastrophe for emergency systems that would face the equivalent to 50 Hurricane Katrinas hitting the

United States all at once. This scenario would leave no one immune and capable of helping out others; communities will have to fend for themselves.



Graph 5.3

In a fully connected three community model, the virus is likely to spread to both the adjacent communities at approximately the same time. Given the interconnected nature of our country, this implies that all cities are likely to be hit within a short time period, and no one will be immune and able to help out others.

5.3.4 Chain Community Model

Next we address how the infection spreads to an indirectly connected community over a longer period of time. We create a chain model where the population consists of 5 communities labeled A through E and all travel is restricted between "adjacent" communities. (i.e., A residents can only visit B, B residents can only visit A or C, etc).

We implemented this multi-community model in Microsoft Excel. ***Figure 5.3*** is a depiction of this chain model.

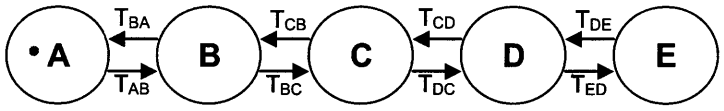
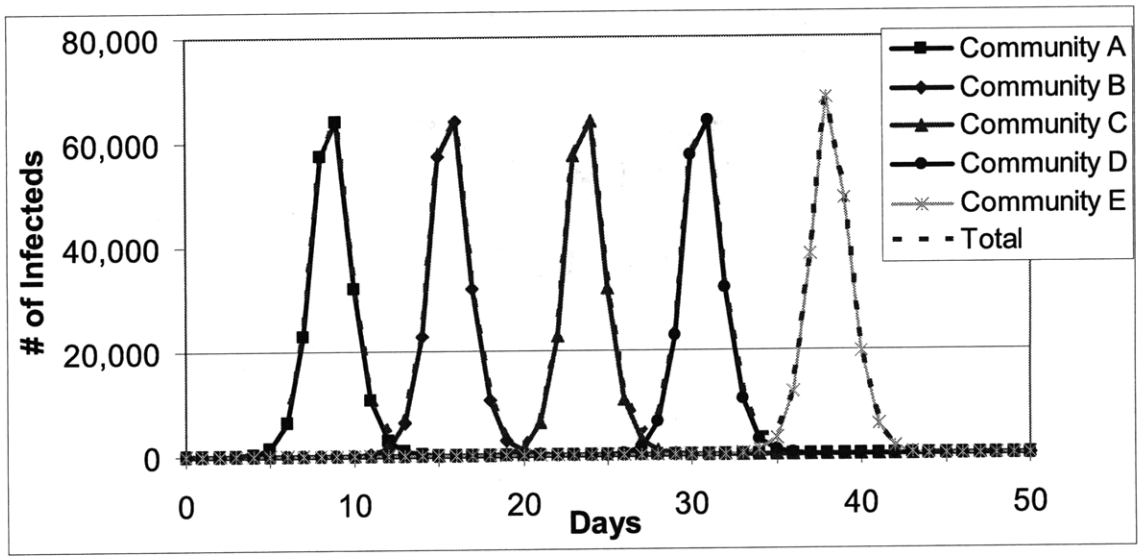


Figure 5.3
A five community chain model

This stylized model allows us to study the spatial disease propagation through a set of towns along the river, interstate or trade route. We avoid creating complicated community connection schematics that would be area specific, but detailed geographically tailored models exist (Ford, 2006; Colizza, 2007).

In addition to insight on infection spread on a larger scale, we can use this model to consider the effectiveness and timing of interventions impacting several communities over time. As seen in ***Graph 5.4***, for our base case with no interventions, once the infection enters a new community, the outbreak scenario is repeated from one community to the next. However in real life, communities that experience the outbreak later on, such as Community E in our model, will react differently than the first community to get infected. As the government and the public learn more about the disease, they will apply the lessons learned in the early infected communities to control and alter the course of the epidemic. A model should incorporate these response and control strategies that occur over the course of the global infection transmission. This provides a direct segway into the next section: modeling preemptive behavior changes that reflect the events of neighboring communities.



Graph 5.4

Default case of infection spread through a chain of communities that do not implement any interventions; the same outbreak scenario repeats over and over again.

5.4 Modeling Preemptive Behavior Changes

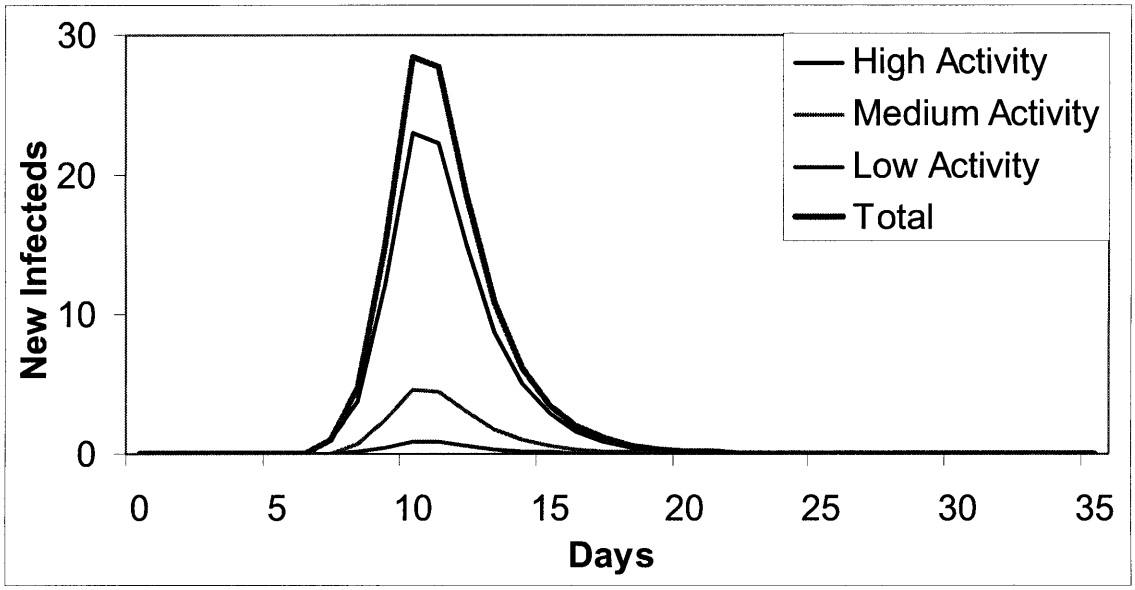
In the case of SARS, researchers recorded that even in regions which were not affected by the disease, people changed their behavior because they were concerned that the infection will eventually enter their community (Shi, 2003). This type of preemptive behavior can be modeled using the concern parameter approach that was presented in ***Section 4.2***. As we mentioned in that section, the outbreak related events occurring within neighboring communities are likely to spur on a response within a community even it has not been infected.

Now that we have a multi community model, we can present the numerical examples of the previously mentioned neighbor based concern factor in evaluating the behavior change feedback parameter, $\pi^3_X(t)$:

$$\pi^{3}_{X}(t, C_3) = \left(1 - \frac{\text{Number of infecteds in all Communities up to and including day } t-1}{\text{The total population in all Communities that have been infected}}\right)^{C_3}$$

C_3 is an input representing the impact of this information. Notice that the denominator is the population of only the infected communities: this reflects a human informational bias that focuses on only the infected communities. It is also important to remember that the concern parameter is a multiplicative factor that decreases the populations' contact rates – λs – and conditional probability of infection – p.

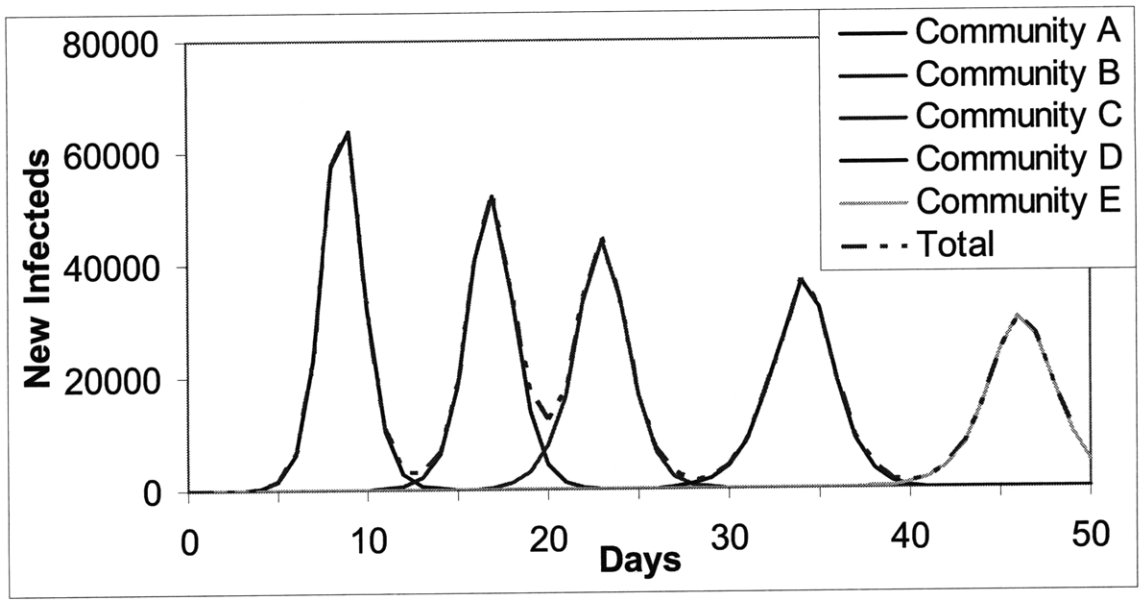
We implemented this multi-community concern factor model in Microsoft Excel and had the following results. In ***Graph 5.5*** we present the case where Community B responds to the outbreak that occurs in Community A. For the horizontal time axis in this graph, day 0 is the first day of flu transmission within Community A, the initial seeder. For the case shown in the graph, the virus enters Community B through one highly active traveler on day 7. Note that since the spread of infection is a Monte Carlo simulation, in other trials the virus could have entered Community B on an earlier or later day. By day 7, the members of Community B have already significantly changed their behavior. By day 11, the third day of infection transmission within Community B, the population has already almost maximally isolated. This very early and maintained behavioral response is the reason that the outbreak only impacts a small fraction of Community B. When comparing this to the scenarios presented in ***Section 4.2***, it is clear that the most cautious communities that change their behavior prior to the infection entrance are the most successful. This voluntary public action will also decrease the probability of the infection entering the community in the first place. However, if the behavioral response is not maintained, the virus can reenter the community and instigate another outbreak.



Graph 5.5

Infection spread within a community that reacts, by social distancing, to news cumulative over all previous days across all communities.

Timely and maintained behavioral changes are an important strategy for mitigating the impact of the pandemic. However, it is highly unlikely that people will drastically alter their behavior based on the experiences of one neighboring community. The behavior changes are likely to be more gradual as communities learn from each others' mistakes. Refer to ***Graph 5.6*** to see how the experiences of prior infected communities can benefit the communities further down the infection chain. This gradual decline in transmission in the communities that experience the outbreak later on was observed in 1918-1919. In the United States, the East coast which was hit first, suffered a higher rate of infection than the West coast. It is impossible to prove that behavior changes and not viral mutations were the reason for this decrease in infection spread. However, the behavior changes observed on the West coast were more dramatic than on the East coast and this could have contributed to the decrease in infection rate over time.



Graph 5.6

Infection spread in a linked chain of five communities where each implements an intermediate level social distancing based on experiences of the previous communities.

While the behavior changes may not be immediately sufficiently stringent, they do have the potential to stop or at least mitigate the impact of an influenza pandemic. Every single individual in the population has the power to alter his or her behavior and change the course of the outbreak. When compared to other intervention strategies, behavior changes are the only approach that empowers the public without relying on medical supplies.

5.5 Vaccination

No country in the world will have sufficient vaccine stockpiles that are ready before the onset of the epidemic to cover the entire population. Given the current practical considerations for vaccine development – manufacturing capacity, ability of

candidate vaccine strains to grow in eggs, and the biological safety containment of parent strains – at least four to six months after the isolation of the virus will be needed to produce the first doses of vaccine (Stohr, 2004). At the same time, many believe that if we are able to slow down or prevent infection spread for those 4 to 6 months, eventually the vaccine will be the ultimate cure for the epidemic (Monto, 2005; GlaxoSmithKline, 2007). New cell based production lines give people hope that the wait for an effective vaccine may be shorter. Since a large fraction of experts are relying on vaccine effectiveness, we briefly propose a method to incorporate vaccination strategies into our model.

We implemented the following vaccination model in Microsoft Excel. In our simple model we assume that vaccination equally changes the conditional probability of infection given contact with an infected individual – p – for all vaccinated individuals. In this model, vaccine efficacy is determined by the parameter v_{eff}. Thus the probability of becoming infected on any given day for a highly active and vaccinated individual from Community A becomes:

$$p_H^{V\,A}(t) = 1 - e^{-\lambda_H{}^A \beta^A(t) p v_{eff}}$$

Note, we acknowledge that there are no vaccines which offer perfect protection, or vaccination strategies that perfectly identify individuals' activity levels. Also, vaccine effectiveness can sometimes manifest itself through a less severe infection in an individual who got infected regardless of the vaccination. Unfortunately there is very limited data that can indicate how effective the pandemic flu vaccine is going to be. Our goal in this section is to gain insight that can be applied to develop reasonable policy recommendations even without precise parameter data.

Since the amount of vaccine, especially early on, will be limited, vaccination plans require judicious and preplanned distribution of this minimal supply. We consider targeting certain population groups as a possible strategy for better vaccine allocation. Before addressing the tradeoffs between vaccine efficacy, vaccine quantity and the delivery time, we confirmed that the most beneficial allocation of limited vaccine is the prioritized distribution of the vaccine to the most socially active individuals, who have not been infected, as early as possible. As discussed in ***Chapter 4***, during a pandemic scenario many members of the community will self isolate. At the same time certain people may not be able to significantly decrease their average daily number of contacts. Doctors, nurses even grocery store cashiers are all likely to still have many contacts and these individuals are the ones that should be the first to receive the limited vaccine. This prioritized distribution will not only ensure the least number of infected individuals, but also provide the most resilient social structure for the duration of the pandemic.

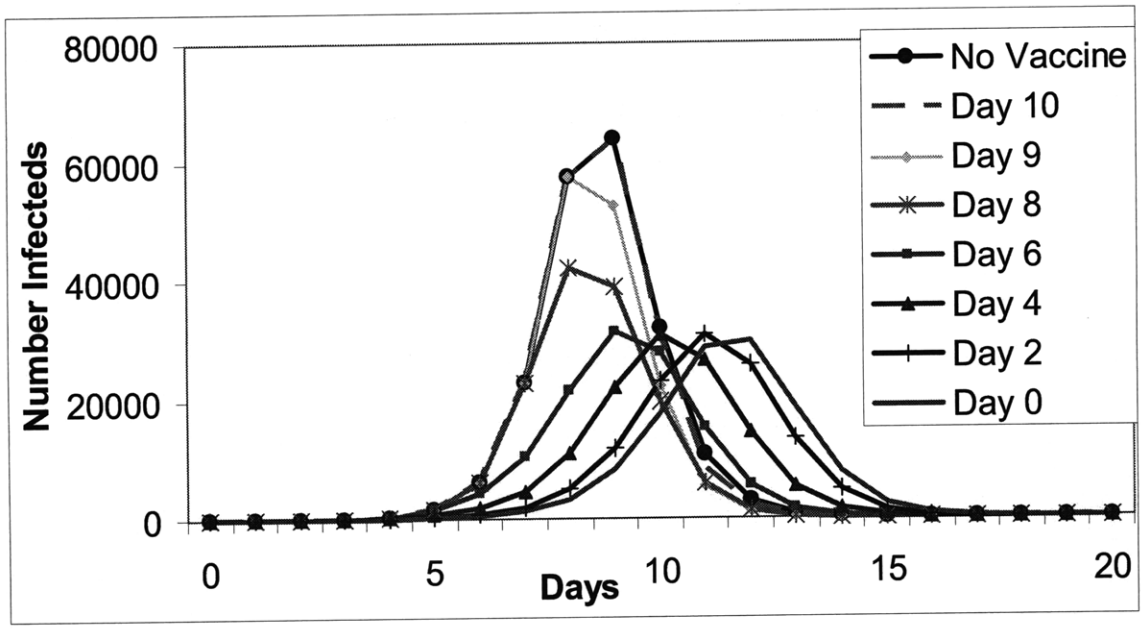
Next we found that given a limited vaccine supply, it is best to focus on stopping the infection in specific cities rather than equally dividing the vaccine amongst all potentially susceptible cities. For example, suppose there is sufficient vaccine for either 1) vaccinating 90% of the highly active population in Community A or 2) vaccinating 45% of the highly active individuals in both communities A and B. While the first vaccination strategy may seem unethical or unfair to members of Community B, it is the better strategy in the sense that it will result in fewer cumulative infections. It will also decrease the likelihood of Community B ever getting infected. While this raises moral concerns, we do not address them in this paper. This implies that in the unlikely case that the United States manages to avoid or delay the spread of influenza until vaccines are

available, the best strategy would be to focus vaccination efforts on major hub cities such as New York, Washington DC, Los Angeles, Chicago, etc. These cities are highly likely to be the first to become infected due to the high number of travelers and commuters. If the infection rates become high in these cities, it becomes very probable that they will cause the infection to spread to many other communities.

Another tradeoff that should be considered is between a larger quantity of less effective vaccine versus a smaller quantity of more effective vaccine. The precise antigenic properties of a nascent pandemic strain cannot be predicted ahead of time; however, stockpiles of vaccine for the expected strain are often created ahead of time. There is even talk of a universal vaccine. This vaccine supply is likely to be poorly antigenically matched to the actual pandemic virus, but it will be available in larger quantities earlier on. First we address the question of quality of effectiveness versus quantity of the vaccine. We compared the pandemic curves between communities where the vaccine effectiveness was the vaccine quantity and vice-versa. For example, we compared a vaccine that is 30% effective and is distributed to 85% of the individuals to a scenario where a vaccine of 85% efficacy is distributed to 30% of the population. The results are practically identical for the two cases. This suggests that stockpiling simply for the sake of quantity may not be the best strategy.

The true benefit of stockpiling lies in the ability to have readily available vaccine very early on. It is clear from ***Graph 5.7***, which depicts the effect of vaccination timing, that the vaccine will only be effective if it takes effect in less than seven days after the virus enters the population. Mass vaccine production takes several months and several weeks are necessary before an administered vaccine becomes effective. This suggests that

unless we can have stockpiled quantities of a viable vaccine we will not be able to rely on vaccination.



Graph 5.7

In all cases 50% of the highly active individuals are inoculated with a 75% effective vaccine. The varying factor is the day that the vaccine starts protecting the vaccinated individuals. In order to significantly reduce the total number of infected individuals vaccination has to be administered very early on.

Since there is no guarantee that the vaccine will be equally effective in all individuals, we consider a possibility where a certain portion of the vaccinated people experiences lesser benefits of the vaccine either as a result of improper administration or biological diversity. This is also similar to administering two types of vaccine: the stockpiled less effective vaccine and the antigenically matched vaccine. We incorporate this by splitting the vaccinated population into further groups, of those who experience the full benefits of the vaccine and those who feel a lesser benefit. Now we define two parameters: v^H_{eff} high vaccine efficacy, v^L_{eff} low vaccine efficacy. The remaining calculations are identical. We compare scenarios where the average vaccine efficacy is

the same regardless of the uniformity of the efficacy. We find that the vaccine that is uniformly effective in all vaccinated individuals is slightly worse than the vaccine that has different benefits for different people. For example, it is preferable to have a vaccine that offers 100% protection in 50% of the vaccinated individuals and 0% protection for the rest then to have a vaccine that provides 50% protection in all of the vaccinated people. It is also clear that the gap defined between these two scenarios grows if we assume optimal allocation and larger quantities of the vaccine.

Given our current egg based production vaccines it is highly unlikely that vaccines will be available early enough. If vaccine manufacturing capability is revolutionized through the usage of cell based vaccine production technology, using vaccines to protect the population becomes a much more important strategy. Regardless, it is clear that in the first months of the outbreak the population will have to rely on behavior changes and other types of NPIs to keep the levels of infection low since initially vaccines will not be available.

5.6 Policy Implications

In this section let us quickly review the policy implications of our spatial spread and vaccination models.

Travel restrictions are impossible and useless once the infection is circulating within the country. There is no easy way to regulate the travel patterns of all individuals through all transportation networks including cars, buses, trains, etc, so the restrictions will be imperfect. Imperfect travel restrictions are extremely costly, but even worse, they are futile. Our recommendation regarding travel restrictions is to avoid government

enforced travel restrictions, but possibly create early travel advisories before the virus enters the country to prevent recreational and voluntary travel and potentially delay the pandemic without severe economic losses.

From our research we find that while these advisories may slightly delay the spread of the flu, they will not stop it from reaching the US. Virtually every community in the US should be prepared that they will become infected. The focus of these communities' mitigation strategies must be inner-community interventions and behavior changes: social distancing, hygienic steps, etc. If communities are able to decrease their maximum number of daily infected individuals they will reduce the probability of intra-community infection transmission as a byproduct of the inner community action.[36] Our findings are encouraging and support the hypothesis that limited interaction will decrease the effect of the pandemic. The deeper insight of this result is that these interventions are effective because they attack the source of the problem by decreasing the exponential growth factor. Preventing exponential explosion of the number of infecteds will prevent the pandemic.

