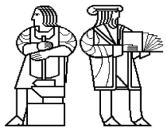

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ENGINEERING RESPONSES TO PANDEMICS

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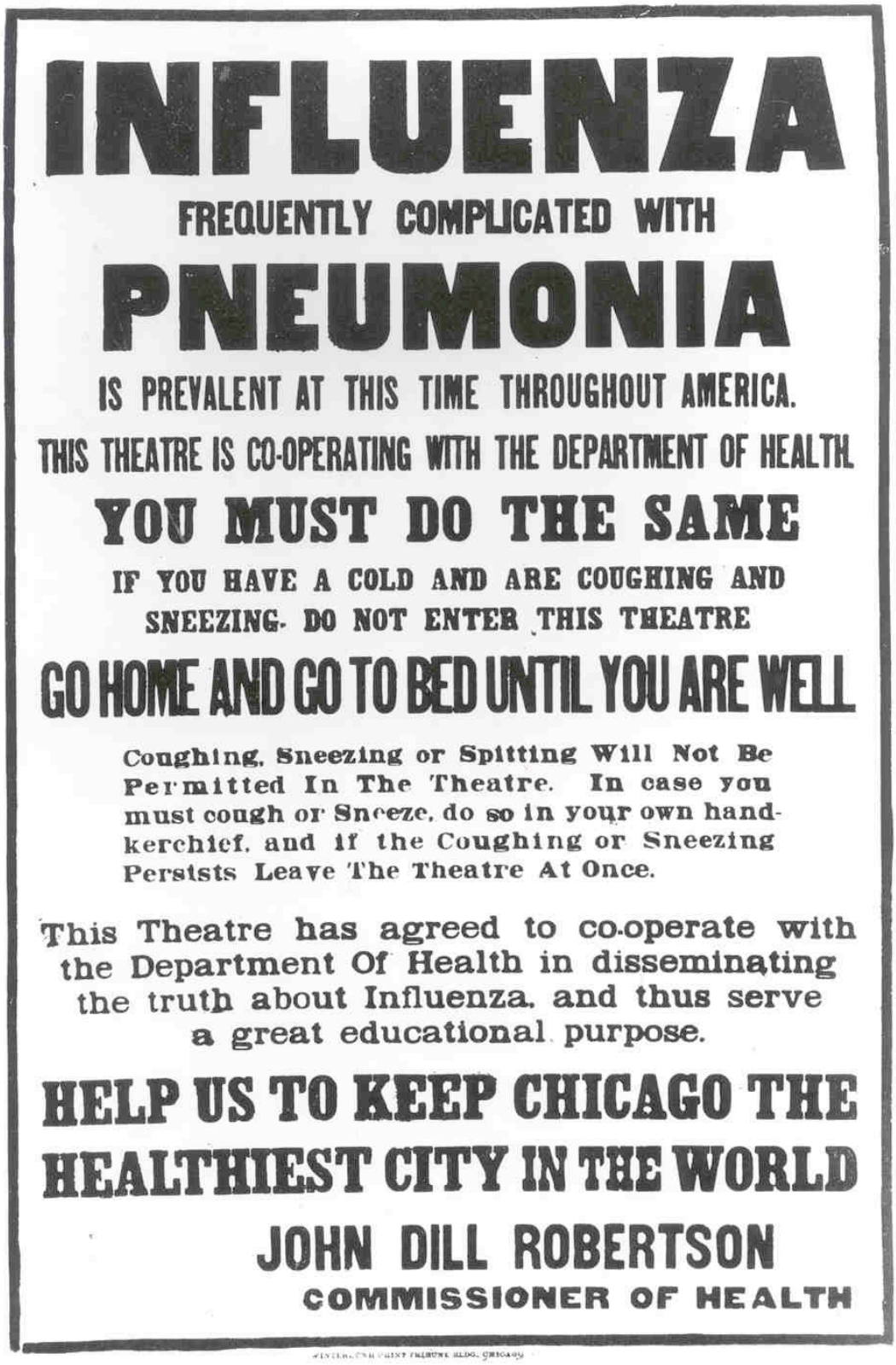
ABSTRACT

Focusing on pandemic influenza, this chapter approaches the planning for and response to such a major worldwide health event as a complex engineering systems problem. Action-oriented analysis of pandemics requires a broad inclusion of academic disciplines since no one domain can cover a significant fraction of the problem. Numerous research papers and action plans have treated pandemics as purely medical happenings, focusing on hospitals, health care professionals, creation and distribution of vaccines and anti-virals, etc. But human behavior with regard to hygiene and social distancing constitutes a first-order partial brake or control of the spread and intensity of infection. Such behavioral options are "non-pharmaceutical interventions." (NPIs) The chapter employs simple mathematical models to study alternative controls of infection, addressing a well-known parameter in epidemiology, R_0, the "reproductive number," defined as the mean number of new infections generated by an index case. Values of R_0 greater than 1.0 usually indicate that the infection begins with exponential growth, the generation-to-generation growth rate being R_0. R_0 is broken down into constituent parts related to the frequency and intensity of human contacts, both partially under our control. It is suggested that any numerical value for R_0 has little meaning outside the social context to which it pertains. Difference equation models are then employed to study the effects of heterogeneity of population social contact rates, the analysis showing that the disease tends to be driven by high frequency individuals. Related analyses show the futility of trying geographically to isolate the disease. Finally, the models are operated under a variety of assumptions related to social distancing and changes in hygienic behavior. The results are promising in terms of potentially reducing the total impact of the pandemic.