Preemptive behavior is effective in decreasing transmission. It is critical for all people to remember the effect of the epidemic and maintain their distance beyond the peak of the outbreak. The media should present information regarding the events over the whole duration of the epidemic, remind communities about the state of other communities, educate individuals and empower them to take preventative action. These informative messages will help shape human behavior and ultimately that will determine the course of the pandemic.

[36] The reverse is not true. Travel restrictions have no impact on inner community infection dynamics.

Vaccination will only be effective if it is administered early on in the outbreak before transmission explodes exponentially. Obviously there is no reason to vaccinate already infected or recovered individuals. Vaccines don't become immediately effective after inoculation, so the population needs to be vaccinated before the virus even enters the community. If the virus is already present in the population, then behavior changes will still need to be maintained for a certain period after the inoculation.

One of the other reasons that we do not put as much focus on vaccination in this thesis is because any vaccination strategy has significant ethical implications. There are three different potential objectives for a vaccination strategy. Two of these are tradeoffs that have been argued in the context of seasonal flu are: 1) protect and vaccinate the individuals who are most likely to die if they become infected or 2) vaccinate the individuals who are the biggest spreaders of infection. The third objective in a pandemic is 3) protect the social infrastructure. In 1992 for seasonal flu, individuals 65 years of age and older accounted for 89% of influenza deaths (MMWR, 15); the elderly consistently have some the highest mortality rates. The age group known to drive the spread of seasonal flu is school aged children, but children are not known to have death rates that are as high as of the elder population. Lastly, the individuals who support the social order and structure are working adults – doctors, policemen, firemen, nurses etc. In order to develop a vaccination strategy one has to rank these objectives. We do not attempt to resolve this ethical debate.

REFERENCES FOR CHAPTER 5

Bell D.M., 2004. "World Health Organization Working Group on Prevention of International and Community Transmission of SARS. Public health interventions and SARS spread, 2003." Emerging Infectious Diseases. <http://www.cdc.gov/ncidod/EID/vol10no11/04-0729.htm>.

Colizza V., Barrat A., Barthelemy M., et al., 2007. "Modeling the Worldwide Spread of Pandemic Influenza: Baseline Case and Containment Interventions." PLoS Medicine. 4(1):95-110. <http://medicine.plosjournals.org/archive/1549-1676/4/1/pdf/10.1371 journal.pmed.0040013-L.pdf>.

Ford D.A., Kaufman J.H., Eiron I., 2006. "An extensible spatial and temporal epidemiological modeling system." International Journal of Health Geographics. 5(4). <http://www.ij-healthgeographics.com/content/5/1/4>.

GlaxoSmithKline, 2007. "New Studies Indicate GSK's Pre-Pandemic Influenza Vaccine Can Protect Against Different Strains Of H5N1." Medican News Today.

Greger M., 2006. "Coming soon to a theater near you. Birdflu a virus of our own hatching." <http://birdflubook.com/g.php?id=5> .

Herda P.S., 1995. "The 1918 influenza pandemic in Fiji, Tonga, and the Samoas." In: Bryder L and Dow DA (eds.), New Countries and Old Medicine: Proceedings of an International Conference on the History of Medicine and Health Auckland, New Zealand: Pyramid Press. 46-53.

Mills C.E., Robins J.M., Lipsitch M., 2004. "Transmissibility of 1918 pandemic influenza." Nature. 432:904-906. <http://www.nature.com/nature/journal/v432/n7019/full/nature03063.html>.

Morbidity and Mortality Weekly Report (MMWR)., 1995. "Pneumonia and Influenza Death Rates – United States, 1974-1994." Center for Disease Control. 44(28):535-537.

Monto A., 2005. "The Threat of an Avian Influenza Pandemic." The New England Journal of Medicine. 352(4):323-327. <http://content.nejm.org/cgi/content/full/352/4/323?ck=nck>.

Shi K., Lu J., Fan H., et al., 2003. "Rationality of 17 cities' public perception of SARS and predictive model of psychological behavior." Chinese Science Bulletin. 48(13):1297-1303.

Shimbun, Y., 2009. "SDF planes to fly home Japanese stranded in event of flu pandemic." Yomiuri Online. <http://www.yomiuri.co.jp/dy/national/20090204TDY02309.htm>.

Smith R. D., 2006. "Responding to global infectious disease outbreaks: Lessons from SARS on the role of risk perception, communication and management." Journal of Social Science and Medicine. 63: 3113-3123.

Stohr K., Esveld M., 2004. "Will vaccines be available for the next influenza pandemic?" Science. 306:2195–2196.

Underwood A., 2005. "Resurrecting a Killer Fly: A scientist explain why he re-created the lethal virus that killed millions in 1918 and what it can teach us about today's flu." Newsweek.

World Health Organization (WHO)., 1972. "Smallpox: Yugoslavia." Weekly Epidemiology Record. 47:161-2.

CHAPTER 6:

PANDEMIC PREPAREDNESS AT UNIVERSITIES: CASE STUDY OF MIT

There are about 17.5 million students attending colleges and universities in the United States. In an influenza pandemic, universities – much like companies and other institutions – would have to make multiple decisions about how to protect their organizations and assets while managing their operations with a limited number of employees, enduring supply chain disruptions and suffering financial losses. Many private firms across the US have begun to acknowledge the potential difficulties that they would encounter in a pandemic and have started to develop preparedness plans in case an outbreak occurs. Universities differ significantly from other private businesses. One substantial distinction is that universities are responsible for a large number of students who are highly active; they attend multiple lectures, participate in clubs, eat in dining halls and live in residential halls, etc. This high level of social and face-to-face academic activity makes university populations highly vulnerable, so academic institutions should create their own pandemic preparedness plans that are tailored to their unique environments.

In order to assist universities and frame the preparations for a pandemic the Department of Health and Human Services (HHS) and the Centers for Disease Control and Prevention (CDC) have developed a checklist for colleges and universities. The checklist is split up into four sections:

1. Planning and Coordination
2. Continuity of Student Learning and Operations
3. Infection Control Policies and Procedures
4. Communications Planning

While this checklist does bring up some very relevant issues that must be addressed by planners at universities, it provides more questions than answers. Furthermore, this checklist provides much more guidance in sections 1 and 4. While it is crucial that universities designate decision making roles and establish communication channels with their own community as well as with outside public health and other government officials, these are only the first steps in a thorough plan. The most challenging aspects are the logistics and implications of various a decisions. Unfortunately, on these matters the HHS and CDC provide little to no guidance.

In this chapter we discuss in detail some of the difficult questions that universities encounter when creating their pandemic flu policies. We use Massachusetts Institute of Technology (MIT) as a concrete example to illustrate our observations and provide analysis. Given that the author of this thesis is a graduate student at MIT, personal insights and experiences are used to support certain claims. In addition, the author's position as a Graduate Resident Tutor for an undergraduate residence hall gives her a unique view into undergraduate dorm life at MIT. Throughout this chapter we will utilize these personal experiences, insights from emergency planners at MIT: Bill VanSchalkwyk, Peggy Enders, Philip Walsh, David Barber and Susan Leite, and

discussions from the Boston Consortium Pandemic Flu Readiness Workshop held on January 23, 2009.

We proceed by first outlining the main priorities of universities in a pandemic. After an initial discussion over a wide range of issues, the chapter focuses upon the difficult, yet pivotal decision regarding where the student body of a university should go; i.e. should the students be sent home or kept on campus? We conclude by mentioning some of the technical difficulties of developing a pandemic plan and provide some possible approaches to encourage the preparation of universities for pandemic influenza.

6.1 What Makes Universities Different?

Most organizations care about the well being of their constituents, but few institutions have the same responsibility over hundreds or thousands, and in some cases tens of thousands of students as colleges or universities do. Unlike a typical employer, a university can not always send a student back home at the end of a day because the university dormitory is their home. The uniqueness of this situation where individuals are on campus day and night is only rivaled by military or penal institutions. Furthermore, these students are usually very active individuals with high contact rates because they attend lectures with dozens of people, participate in club activities, study together and share living quarters. From personal experience, as a graduate student who no longer attends lectures with a hundred or more people in the audience, the author's average number of face-to-face contacts is approximately 40 people/day. Thus according to our findings in ***Chapter 3***, university students are at high risk for early infection. Assuming

there are no radical age group dependencies in susceptibility or infectivity, the reproductive number, R_0 of most university populations is likely to be significantly higher than that of the overall population. In order to stop or reduce transmission, the behavior changes in the university population will have to be more drastic than in the overall population.

One substantial core difference between universities and private companies is the mission statement. While firms focus on making profit, the intentions of a university are to educate students and advance knowledge. Consequently, in a pandemic, the objectives of a for-profit firm and an academic institution differ. In ***Figure 6.1*** we present the main objectives of a university in a pandemic and provide examples of how to achieve them. As mentioned earlier, the well being of the community is the primary priority of any organization. In addition to maintaining the buildings, equipment and other facilities, the next priority of a research university, such as MIT, is to not lose decades of research. This may mean keeping thousands of laboratory animals alive or making sure that the nitrogen tanks are sufficiently full and maintained to cool sensitive laboratory equipment. Any academic institution will also have to determine how to best continue their educational and research missions given the importance of limiting interactions in an outbreak. While the financial burdens for universities are likely to be very significant, Longwood University even says that the "continuations of ... teaching, research and service activities will be a foremost goal of [pandemic] planning and policymaking" (Longwood, 2006).

Lastly, in order to ensure that people understand the situation and comply with the necessary policies, the universities need to establish clear, non-conflicting and timely

communication with the entire community. Communication will be a critical component of a successfully implemented pandemic flu plan at a university. The university culture of consensus and decision making by committees is not suited for emergency situations. In a pandemic, a clear line of emergency decision making authorities will need to ensure rapid and appropriate communication. The student body is likely to stay very active unless they are properly informed about the risks of infection. Educating the students will be vital in encouraging effective behavior changes that we presented in ***Chapter 4***. Canceling classes, suspending on-campus research, stopping club activities and decreasing the interaction within dorms by sending some students home are also approaches to reducing contact rates.

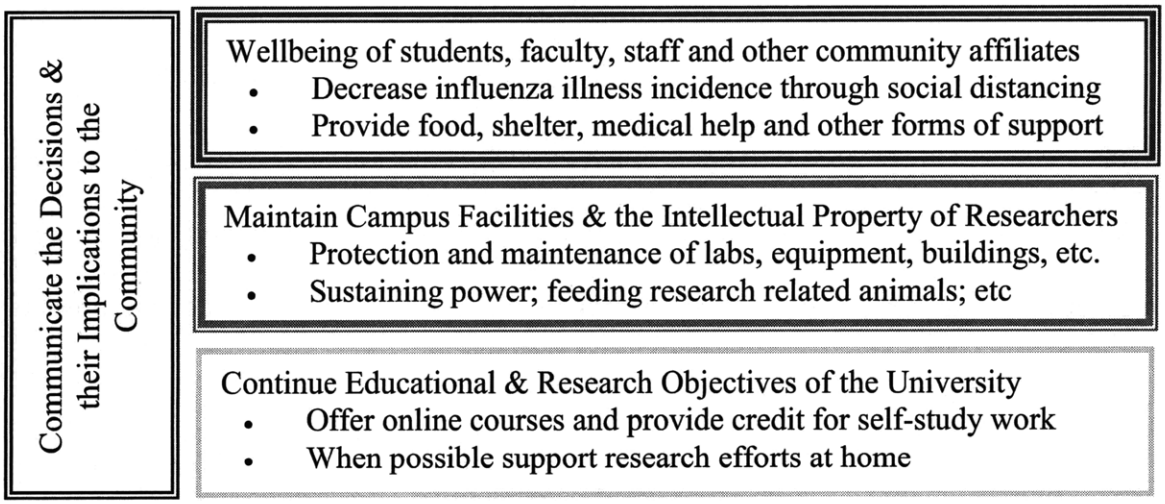


Figure 6.1
Priorities of a University in a Pandemic

During the 1918-1919 pandemic, priorities were skewed by World War I, but even then some universities implemented non-pharmaceutical precautionary measures to reduce flu transmission. The main focus at MIT during the fall of 1918 seemed to be on the war and the completion of new barracks (The Tech, 1918). Registration was delayed

till mid October because of the flu, but there were several pneumonia deaths later on in the semester (The Tech, 1918). Harvard University implemented partial quarantines, but still had two students die of influenza (Bernstein, 2008). Princeton University used a strategy known as protective sequestration which is designed to protect the healthy people from contacting the infection that is present elsewhere. Princeton was one of the luckiest schools to escape with no deaths on campus. Why some schools were spared any deaths and others had dozens is still a matter of some question, but there does appear to be some evidence that students at schools with well implemented NPIs may have been less severely afflicted by the flu. This suggests that in order to mitigate the impact of the next pandemic, universities need to develop response plans for the flu.

6.2 MIT

Before we dive into the problems that universities will have to address in a pandemic, let us describe the academic institution that we will be using as an example to illustrate our ideas. The Massachusetts Institute of Technology (MIT) is a world-renowned research institution that strives to "advance knowledge and educate students in science." The Institute is located in Cambridge, Massachusetts and has a student body of over 4,000 undergraduate and 6,000 graduate students, including approximately 3,000 international students. Most undergraduates – about 3,000 – live on campus in one of MIT's 11 Institute residential halls or 36 affiliated fraternities, sororities and living groups. More than 2,000 graduate students also reside in one of the 7 houses on campus. The Institute employs about 11,500 individuals on campus, including about 1,000 faculty

members and many staff members in research, administrative, libraries and other support areas.

MIT's location and proximity to Boston places it in an urban center with more than 40 other colleges and universities including Harvard University, Boston College, Boston University, Northestern University and Tufts University (Wikipedia, 2009). Example sizes of the student bodies from some of the larger schools are included in ***Table 6.1***. The overall student body in the state of Massachusetts is close to half a million spread over more than 100 institutions; the number of students in the Boston and Cambridge areas alone exceeds two hundred thousand (Wikipedia, 2009). ***Appendix K*** contains a map of some of the educational institutions in the area. As an educational Mecca, the area houses many students who are far away from their families and would not be able to get home in the case of a pandemic. From ***Chapter 5*** we know that quarantining the university populations from the rest of the city will be ineffective. Accordingly, if the universities and colleges in the area have a high number of sick and infectious students because of poor planning, Boston and Cambridge populations will also have higher risks of infection.

University	**Size of Student Body**
Boston University	32,735 (BU, 2009)
Northeastern University	24,752 (Northeastern, 2009)
Harvard University	20,222 (Harvard, 2008)
Boston College	14,395 (BC, 2009)
Massachusetts Institute of Technology	10,299 (MIT, 2009)
Tufts University	10,030 (ASEE, 2009)
Total of 6 schools	**112,433**
Student body in Boston/Cambridge Area	***>200,000***

Table 6.1

Student Body in the Boston and Cambridge Universities

When compared to other universities, MIT is an intermediate sized school, but there are several aspects about the Institute that distinguish it from the average university and are relevant in pandemic planning. For example, MIT is highly research focused with many research grants and contracts supporting many hundreds of researchers and students. A large fraction of the student body, about 30%, is international students. In addition, the University has residential halls that house about half of the student body. These and other characteristics that a university needs to take into account when developing its plan are described in ***Appendix L***.

Like other organizations, MIT is a complex structure with multiple stakeholders and players who will all have to take part in managing the situation in the case of a pandemic. ***Figure 6.2*** is a diagram of the main structures within MIT that will be involved in pandemic planning. While the Emergency Executive Council, comprised of senior level administrators, would be responsible for making decisions in a pandemic, to be successful, all the different units would have to depend on each other. For instance, without the facilities department electric power could go out and the medical facilities would not be able to function, or the heat could go out and students in dormitories would be left to freeze. If the campus police were not able to perform their duties, looting of medical supplies and food and other crimes could become frequent on campus and cause panic and employee absenteeism. A breakdown in the medical department could lead to unnecessary deaths in any of the described departments, further decreasing the employee base. The common factor is that all of these units depend on their human assets and will suffer from a shortage of employees in an outbreak. It is clear that in order to best

mitigate a serious outbreak, all the key units must be identified, individually prepared, but also ready to coordinate and help each other.

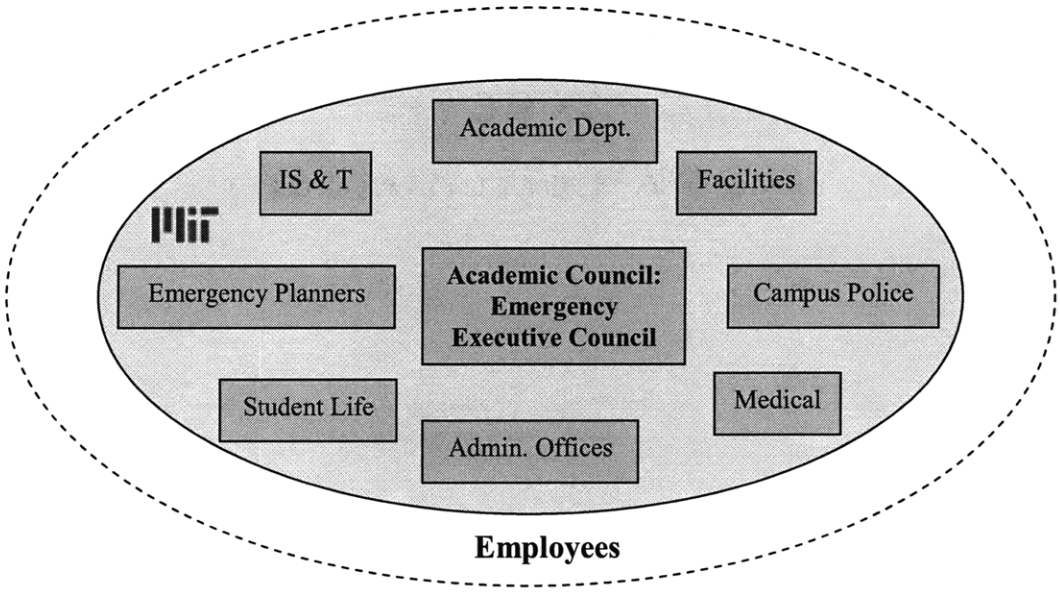


Figure 6.2
Different organizational units within MIT, which would be involved in managing a pandemic. A vital asset to all of these structures is the employees.

In a pandemic, MIT would also depend on multiple outside structures and decisions that are beyond its control. ***Figure 6.3*** identifies some of the important services, supplies and policies that come from outside of MIT. Supplies including lab equipment, food, cleaning or medical supplies are all necessary, but may become unavailable during a crisis, such as an influenza outbreak, that disrupts the supply chains. While MIT generates about 80% of its own power needs at its Cogeneration plant, it still uses city water and other services such as postal and waste disposal. In a pandemic, these outside services may be disrupted because of high levels of worker absenteeism. Furthermore, local, state and federal public health and other government offices are likely to implement

pandemic policies that will impact MIT. Whether the local government requests that MIT helps by assembling and equipping an Influenza Specialty Care Unit (ISCU) on its campus or implements quarantine and isolation policies for the region, MIT is obliged to comply. While internal preparation is important, many issues will be unpredictable and outside of the university's control.

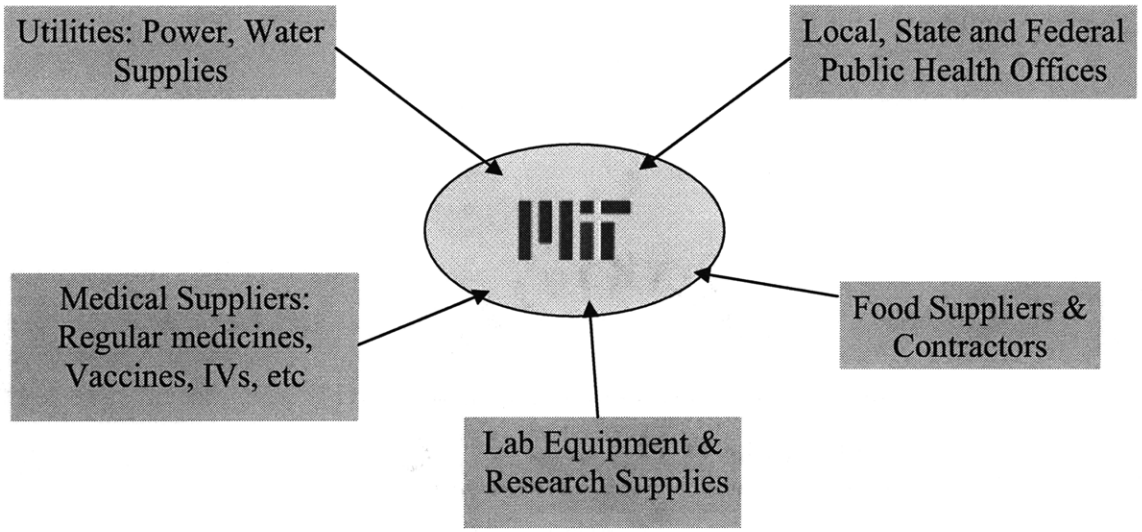


Figure 6.3
MIT relies on the provisions of many outside services and supplies, some of the major ones are included in this diagram.

6.3 Preparing for a Pandemic in a University

There are several difficult questions that universities have to answer when developing a preparedness plan for a pandemic. Should a university suspend normal campus activities in order to encourage contact limiting behavior changes? Should students be kept on campus or asked to leave? What is the appropriate timing for these

decisions? What are the obligations of the university to the outside community? How does a university continue vital operations with a limited employee base?

Smaller schools may have the ability to completely shut down and thus may not have to deal with all of these complications. For example, Craig Andrade and John Sullivan, planners at Wheaton College, assert that the faculty and decision makers agreed to cancel classes, euthanize laboratory animals and do everything necessary to close down the college in the case of a pandemic (Boston Consortium, 2009). Middlebury College also plans almost a complete shut down of their campus (Middlebury, 2007). At the same time, according to Bill VanSchalkwyk of MIT, for most universities, including MIT, shutting down completely is not an option.

In this section, we list some of the complex issues that MIT has been attempting to resolve. This section can serve as an attachment to the HHS/CDC checklist to help catalyze and advance the discussion for university planners. We also provide some potential options for resolving some of these challenges which will inevitably come up in contingency planning discussions in ***Appendix M***.

6.3.1 Suspending Classes

Emergency planners at most universities and colleges, including MIT, expect that in a pandemic they will have to cancel classes for a protracted period of time. This is a very reasonable course of action especially given how often we have stressed the importance of decreasing peoples' activity levels throughout this thesis. Suspending classes should theoretically lead to the effective behavior changes described in ***Chapter 4***. Some schools, such as Longwood University, expect that even without official class

cancellations, students will choose to skip classes and/or leave the university to shield themselves from the flu (Longwood, 2006). There are many logistical implications of either formally suspending or just having high student absentee rates at lectures. Below we list some of the resulting complications. Refer to ***Appendix M*** for some potential resolutions to these issues.

- At what point should classes be suspended? Should all classes be canceled simultaneously or should the largest lectures be the first to cease in-class sessions?
- How does a university continue its educational mission in the absence of in-class sessions?
- How should a university assign credit for courses when classes are suspended before the end of the semester?
- How can students stay on track to graduate without completing the full term of course credits?
- Will the university refund tuition for partial loss of term? What happens to the tuition of students on various forms of financial aid?
- Should the university postpone or cancel special events such as orientation programs, preview weekends, or exams?
- How and when should the university resume the educational program?
- If classes are cancelled, what will students do to occupy their time? Will it decrease their interaction levels?

In addition to the logistical challenges of suspending classes, there is an implicit assumption that as a result students will decrease their number of daily contacts. This assumption is highly suspect in the case of MIT, and other residential schools, since many students reside in dormitories. If students are not occupied with course work, the increased interaction in dorms could make up for the decreased interaction from cancelled lectures. In order to achieve the necessary behavior changes, the university may need to take further steps.

6.3.2 Closing Laboratories and Suspending Research

In order to reduce the contact rates of the university community and thereby decrease transmission, labs are likely to be shut down which will result in a lot of suspended research. The findings in ***Chapter 4*** underline the potential value of these behavior changes especially during the peak of the outbreak. There are numerous implications of this action, especially for research universities that have a large graduate student community. In the case of MIT, this decision is likely to be met with some resistance on the behalf of both some graduate students and some faculty. As a consequence of suspending research, the university would have to address the following issues:

- Who prioritizes research continuation and how?
- What are the triggers for suspending and resuming research?
- What are the obligations of externally funded projects? What happens when the research team cannot meet their deadlines?
- Would the university discontinue research assistantship (RA) and teaching assistantship (TA) stipends?
- What happens to tenure track professors who lose their research as a result?
- How can the university attempt to prevent the loss of legacy research?
- What is the procedure, if students or faculty do not comply?

6.3.3 Student Life on Campus

A primary concern of planners when considering the impact of a pandemic is the effect on the student body. What will happen when supply chains are disrupted, students get sick and housing accommodations aren't sufficient to isolate the sick students from

the healthy ones? For example, Columbia University plans on having social isolation sites to decrease transmission and mentions that relocation of students in residence halls may be necessary to accomplish this goal (Columbia, 2009). However the report provides no further details regarding the logistics of such relocation. Overall, ensuring the wellbeing of the student population is a complex task requiring the cooperation of many individuals. Below is a list of issues that the student life offices at MIT have been attempting to resolve.

Dining:

- Currently MIT only has enough food on campus for 3-5 days. In the case of a pandemic the supply chain is likely to be broken, so how should the university feed the students who remain on campus?
- If the university establishes contracts with suppliers in the case of an emergency how can they guarantee that the suppliers will not renege on those contracts?
- Where on campus can the university store a significant amount of food? Refrigerated space limitations may imply that food requiring refrigeration is not appropriate.
- How can food be distributed while preserving social distancing measures for students?

Housing:

- How can dormitories accommodate both healthy and sick students?
- What is the procedure if a healthy student's roommate gets sick?
- Should the university allocate certain residence halls for quarantined and isolated students?
- Students who currently reside off-campus may choose to come and stay on campus if they feel the university is better protected. At MIT, fraternities, sororities and independent living groups may shut down and cause a large number of students to seek shelter in residential halls. How can the school accommodate the influx of these students?

Other Issues:

- What is the best way to provide attention for sick students who do not require hospitalization?
- How can the school promote non-pharmaceutical measures such as hygiene practices and social distancing without inciting panic?
- What kind of hygiene related supplies should the university stockpile?
- What is the best way to provide mental and emotional support for students?
- How can the university use students as volunteers? What kinds of tasks would student volunteers be asked to do? What are the legal and ethical ramifications of this action?
- Which student facilities should remain open and which should be closed? (e.g. athletic facilities, student center, dining halls, etc.)
- What can the university do to occupy students remaining on campus while limiting their interaction and decreasing transmission?

6.3.4 Medical Facility Preparations

An influx of sick patients in a pandemic is sure to overwhelm any university's medical infrastructure. Since a pandemic is a public health crisis, it is clear that preparations in the medical department are vital. In the case of MIT, the medical facility on campus serves the population of the entire university including students, faculty, staff and often their respective families. At the same time many of the doctors and other staff at MIT Medical are also affiliated with other medical institutions and hospitals, and it is unclear where they would provide their highly sought after services in a pandemic. Furthermore, uninfected individuals who come to the medical facility, to visit a loved one or seek non-flu treatment, may end up having a high number of contacts with the crowd of individuals possibly sick with the flu. It would be important to ensure that the medical

facility does not become a breeding ground for infection. Here are some of the problems that any university with a medical facility will have to address in a pandemic:

- What is the best way to continue operations and treat patients given capacity limitations, from lack of cots to limited supplies and medications?
- While supplies and cots can be purchased and stockpiled, what can the university do when the number of doctors and nurses is insufficient?
- It is likely that many voluntary visits and treatments will be postponed, but what is the best way to continue first aid treatment and other vital care to non-influenza patients without exposing them to the virus?
- How can the university continue distributing pharmaceutical supplies and medicines when there are disruptions in the supply chain?
- What is the best approach to diagnosing people who do not feel well without creating unnecessary contact that furthers the spread of infection?
- Should the triage policies change? If so, how?
- When should people come to the medical facility for treatment and when should they stay at home?
- What is the best way for the university to provide medical and emotional support to grieving or upset students?
- What should be the policy if an unaffiliated individual seeks medical help at the facility? What if the individual is a resident of the local region? What if the individual is a guest or visitor of the university?

6.3.5 Administrative and Operational Issues

One of the biggest challenges for maintaining university operations in a pandemic will be the shortage of able-bodied and willing employees. Not only will many be at home because of their own illness, but many will be at home providing care to ill family members. Some may be too afraid to come to work and risk becoming infected. The US government projections forecast that up to 40% of employees will remain at home at the height of the outbreak (HHS, 2009). It is important to realize that employee absenteeism

will not be evenly distributed amongst all the departments. Some groups may be hit much worse than others, thus coordination amongst various groups within the university will be necessary. At the same time some employees may insist on coming to work even when indicated to stay at home; employee "presenteeism" presents its own set of challenges. Below are a set of issues that will need to be resolved by administrative offices to ensure the continuation of vital operations.

Payroll and Human Resources

- How can the university encourage the vital employees to come to work in a pandemic?
- Should the university alter its sick leave policy during a pandemic? If so, what kind of policy should it be?
- What should be the changes in policies for job termination, furlough, extended sick leave, union contracts and need based hiring?
- If employees are quarantined or isolated, what will the pay policies be during extended confinement?
- Many universities employ union workers, but union contracts often do not include anything about a pandemic scenario. How can the university ensure that it does not break any union agreements?
- What will the policy be on employee cross training? How will the university compensate and motivate employees to attend pandemic or pre-pandemic cross training? How and when should the university decide that cross training is necessary?
- How will the decision be made to redistribute employees to other workplace areas in the university? Should such employees receive additional pay?
- What should happen if a worker gets sick as a result of their work requirements? Should he or she be compensated?

Administrative offices will have to also manage other problems that will emerge because of various pandemic related decisions. We describe some of the questions that different offices are likely to encounter:

Payroll Office

- If research is suspended, how will payroll compensate staff and students who were paid through grants and outside contracts? For example, if a graduate student's RA came from an outside research grant, would the university cover the RA stipend if research of the externally funded project was suspended?

- What will the impact be of research and class suspension on the student payroll?

Finance Office

- Will students' tuition be reimbursed? Will this money be withdrawn from the university's general funds? Will tuition credit be kept on record to cover next semester?

- What policies should be in place for students who receive financial aid from inside or outside of the university?

- How will this change the situation for students who depend on financial aid to cover living and/or residential expenses? What will the university do to help these students if their financial aid is revoked?

Registrar, Undergraduate and Graduate Offices

- As students chose or are asked to leave campus, how will the university stay aware of their status?

- How will the university keep track of student wellbeing?

- What will happen to conference participants or other university visitors who are on campus in an outbreak?

Study Abroad Office

- How should students be prepared in advance to cope with the possibility of a pandemic while they are abroad?

- What should the office tell students who are studying abroad? Should they stay abroad? Should they return to the university? Should they return home?

- What will the office advise international students who are visiting the university on an exchange program?

Legal and Ethical Concerns

- What kind of legal responsibility does the university have to its community and visitors in this emergency?

- What kind of ethical responsibility does the university have to its community and visitors in this emergency?
- What is the university's responsibility to the surrounding community?
- What level of preparation will ensure that the university would not be held liable for being "unprepared" for a pandemic?

6.3.6 Overall

In conclusion, there are several takeaways from this section. First, it is important to think deeper about the logistical and other implications of any policy recommendations. For example, we showed how the decision to suspend classes has multiple cascading effects that will have to be addressed as well. Second, adequate infrastructure must be put in place ahead of time: student information databases, emergency communication channels, etc should be created before a pandemic hits. Third, university planners need to think beyond the HHS/CDC checklist when creating their pandemic preparedness plans.

At the same time, it is impossible to predict all the unusual circumstances that will come up in a pandemic. Many decisions will be made at the spur of the moment and cannot be planned out ahead of time. Some decisions may even be reversed as more information becomes available. No plan can cover and have contingency procedures for every possible scenario. This does not mean that planning is unimportant. Decision makers must think about the pandemic ahead of time, but also be prepared to think on their feet.

It is vital that all members of the decision making group know each other and know the university. Small emergencies help bring together first responders and keep them aware of and familiar with each other and their responsibilities. Drill operations and

decision making simulation exercises are valuable because they act in a similar fashion, bringing together the same people as would a real emergency. These exercises should include not only university decision makers and students, but also government decision makers. BIRDFLUPLEX is an example of such a simulation drill that was held at Boston University (Vanderschmidt, 2006). Additionally, it is important to have individuals who could step into the role of current first responders. Some decision makers may get sick and backup individuals, who are familiar with all the issues, should be able to step in if necessary. The university with the most cohesive, responsive and collaborative decision making team, and not the university with the most thorough plan, will be best prepared for a pandemic.

Finally, we would like to point the interested reader to review the University of Minnesota Twin Cities pandemic plan for some general preparation practices and the University of North Carolina plan for suggestions on how to address administrative issues that are likely to arise in a pandemic (UM, 2008; UNC, 2008).

6.4 Evacuate or Shelter-In-Place?

All universities will have to make the pivotal decision in a pandemic of what to do with the student body in the case of an outbreak – evacuate or shelter-in-place. This question is likely to come up early in the outbreak, and the outcome from this decision will have multiple implications. While some universities may have a large number of local students who do not rely on the school's resources, this is not the case for MIT. Reducing the size of the student body is very important because otherwise the capabilities

of the Institute functioning with a reduced staff would be overwhelmed in a pandemic. At the same time, putting students on trains, buses and planes in the middle of an outbreak may result in many of them getting ill and spreading the infection. It is unclear that by sending students home, the university is ensuring that they will be in a better environment than if they remained on campus. In this section, we will discuss the benefits, drawbacks, implications, timing and logistics of the decision to decrease the size of the student on campus population.

6.4.1 Benefits and Drawbacks of an Evacuation

Benefits:

Since university resources will be limited in a pandemic, many decision makers believe that it would be beneficial to send students back home. They believe that this will not only ensure that the remaining members of the university community will be better served, but that the students who go home will receive better care in their home community. Food supplies may be dwindling at university campuses, if food distributor supply chains are disrupted; at MIT there would only be enough food for 2-4 days. The belief is that in this crisis, parents will be able to provide these basic care and necessities to their children better than the university. Furthermore, it is expected that if students become ill without requiring hospitalization in their home, their family members are more likely to provide better care than the university, if they stayed on campus. The mental and emotional support that family can provide is also likely to be superior to the thinly stretched capacity of the university. Lastly, removing students from the university

dorm environment where students are highly interactive, theoretically, should change their behavior enough that their chances of becoming infected are reduced.

When focusing on MIT, diminishing the size of the population on campus would also improve the level of service for those who remain on campus. For example, the MIT Medical Department, which serves the entire MIT community as well as the families of many MIT affiliates, only has about 30 beds and is likely to be overwhelmed in a pandemic regardless of the number of students on campus. However, if all students remain on campus, the shortage in the medical department would be even more severe, and it is likely that as a result all patients would receive a lower level of treatment. Mental health support services are also likely to be in high demand in a pandemic, and while pastoral and other guidance services can be used to manage the demand, it is likely that MIT Mental health will still be overwhelmed. Planners at MIT also believe that some remaining students who currently live in non-campus housing, including fraternities, sororities and independent living groups, will attempt to seek shelter at MIT. It would be very convenient, if some number of students had gone home, leaving their dorm rooms available to accommodate this surge. All of these points argue for the need to evacuate the students. Schools such as Stanford University, St. Lawrence University and many others use these reasons to support their policy of sending a sizeable fraction of their students back home (Stanford, 2008; St. Lawrence, 2009). Other schools, such as Middlebury College take this as far as to state that "a pandemic will warrant a complete closure and all students will be required to vacate the campus until it is deemed safe to return" (Middlebury, 2009).

Drawbacks:

The main argument for keeping students on campus is that requiring students to travel back home in a pandemic will subject them to additional exposure to infection. Planes, trains and buses are confined spaces that transport many individuals and are believed to have increased levels transmission. Forcing students to travel home during an outbreak of a virulent virus puts them in danger of becoming sick. From the multi-community model presented in ***Chapter 5*** we can infer that students traveling home may become carriers of infection. By returning home these students could pose greater risks of infection to their home communities. While as shown in ***Chapter 5,*** geographical disparity in the transmission of the flu is not likely to be sustained for a long time,[37] it could present problems for evacuation. If influenza is widespread on the West coast, schools on the East coast would put their West coast students in a dangerous environment, if they were to send them back home. For the same scenario, schools on the West coast could be contributing to transmission, if they sent their potentially infected students back home to the East coast. Overall, requiring students to leave the safety of campus may be unethical and even present legal problems.

The other reason supporting the decision to shelter-in-place is that it would be impossible to send the entire student body back home. At MIT many undergraduate students would feel comfortable returning home to their families, but many graduate students would not be able to leave since they consider Boston or Cambridge their home. Financial restrictions may also make it impossible for certain students to return home. In a pandemic, international travel is likely to be severely restricted, so the international

[37] In ***Chapter 5*** we have shown that travel restrictions are not effective if the virus is widespread in the seed population.

contingent at MIT – that is 30% of its student body – would be unable to leave the area. Transportation infrastructure capacity restrictions may make it impossible to send domestic students home. Airports, train and bus stations – and even interstate highways – could be shut down in an attempt to decrease intra-city transmission. Many campuses are likely to attempt sending their students home at approximately the same time, so any remaining modes of transportation in a city with many schools, such as Boston, may be insufficient to handle the surge in demand.

Recommendation:

Considering all the arguments for and against an evacuation suggests that the best policy is to advise, but not require, students to leave campus. This is not a binary, yes or no, decision. Students should be well informed of the drawbacks and risks of remaining at the university, but they should have the option to stay on campus if they feel that it is in their best interest. The university should also attempt to help the students who want to return home, but aren't able to do so on their own devices. It is anticipated that many parents will choose to come and take their children back home before the university even makes a decision to evacuate the student body. For example, when there was a meningitis scare at the University of Richmond, some parents quickly summoned their children home (Schachter, 2007). A certain degree of reduction of the student body would be unavoidable, but evacuating the entire student population would be virtually impossible.

At the same time, it is almost guaranteed that there will be some deeper, potentially unanticipated complexities after the university advises that willing members of the student body leave campus. One example is that certain students, who are over the

age of 18 and are therefore legally considered adults, may disagree with their tuition paying parents regarding whether to stay on campus or return home. It is unclear who the university should support in this scenario, but having unaccounted for students staying around in their friends' dorm rooms is highly undesirable. Another example of a challenging situation would be if instead of leaving campus, some students decided not only to remain, but also attempt to provide shelter for friends or family members who are not affiliated with the university. This type of behavior would increase the population residing on campus and blur the responsibility of the university to the guest individuals. While we attempt to provide specific suggestions in an attempt to provide clarity about how to reduce the student population, it is clear that there are many additional complexities that will come up and cannot be anticipated ahead of time.

6.4.2 Timing of Evacuation

The drawbacks described above suggest that the best way to get around the difficulties of an evacuation is to send students home very early on, potentially before the virus enters the country. At the same time, in the early stages of transmission people may misinterpret the potential of a novel strain of influenza. It is possible that initial transmission may die out on its own without becoming widespread or damaging. On the other hand, it could spread quickly and kill many people. There is no simple indicator of what an emergent strain will do, and decision makers do not want to trigger a false alarm. Given these considerations, what should the trigger be to send students home?

Universities have determined different trigger points for an evacuation. Some, such as University of Minnesota Twin Cities, will send students home if there are cases

of the flu in the local region, while others, such as Middlebury College, plan on initiating the evacuation as soon as there are pandemic influenza cases anywhere in North America (UM, 2008; Middlebury, 2007). Carnegie Mellon University is considering the trigger of a case discovered at an international airport in a major American city (Schachter, 2007). By waiting for the virus to become a local problem, universities increase the size of the student body that will remain on campus, but reduce the risk of triggering an unnecessary student exodus. Given our conclusions regarding the ineffectiveness of travel restrictions, our recommendation is that the evacuation needs to occur earlier. Unless incredibly high tech surveillance and rapid educational measures are put in place, initially people will not be aware of the seriousness of the infection and maintain normal behavior which allows the virus to transmit to a significant number of people. Even with SARS the disease quickly spread to multiple countries, in the case of the flu this global transmission is even more likely. The potential speed of global influenza transmission supports an early trigger for initiating the student exodus.

Overall, it will not be easy to send the students back home, and we believe that the formation of this decision will span over several days and the implementation will be somewhat gradual. It may be very helpful to prepare the student body for this type of scenario as soon as sizeable clusters of human influenza are found anywhere in the world, so in case it becomes necessary, students are prepared to leave. Asking students to think about a contingency plan, in case they are advised to leave campus may be helpful. Suggesting that they prepare a just-in-case suitcase and organize their dorm rooms ahead of time in case their rooms will have to be occupied by someone else will help speed up the process. Requesting that students review their emergency contact or evacuation

relevant information in the university database will help maintain current records. While it is important not to create an unnecessary panic, preparing students for the possible risks in advance should help manage the situation if the spread of infection starts to accelerate.

It is likely that early on in the pandemic there will be a certain degree of resistance to a formal request that students leave campus, but the trickle of people leaving campus can be initiated by the university before the advisory to leave campus is made official. It would be most sensible and effective, if the recommendation for returning home was to follow or coincide with the suspension of classes. However, even a public announcement of canceling or postponing all conferences hosted on campus would send a message to the public. Some parents are likely to use such an announcement as an indictor the campus is not safe and take their children home before the university makes the decision.

6.4.3 Facilitating the Student Evacuation

In many cases even if a university initiated a voluntary student evacuation, certain students who want to go home would not be able to without the help of the university. It would be very challenging to ensure that students return home, if their homes are far away. Additionally, in a university such as MIT, the majority of students do not have cars on campus and even students from nearby cities such as New York would have a difficult time returning home. Financial constraints may also hinder certain students from returning home.

We have several suggestions on steps that especially larger universities may want to take to further facilitate the student exodus. Financial support for travel expenses

would help increase the number of students returning home. Providing students on financial aid with $100-$500 debit cards that can be used to cover travel expenses will provide these financially constrained students with the option to go home.

In the case of MIT, many students are from the New York City area. In order to ensure the safe return of these students home it would be beneficial for MIT to charter several buses that transport them to an easily accessible location in New York where parents could pick them up. Chartering buses to several other cities that are within several hundred miles – one days drive, such as Philadelphia, Hartford and maybe even Washington DC and Buffalo will help many students get home. By providing transportation, the university can make returning home not only more convenient, but also cheaper and safer. In order to implement this plan, it is essential that universities that plan to charter buses establish contracts with bus companies before the outbreak becomes a widespread problem. We also suggest that certain smaller schools collaborate and charter buses to the same locations together. Even larger schools could collaborate to charter one bus to a town that is home to several students from each of the schools.