Posted in Chicago, 1918.
http://1918.pandemicflu.gov/pics/posters/Chicago_Poster_1918.jpg

1. Introduction

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 "Spanish Flu" that 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. At the writing of this chapter there is a novel flu strain – A(H1N1), commonly referred to as the "Swine flu" – circulating through the globe and sparking fears that it may mutate and become a deadly killer. While medical advances over the past century have been significant, we still don't have a simple cure for the flu, and when a severe 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 U.S. federal government projects 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. High rates of worker absenteeism could in turn affect critical infrastructure, including the operations of water treatment facilities and power plants, while efforts to slow the spread of disease could limit the availability of food. A pandemic could 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). It is for these reasons, and more – discussed below -- that we select **influenza** pandemics as our focus in a chapter entitled, ***Engineering Responses to Pandemics.***

A common definition of "engineering' is as follows: *"The application of scientific and mathematical principles to practical ends such as the design, manufacture, and operation of efficient and economical structures, machines, processes, and systems."*[1] In engineering the response to a pandemic, we need to use "scientific and mathematical principles" to design processes and systems to mitigate the seriousness and consequences of the flu and to create a total system response to it.

A standard engineering approach towards pandemic flu has been to tackle obvious more traditional engineering problems. These problems range from "optimizing" vaccine and anti-viral distribution and stockpiling strategies, to hospital surge capacity analysis, to developing solutions to supply chain disruptions that are almost guaranteed in a pandemic. See, for example work by Chick et al., 2006 or Ekici et al., 2008 or Itzwerth et al., 2006. However, a broad engineering mindset allows going beyond the study of isolated subsystems and well-defined operational problems to develop models of disease spread and – to some extent -- control. Understanding disease dynamics to help anticipate the impact of the infection would in turn help develop more applicable preparedness and response plans. *The key here:* The disease dynamics are partly under our individual and collective control. Any engineered system in anticipation of the flu must take this into account.

[1] http://www.answers.com/topic/engineering Cited July 9, 2009.

Pervasive pandemic preparedness at all levels will be essential in mitigating the flu, but many current plans – especially at the state level in the U.S. -- lack details and implementation logistics, often skirting the complex issues. Some unknowns including the virulence, morbidity and speed of transmission of the viral strain hamper precise planning. Since there is no way to test run a pandemic, policy makers must often rely on mathematical models to guide their decision making and evaluate "what-if" scenarios. These models can help systematically to gauge the effectiveness of medical and government imposed interventions, medical measures as well as social distancing and hygiene behavioral changes. Understandably, the epidemiology community has done the majority of the work in the area of pandemic transmission modeling.

The "Engineering" for systems problems as complex as pandemic influenza needs to encompass many aspects of the problem, drawing on ideas and methods not only from traditional engineering, but also from the management sciences and – especially – the social sciences. Human behavioral response to pandemic flu is a first-order characteristic of any realistic model of flu progression. Highly stylized mechanistic problem formulations, sometimes derisively labeled 'toy problems,' are not applicable in these settings. But that is not to say that simplicity is bad *per se*. Albert Einstein said, "*Keep it simple but not too simple*!" The idea is to simplify the analysis but only to the point that needed insights from the analysis are retained.

With pandemic influenza, we are dealing with a worldwide problem involving decisions by literally billions of people. Initially the physics of flu transmission is governed by the inherent purely scientific properties of the novel flu virus. These properties relate to aerosol flu in-air latency time in rooms and other closed places, half-life of flu virus particles on various surfaces, efficiency of infectivity (i.e., ease of passing the virus from person to person and creating a newly infected person), levels of morbidity and mortality by age and other population descriptors, etc. But once the flu has emerged and is recognized as the danger that it is, myriad decision makers come into play. These include governments at all levels – local, regional and federal --- that initiate steps in response to the flu. These steps can be medical, such as supporting research leading to a new vaccine, or managerial, such as convening various stakeholders and starting to execute a flu response plan. These plans contain many elements, including steps to limit human-to-human interactions that may otherwise accelerate the propagation of the virus. Examples of governmental steps to reduce virus transmission include the prohibition of certain public events, the closing of schools, quarantining and forced self-isolation. Simultaneously with government-mandated steps, individuals within the population begin to change their behavior, perhaps seeing fewer people on a day-to-day basis, washing hands more frequently, coughing into their elbows, not shaking hands or kissing upon greetings, wearing face masks, etc.

Both governmental 'top-down' and individual 'bottom up' behavioral changes can affect dramatically the propagation properties of the flu, and ultimately the total number of people who will become infected. Beforehand, no one knows exactly how these steps will play out. Added to this complexity is the fact that flu viruses mutate continuously. A mild virus in June may become a lethal virulent virus in October. No

one knows how these mutations will evolve. Thus, we have a complex stochastic global system with unknown emergent properties, yet demanding timely informed decisions by decision makers at all levels (Lipsitch, et al., 2009). Risks are high. Do nothing and the flu may infect over 40 percent of the population and kill tens of millions. Or, take steps believed to reduce levels of infection, and one disrupts daily lives, the economy, children's education, etc., but likely reduces the severity of the flu pandemic.