However, this will not help international or other students who live more than 500 miles away. Some students, whose parents are far away, have other relatives in the nearby area. While these students shouldn't be forced to leave the campus to stay with their relatives, they should be reminded of this option and encouraged to take it. Another approach to decrease the student population is to encourage students from the area to take home a friend who is not able to return home – an emergency buddy system. Some host families could be asked to accommodate international students. It may be helpful to extend this further and suggest that university staff house students for the duration of the

outbreak. While it is clear that given the contagious nature of the infection many people will refrain from taking in people who are not members of their family. However, even if only one person benefits, it is worth suggesting these options to the community. No one policy, but the combination of them all is necessary to most effectively reduce the size of the student population.

6.4.4 Student Database

Most of the decisions regarding how to best address the needs of the students will depend on information regarding the nature of the virus and will thus have to be made during the outbreak. However, certain preparations and principles can be developed now to ensure smoother execution of decisions made in a pandemic. In a crisis situation such as a pandemic, parents may attempt to contact the university to find out the location and wellbeing of their children. Regardless of whether the university is able to send the students home or decides to shelter-in-place, it is the school's responsibility to keep track of the students.

We suggest that all universities develop and maintain an easily updatable student emergency information database. The information in this database would be beneficial in other emergencies in addition to a pandemic. This database should contain the name and contact information of every student as well as the emergency contact information for all students. MITAlert is this type of database, however it may benefit from the addition of a section that enables students to register an evacuation contingency plan. Such a plan would provide students the opportunity to indicate that they do not have any family or friends in the nearby area and would not be able to leave campus without the help of the

university. When possible, students would be able to indicate where they could go, if they were asked to leave campus.

This database should also be accessible by students in an emergency. In a pandemic, students should be queried about their current location and health status. When students leave campus they should promptly notify the university of their departure through this system. Students, especially those remaining on campus, should regularly update their health status in the database. Stressing that students keep their database information current is vital. If current, this information will not only help keep track of the students and their status, but help in the overall decision making process. As a live census it would help track the progression of infection, be used by the medical staff for triage, utilized by the housing staff to move students to empty available rooms, used by dining to determine food distribution demands, etc. Since having accurate information is critical for making good decisions, this type of database would be a very valuable resource.

6.5 General Recommendations

The reason that preparing for a pandemic is very challenging for all organizations is that there are so many unknown parameters about the next pandemic. The next pandemic strain is still unknown, and as a result no one knows how contagious, virulent or deadly it is going to be. It is unclear whether the virus will target any portion or age group in the population. How quickly will it spread across the globe and will there be any warning time before it enters the US? The durations of outbreaks at the local and global

levels are also uncertain. The most vexing question of all is, in any given year how likely is a pandemic and is it even worth preparing for something that is so improbable and depressing?

We strongly believe that in advance preparation will help decision makers manage the consequences of a pandemic outbreak. Since it is very difficult to motivate planners to focus on pandemic flu given the low probability of this emergency, some have proposed taking an all hazards approach and simply preparing for any emergency. While taking an all hazards approach battles "flu fatigue" it is not specific enough because there are several aspects that differentiate a pandemic from other emergencies:

- It has the potential to be a long lasting crisis that results in an extended outage for the university.
- The contagiousness of the flu is likely to result in people avoiding social contact and having less desire to help others.
- The universal impact of the virus is likely to leave no one immune; everyone will have to fend for themselves.

While overall emergency planning is a very unpleasant experience, the above reasons make a pandemic one of the worst case scenarios for any institution.

One potential motivation to focus on pandemic preparedness is if we are ready for the worst case, we can handle everything else. ***Section 6.2*** provides a list of specific questions that require careful thought and deliberation. While we do not claim that this list is exhaustive nor that answering those questions will ensure pandemic preparedness, it will help familiarize the decision makers with the real issues. In order to motivate planners to develop possible solutions for this set of seemingly unlikely dilemmas, we

suggest identifying several different crises that would cause the same problem. A pandemic is not the only possible trigger for a student body evacuation; a terrorist attack in the Boston/Cambridge area, a nuclear power plant meltdown or a natural disaster are other examples that would require reducing the student presence on campus.

We would also like to encourage universities to educate their students about the importance of proper hygiene on a regular basis, so that people automatically wash their hands and cough into their elbows. It would be even better if this type of behavior was instilled in the population early on in their lives, such as elementary school. However, for now universities can step up their hygiene campaigns and ensure that hygiene supplies such as soap or hand sanitizer are found throughout campus.

Lastly, we encourage universities to continue developing their plans, but also recommend that the government provide more guidance to universities on triggers for campus closure and evacuation, materials to stockpile, policies for refunding tuition, adjusting credits for missed coursework, legal concerns, as well as other issues described in this chapter. Information on how government financial aid and grant policies may be adjusted during protracted emergencies would also be very valuable. Successful management of the pandemic at universities will not only help the 17.5 million students in this country, but also the people in cities and towns that have high student populations. Preparing for a pandemic has the potential to save lives in the case of a global outbreak. Such preparation may even be helpful in dealing with many other emergencies that could strike any place and at any time.

REFERENCES FOR CHAPTER 6

American Society for Engineering Education (ASEE)., 2008. "Tufts University Institution Information." <http://profiles.asee.org/profiles/3980/screen/2?school_name=Tufts+University>.

Bernstein M.F., 2008. "Why Princeton was spared." Princeton Alumni Weekly.

Boston College (BC)., 2009. "Boston College Facts." <http://www.bc.edu/about/bc-facts.html>.

Boston Consortium, 2009. "Pandemic Flu Readiness Workshop held on January 23, 2009."

Boston University (BU)., 2009. <http://www.bu.edu/info/about/>

Columbia University, 2009. "Pandemic Flu Response." <http://www.columbia.edu/cu/studentservices/preparedness/docs/General_Info/index.html> .

Department of Health and Human Services (HHS), Center for Disease Control and Prevention (CDC)., 2009. "Colleges and Universities Pandemic Influenza Planning Checklist." <http://www.pandemicflu.gov/plan/pdf/colleges_universities.pdf>.

Harvard University, 2008. "Degree Student Head Count: Fall 2008." <http://www.provost.harvard.edu/institutional_research/FB2008_09_Enrollments.pdf>.

Massachusetts Institute of Technology (MIT)., 2009. "Enrollment 2008-2009." <http://web.mit.edu/facts/enrollment.html>.

Middlebury College, 2007. "Pandemic Health Protection Response Protocol."

<http://www.middlebury.edu/NR/rdonlyres/9BD41B34-CB6E-4125-A335-1610941F1D2F/0/MiddleburyCollegePandemicHealthProtectionResponseProtocol31507.pdf>.

Middlebury College, 2009. "Pandemic- Campus Evacuation." <http://www.middlebury.edu/administration/publicsafety/er/pandemic.htm>.

Northeastern University, 2009. "Student Enrollment Data." <http://www.northeastern.edu/oir/pdfs/reaccreditation08/appendix2-08/form7.pdf>.

Longwood University, 2006. "Pandemic Flu, Social Distancing Measures, and Business Continuation at Longwood University." <http://www.longwood.edu/health/education/health/pandemicflu/docs/pandemic_flu_social_distancing_measures_and_business_continuation_at_longwood_university.pdf>.

Schachter R., 2007. "Flu Pandemic Prep. University Business." <http://www.universitybusiness.com/viewarticle.aspx?articleid=669>.

St. Lawrence University, 2009. "Pandemic Flu." <http://www.stlawu.edu/ucomm/flu.html>.

Stanford University, 2008. "Information About Pandemic Influenza." <http://www.stanford.edu/dept/ucomm/news/avianflu.html>.

The Tech. 1918. Volume 38. Issues 51-63. <http://tech.mit.edu/V38/>.

University of Minnesota Twin Cities, 2008. "What the University of Minnesota is Doing to Prepare for Pandemic Influenza." <http://www1.umn.edu/prepared/ahc_prepared/flu/index.html>.

University of North Carolina, 2008. "UNC Pandemic and Communicable Disease Emergency Policy, Policy 300.2.15."

<http://intranet.northcarolina.edu/docs/legal/policymanual/2008/Updates%20of%20October%2017,%202008/Policy_300.2.15_UNC_Pandemic_and_Comm_Disease.pdf>.

U.S. Department of Health and Human Services (HHS). 2009. "Pandemic Planning Assumptions." <http://www.pandemicflu.gov/plan/pandplan.html>.

Vanderschmidt H., 2006. "Bird Flu Simulation Workshop Fri., Feb 17. Boston University." <http://sph.bu.edu/insider/index.php?option=com_content&task=view&id=131>.

Wikipedia contributors, 2009. "List of colleges and universities in Massachusetts." Wikipedia, The Free Encyclopedia. <http://en.wikipedia.org/w/index.php?title=List_of_colleges_and_universities_in_Massachusetts&oldid=284700611>.

CHAPTER 7:
CONCLUSIONS & FUTURE WORK

"How would a nation so greatly moved and touched by the 3,000 dead of September 11th react to half a million dead? ... to 5 or 50 million dead?"
– Bill Frist[38]

7.1 Summary

Human deaths due to infection with the highly pathogenic H5N1 avian influenza A virus have elicited the specter of a catastrophic flu pandemic like that of 1918-1919. Regardless of whether H5N1 or another flu strain mutates to become easily transmissible among humans, most experts agree that the next pandemic is inevitable. Pandemic preparedness at all levels will be essential in mitigating the flu, but existing plans often lack details and implementation logistics, often skirting the complex issues. Precise planning is hampered by some unknowns including the virulence, morbidity and speed of transmission of the next pandemic strain. Since there is no way to test run a pandemic, policy makers must often rely on models to guide their decision making.

In this thesis we have developed a simple analytical model of disease transmission in a heterogeneous population. Diversities in activity, susceptibility and infectivity were integrated individually and collectively in order to reveal the most significant population

[38] Talking about pandemic influenza in 2005.

distributional attributes. Our results indicate that activity level is likely to be the most important driver; individuals with high contact rates are likely to be the first to become ill and consequently spread the infection to many others. It appears that heterogeneity in either susceptibility or infectivity independently also has the potential to change the course of the outbreak. Yet the individuals who are both highly infective and highly susceptible are the ones to really propel the spread of the flu. Given the challenge of identifying the highly susceptible and infectious persons, we believe that initially focusing on the highly active individuals may be a better strategy.

In a severe outbreak people are likely to dynamically alter their behavior, including reducing their contact rates, thus we extended our model to include behavior changes. Since very limited work exists in the area of influenza based behavioral responses, data on STDs and SARS driven behavior was used to support some anecdotal observations of what occurred in the 1918 pandemic. From this information, four completely novel approaches to modeling peoples' behavior changes were proposed. Simple algebraic formulations, cost-benefit balancing calculation and dynamic programming approaches were used in these behavior change models. Our results show that behavior changes ranging from reduced interaction to improved hygiene have the potential to significantly decrease the transmission of the virus.

The model was also expanded to include a spatial component, where several communities were linked through a few traveling individuals. Monte Carlo simulation was employed to establish how quickly the virus would spread from one community to the next. Varying the number of travelers between communities demonstrated that

realistic, but imperfect, travel restrictions are not effective at stopping the spread of infection.

The last facet that we added to our model is vaccination strategies; the goal was to evaluate the importance of vaccine efficacy, quantity and timing in decreasing influenza transmission. The findings indicate that unless vaccination occurs very early on in the outbreak, it can be ineffective. Since current egg based production technologies require a minimum of six months to produce the initial doses, it is unlikely that vaccines will be available in time, so well executed NPIs are likely to be indispensable.

After developing and building on our model, the focus of the thesis shifted to analyzing the potential impact of a pandemic on universities. The objective was to use insights gained from the modeling work to help make specific recommendations that would help assure the wellbeing of the uniquely active student population. The question of whether students should be evacuated home or allowed to stay on campus is one of the most pressing for university emergency planners. We suggest that a degree of reduction in the size of the student population is inevitable and should be encouraged; however, the university should also be prepared to support and care for a large portion of remaining students. Furthermore, universities should cope with and address the ethical and other complex pandemic driven dilemmas now; otherwise, they will consume crucial time when our society should be taking action. Overall, many organizations could benefit from a new mindset of emergency preparedness.

7.2 Policy Implications

Detailed and thorough plans that are prepared and reviewed before the outbreak, should be implemented immediately at the first sign of a dangerous easily transmissible flu strain. While it is impossible to validate any model with experimental trials, they do provide an approach to systematically evaluating different policies and scenarios. The results and insights developed from models proposed in this thesis can be used to carefully guide some pandemic policies.

Even highly effective travel restrictions, unless airtight, are likely to be useless once the infection is circulating in several communities. There is no easy way to regulate the travel patterns of all individuals through all transportation networks including planes, cars, buses, trains, etc, so the restrictions will be imperfect, costly and futile. We recommend avoiding government-enforced travel restrictions, but possibly creating early travel advisories before the virus enters the country to prevent recreational and voluntary travel and potentially delay the pandemic without severe economic losses.

From our research we find that while these advisories may slightly delay the spread of the flu, they are not likely to stop it from reaching the US. Virtually every community in the US should be prepared for infection. The focus of these communities' mitigation strategies should be a combination of inner-community interventions: social distancing, hygienic steps, closings, pre-pandemic vaccine inoculation, etc. No one intervention is likely to be the silver bullet that stops the pandemic, but a layered combination of multiple measures has a high likelihood of successfully decreasing infection incidence. If communities are able to decrease their maximum number of daily

infected individuals, they will reduce the probability of intra-community infection transmission as a byproduct of the inner community action.[39]

The large scale findings are encouraging and support the assumption that *limiting interaction* within the population will decrease the effect of the pandemic. The deeper, mathematical insight of this result is that social distancing is effective because it attacks the source of the problem by decreasing the exponential growth factor. Preventing exponential explosion of the number of infecteds has the potential to prevent the pandemic.

Another result is that the focus should be on the group most culpable for infection spread: highly active individuals as well as people who are both highly susceptible and highly infectious. They are the drivers of the flu and it is important to ensure that these people alter their behavior in an outbreak. Most children are highly active, infective and susceptible, thus school closures and other ways of socially distancing children are likely to be instrumental in mitigating the flu.

At the same time, the overall goal should be to get as many people to alter their behavior as possible. Even small changes in behavior, implemented on a global scale, can make a very big difference. The government should educate as many people as possible about appropriate flu prevention measures. It may be helpful to explain to people that by avoiding infection, they not only protect their own wellbeing, but they also prevent their ability to spread the disease to their loved ones at home.

The most effective timing of these measures, in the absence of vaccines, is preemptive and maintained implementation of non-pharmaceutical interventions. As long as neighboring communities are infective, a community would need to maintain

[39] The reverse is not true. Travel restrictions have no impact on inner community infection dynamics.

preventative measures to avoid entry or reentry of the infection. However, for those communities that are not able to drastically alter and maintain their behavior changes, even altering behavior only during the peak days of the infection should decrease the overall infection rate.

Lastly, our conclusion regarding vaccines is that while they have the potential to be tremendously helpful if people are inoculated early, current production makes this highly improbable. In the case that pre-pandemic less effective vaccine is available, we recommend focusing those limited doses on doctors, nurses, law enforcement personnel, etc; these individuals will be important in ensuring the sustainability of social order. However, if researchers master the use of cell-based vaccine production or create a universal vaccine, the importance of vaccination will be significantly higher.

7.3 Future Work

There are several different areas of research that we suggest for future study. There is significant work to be done ranging from quantitative research such as data collection and modeling to biological studies and policy analysis.

One of the biggest areas for future research is in the area of developing and validating models of reactive behavior change. This thesis is one of the first attempts at dynamically modeling human behavior, and the lack of data makes it impossible to compare the usefulness or reliability of our four different approaches. At the same time, we were able to show that behavior changes are going to significantly alter the course of the epidemic, and thus must be studied further.

The rarity of influenza pandemics makes it difficult to collect data on human behavior in a flu pandemic. We looked at the data from the 1918-1919 Spanish flu, but unfortunately it was very limited and more anecdotal in nature. Future work could focus on the more recent 1957-1958 Asian and 1968-1969 Hong Kong pandemics which seem somewhat understudied. Furthermore, data on human behavior as a result of other infectious diseases from measles to cholera could be helpful in identifying standard patterns in reactive behavior.

The development of other reactive behavior models is another area of research that requires the collaboration of social scientists and modelers. Existing models are qualitative – they describe which factors are important, but do not quantify the importance of these factors. More data on human behavior will act as a catalyst in the development of these more quantitative models.

More data on human activity levels, similar to the research done by Yang-chih Fu in Taiwan, will help quantify the impact of highly active individuals. In our research, we have shown that highly active individuals act as drivers of transmission, however there is limited data quantifying the activity levels of the US population. Identifying the members of the highly active group by profession or some other easily identifiable characteristic will help target and educate these individuals in an outbreak.

An idea, which was briefly described in ***Chapter 5,*** that we believe merits further research and development, is the creation of the multidimensional tent-like boundary for sets of interventions that will result in a R_0 less than 1. It is unlikely that any one intervention will be implemented to the extreme necessary to stop the flu, but combinations of several measures may be able to decrease R_0 to below 1. There has been

limited research analyzing the interplay of layered interventions. We suggest an approach to visualizing these results through the creation of a tool that decision makers could use to test out possible policies.

Another promising area of research is in the fields of biology and particle physics. Currently, the mode of transmission for influenza is highly debated. It is unclear whether large droplet, and the resulting contact based transmission, or aerosol transmission is the predominant form of transmission. Understanding how each type of transmission contributes to overall disease spread will allow researchers to develop more accurate mathematical models and appropriate intervention strategies.

Lastly, we have identified a significant lack of understanding of and preparation for a pandemic at the organizational level. We do not suggest that institutions should scare their respective members about the possibility and impact of a pandemic. However, many organizations have not thought about the details and implications of their decisions and actions. We encourage businesses, law enforcement offices, utilities, universities, churches and other organizational structures to develop emergency plans including one for pandemic flu.

7.4 Conclusions

The irony of a pandemic is that it is a worldwide catastrophe that will be felt intensely at the local level since there is no one who will be "outside" of the pandemic to send help (Greger, 2006; USDA., 2006). Communities will have to use their own resources to cope with the pandemic. Therefore, it is vital that all levels of society:

families, businesses, cities, states, countries, are all prepared for the pandemic. The best plan will require the cooperation of the American people. In order to gain the trust and understanding of 300 million people, we must be prepared to educate the public on the important factors of the infection.

While epidemiologists sometimes refer to a lack of parameter knowledge as reason to avoid adding complexity to models, we believe that an intuitive understanding of disease dynamics can only be improved by looking at lessons learned from experience, logic, and most importantly well structured models. We hope that the findings described in this thesis not only advance the field, but are also helpful in case there is a pandemic. In the end we also acknowledge the limitations of our work, mathematical models remain just that – models, not real life. All models use assumptions and simplifying approaches and no approach should be thought of as the only modeling strategy. Even the most established modeling approaches should not be seen as boundaries, but rather as starting points for future work. By moving beyond the highly used R_0 parameter in our modeling work, we were able to observe the importance of highly active individuals and include a dynamic feedback component to describe reactive behavior changes. This research provides actionable insights on the effectiveness of mostly non-pharmaceutical interventions in reducing illness and death from pandemic influenza. In case of a pandemic, hopefully this work can help save peoples' lives.

REFERENCES FOR CHAPTER 7

Greger M., 2006. "Coming soon to a theater near you. Birdflu a virus of our own hatching." <http://birdflubook.com/g.php?id=5>.

U.S. Department of Agriculture National Agricultural Statistics Service (USDA)., 2006. "Poultry slaughter-2005 annual summary." <http://usda.mannlib.cornell.edu/usda/cur...lauSu-02-28-2006.pdf>.

APPENDIX A

MODEL FLOW CHARTS FOR INFLUENZA

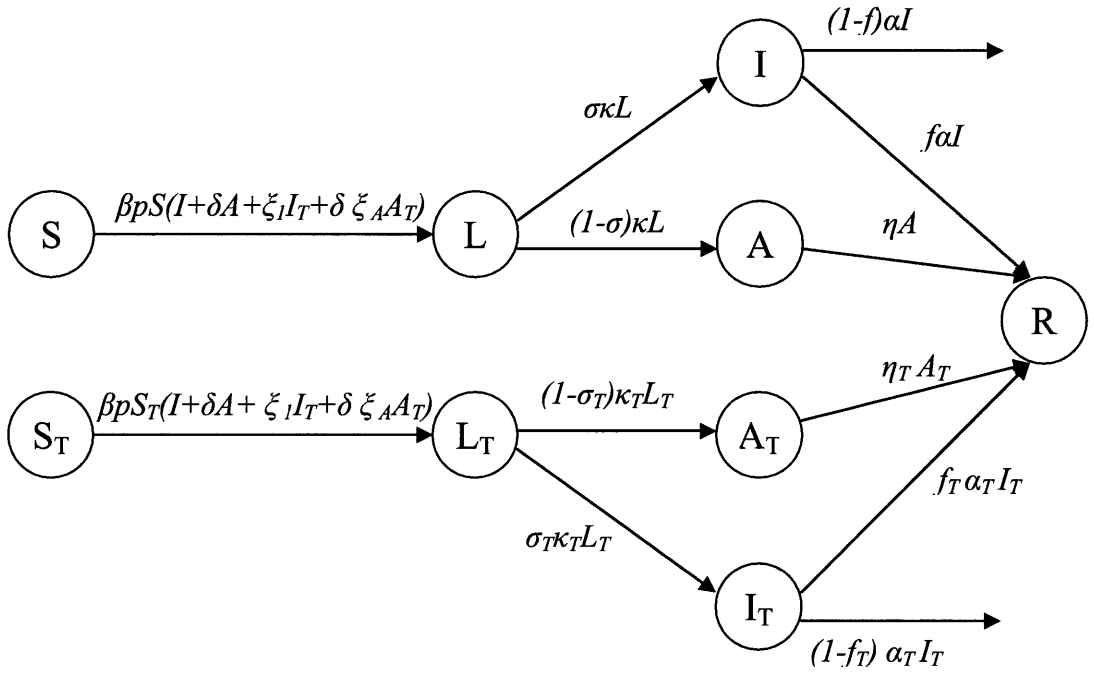


Figure A.1
Vaccination model flow chart.