We believe that mathematical models that are simple, but not too simple, can add significant insight into what to do in the case of a pandemic flu. This is the classic paradigm in engineering science, the use of mathematical models for circuit design, for bridge building, for creating mechanical devises, etc. But we are humble in face of the flu, as the dynamics are always changing, and no model will be anywhere near perfect. For pandemic flu, there are no known equivalents to Newton's laws of physics or Kirchoff's circuit laws. All current models are flawed. But we can rely on data from past pandemics and axiomatic reasoning to develop models to obtain decision insights. That is our goal. We recommend that the word "optimal" be avoided when analyzing pandemic flu since (1) the disease dynamics are *a priori* unknown and emergent; (2) the existence of numerous stakeholders precludes the existence of an uncontested single objective function; and (3) there exists no uncontested set of constraints.

This chapter will describe models that provide insight into disease transmission dynamics. Several important epidemiological concepts including the basic reproductive number – R_0 will be discussed. A basic understanding of transmission dynamics makes very clear the impact that human behavior has on the spread of infection. A public well educated about the infection and regularly updated on the extent of infection spread will react and alter their daily behavior in attempts to protect themselves from becoming ill. The resulting behavioral changes have the potential to 'mitigate' the outbreak. This chapter will show that peoples' behavior is a first-order effect and must be included in any engineered design for a flu preparedness and response system.

We recognize that, in writing this chapter, we are addressing at least two different audiences with two distinctly different cultures. The two professional groups -- engineering and medicine -- are quite different culturally and in other ways. We see this chapter as primarily engineering-oriented with considerable input from the medical research community, especially epidemiology. The engineering approach gives rise to the references to Kirchoff's Laws, Newtonian physics, etc. The idea is that there are a few fundamental laws of nature in the domain you are studying, and – as any engineer would attempt to do - you try to design a good system utilizing these laws. Much of the medical community focuses on 'evidence-based medicine,' often with the bar set very high in terms of randomized controlled experimentation. But this research paradigm is very difficult with pandemic influenza, a world-wide occurrence only a few times per century. We will attempt to address these cultural differences and explain how our modest contribution fits into the bigger picture.

2. Background: What is a pandemic?

Influenza pandemics are usually associated with high morbidity, excess mortality as well as economic and social disruptions. As defined by the World Health Organization (WHO), influenza pandemics arise when:

1. A "novel" influenza virus subtype, to which the general population has no pre-existing immunological protection, emerges. [2]
2. The virus infects humans and causes serious illness.
3. It spreads efficiently amongst people with sustained chains of transmission.

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.

From the year 2000 until early 2009, the most discussed strain of flu with pandemic potential was H5N1, also referred to as the "Avian Flu". This virus has infected birds in over 35 countries becoming endemic in Southeast Asia and has resulted in the deaths, through illness and culling, of over 200 million birds across Asia. The H5N1 virus has been reported to have infected 436 people in 15 countries, resulting in 262 deaths (WHO, 2009). This subtype has not yet shown an ability to transmit efficiently between humans, but many caution that it is important to maintain a high level of vigilance because another strain may cause the next pandemic.

In late April 2009 in Mexico these warnings became reality. H1N1, a viral strain referred to as the "swine flu" was identified and began to spread to other countries. While the estimated death toll at time of writing (July 2009) has been more consistent with expectations for seasonal flu, the socio-economic losses are significant (Lipsitch, et al., 2009). The WHO has already declared the H1N1 strain as a full-fledged pandemic even though the death toll has remained at seasonal flu levels. Since viral mutations are almost impossible to predict, at the writing of this chapter, it is too early to tell what total costs the world will incur as a result of this virus, but already this strain has highlighted the importance of pandemic preparedness at all levels. At this point, antiviral medications such as Tamiflu are effective for the H1N1 strain, but it is very unclear whether the virus will develop resistance to the drugs or if our infrastructure will be sufficient to administer the limited antiviral stockpiles rapidly enough. Sufficient vaccine doses require 6-9 months of production time, as a result even with a virus that emerged in the spring we are naked against a fall wave of the flu.

The lack of vaccines does not need to spell out a doomsday scenario because *even without medical interventions regular people have the ability to decrease the cumulative amount of flu transmission through behavioral change*. Often this point is overlooked by models that inherently assume that individuals maintain their behavior throughout the entire outbreak regardless of its severity. Furthermore, some epidemiologists argue that while behavioral changes do indeed decrease the burden of infection at the peak of the

[2] This also implies that no vaccine is available at the onset of the outbreak.

pandemic, they don't change the cumulative number of people who become ill over the entire outbreak (Oshitani 2006). Using mathematical models we argue the overall effectiveness of non-pharmaceutical interventions (NPIs) and demonstrate the potential control the population can have over disease dynamics.

3. Modeling Approaches

The types of models that have been used to describe the spread of infection range from basic deterministic differential equations to detailed stochastic agent-based models. The basic compartmental models are contained within a series of three 1930's papers by W.O. Kermack and A.G. McKendrick (Kermack & McKendrick, 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. A set of partial differential equations then describes the transfer rate of individuals from one compartment to the next. For more on compartmental models refer to *Mathematical Epidemiology*, Allen L.J.S., Springer, 2008.