Assumptions:

1. An average member of the population makes βN contacts per unit of time.
2. The probability of infection spreading from an infected to a susceptible individual per contact is p.
3. A fraction of the population is vaccinated and is in the T compartments.
4. Infected individuals leave the I group at a rate of αI and the I_T group at a rate of $\alpha_T I_T$.
5. Asymptomatic individuals leave groups A and A_T at rates ηA and $\eta_T A_T$ respectively.
6. Members of the vaccinated group marked as T has susceptibility, infectivity in I and A reduced by ξ_S, ξ_I, ξ_A.
7. The recovery rates are f and f_T.
8. Vaccination decreases the fraction of latent members who develop symptoms by τ.

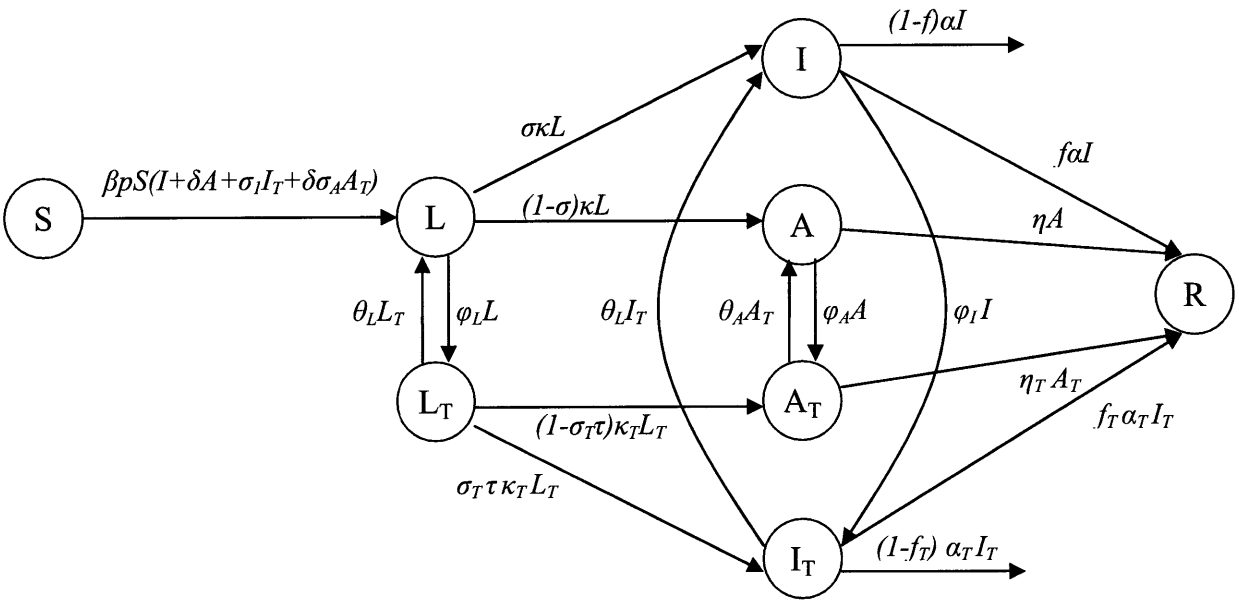


Figure A.2
Antiviral treatment model flow chart.

Assumptions:

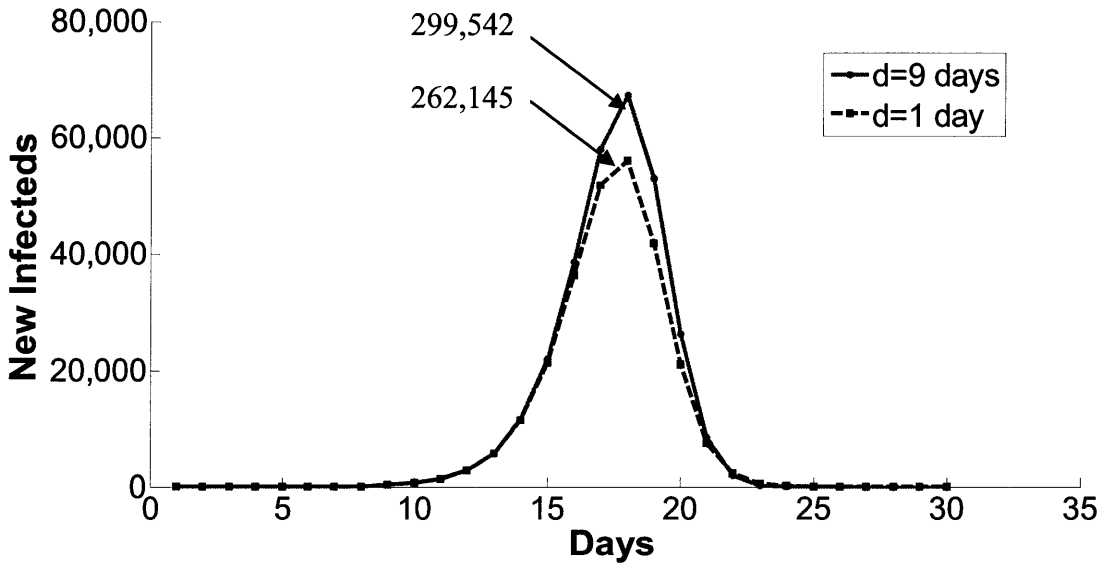
1. An average member of the population makes βN contacts per unit of time.
2. The probability of infection spreading from an infected to a susceptible individual per contact is p.
3. There is a treatment rate of φ and a θ rate of relapse in the different compartments.
4. Infected individuals leave the I group at a rate of αI and the I_T group at a rate of $\alpha_T I_T$
5. Asymptomatic individuals leave groups A and A_T at rates ηA and $\eta_T A_T$ respectively.
6. Antivirals decrease the fraction of latent patients who go to the infectious rate by τ.
7. Members of the treated group marked as T has infectivity in I and A reduced by ξ_I, ξ_A.
8. The recovery rates are f and f_T.

APPENDIX B

IMPACT OF VARYING THE DURATION OF ILLNESS – D, OR THE PERCENTAGE OF PEOPLE WHO RECOVER – H.

Consider a population where the rate of contact for the entire population is λ=20.666 people/day and the conditional probability of infection is p=0.1 for the entire population. (Note, we will be considering the standard incidence model).

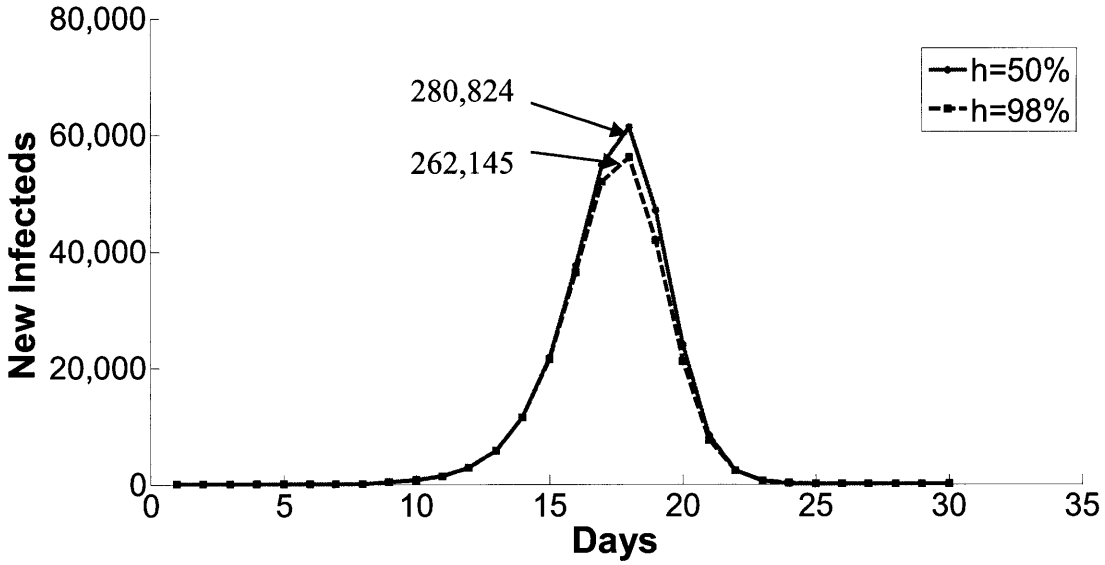
Let us vary the duration of the sickness, from d=9 days, down to d=1 day[40] while keeping the fraction of recovering people who reenter the population at h=98%. As shown in Graph B.1, we see that the number of people infected is reduced.



Graph B.1
Varying the duration of illness.

Let us vary the fraction of people who recover from h=98% down to h=50% while keeping the duration of sickness at d=*1*. As shown in ***Graph B.2*** we see that the number of infected individuals is increased.

[40] The duration of illness starting the day of infection, d cannot be less than 1. So for the case where d=1, the individual does not stay at home as a result of the virus, but returns right away with immunity to the active population after surviving the virus.



Graph B.1

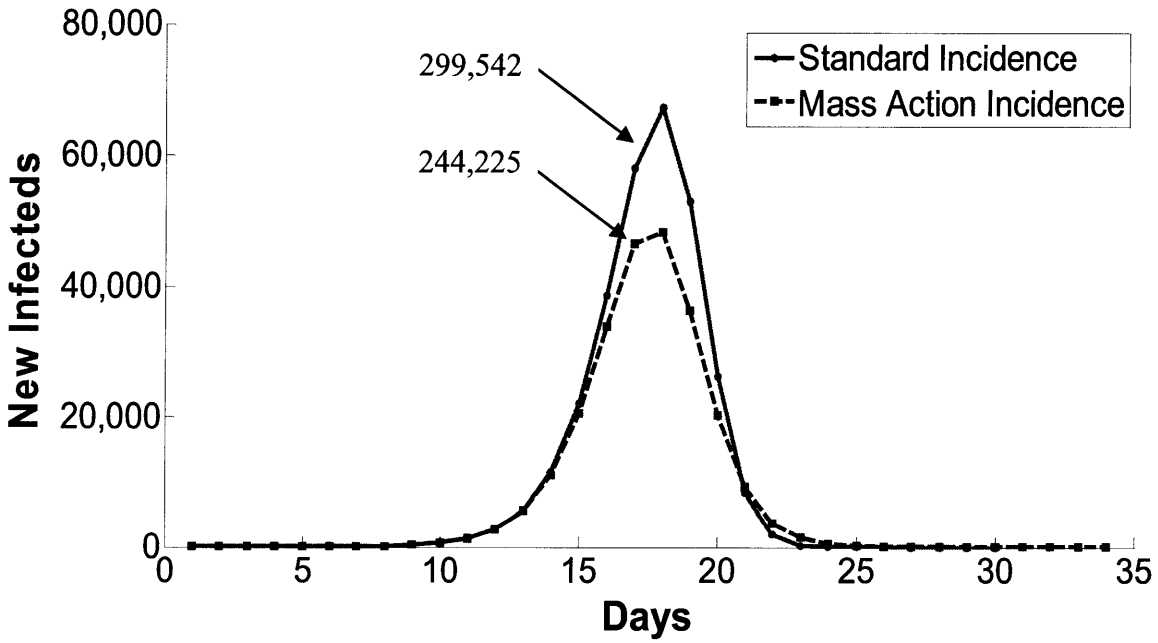
Varying the percentage of people who recover and reenter the population.

For both cases, decreasing d and increasing *h*, the effect is that the active population is diluted by individuals who are no longer susceptible nor infectious. This immune population "absorbs" some of the interactions with the infectious individuals and as a result reduces the infection rate for the overall population.

APPENDIX C

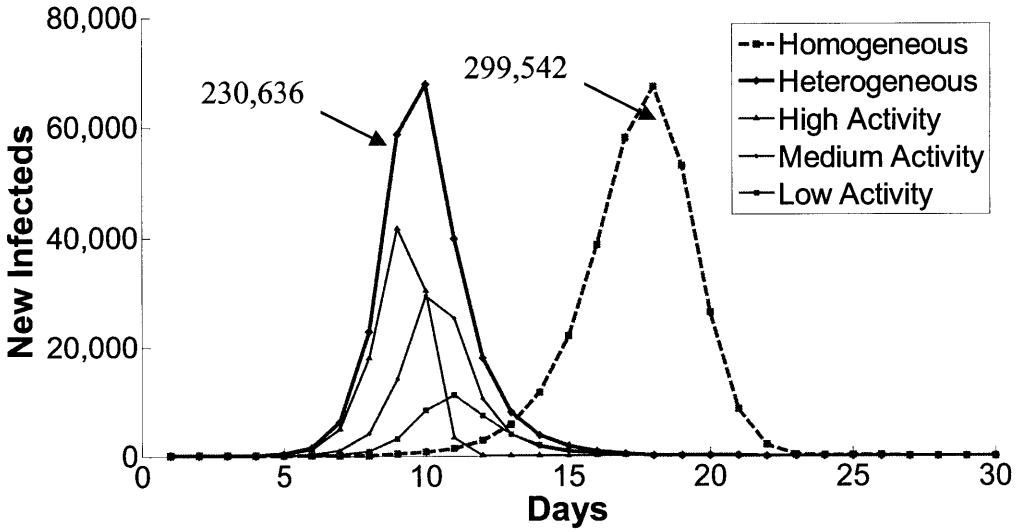
STANDARD INCIDENCE MODEL

The difference between the two modeling approaches is significant in cases where there is a slower initial growth of the infection. For example when we have a completely homogeneous population as in ***Graph B.1A*** the initial spread of the flu is slower than in a heterogeneous population as shown in ***Graph 3.1***. If we shorten the duration of sickness to only 1 day, or increase the mortality rate from 2% to 50%, the difference between the two models is a little smaller, but still significant.



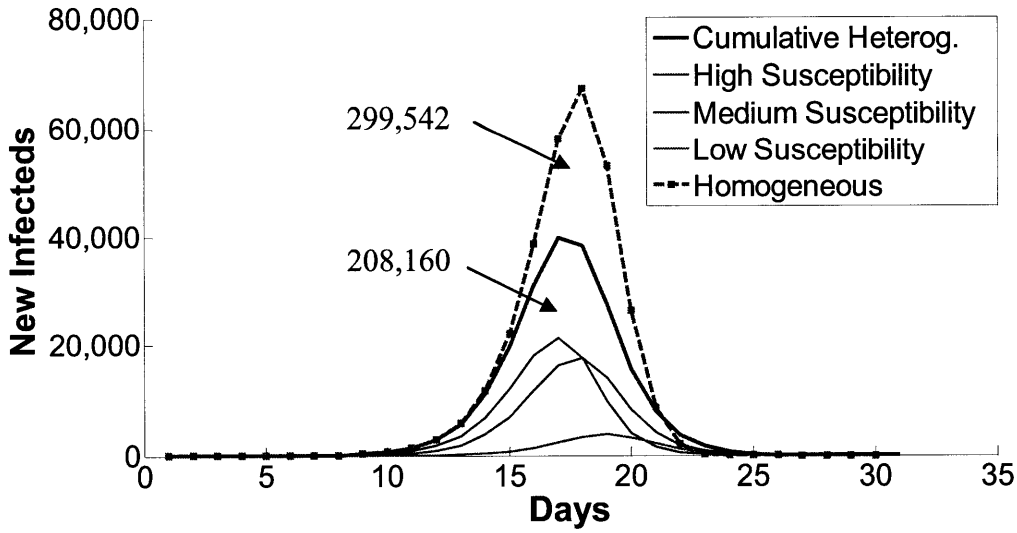
Graph C.1

Comparison of the Standard and Mass Action Incidence models for a homogeneous population. The rate of contact for the entire population is $\lambda = \lambda(0) = 20.666$ people/day. The conditional probability of infection is $p = 0.1$ for the entire population. The duration of illness since infection is 9 days.



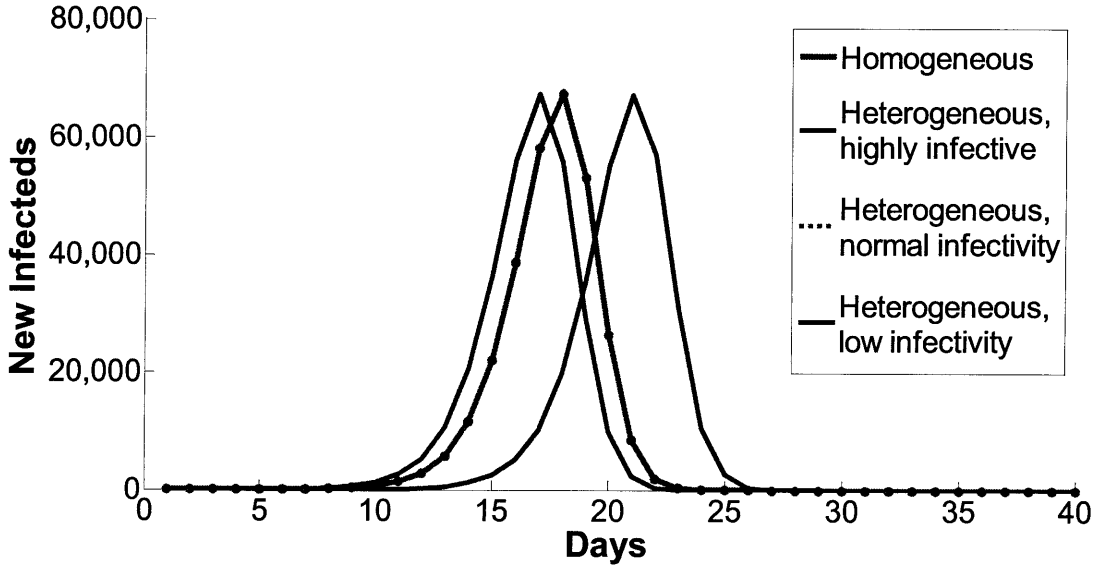
Graph C.2

The equivalent of ***Graph 3.2*** for the Standard Incidence Model. Comparing spread of infection between heterogeneously and uniformly active communities of 300,000 individuals. The homogeneous population has a rate of contact 20.66 people/day. The rest of the input data can be found in ***Table 3.1***. All the highly active, 91% of the medium activity and 39% of the low activity people get sick.



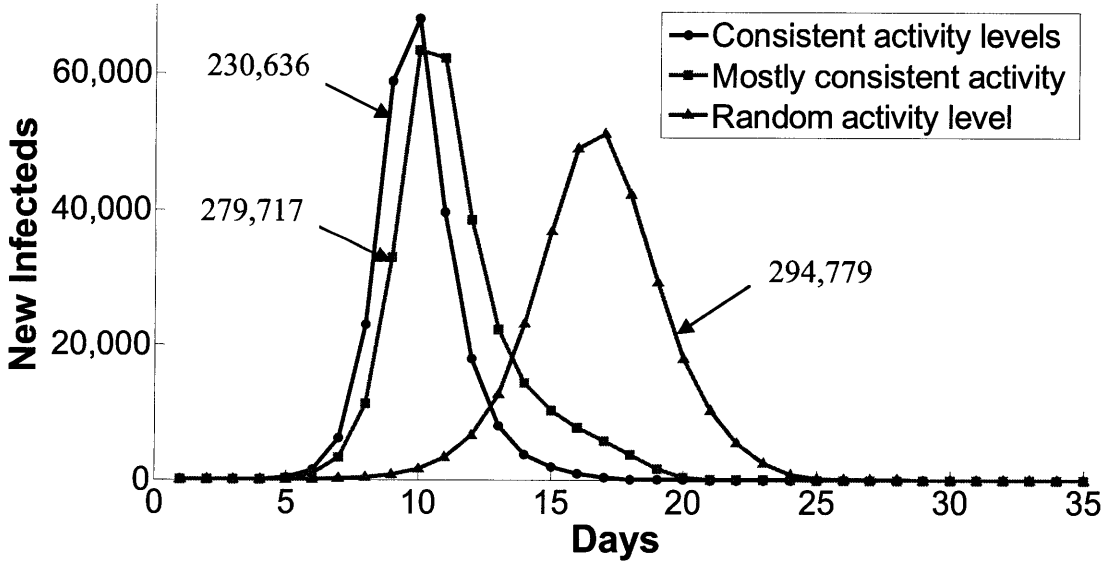
Graph C.3

The equivalent of ***Graph 3.3*** for the Standard Incidence Model. Comparing spread of infection between heterogeneously and uniformly susceptible population of 300,000 individuals. The susceptibility of the individuals in the heterogeneous population is shown in ***Table 3.3*** and for the homogeneous population p=1.Compared to 20% of the low susceptibility group, over 98% of the high susceptibility group become infected.



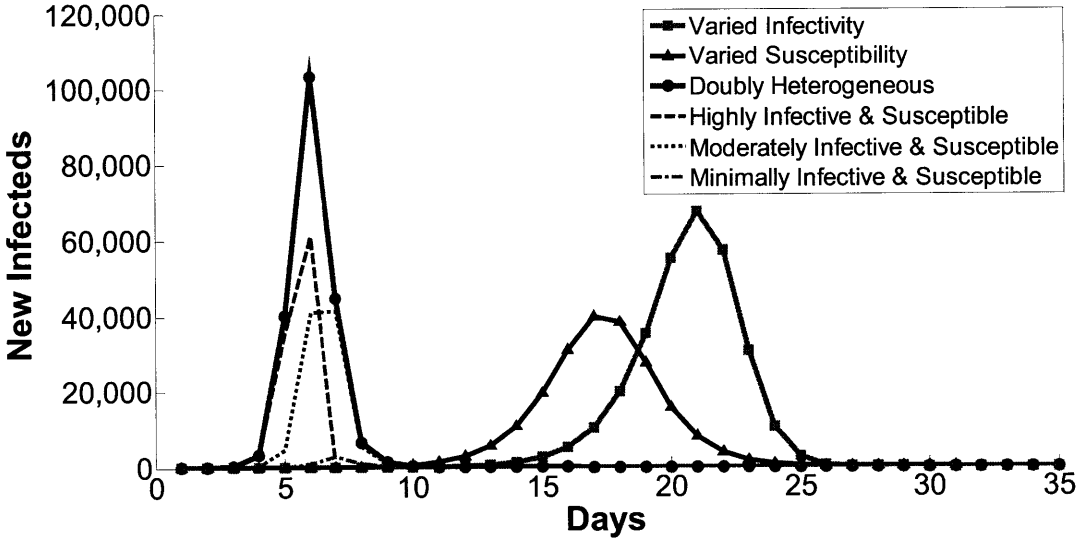
Graph C.4

The equivalent of ***Graph 3.4*** for the Standard Incidence Model. The cumulative number of people infected is constant regardless of the heterogeneous or homogeneous model; 299,542 people get infected.



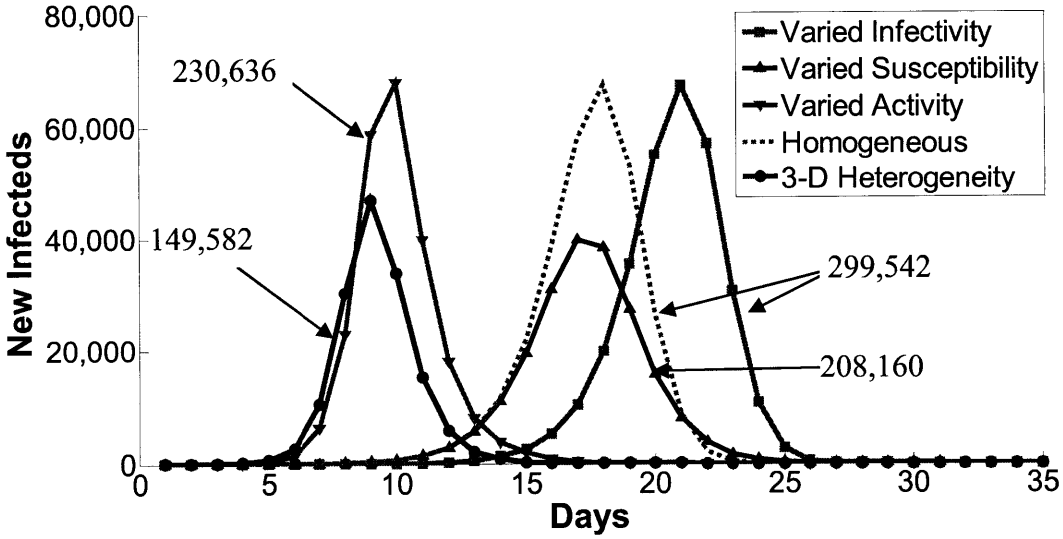
Graph C.5

The equivalent of Graph 3.5 for the Standard Incidence Model. The impact of inconsistent behavior in the population on the epidemic curve. If people can change their activity levels the speed of transmission is decreased.



Graph C.6

The equivalent of ***Graph 3.6*** for the Standard Incidence Model. Heterogeneity in two dimensions: susceptibility and infectivity. The simultaneous presence of both high susceptibility and high infectivity results in an explosive outbreak that is driven by this doubly dangerous group.



Graph C.7

The equivalent of ***Graph 3.7*** for the Standard Incidence Model. Heterogeneity in all dimensions: activity level, susceptibility and infectivity. The highly active, highly susceptible and highly infective individuals are the drivers of infection of spread. The low activity, low susceptibility and low infectivity decrease the cumulative impact of the outbreak on the population

APPENDIX D

MATLAB CODES FOR CHAPTER 3

```
function OneCommunityBasicProporationalBeta
  % allows for both standard and mass action incidence model
  % heterogeneity in activity levels: different lambda's
  % heterogeneity in susceptibility levels: different p's

n=3;                          %number of activity groups

lambda = [50, 10, 2];         % average number of contacts
p = [0.1, 0.1, 0.1];          % conditional probability of infection
N = [100000, 100000, 0];      % number of people in each category

t=1; % day
T=30;

duration=9;                   %duration of sickness till reentry into
                                 circulation population
survive=.98;                  %fraction of people to survive and
                                 reenter into circulation

beta=zeros(T,1);
prop=zeros(T,1);              %impact of population size on lambda
prob=zeros(T,n);
I=zeros(T,n);
S=zeros(T,n);
Active=zeros(T,n);
I_Total =zeros(T,1);

I(t,1)=1;
I(t,2)=0;
I(t,3)=0;

S(t,1)= N(1) - I(t,1);
S(t,2)= N(2) - I(t,2);
S(t,3)= N(3) - I(t,3);

Active(t,1)=N(1);
Active(t,2)=N(2);
Active(t,3)=N(3);

I_Total(t)= sum(I(t,:));

while I_Total(t)>.1
    beta(t) = (I(t,:) * lambda')/((Active(t,:)) * lambda');
    %prop(t)=sum(Active(t,:))/sum(N);   %used for mass action incidence
                                          model
    prop(t)=1;                          %used for standard incidence
                                          model

    for i=1:n     % The interactions throughout the day that result in
                    new infections
```

```
        prob(t,i) = 1 - exp(-lambda(i) * beta(t)*prop(t) * p(i));
        I(t+1,i) = prob(t,i) * S(t,i);
        S(t+1,i) = S(t,i) - I(t+1,i);
        if t-duration>0
            Active(t+1,i)=Active(t,i)-I(t,i)+survive*I(t-duration, i);
        else
            Active(t+1,i)=Active(t,i)-I(t,i);
        end
    end
    t=t+1;
    I_Total(t)= sum(I(t,:));
end

hold on
plot (I_Total,'g');
% plot(I(:,1),'b')
% plot(I(:,2),'m')
% plot(I(:,3),'g')
sum(I_Total);
```

```
function CommVariedInfectivityModel
  % allows for both standard and mass action incidence model
  % heterogeneity in infectivity levels: different p's

n=3;                                %number of activity groups

lambda = [20.66, 20.66, 20.66]; % average number of contacts
p = [0.19, 0.1, 0.01];          % conditional probability of infection
N = [100000, 100000, 100000];   % number of people in each category

t=1; % day
T=55;

duration=9;

beta=zeros(T,n);                %beta for each infection level group
prop=zeros(T,1);
power=zeros(T,1);
prob=zeros(T,n);
I=zeros(T,n);
S=zeros(T,n);
Active=zeros(T,n);
I_Total =zeros(T,1);

I(t,1)=1;
I(t,2)=0;
I(t,3)=0;
```

APPENDIX D
(CONTINUED)

```
S(t,1)= N(1) - I(t,1);
S(t,2)= N(2) - I(t,2);
S(t,3)= N(3) - I(t,3);

Active(t,1)=N(1);
Active(t,2)=N(2);
Active(t,3)=N(3);

I_Total(t)= sum(I(t,:));

while I_Total(t)>.1
    for i=1:n
        beta(t,i)=I(t,i)*lambda(i)/((Active(t,:)) * lambda');
    end

    for i=1:n
        power(t)=power(t)+beta(t,i)*p(i);
    end

    %prop(t)=sum(Active(t,:))/sum(N);
    prop(t)=1;

    for i=1:n     % interactions throughout the day resulting in new
                    infections
        prob(t,i) = 1 - exp((-lambda(i)*prop(t)) * power(t));
        I(t+1,i) = prob(t,i) * S(t,i);
        S(t+1,i) = S(t,i) - I(t+1,i);
        if t-duration>0
            Active(t+1,i)=Active(t,i)-I(t,i)+.98*I(t-duration, i);

        else
            Active(t+1,i)=Active(t,i)-I(t,i);
        end
    end
    t=t+1;
    I_Total(t)= sum(I(t,:));
end

hold on

plot (I_Total,'k');
% plot(I(:,1),'b')
% plot(I(:,2),'m')
% plot(I(:,3),'g')
sum(I_Total)
```

APPENDIX D
(CONTINUED)

```
function ModelingInconsistentBehavior
  %modeling inconsistent behavior
  %allows for standard and mass action incidence model

n=3;                    %number of activity groups

lambda = [50, 10, 2];  % average number of contacts
p = [0.1, 0.1, 0.1];
N = [100000, 100000, 100000]; % number of people in each category

t=1; % day
T=35;
duration=9;
survive=.98;

beta=zeros(T,1);
prop=zeros(T,1);
prob=zeros(T,n);

I_Start=zeros(T,n);
S_Start=zeros(T,n);
I_End=zeros(T,n);
S_End=zeros(T,n);
I_Total_Start=zeros(T,1);
R_Start=zeros(T,n);
R_End=zeros(T,n);
Active_Start=zeros(T,n);
Active_End=zeros(T,n);

I_Start(t,1)=1;
I_Start(t,2)=0;
I_Start(t,3)=0;
S_Start(t,1)= N(1) - I_Start(t,1);
S_Start(t,2)= N(2) - I_Start(t,2);
S_Start(t,3)= N(3) - I_Start(t,3);
R_Start(t,1)= 0;
R_Start(t,2)= 0;
R_Start(t,3)= 0;

Active_Start(t,1)= N(1);
Active_Start(t,2)= N(2);
Active_Start(t,3)= N(3);

I_Total_Start(t)= sum(I_Start(t,:));

%Q=eye(n,n);
%Q=[17/20, 2/20, 1/20; 3/40, 17/20, 3/40;  1/20, 2/20, 17/20; ];
%Q=[2/3, 1/3, 0; 1/3, 2/3, 0;  0, 0, 1; ];
Q=[1/3, 1/3, 1/3; 1/3, 1/3, 1/3;  1/3, 1/3, 1/3; ];
%Q=[1/3, 2/3, 0; 2/3, 1/3, 0; 0, 0, 1; ];
%Q=[0, 1, 0; 0, 0, 1; 1, 0, 0; ];
```

APPENDIX D
(CONTINUED)

```
while I_Total_Start(t)>.5
    beta(t) = (I_Start(t,:) * lambda')/((Active_Start(t,:)) * lambda');
    prop(t)=1;                                  %used for standard incidence
                                                     model
    %prop(t)=sum(Active_Start(t,:))/sum(N); %used for mass action
                                                  incidence model

    for i=1:n     % The interactions throughout the day that result in
                      new infections
        prob(t,i) = 1 - exp(-lambda(i) * beta(t)* prop(t)* p(i));
        I_End(t,i) = prob(t,i) * S_Start(t,i);
        S_End(t,i) = S_Start(t,i) - I_End(t,i);
        if t-duration>0
            R_End(t,i)=R_Start(t,i)+ survive * I_Start(t-duration,i);
        else
            R_End(t,i)=R_Start(t,i);
        end
        Active_End(t,i)=Active_Start(t,i)-I_Start(t,i)+ R_End(t,i);
    end

    for i=1:n      % People changing behavior overnight
        I_Start(t+1,i) = Q(1,i)*I_End(t,1) + Q(2,i)*I_End(t,2) +
                         Q(3,i)*I_End(t,3);
        S_Start(t+1,i) = Q(1,i)*S_End(t,1) + Q(2,i)*S_End(t,2) +
                         Q(3,i)*S_End(t,3);
        R_Start(t+1,i)= Q(1,i)*R_End(t,1) + Q(2,i)*R_End(t,2) +
                        Q(3,i)*R_End(t,3);

        Active_Start(t+1,i)= S_Start(t+1,i) + I_Start(t+1,i) +
                             R_Start(t+1,i);
    end
    t=t+1;
    I_Total_Start(t)= sum(I_Start(t,:));
end

hold on
plot (I_Total_Start, 'k');
x=sum(I_Total_Start)
```

```
function OneCommunityBasicThreeHeterogeneities27_WORKS
  %allows for both standard and mass action incidence models
  %heterogeneity in all three different dimensions

n=27;                              %number of activity groups

%lambda = [50, 10, 2];             % average number of contacts
%p = [.361, .19, .019; 0.19, 0.1, 0.01; 0.019, 0.01, 0.001;];
% conditional probability of infection
%N = [100000, 100000, 100000];    % number of people in each category
```

APPENDIX D
(CONTINUED)

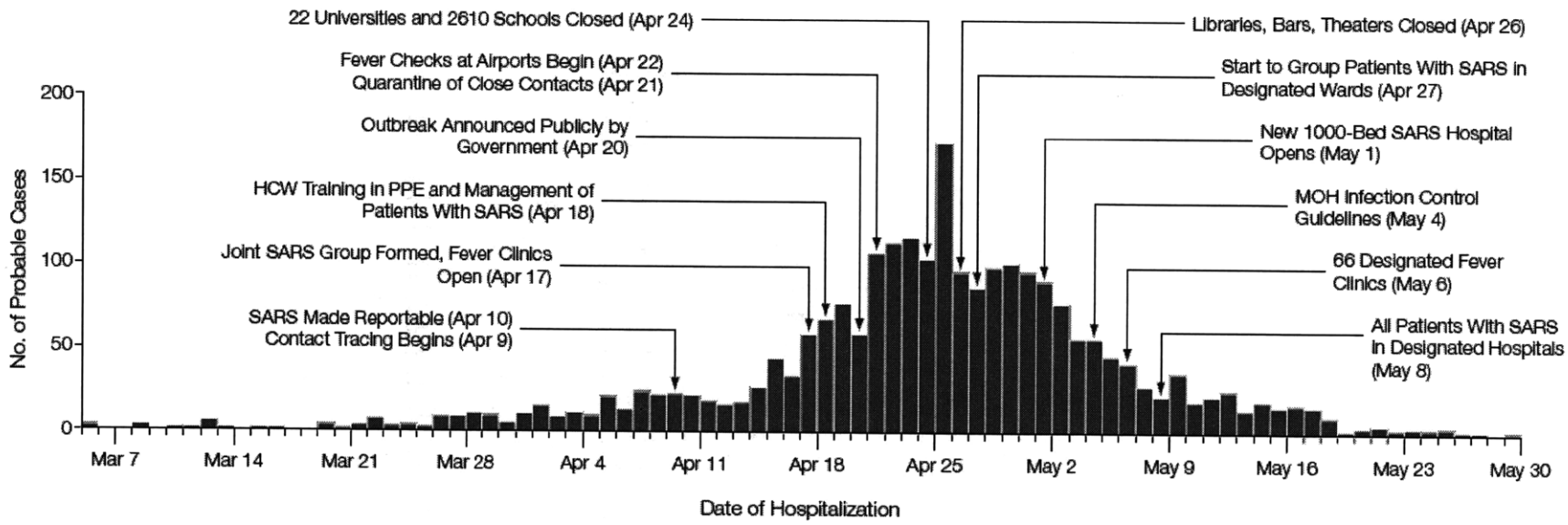
```
p=zeros(n,n);
lambda=zeros(n,1);
N=zeros(n,1);

t=1; % day
T=35;

duration=9;

beta=zeros(T,n);                    %beta for each infection level group
prop=zeros(T,n);
power=zeros(T,n);
prob=zeros(T,n);
I=zeros(T,n);
S=zeros(T,n);
Active=zeros(T,n);
I_Total =zeros(T,1);

I(t,1)=1;

for i=1:27
    if i<10
        lambda(i)=50;
    elseif (i>9 && i<19)
        lambda(i)=10;
    else
        lambda(i)=2;
    end

    N(i)=11111;
    Active(t,i)=N(i);
    S(t,i)= N(i) - I(t,i);

    for j=1:27
        if (i==1||i==4||i==7||i==10||i==13||i==16||i==19||i==22||i==25)
            if ((j<4)||(j<13&&j>9)||(j<22&&j>18))
                p(i,j)=0.361;
            elseif((j<7&&j>3)||(j<16&&j>12)||(j<25&&j>21))
                p(i,j)=.19;
            else
                p(i,j)=.019;
            end

elseif(i==2||i==5||i==8||i==11||i==14||i==17||i==20||i==23||i==26)
            if ((j<4)||(j<13&&j>9)||(j<22&&j>18))
                p(i,j)=0.19;
            elseif((j<7&&j>3)||(j<16&&j>12)||(j<25&&j>21))
                p(i,j)=.1;
            else
                p(i,j)=.001;
            end
```

APPENDIX D
(CONTINUED)

```
        else
            if ((j<4)||(j<13&&j>9)||(j<22&&j>18))
                p(i,j)=0.019;
            elseif((j<7&&j>3)||(j<16&&j>12)||(j<25&&j>21))
                p(i,j)=.01;
            else
                p(i,j)=.001;
            end
        end
    end
end

I_Total(t)= sum(I(t,:));


while I_Total(t)>.1
    for i=1:n
        beta(t,i)=I(t,i)*lambda(i)/((Active(t,:)) * lambda);
    end

    for i=1:n
        for j=1:n
            power(t,j)=power(t,j)+beta(t,i)*p(i,j);
        end
    end

    %prop(t)=sum(Active(t,:))/sum(N);
    prop(t)=1;

    for i=1:n     % The interactions throughout the day that result in
                      new infections
        prob(t,i) = 1 - exp((-lambda(i)*prop(t)) * power(t,i));
        I(t+1,i) = prob(t,i) * S(t,i);
        S(t+1,i) = S(t,i) - I(t+1,i);
        if t-duration>0
            Active(t+1,i)=Active(t,i)-I(t,i)+.98*I(t-duration, i);

        else
            Active(t+1,i)=Active(t,i)-I(t,i);
        end
    end
    t=t+1;
    I_Total(t)= sum(I(t,:));
end


hold on

plot (I_Total,'b');

x=sum(I_Total)
```

APPENDIX E

SARS OUTBREAK IN BEIJING



Epidemic Curve for Beijing SARS Outbreak and Timeline of Major Control Measures from March 5 to May 29, 2003. (Timeline from Pang, 2003)

APPENDIX F

MODELING EXPONENTIALLY DECAYING MEMORY

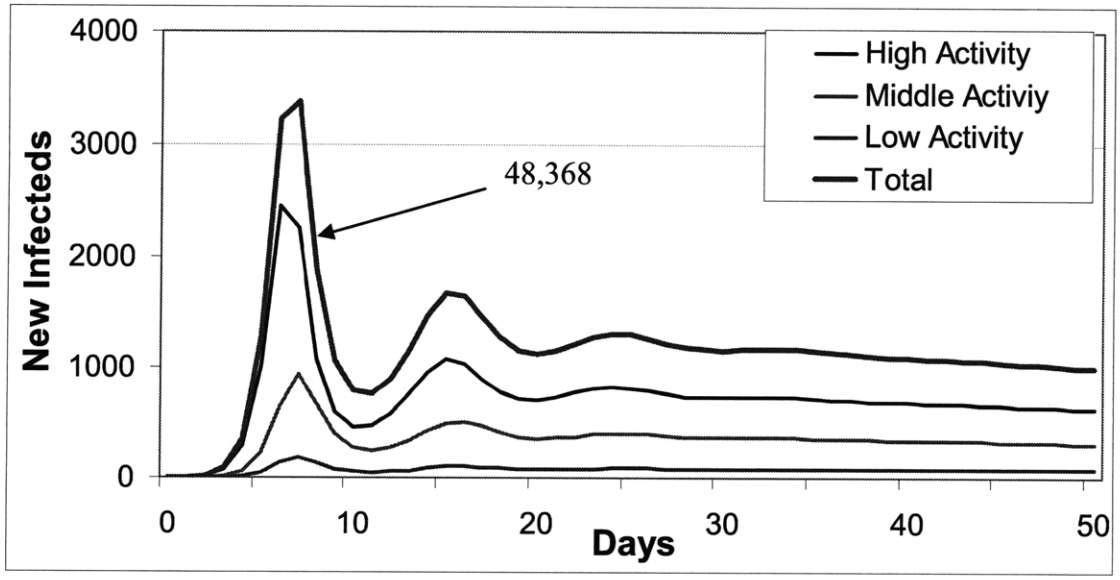
We will present the result of modeling behavior using the concern factor approach, where people's memories of past events decay exponentially. We will use the following approach to calculate the concern parameter:

$$\pi_X(t,C,\alpha)=\prod_{i=0}\left(1-\frac{\text{Number of infected people in Community X on day } t\text{-}1\text{-}i}{\text{The total population in Community X}}\right)^{\frac{C}{\alpha^i}}$$

We will now assume that people reduce their contact rate in accordance to their concern level, so the effective contact rate becomes:

$$\lambda(t)=\lambda\,\pi_X(t,C,\alpha)$$

The impact of this type of behavior change is shown in ***Graph F.1***.