Many recent models incorporate information about social network structures in order to understand the impact of social mixing patterns. Network models can range from simple lattice and random mixing networks, to small-world graphs or incredibly detailed social networks where nodes represent people, and edges represent specified relationships or interactions. 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. These studies have shown that the degree, 'betweenness' and farness of nodes alter disease dynamics (Christley, 2005). The most computationally intensive agent-based stochastic simulation models have been used to "play out" more specific scenarios (Ferguson, 2005; German, 2006; Longini, 2005).

The simulation models include an incredibly detailed level of granularity, while many compartmental models assume inter-connected sets of homogeneous groups within the population. Any one model may be most applicable in a given setting, depending on the question that is being addressed. In general, an insightful model should provide a balance of the extreme of simplified abstraction that makes the model virtually useless in practice and the other extreme of meticulous detailed complexity that is time consuming, difficult to verify while giving the appearance of accuracy and completeness, but providing little intuition. The models presented later in this chapter attempt to achieve this sort of balance.

4. R_0, the Basic Reproductive Number

In virtually all epidemiological models one of the most commonly referred to parameters is R_0. The *basic reproductive number* – R_0, is defined to be the expected number of secondary infections produced by a typical index case in a completely susceptible population (van den Driessche, 2008). As the population of susceptibles is depleted, the generation-specific reproductive number, $R(t)$, is called the *effective*

reproductive number. *R(t)* is the mean number of secondary infections that will result from each newly infected individual in generation *t.*

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. Usually, a value of 2 for R_0 is thought to result in a doubling of the number newly infected with each generation of the flu. But consider a population where half of the population – group 1 – because of behavioral and immunological reasons, will 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. We can write an equation from which we can compute the exact value for the self-extinction probability, which we will call P_E. For our simple example, we can write

$$P_E = (1/2) + (1/2)P_E^4 .$$

The logic is this: P_E is equal to 1/2, due to the 50% chance that patient zero will infect no others, plus (1/2) times the probability that each of the four people infected under the second possibility for patient zero will themselves spawn an infection process that dies out – each independently and each with probability P_E. The numerical solution to this equation is $P_E = 0.543$. So, we have a feasible situation in which R_0 is 2.0 and yet 54.3% of the 'epidemics'' die out very quickly on their own. There is no exponential growth, obviously, for such cases.

As described by Heesterbeek (Heesterbeek, 2002), R_0 was conceived in Germany by demographers in the 1880's and formalized in 1925 to model the progression of a country's population. The original R_0 was defined to be the average number of female offspring born to one female over her entire life. For the year 1879, this number for Germany was estimated by Richard Bockh to be 1.06. The time scale was decades and the system was in approximate equilibrium. With an influenza epidemic, the time scale is in days and weeks and nothing approximating equilibrium exists. To the contrary, the system is characterized by markedly changing parameter values as society copes daily with the influenza's evolution. Over the last three decades, epidemiologists have adopted the R_0 concept and applied it to a variety of diseases, some of which (e.g., malaria) exist in a type of quasi-equilibrium similar to that of population demographics. But the original demographic motivation and near steady state environment supporting R_0 simply do not exist in a dynamic influenza epidemic situation. In summary, R_0 and its successor $R(t)$ as fixed-trajectory concepts in rapidly evolving infectious disease epidemics are of limited value at best.

We often hear epidemiologists attach to an infectious disease a given number for R_0, as if that number characterizes some constant of nature, independent of

anything else. One might hear, "Consider an infectious disease with R_0 equal to 3.14159, etc., etc." One mathematical researcher even calls R_0 the "…one parameter that (almost) does it all" (Keeling, 2001). For the H1N1 swine flu in circulation as of this writing, the WHO (World Health Organization) has estimated R_0 for H1N1 to be between 1.4 and 1.6. The very form of the statement implies that R_0 exists as a defined constant of the H1N1 flu, independent of the contextual social and physical environments in which the disease is developing. But disease environments play a significant role in determining the numerical value for R_0 and for subsequent values of $R(t)$. Our own research into tracking of H1N1 has shown that fitting exponential growth curves to the daily numbers of confirmed cases of H1N1 demonstrates that statistical estimates of R_0 vary widely among states and among countries (Hashmi et al 2009). Yet, many authors discussing R_0 describe it as if there is one correct numerical value, worldwide, and discrepancies in estimated values are usually attributed to statistical noise and reporting errors. Even in demography, where quasi steady-state operation supports use of the R_0 concept, human behavior demonstrates that the birth rate defined R_0 is far from an immutable constant. In Germany today, more than a century after the first estimate of Germany's R_0, the current R_0 is estimated to be about 0.70, a 33 percent drop from Bockh's 1879 estimate of 1.06. Worldwide, the demography interpretation of R_0 today varies by a factor of seven, from over 3.5 daughters per female (Mali and Niger) to under 0.5 (Hong Kong). In demography, we see that the numerical value of R_0 depends strongly on social and environmental context. It is not a constant of nature. So too in infectious disease applications we should expect R_0 to depend on context. In influenza, as in demography, the numerical value of R_0 depends strongly on the societal situation in which it is embedded. In some existential sense then, R_0 does not exist as a number independent of context.

The consensus definition of R_0 states that it is the mean value of a random variable. As in all probabilistic situations, the mean of a random variable conveys some useful information. But expressing the mean in terms of other more fundamental quantities can yield additional insights. Suppose I come face to face with λ people on a day that I am infectious but asymptomatic. We select the Greek letter lambda (λ) since in modeling analyses it often refers to frequency of occurrence, such as the daily frequency of interacting with other people. Many people who become infected with the flu have one such day before they feel and appear sick, and not being able to identify these people is what makes eradication of the flu so difficult. Define an 'indicator variable' as follows:

$$X_i = \begin{cases} 1 \text{ if person } i \text{ becomes sick as a result of exposure to me} \\ 0 \text{ if person } i \text{ does not become sick as a result of exposure to me} \end{cases}$$

Now, we let NI be defined to be the number of people I will infect on this day. NI can be written as simply counting the indicator variables,

$$NI = X_1 + X_2 + X_3 + \ldots = \sum_{i=1}^{\lambda} X_i$$

Suppose for example $\lambda = 50$ and that all X_i's are 0 except for X_9, X_{18} and X_{45}, each being equal to one. In that case, I have infected 3 of the 50 individuals that I have come face to face with on this day. Now, at any given level of intensity of face-to-face contact, there is a probability p that I will pass the infection on to the person I am facing. Sometimes p is called the "transmission probability." We can now write an expression for the mean number of people I will infect on this day. It is simply the mean of $NI = X_1 + X_2 + X_3 + ... = \sum_{i=1}^{\lambda} X_i$, which equals λp. We thus have a simple expression for R_0, and that is

$$R_0 = \lambda p. \qquad (1)$$

Flu is an infectious respiratory disease, spread by human contacts. Reduce human contacts, and reduce prevalence of the flu. By writing $R_0 = \lambda p$, we have expressed R_0 in terms of two other parameters, each of which we can control to some extent. We have a fighting chance of reducing R_0, perhaps a little, perhaps even to below 1.0, the critical value to assure that the disease dies away rather than grows exponentially. In the sense of this discussion, R_0 indeed does not exist as a separate quantity. It is a function of both the inherent properties of the given virus *and* the population's behavioral responses to it.

How do we control λ and p? One reduces λ simply by reducing the number of face-to-face contacts we have each day. If a parent is shopping for groceries, rather than following the European tradition of daily shopping, perhaps one switches to weekly shopping, or, better yet, to groceries delivered to one's door. If you manage a team of employees, rather than have face-to-face meetings during a flu emergency, have conference calls instead, with many workers telecommuting. Many companies have already created comprehensive pandemic flu plans that include telecommuting, reduced face-to-face encounters and even minimum desk spacing between workers. The desk spacing idea relates more to the parameter p, the probability that any given face-to-face contact will result in a new infection. How else can we reduce p? Wash hands with hot water and soap several times daily. Do not shake hands during greetings with colleagues. Cough or sneeze into your elbow, not into the open air or your bare hand. Be careful not to touch surfaces that might have recently been contaminated with flu virus. Encourage your city's large employers to stagger work hours, so that public transportation subways and busses are less crowded during now-stretched-out rush hours. Even run the subways and busses with windows opened. The key here is that R_0 is a direct function of social context and human behavior, behavior that can be altered to reduce the numerical value of R_0.

Reducing the number and intensity of human-to-human contacts has been called "social distancing." It is a key control parameter in any engineered response to the flu. Social distancing has roots over centuries, often as a type of group evolutionary survival mechanism. In rural India in the 19th and early 20th Centuries, subsistence farm families who lived closely together in villages but who worked separate land plots outside of the villages, left the villages and lived separately on their land whenever they heard from a trusted messenger that 'a plague' was 'in the vicinity.' They returned to their village

homes once the signal was given that the risk of plague had subsided, the duration of the distancing typically being about two weeks[3]. While this policy seemed to work well for rural subsistence farmers, we may well ask, "What is the analogue to the movement to the land in our highly-networked interconnected Western style of life?" We are not self sufficient and we rely on others to provide virtually all essential services and products for living. Given all the interconnected networks upon which we rely, is social distancing itself, in the simple ways in which we can do it, sufficient to control the evolution and penetration of a flu pandemic? This question is a major challenge when addressing response to pandemic flu.

Of course there are limitations to our analysis. The causal model creating infection is more complex than just counting the numbers of face-to-face contacts. One can touch surfaces contaminated minutes or perhaps even hours before by individuals who we do not see face to face. If contaminated hands then touch one's mouth or eyes, infection can result. With SARS (Severe Acute Respiratory Syndrome), residents of a Hong Kong high-rise apartment complex became infected by a faulty sewage system, again not 'seeing' the infected person responsible for spreading the infection. But we believe that a model that counts the number of face-to-face contacts and includes the intensity of these contacts represents a valid primary mechanism for depicting how the disease propagates through the population. Adding complexities such as the two just cited does not alter the main conclusions of our arguments. Our approach is buttressed by findings of others. For instance, Riley et al. (Riley, et al., 2003) credits reduction in the number of face-to-face contacts in Hong Kong as the primary cause for reduction in spread of SARS.

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, et al., 2005). While using $R(t)$ or R_0 provides a computationally intuitive basis for describing disease dynamics, this approach neglects important complexities related to heterogeneities and uncertainties (Eubank, 2004; Larson, 2007).

From an engineering point of view that is taken in this paper, expressing R_0 as the product of λ and p is good news. Both λ and p are controllable to some extent, so R_0 is controllable to some extent. Behavioral changes can reduce R_0 and as a result, reduce the chance that you or a loved one becomes infected with the flu.