Graph F.1

For a concern factor that has an exponentially decaying memory of what happened in the past the outbreak persists for a long period of time. In this case, after the initial drop in contact rates, the contact rates rebound and stay around $\lambda_H \approx 15$, $\lambda_M \approx 7$, $\lambda_H \approx 1.5$ while the conditional probability of infection is held constant at $p=0.1$.

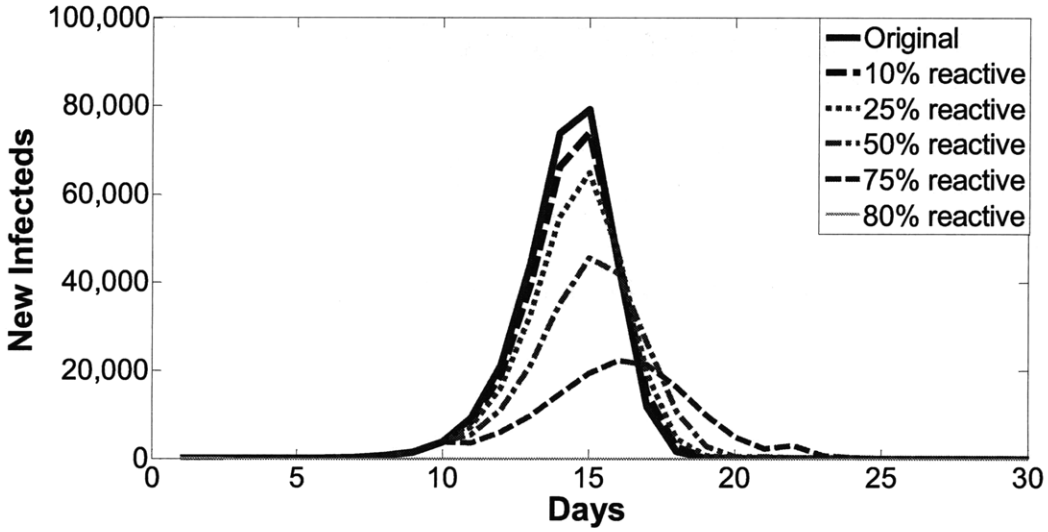
APPENDIX F
(CONTINUED)

If people over time forget the anxiety that they initially experienced, the virus can persist in the population as long as the susceptible pool is large enough. In the case where people only remember yesterday's events they don't react as strongly as they do here and as a result in the other model, the number of susceptibles is depleted. In the extreme case where people remember everything, their behavior changes are extreme enough to completely stop the outbreak. This case is intermediate: the behavior changes are significant at first when the virus takes off, and it seems like the flu is under control. But as time passes people start to forget the seriousness of past events and start behaving somewhat cautiously, so that the virus never takes off; but not cautiously enough to stop its spread. Thus the epidemic persists until the number of susceptibles is finally diminished.

APPENDIX G

ANOTHER EXAMPLE OF THE TRADEOFF MODEL

Another example of the tradeoff model presented in ***Section 4.3***. The parameters for this model are $\lambda=25$ contacts/day; the conditional probability of infection is $p=0.1$ and $\Lambda=\{25,20,15,10,5\}$.



Graph G.1

The impact of varying sized reactive groups on the epidemic curve. The larger the reactive group the less the burden of the infection.

	Infection rate for Non-Reactive group (%)	Infection rate for Reactive group (%)	Cumulative Infection rate (%)
0% reactive	97.1	52.4*	97.1
10% reactive	96.9	50.9	92.3
25% reactive	96.3	49.4	84.6
50% reactive	94.2	45.4	69.8
75% reactive	85.5	34.2	47.0
77% reactive	84.4	34.6	46.1
80% reactive	~ 0	~ 0	~ 0

Table G.1

The infection rates for different groups of the population. Notice that in this case the rate of infection within the reactive group is not decreasing as the size of the reactive group increases, in fact it is almost the opposite. However, the relationship is not completely monotonic and the rate of infection is a tiny bit higher in the case of a 77% reactive group than for a 75% reactive group.

** If 1 individual changes his or her behavior, the probability of infection for that individual will be 52.4%*

APPENDIX H

BEHAVIOR CHANGE MATLAB CODE FOR TRADEOFF MODEL

```
function RunFiveIterations(fraction)

hold off
hold on
decision = Individual_NO_Feedback();
IndividualDecision = IterationOfGroupDecision(decision, fraction,
                        ':g');
IndividualDecision = IterationOfGroupDecision(IndividualDecision,
                        fraction, ':g');
IndividualDecision = IterationOfGroupDecision(IndividualDecision,
                        fraction, ':g');
IndividualDecision = IterationOfGroupDecision(IndividualDecision,
                        fraction, '-r');
```

```
function [decision]=Individual_NO_Feedback()

N=300000;     %population total
n=5;          %number of choices an individual has
lambda = 30;
Ind_lambda = [30, 20, 15, 10, 5]; %decision maker's options
p=.05;

t=1;   %start day
T=50;  %end day

duration_illness = 2;
delta = 1000;     %balloon cost of illness
survival_rate=.98;
cost_per_interaction = 5;

% Code, not to be changed during sensitivity analysis
I=zeros(T,1); % # infecteds at the start of day t
S=zeros(T,1); % # susceptibles at the start of day t
R=zeros(T,1); % # newly recovered at the END of day t
Active_Pop=zeros(T,1); % # of people interacting on day t
                        (susceptibles, infecteds and recovereds)
Ind_prob = zeros(n,T); %probability of getting infected given choice n
                        and day T
Ind_beta = zeros(n,T);
prob = zeros(T,1);
beta = zeros(T,1);
prop = zeros(T,1);

I(t)=1;            %day 0, 1 person initiates the virus
S(t)= N - I(t);    %day 0, all but initial case susceptible
Active_Pop(t)= N; %day 0, everyone is active
```

APPENDIX H
(CONTINUED)

```
for i=1:duration_illness
    R(i)=0;          % there are no recovered people until the first
                         person recovers
end

Reward_Healthy=zeros(n,1);
Reward_Ill=zeros(n,1);
decision=ones(T,1);
decision(1)=1;
IndProbHealth=1;

for i=1:n
      %benefit from choice (of lambda) 1
    %Reward_Healthy(i) = Ind_lambda(i)*cost_per_interaction;
    %Reward_Ill(i) = Ind_lambda(i)*cost_per_interaction-
(duration_illness * (mean(Ind_lambda))*cost_per_interaction) - delta;

    Reward_Healthy(i) = sqrt(Ind_lambda(i))*cost_per_interaction;
      %benefit from choice (of lambda) 1
    Reward_Ill(i) = sqrt(Ind_lambda(i))*cost_per_interaction-
(duration_illness * sqrt((mean(Ind_lambda)))*cost_per_interaction) -
delta;

end

E_Reward=zeros(n,1);
Max_Reward=zeros(T,1); % maximum expected reward on day t

while I(t)>.5

    %prop(t)=sum(Active_Pop(t))/N;
    prop(t)=1;

    for i=1:n
        Ind_beta(i,t) = lambda*(I(t)) /(lambda*(Active_Pop(t)));
        Ind_prob(i,t) = 1 - exp(-Ind_lambda(i) * prop(t) *
            Ind_beta(i,t) * p);
        E_Reward(i)= Ind_prob(i,t)*Reward_Ill(i) +(1-Ind_prob(i,t)) *
            Reward_Healthy(i);   %expected reward for choice i on day t
    end


    [x,choice] = max(E_Reward(:,1));
    decision(t)=choice;
    Max_Reward(t)=x;

    IndProbHealth=IndProbHealth*(1-Ind_prob(decision(t),t));

    beta(t) = lambda*(I(t)) /(lambda*(Active_Pop(t)));
    prob(t)= 1 - exp(-(lambda)*beta(t)*p);
```

APPENDIX H
(CONTINUED)

```
    I(t+1)= S(t) * prob(t); %number to actually getsick
    S(t+1)= S(t) - I(t+1); %number to be susceptible

    if t > duration_illness
        R(t)=I(t-duration_illness)*survival_rate;
    end
    Active_Pop(t+1)=Active_Pop(t)-I(t)+R(t); %yesterdays actives
                                                  without the
    t=t+1;
end

hold on
plot(I,'LineWidth', 6)
plot(decision*2500,'r.')
PopulationHealth=1-sum(I)/N
IndProbHealth
```

```
function [IndividualDecision] = IterationOfGroupDecision(GroupDecision,
fraction, iteration);
N=300000; %population total
n=5; %number of choices an individual has
lambda = 30;
LengthLastTime=length(GroupDecision);

Ind_lambda = [ 30, 20, 15, 10, 5]; %decision maker's options

p=.05;

t=1; %start day
T=50;  %end day

duration_illness = 2;
delta = 1000; %baloon cost of illness
survival_rate=.98;
cost_per_interaction = 1;


% Code, not to be changed during sensitivity analysis
I=zeros(T,1); % # infecteds at the start of day t
S=zeros(T,1); % # susceptibles at the start of day t
R=zeros(T,1); % # newly recovered at the END of day t
I_Group=zeros(T,1);
S_Group=zeros(T,1);
R_Group=zeros(T,1);
Active_Pop=zeros(T,1); % # of people interacting on day t
                        (susceptibles, infecteds and recovereds)
Active_Group=zeros(T,1);
Active_Tot=zeros(T,1);
```

APPENDIX H
(CONTINUED)

```
Ind_prob = zeros(n,T); %probability of getting infected given choice n
                        and day T used by the INDIVIDUAL
Ind_beta = zeros(n,T); %USED BY THE INDIVIDUAL

prob = zeros(T,1);
prop = zeros(T,1);
prob_Group = zeros(T,1);
beta = zeros(T,1);

I(t)=1;  %day 0, 1 person initiates the virus
S(t)= N * (1-fraction) - I(t); %day 0, all but initial case susceptible
Active_Pop(t)= N * (1-fraction); %day 0, everyone is active

I_Group(t)=0;
S_Group(t)= N - I_Group(t) - I(t) - S(t);
Active_Group(t)=N * (fraction);

Active_Tot(t)=Active_Pop(t)+Active_Group(t);

for i=1:duration_illness
    R(i)=0;          % there are no recovered people until the first
                        person recovers
    R_Group(i)=0;
end

Reward_Healthy=zeros(n,1);
Reward_Ill=zeros(n,1);
decision=ones(T,1);
decision(1)=1;

for i=1:n
    Reward_Healthy(i) = Ind_lambda(i)*cost_per_interaction;
                                %benefit from choice (of lambda) 1
    Reward_Ill(i) = Ind_lambda(i)*cost_per_interaction-
(duration_illness * (mean(Ind_lambda))*cost_per_interaction) - delta;
    %Reward_Healthy(i) = sqrt(Ind_lambda(i))*cost_per_interaction;
                                %benefit from choice (of lambda) 1
    %Reward_Ill(i) = sqrt(Ind_lambda(i))*cost_per_interaction-
(duration_illness * sqrt((mean(Ind_lambda)))*cost_per_interaction) -
delta;
end

E_Reward=zeros(n,1);
Max_Reward=zeros(T,1); % maximum expected reward on day t

while I(t)>.5
    if t>LengthLastTime
        GroupDecision(t)=1;
    end
```

APPENDIX H
(CONTINUED)

```
    %prop(t)=sum(Active_Pop(t))/N;
    prop(t)=1;

    for i=1:n
        Ind_beta(i,t) = (lambda*(I(t))+
        Ind_lambda(GroupDecision(t))*I_Group(t))/( lambda*
      (Active_Pop(t))+ Ind_lambda(GroupDecision(t))*Active_Group(t));
        Ind_prob(i,t) = 1 - exp(-Ind_lambda(i) * Ind_beta(i,t) * p);
        E_Reward(i)= Ind_prob(i,t)*Reward_Ill(i) +(1-
                        Ind_prob(i,t))*Reward_Healthy(i);
            %expected reward for choice i on day t
    end

    [x,choice] = max(E_Reward(:,1));
    decision(t)=choice;
    Max_Reward(t)=x;


    beta(t) = (lambda*(I(t))+
    Ind_lambda(GroupDecision(t))*I_Group(t))/(lambda* (Active_Pop(t))+
    Ind_lambda(GroupDecision(t))*Active_Group(t));
    prob(t)= 1 - exp(-(lambda)*beta(t)*p);
    prob_Group(t)=1-exp(-Ind_lambda(GroupDecision(t))*beta(t)*p);

    I(t+1)= S(t) * prob(t); %number to actually getsick
    S(t+1)= S(t) - I(t+1); %number to be susceptible
    I_Group(t+1) = S_Group(t) * prob_Group(t);
    S_Group(t+1) = S_Group(t) - I_Group(t+1);

    if t > duration_illness
        R(t)=I(t-duration_illness)*survival_rate;
        R_Group(t)=I_Group(t-duration_illness)*survival_rate;
    end
    Active_Pop(t+1)=Active_Pop(t)-I(t)+R(t); %yesterdays actives
                                                 without the
    Active_Group(t+1)=Active_Group(t)-I_Group(t)+R_Group(t);
    t=t+1;
end

IndividualDecision = decision;

I_total=I+I_Group;

plot(I_total, iteration, 'LineWidth', 1.75)
%plot(decision*10000, '*r')
%plot(I)

ReactiveGroupInfected=sum(I_Group)/(N*fraction)
NonReactiveInfected=sum(I)/(N*(1-fraction))
                    CumulativeInfected=sum(I_total)/N;
```

APPENDIX I

BEHAVIOR CHANGE MATLAB CODE FOR FULFILLING BEHAVIORAL CONSTRAINTS

```
function RunFiveIterationsDP(fraction)

%initialize
N=1000000; %population total
n=3; %choices a person has
lambda = [30, 20, 10];
p=.05;

t=1; %start day
T=50;  %end day
duration_illness = 2;
delta = 10000; %baloon cost of illness
survival_rate=.98;
cost_interaction=1;

% Code, not to be changed during sensitivity analysis
I=zeros(T,1); % # infecteds on day t
S=zeros(T,1); % # susceptibles on day t
R=zeros(T,1); % # recovered on day t
Active_Pop=zeros(T,1); % # of people interacting on day t
(susceptibles, infecteds and recovereds)
prob = zeros(n,T); %probability of getting infected given choice n and
day T
beta = zeros(n,T);

I(t)=1;  %day 0, 1 person initiates the virus
S(t)= N - I(t); %day 0, all but initial case susceptible
Active_Pop(t)= N; %day 0, everyone is active

for i=1:duration_illness
    R(i)=0;          % there are no recovered people until the first
person recoveres
end

while I(t)>=1.0

    for i=1:n
        beta(i,t) = lambda(i)*I(t) /(lambda(i)*Active_Pop(t));
        prob(i,t) = 1 - exp(-lambda(i) * beta(i,t) * p);
    end
    I(t+1)= S(t) * prob(1, t); %number to actually getsick
    S(t+1)= S(t) - I(t+1); %number to be susceptible
    if t > duration_illness
        R(t)=I(t-duration_illness)*survival_rate;
    end
    Active_Pop(t+1)=Active_Pop(t)-I(t)+R(t); %yesterdays actives
without the
    t=t+1;
end

sum(I)/N
```

APPENDIX I
(CONTINUED)

```
%At this point we have our initial epidemic curve

%Lets program in that people can't stay at home for more than 3 days
out of
%4 days
T=t-1;
k=4; %number of days you need to carry with you
f=ones(T,n,n,n,n); %the number of n's should be the number of k's
% f(t,i,j,l,r) is the probability that the individual will stay healthy
% from day t till the end of the epidemic while his current state is r
% and his overall state is (i,j,l,r)
pred=zeros(T,n,n,n,n);

for i=1:n           %initialize all the states for the final day
    for j=1:n
        for l=1:n
            for r=1:n
                if i+j+l+r<=8
                    f(T,i,j,l,r)= 1-prob(r,T);
                else
                    f(T,i,j,l,r)= 0; % this is not allowed (4 days out
                                        of 4 at home not acceptable)
                    pred(T,i,j,l,r)=1000;
                end
            end
        end
    end
end

for t=T-1:-1:1       %recalculate the behavior at each step
    for i=1:n
        for j=1:n
            for l=1:n
                for r=1:n
                    if i+j+l+r<=8
                        [x,choice]=max(f(t+1,j,l,r,:));
                        pred(t,i,j,l,r)=choice;
                        f(t,i,j,l,r)=(1-prob(r,t))*x;
                    else
                        f(t,i,j,l,r)= 0;
                    end
                end
            end
        end
    end
end

behavior=zeros(T,1);

for t=1:k
    behavior(t)=1;
end
```

APPENDIX I
(CONTINUED)

```
for t=k+1:T
    behavior(t)=pred(t-1, behavior(t-k), behavior(t-(k-1)), behavior(t-
(k-2)), behavior(t-(k-3)));
end

plot(I)

IndProbHealth=1;

for t=1:T
    IndProbHealth=IndProbHealth*(1-prob(behavior(t),t));
end

IndProbHealth

%initialization is complete
%plot(behavior*10000, 'r.');


IndividualDecisionDP = IterationOfGroupDecisionDP(behavior, fraction,
                        'm');
IndividualDecisionDP = IterationOfGroupDecisionDP(IndividualDecisionDP,
                        fraction, '--c');
IndividualDecisionDP = IterationOfGroupDecisionDP(IndividualDecisionDP,
                        fraction, '-g');
IndividualDecisionDP = IterationOfGroupDecisionDP(IndividualDecisionDP,
                        fraction, '--k');


.....

function [IndividualDecision] =
      IterationOfGroupDecisionDP(GroupDecision, fraction, iteration);

N=1000000; %population total
n=3; %number of choices an individual has
lambda = 30;
LengthLastTime=length(GroupDecision);

Ind_lambda = [30,20,10]; %decision maker's options

p=.05;

t=1; %start day
T=50;  %end day

duration_illness = 2;
delta = 1000; %balloon cost of illness
survival_rate=.98;
cost_per_interaction = 1;
```

APPENDIX I
(CONTINUED)

```
% Code, not to be changed during sensitivity analysis
I=zeros(T,1); % # infecteds at the start of day t
S=zeros(T,1); % # susceptibles at the start of day t
R=zeros(T,1); % # newly recovered at the END of day t
I_Group=zeros(T,1);
S_Group=zeros(T,1);
R_Group=zeros(T,1);
Active_Pop=zeros(T,1); % # of people interacting on day t
                        (susceptibles, infecteds and recovereds)
Active_Group=zeros(T,1);
Active_Tot=zeros(T,1);

Ind_prob = zeros(n,T); %probability of getting infected given choice n
                        and day T used by the INDIVIDUAL
Ind_beta = zeros(n,T); %USED BY THE INDIVIDUAL

prob = zeros(n,T);
prob_Group = zeros(T,1);
beta = zeros(n,T);

I(t)=1;  %day 0, 1 person initiates the virus
S(t)= N * (1-fraction) - I(t); %day 0, all but initial case susceptible
Active_Pop(t)= N * (1-fraction); %day 0, everyone is active

I_Group(t)=0;
S_Group(t)= N - I_Group(t) - I(t) - S(t);
Active_Group(t)=N * (fraction);

Active_Tot(t)=Active_Pop(t)+Active_Group(t);

for i=1:duration_illness
    R(i)=0;          % there are no recovered people until the first
                        person recovers
    R_Group(i)=0;
end

while I(t)>.5
    if t>LengthLastTime
        GroupDecision(t)=1;
    end

    beta(t) = (lambda*(I(t))+
Ind_lambda(GroupDecision(t))*I_Group(t))/(lambda*(Active_Pop(t))+
Ind_lambda(GroupDecision(t))*Active_Group(t));
    prob(t)= 1 - exp(-(lambda)*beta(t)*p);
    prob_Group(t)=1-exp(-Ind_lambda(GroupDecision(t))*beta(t)*p);

    for i=1:n      %This is to determine the individual's behavior which
                   is used later on
```

APPENDIX I
(CONTINUED)

```
        %Ind_beta(i,t) = (lambda*(I(t))+
            Ind_lambda(GroupDecision(t))*I_Group(t))/(lambda*
            (Active_Pop(t)) + Ind_lambda(GroupDecision(t))*
            Active_Group(t));
        Ind_prob(i,t) = 1 - exp(-(Ind_lambda(i))*beta(t)*p);
    end

    I(t+1)= S(t) * prob(t); %number to actually get sick
    S(t+1)= S(t) - I(t+1); %number to be susceptible
    I_Group(t+1) = S_Group(t) * prob_Group(t);
    S_Group(t+1) = S_Group(t) - I_Group(t+1);

    if t > duration_illness
        R(t)=I(t-duration_illness)*survival_rate;
        R_Group(t)=I_Group(t-duration_illness)*survival_rate;
    end
    Active_Pop(t+1)=Active_Pop(t)-I(t)+R(t); %yesterdays actives
without the
    Active_Group(t+1)=Active_Group(t)-I_Group(t)+R_Group(t);
    t=t+1;
end

I_total=I+I_Group;

plot(I_total, iteration, 'LineWidth', 1.75)
%plot(I)
%plot(I_Group)
sum(I_total)

%At this point we have our initial epidemic curve

%Lets program in that people can't stay at home for more than 3 days
% out of 4 days
T=t-1;
k=4; %number of days you need to carry with you
f=ones(T,n,n,n,n); %the number of n's should be the number of k's
% f(t,i,j,l,r) is the probability that the individual will stay healthy
% from day t till the end of the epidemic while his current state is r
% and his overall state is (i,j,l,r)
pred=zeros(T,n,n,n,n);

for i=1:n           %initialize all the states for the final day
    for j=1:n
        for l=1:n
            for r=1:n
                if i+j+l+r<=8
                    f(T,i,j,l,r)= 1-Ind_prob(r,T);
                else
                    f(T,i,j,l,r)= 0; % this is not allowed (4 days out
                                       of 4 at home not acceptable)
                    pred(T,i,j,l,r)=1000;
```