[3.] This policy of Indian farm families was presented to the author by Dr. Nitin Patel whose father reported that tradition to him. Dr. Patel's father was born in 1909 and lived in the rural village of Karamsad, state of Gujarat, India. Once as a boy he had to leave the village with his family to avoid 'the plague.' Our hypothesis is that the terminology 'the plague' related to several different serious and sometimes fatal diseases and did not precisely refer to any specific plague such as the bubonic plague. (Paragraph and footnote taken from Larson [2007].)

5. Basic Model

In this model one community is divided into several groups based on their daily social activity levels.[4] 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, as most other models, that face-to-face contact is the major method of influenza transmission.[5] 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. 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, N_M, N_L - Initial total populations of High, Medium and Low activity persons, respectively

$N_H(t)$ - 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.*

This notation continues in the same manner for the other populations, *M* and *L*. Let us clarify that throughout the remainder of this chapter 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 to 3 actual 24-hour days.

[4] The model presented is 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).

[5] 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. Within the context of our model we assume that the majority of transmission occurs during direct interaction.

The outbreak is initiated by 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 (Larson, 2007) we know that for a random person on day *t* the probability that the next interaction will be with an infected individual is:

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

β(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,

$$N_H(t+1) = N_H(t) - I_h(t) + hI_H(t-d)$$ [6]

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):

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

In ***Table 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.

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

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 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 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 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 λ's 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,

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

The cumulative number of infected individuals, as well as the infection peak, is higher for the standard incidence model.[7]

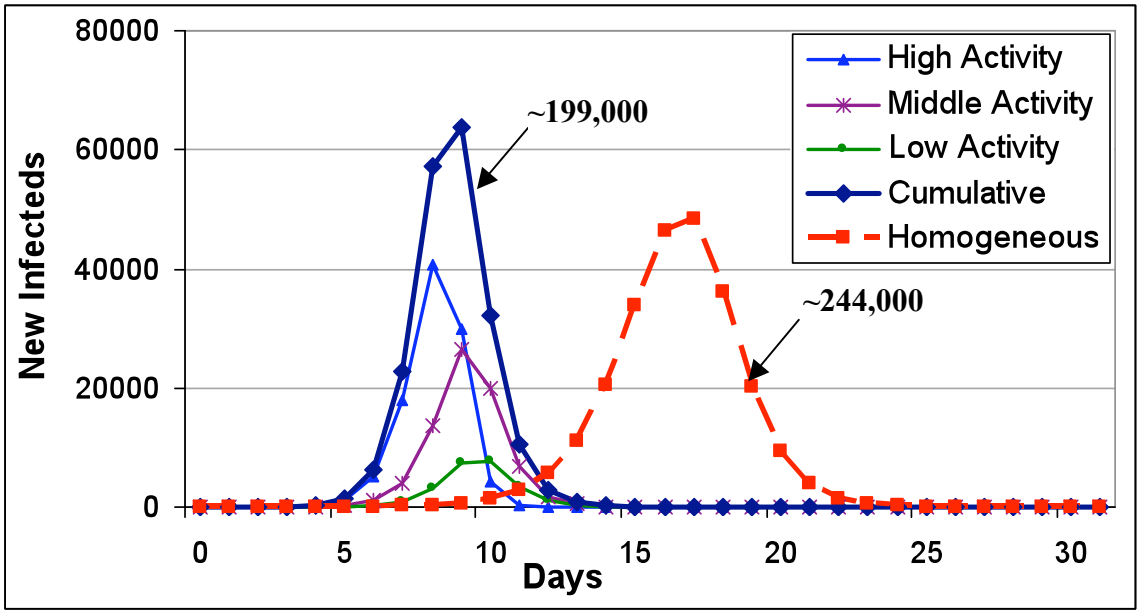
Let us focus on the mass action incidence model and the input values in ***Table 1.*** The expected infection transmission for the hypothetical heterogeneous community is compared to the disease dynamics in a similar homogeneous community in ***Graph 1***. Notice that the virus spreads faster through a population with several activity levels when compared to a homogeneous community with an equivalent average activity level. Furthermore, 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. 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. Because of their behavioral characteristics[8], the high activity people are the drivers of influenza transmission.[9]

[7] For more on the comparison of the Standard Incidence and Mass Action models refer to thesis by Nigmatulina, 2009.

[8] The behavioral traits and not the biological propensity to shed the virus cause these individuals to be the drivers of infection.

[9] 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).

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 1*** illustrates a fundamental flaw in the usage one averaging parameter such as R_0 (or $R(t)$) as the sole modeling factor.



Graph 1
Comparing spread of infection between heterogeneously and uniformly active communities of 300,000 individuals.

Other types of heterogeneities also exist and can be similarly modeled. Diverse susceptibility levels and varying infectivity levels are just two more examples of heterogeneities present in the population.[10] In reality our population can be described by a complex combination of many different types of heterogeneities. When compared to heterogeneity in susceptibility and infectivity levels, diversity of activity levels is the most influential and easily observable type of heterogeneity. It is also a behavior that people have the ability to alter in the case of a pandemic.

6. Multi-Community Model

The basic model assumes that there is random mixing within the community, so that a randomly selected individual has a chance of encountering any other individual. While this isn't precisely true because often people interact within smaller social

[10] For details on modeling these types of heterogeneities refer to Thesis by Nigmatulina, 2009.

networks such as family, friends or colleagues, but it is still possible that an individual would have an unplanned encounter with a stranger at a grocery store, bus, movie theater etc. Yet this complete mixing assumption doesn't hold when describing people in two different cities. Thus the next step is to expand our one-community model to a multi-community structure and determine whether travel restrictions between communities have the potential to stop its spread.

Spatial complexity can be modeled through a loosely connected multi-community structure based on Monte Carlo simulation to model disease spread between cities. Consider a two community model – Community A and Community B – each has its own demographic and epidemiological composition. A and B are two communities – each with 300,000 people --- with identical compositions: 100,000 people, respectively, in each activity level, high, medium and low. These 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.

The outbreak is initiated with an infectious seed in Community A, and the disease propagates to other individuals within this community. 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. 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.

The two processes compete to bring the pandemic to Community B. After the pandemic is in both populations, 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. One question is: 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. Recall that whenever we refer to a 'day' 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 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:

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

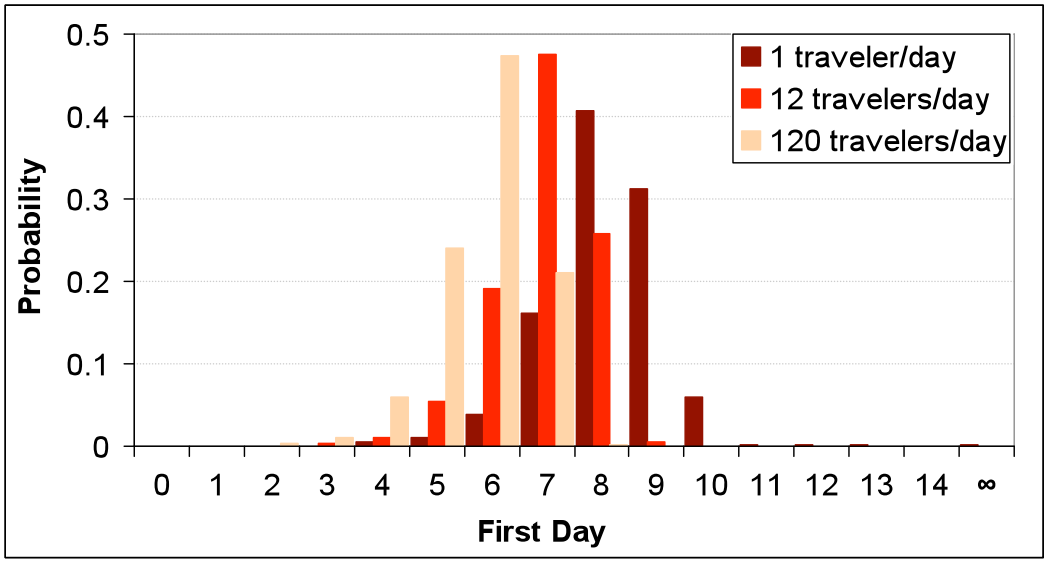
Notice that the probability of never infecting a neighboring community is greater than 0, thus the expected time until the next community gets contaminated is infinity. Instead one can determine the probability that day t is the first day of infection entering into the neighboring community. These calculations show that the probability of infection spread is almost certain if the twelve travelers maintain their trips and if the virus is relatively transmissible amongst individuals. Furthermore, the high activity travelers are very likely to be infected during the peak times of the community outbreak.

These calculations are supported by historical examples demonstrating 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).

7. Travel Restrictions

During SARS, some governments enforced travel restrictions. 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. To model this, one can vary the number of travelers between the cities. For numerical calculations, change the number of travelers from the baseline number of 12 daily[11] 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 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 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 geographical 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.



Graph 2.
A histogram of the first day of infection spread in Community B that 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.

[11] Recall, "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 and sustained beyond the peak until the threat of the transition is small. 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.

It is almost impossible to completely stop the movement of people across borders. In the case of SARS, studies indicate that thermal screening and health declarations of travelers did not 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). Overall, travel restrictions are expensive, almost impossible to implement and are often ineffective.

Taking the model a step further highlights that in today's very interconnected world the virus will spread very quickly to many geographical areas. Consider a fully interconnected three community model with one initially infected community and two neighboring susceptible communities. In this case the disease spreads almost concurrently to both 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. The number of commuters between nearby cities is high. Management consultants are examples of people who are likely to crisscross the world in the course of a week. This type of global connectedness could be catastrophic for emergency systems that, in a pandemic, would face the equivalent to 50 Hurricane Katrina's 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. Current events support this finding; the rapid geographical spread of the swine flu in 2009 is an example. This suggests that, instead of controlling transmission between communities, managing the infection's spread within communities is likely to be the more effective strategy.

In summary, geographical isolation of the flu is almost impossible; reducing the prevalence – the number infected -- within a given geographical region ***is*** possible.

8. Behavioral Changes

When studying and modeling sexually transmitted diseases, especially HIV/AIDS, behavioral changes are often cited as the main factors determining transmission dynamics, but when it comes to modeling flu, behavior is almost always ignored. Few would argue that:

1) People will alter their behavior in a pandemic by becoming more aware of hygiene and decreasing their human contacts.[12]
2) Limiting the number of daily interactions and improving hygiene decrease transmission.