APPENDIX I
(CONTINUED)

```
                end
            end
        end
    end
end

for t=T-1:-1:1       %recalculate the behavior at each step
    for i=1:n
        for j=1:n
            for l=1:n
                for r=1:n
                    if i+j+l+r<=8 %(i==1)||(j==1)||(l==1)||(r==1)
                        [x,choice]=max(f(t+1,j,l,r,:));
                        pred(t,i,j,l,r)=choice;
                        f(t,i,j,l,r)=(1-Ind_prob(r,t))*x;
                    else
                        f(t,i,j,l,r)= 0;
                    end
                end
            end
        end
    end
end

behavior=zeros(T,1);

for t=1:k
    behavior(t)=1;
end

for t=k+1:T
    behavior(t)=pred(t-1, behavior(t-k), behavior(t-(k-1)), behavior(t-
(k-2)), behavior(t-(k-3)));
end

IndividualDecision = behavior;
ReactiveGroupInfected=sum(I_Group)/(N*fraction)
NonReactiveInfected=sum(I)/(N*(1-fraction))
CumulativeInfected=sum(I_total)/N
```

APPENDIX J

BEHAVIOR CHANGE MATLAB CODE FOR BOTH SELECTING TRADEOFFS AND FULFILLING BEHAVIORAL CONSTRAINTS

```
function RunFiveIterationsCombo(fraction)
%initialize
N=1000000; %population total
n=3; %choices a person has
lambda = [30, 20, 10];
p=.05;

t=1; %start day
T=50;  %end day
duration_illness = 2;
delta = 10000; %baloon cost of illness
survival_rate=.98;
cost_per_interaction=1;

Reward_Healthy=zeros(n,1);
Reward_Ill=zeros(n,1);

for i=1:n
    Reward_Healthy(i) = lambda(i)*cost_per_interaction;
                                    %benefit from choice (of lambda) 1
    Reward_Ill(i) = lambda(i)*cost_per_interaction- (duration_illness *
                        (mean(lambda))*cost_per_interaction) - delta;
end

% Code, not to be changed during sensitivity analysis
I=zeros(T,1); % # infecteds on day t
S=zeros(T,1); % # susceptibles on day t
R=zeros(T,1); % # recovered on day t
Active_Pop=zeros(T,1); % # of people interacting on day t
                        (susceptibles, infecteds and recovereds)
prob = zeros(n,T); %probability of getting infected given choice n and
                        day T
beta = zeros(n,T);

I(t)=1;  %day 0, 1 person initiates the virus
S(t)= N - I(t); %day 0, all but initial case susceptible
Active_Pop(t)= N; %day 0, everyone is active

for i=1:duration_illness
    R(i)=0;         % there are no recovered people until the first
                        person recovers
end

while I(t)>=1.0
    for i=1:n
        beta(i,t) = lambda(i)*I(t) /(lambda(i)*Active_Pop(t));
        prob(i,t) = 1 - exp(-lambda(i) * beta(i,t) * p);
    end
```

APPENDIX J
(CONTINUED)

```
    I(t+1)= S(t) * prob(1, t); %number to actually getsick
    S(t+1)= S(t) - I(t+1); %number to be susceptible
    if t > duration_illness
        R(t)=I(t-duration_illness)*survival_rate;
    end
    Active_Pop(t+1)=Active_Pop(t)-I(t)+R(t); %yesterdays actives
without the
    t=t+1;
end

sum(I)/N;

%At this point we have our initial epidemic curve

%Lets program in that people can't stay at home for more than 3 days
out of
%4 days
T=t-1;
k=4; %number of days you need to carry with you
f=ones(T,n,n,n,n); %the number of n's should be the number of k's
% f(t,i,j,l,r) is the probability that the individual will stay healthy
% from day t till the end of the epidemic while his current state is r
% and his overall state is (i,j,l,r)
pred=zeros(T,n,n,n,n);

for i=1:n           %initialize all the states for the final day
    for j=1:n
        for l=1:n
            for r=1:n
                if i+j+l+r<=10
                    f(T,i,j,l,r)= 1-prob(r,T);
                else
                    f(T,i,j,l,r)= 0; % this is not allowed (4 days out
                                        of 4 at home not acceptable)
                    pred(T,i,j,l,r)=1000;
                end
            end
        end
    end
end


for t=T-1:-1:1       %recalculate the behavior at each step
    for i=1:n
        for j=1:n
            for l=1:n
                for r=1:n
                    if i+j+l+r<=10
                        [x,choice]=max(f(t+1,j,l,r,:));
                        pred(t,i,j,l,r)=choice;
                        f(t,i,j,l,r)=(1-prob(r,t))*x;
```

APPENDIX J
(CONTINUED)

```
                    else
                        f(t,i,j,l,r)= 0;
                    end
                end
            end
        end
    end
end

behavior=zeros(T,1);

for t=1:k
    behavior(t)=1;
end

for t=k+1:T
    behavior(t)=pred(t-1, behavior(t-k), behavior(t-(k-1)), behavior(t-
(k-2)), behavior(t-(k-3)));
end

E_Reward=zeros(n,T);

for t=1:T
    if behavior(t)~=1
        for l=1:behavior(t)
            E_Reward(l,t)= prob(l,t)*Reward_Ill(l) +(1-
                           prob(l,t))*Reward_Healthy(l);
                  %expected reward for choice i on day t
        end
        [x,choice] = max(E_Reward(:,t));
        if behavior(t)~=choice
            behavior(t)=choice;
        end
    end
end

hold off
hold on
plot(I,'k')
%plot(behavior*10000, 'm.')

IndProbHealth=1;

for t=1:T
    IndProbHealth=IndProbHealth*(1-prob(behavior(t),t));
end

IndProbHealth

%initialization is complete
%plot(behavior*10000, 'r.');
```

APPENDIX J
(CONTINUED)

```
IndividualDecisionCombo = IterationOfGroupDecisionCombo(behavior,
                          fraction, '.w');
IndividualDecisionCombo = IterationOfGroupDecisionCombo
                          (IndividualDecisionCombo, fraction, '.w');
IndividualDecisionCombo = IterationOfGroupDecisionCombo
                          (IndividualDecisionCombo, fraction, '.w');
IndividualDecisionCombo = IterationOfGroupDecisionCombo
                          (IndividualDecisionCombo, fraction, '--g');

.....

function [IndividualDecision] = IterationOfGroupDecisionCombo
                                 (GroupDecision, fraction, iteration);

n=3; %number of choices an individual has
N=1000000; %population total
lambda = 30;
LengthLastTime=length(GroupDecision);

Ind_lambda = [30,20,10]; %decision maker's options

p=.05;

t=1; %start day
T=50;  %end day

duration_illness = 2;
delta = 1000; %baloon cost of illness
survival_rate=.98;

% Code, not to be changed during sensitivity analysis
I=zeros(T,1); % # infecteds at the start of day t
S=zeros(T,1); % # susceptibles at the start of day t
R=zeros(T,1); % # newly recovered at the END of day t
I_Group=zeros(T,1);
S_Group=zeros(T,1);
R_Group=zeros(T,1);
Active_Pop=zeros(T,1); % # of people interacting on day t
(susceptibles, infecteds and recovereds)
Active_Group=zeros(T,1);
Active_Tot=zeros(T,1);

Ind_prob = zeros(n,T); %probability of getting infected given choice n
and day T used by the INDIVIDUAL
Ind_beta = zeros(n,T); %USED BY THE INDIVIDUAL

prob = zeros(n,T);
prob_Group = zeros(T,1);
beta = zeros(n,T);
```

APPENDIX J
(CONTINUED)

```
Reward_Healthy=zeros(n,1);
Reward_Ill=zeros(n,1);
cost_per_interaction=1;

for i=1:n
    Reward_Healthy(i) = Ind_lambda(i)*cost_per_interaction;
                                    %benefit from choice (of lambda) 1
    Reward_Ill(i) = Ind_lambda(i)*cost_per_interaction-
                        (duration_illness * (mean(Ind_lambda)) *
                        cost_per_interaction) - delta;
end

I(t)=1;  %day 0, 1 person initiates the virus
S(t)= N * (1-fraction) - I(t); %day 0, all but initial case susceptible
Active_Pop(t)= N * (1-fraction); %day 0, everyone is active

I_Group(t)=0;
S_Group(t)= N - I_Group(t) - I(t) - S(t);
Active_Group(t)=N * (fraction);
Active_Tot(t)=Active_Pop(t)+Active_Group(t);

for i=1:duration_illness
    R(i)=0;          % there are no recovered people until the first
                        person recovers
    R_Group(i)=0;
end



while I(t)>.5
    if t>LengthLastTime
        GroupDecision(t)=1;
    end

    beta(t) = (lambda*(I(t))+ Ind_lambda(GroupDecision(t))*
               I_Group(t))/(lambda*(Active_Pop(t))+
               Ind_lambda(GroupDecision(t))*Active_Group(t));
    prob(t)= 1 - exp(-(lambda)*beta(t)*p);
    prob_Group(t)=1-exp(-Ind_lambda(GroupDecision(t))*beta(t)*p);

    for i=1:n      %This is to determine the individual's behavior which
                   is used later on
        %Ind_beta(i,t) = (lambda*(I(t))+ Ind_lambda(GroupDecision(t))*
                         I_Group(t))/(lambda*(Active_Pop(t))+
                         Ind_lambda(GroupDecision(t))*Active_Group(t));
        Ind_prob(i,t) = 1 - exp(-(Ind_lambda(i))*beta(t)*p);
    end

        I(t+1)= S(t) * prob(t); %number to actually getsick
    S(t+1)= S(t) - I(t+1); %number to be susceptible
    I_Group(t+1) = S_Group(t) * prob_Group(t);
    S_Group(t+1) = S_Group(t) - I_Group(t+1);
```

APPENDIX J
(CONTINUED)

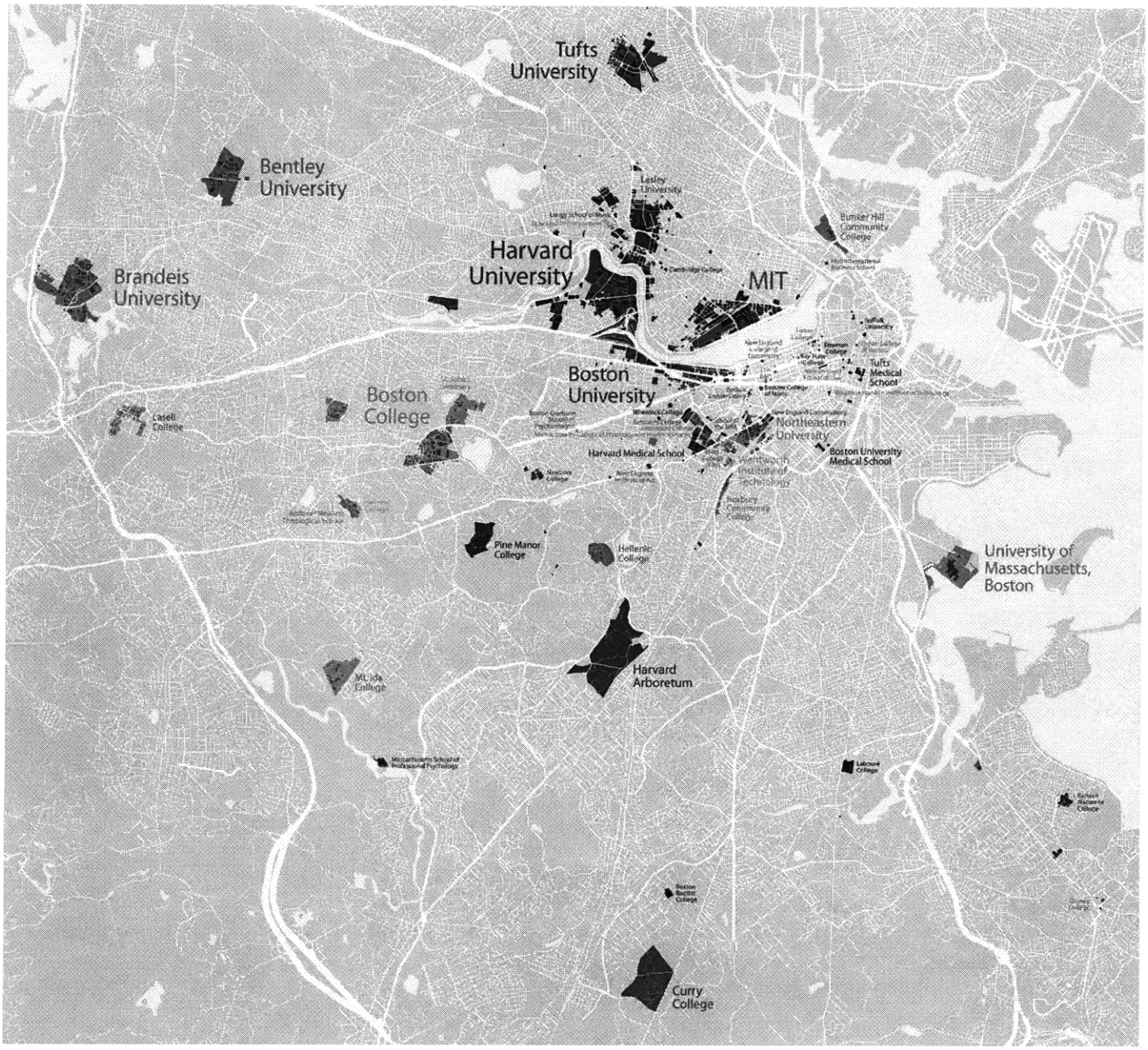
```
    if t > duration_illness
        R(t)=I(t-duration_illness)*survival_rate;
        R_Group(t)=I_Group(t-duration_illness)*survival_rate;
    end
    Active_Pop(t+1)=Active_Pop(t)-I(t)+R(t);
                        %yesterdays actives without the
    Active_Group(t+1)=Active_Group(t)-I_Group(t)+R_Group(t);
    t=t+1;
end

I_total=I+I_Group;
plot(I_total, iteration, 'LineWidth', 1.75)
sum(I_total)

%At this point we have our initial epidemic curve

%Lets program in that people can't stay at home for more than 3 days
% out of 4 days
T=t-1;
k=4; %number of days you need to carry with you
f=ones(T,n,n,n,n); %the number of n's should be the number of k's
% f(t,i,j,l,r) is the probability that the individual will stay healthy
% from day t till the end of the epidemic while his current state is r
% and his overall state is (i,j,l,r)
pred=zeros(T,n,n,n,n);

for i=1:n           %initialize all the states for the final day
    for j=1:n
        for l=1:n
            for r=1:n
                if i+j+l+r<=10
                    f(T,i,j,l,r)= 1-Ind_prob(r,T);
                else
                    f(T,i,j,l,r)= 0; % this is not allowed (4 days out
                                        of 4 at home not acceptable)
                    pred(T,i,j,l,r)=1000;
                end
            end
        end
    end
end

for t=T-1:-1:1       %recalculate the behavior at each step
    for i=1:n
        for j=1:n
            for l=1:n
                for r=1:n
                    if i+j+l+r<=10 %(i==1)||(j==1)||(l==1)||(r==1)
                        [x,choice]=max(f(t+1,j,l,r,:));
                        pred(t,i,j,l,r)=choice;
                        f(t,i,j,l,r)=(1-Ind_prob(r,t))*x;
```

APPENDIX J
(CONTINUED)

```
                    else
                        f(t,i,j,l,r)= 0;
                    end
                end
            end
        end
    end
end

behavior=zeros(T,1);

for t=1:k
    behavior(t)=1;
end

for t=k+1:T
    behavior(t)=pred(t-1, behavior(t-k), behavior(t-(k-1)), behavior(t-
(k-2)), behavior(t-(k-3)));
end

E_Reward=zeros(n,T);

for t=1:T
    if behavior(t)~=1
        for l=1:behavior(t)
            E_Reward(l,t)= Ind_prob(l,t)*Reward_Ill(l) +(1-
Ind_prob(l,t))*Reward_Healthy(l); %expected reward for choice i on day
t
        end
        [x,choice] = max(E_Reward(:,t));
        if behavior(t)~=choice
            behavior(t)=choice;
        end
    end
end

IndividualDecision = behavior;
ReactiveGroupInfected=sum(I_Group)/(N*fraction)
NonReactiveInfected=sum(I)/(N*(1-fraction))
CumulativeInfected=sum(I_total)/N
```

APPENDIX K

MAP OF COLLEGES AND UNIVERSITIES IN THE BOSTON, MASSACHUSETTS AREA



APPENDIX L

UNIVERSITY CHARACTERISTICS THAT ARE IMPORTANT WHEN DEVELOPING A PANDEMIC PREPAREDNESS PLAN.

Size

1. Size of university (large/moderate/small).
2. Fraction of student body residing on campus.
3. Fraction of student body who comes from farther than 150 miles.

Location

4. Location of campus (urban/rural/near a metropolis).
5. Proximity to train or bus stations and airports.
6. Presence of other colleges or universities in the area (many/few/none).

Research

7. Importance and size of the research mission (crucial/important/flexible).
8. Graduate students in the population (majority/minority/none).

Medical

9. Medical facilities on campus (fully functioning medical facility/infirmary/none).
10. Academic program in medicine (medical school/veterinary school/none).

Internal

11. Identify all the different administrative and operational departments.

External

12. Identify all the different supplies and services that the university receives from outside.
13. Characterize the relationship with the local community and other colleges in the area.

APPENDIX M

POSSIBLE SUGGESTIONS FOR UNIVERSITY RELATED QUESTIONS

Issue	Possible Resolution
Canceling Classes	
How does MIT continue the educational mission of the university without ongoing classes?	• Use existing online educational tools such as: OpenCourseWare, Stellar, etc. • Continue classes through remote lecture and online assignment submission. • Encourage students to start independent work or research that can be done remotely and presented to a willing faculty member for credit. • Provide credit for volunteer work.
How to assign credit for courses when classes are canceled before the end of the semester?	• If classes are cancelled in the first third of a semester, give no credit. • If classes are cancelled in the middle third of a semester encourage students to prepare and submit relevant independent work for credit on a case-by-case basis. • If classes are canceled in the last third of the semester before finals, use existing student scores to assign P/D/F style grades.
How can students stay on track to graduate at the same time as before without the appropriate course credit?	• Ask departments to review their requirements and determine a "forgiveness policy" when appropriate. • Create summer courses to make up for loss of term. While this is an option it may be difficult to coordinate amongst faculty, graduate teaching staff and students.
Will the university refund tuition? What happens to the tuition of students on financial aid?	• Use the same division of the semester into 3 parts are provide full, half or no refund according to which portion of the semester classes are cancelled.
Should the university postpone or cancel special events such as orientation programs, preview weekends or exams?	• Make case by case decisions, but universities should expect that many participants are likely to withdraw from attending any voluntary events such as Campus Preview Weekend.
How and when should the university resume the educational program?	• Classes should not resume until the outbreak has flared off and there is no fear that it will resume. • Another trigger point for recommencing educational programs is when the majority of the student body has been vaccinated.
Student Life on Campus	
In the case of a pandemic the food supply chain is likely to be broken, so how should the	• One solution could be to provide students with debit cards with a fixed amount of money to be used for food at local establishments.

university feed the student body remaining on campus?	• Establishing contracts with local restaurants to feed students with university IDs may be another approach.
How can food be distributed while implementing social distancing measures for students?	• If the dining staff limitation forces students to receive food in dining halls, several lunch shifts could be established to de-crowd the dinning halls. • A distribution system of leaving food at the door could be used to feed the sick and quarantined students.
How can the school promote NPIs, such as hygiene practices and social distancing, without inciting panic?	• It is important to instill good hygiene practices in the population before a pandemic strain emerges. • In a pandemic, students could be asked to take an online tutorial on how to avoid the flu. • The university could encourage students to learn more about the flu by creating some motivation for them to research information about the virus. For example, the university could develop a prize contest of the best paper that describes how to avoid the flu. Maybe course credit can be given to students who do research projects about the flu and how one can avoid it.
Administrative and Operational Issues	
How can the university encourage the right employees to come to work?	• Compensating essential employees with time and a half pay should help encourage them to come in. • Advice and policies to discourage "presenteeism" will help discourage non-vital worked from coming in unnecessarily. • Union contracts should be renegotiated to allow other employees and volunteers to do some union work in an emergency.
What should the sick leave policy be?	• Anyone who is sick should remain at home until their symptoms have subsided and they are no longer infectious. • There should be some additional flexibility for employees who have to stay at home to take care of sick family members. • Nonessential employees with sick family members could be asked to self quarantine, if they are unsure about their health status.
How can the university keep track of students as they leave campus?	• Please refer to ***Section 6.4.4***.
What will happen to conference participants?	• Conferences and other events that bring non-affiliates individuals to campus should be canceled or postponed early on in the outbreak.