It is unlikely that society will implement severe measures as they did in 1918-1919 making it "unlawful to cough and sneeze" punishing violators with up to a year in jail (Hudson, 1999). However, even without forceful implementation people are likely to 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 will probably 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 behavioral 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

[12] There are also potential negative behavior changes. An example is the "worried well" phenomenon where healthy people seek medical assistance because of their concerns about possibly being ill.

that many people took precautionary measures as a result, and the outcome in Hong Kong was the 90% decrease in the reported 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 does not 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.

Various interventions, both behavioral and technological, have been shown to decrease transmission of the flu. Improved hygiene, including hand washing and using alcohol-based hand sanitizer, has been shown 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 (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, 2007). In addition, ultra-violet light, specifically UV-C, has the potential to disinfect air by inactivating virus-containing aerosols (Weiss, 2007).

9. Data on Behavior Changes

The most relevant data for creating mathematical models on reactive behavior comes from SARS. 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, with 8,096 known infection cases and 774 deaths.

Some of the best data on SARS comes from studies and surveys of 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 progressions 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 3*** 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 3

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 high[13] 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. Later in this chapter we will propose several approaches to including these human behaviors into our model.

10. Herd Immunity: What It Means in Terms of Total Number Infected

As mentioned before, there are many who agree that implementation of NPI's indeed does reduce the peak severity of the pandemic, in terms of maximum number infected at any time, and this is good for managing hospital surge capacity. But some also suggest that use of NPI's may only prolong the pandemic period, ultimately infecting as many people as would have been infected without use of NPI's (Cauchemez, et al 2009). Our modeling analysis and recent work of others (Germann et al 2006; Kelso et al 2009; Jefferson et al 2008; Caley et al 2008) have shown that this need not be true. Given our model assumptions, with NPI's the total number infected is almost always less, sometimes significantly so.

We can demonstrate this property with a simple back-of-the-envelope analysis, invoking the concept of herd immunity. All else being equal, herd immunity occurs in a population when the infectious disease no longer grows exponentially, and starts to die out geometrically from generation to generation. Herd immunity occurs when the effective reproductive number drops to $R(t) = 1$, signifying that each newly infected person infects – on average -- only one additional person. At this point in the evolution of the pandemic, no further exponential increase occurs. Usually herd immunity is achieved because a significant fraction of the population has become immune to the disease, either by vaccination or by having had the disease and being recovered and immune to further infection. Let us call $R(0) = R_0 > 1$. Recall from Eq. (1) that $R_0 = \lambda p$, where λ is the pre-intervention mean number of daily face-to-face contacts by a random member of the population, and p is the initial conditional probability of passing on the infection to the person in a random face-to-face contact. Define the "critical time" t_c such that $R(t_c) = 1$. The critical time is the time at which herd immunity is achieved.

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

Let's first do this without NPI's. At $R(t_c) = 1 = \lambda_{t_c} p_{t_c}$, we assume that the frequency of day-to-day contacts $\lambda_{t_c} = \lambda$ is unchanged during the pandemic[14]. Thus, for this equation to work, we need a reduction in p so that $p_{t_c} < p$. We get this because some face-to-face contacts are recovered or vaccinated and now immune to further infection. Suppose at time t_c, the time of herd immunity, we have a fraction f of the population in state ***R***, immune to re-infection, and the residual (1-f) still susceptible. For those who are still susceptible, the conditional probability of infection given exposure from a face-to-face contact remains unchanged at p. Thus $p_{t_c} = p(1-f)$. Then we must have $\lambda p_{t_c} = \lambda p(1-f) = 1$ or $f = (\lambda p - 1)/\lambda p = 1 - 1/R_0 > 0$. To see if this makes sense, we try $R_0 = \lambda p = 2$ and obtain $f = 1 - 1/2 = 1/2$. This makes sense: with R_0 = 2, one half of the population needs to be immune for herd immunity to occur. Other numerical examples are similarly intuitively appealing. (For additional discussion of herd immunity, consult any textbook on mathematical epidemiology such as Nelson and Williams, 2006, p. 627.)

Now, let's redo this exercise having $R_0 = \lambda p = 2$, but with NPI's. Suppose we alter daily behavior to reduce λ by a factor of $1/\sqrt{2}$, that is we have a new λ, call it λ', such that $\lambda' = \lambda/\sqrt{2}$, roughly a 30% reduction in daily contacts. Suppose by social distancing and hygienic steps we also reduce p by a factor of $1/\sqrt{2}$, defining a new p, call it p', such that $p' = p/\sqrt{2}$, which is roughly a 30% reduction in infection probability, given face to face contact. If we can all do that by invoking NPI's, then the new R_0, call it R_0', becomes $R_0' = \lambda' p' = (\lambda/\sqrt{2})(p/\sqrt{2}) = \lambda p/2 = 2/2 = 1$. That is, we can start the pandemic at herd immunity level by invoking NPI's at the beginning. If we could do that, the pandemic would never grow exponentially and would die off geometrically instead. This is most likely impossible in practice, since time is required for officials to observe and recognize a new and novel flu virus, one that could grow to epidemic and then pandemic levels. But the point remains: We individually and collectively have the power through self-selected behavioral changes to alter dramatically the course of the flu. To avoid a dangerous re-emergence, perhaps a 'second wave' after NPI's have squelched the first wave, these behavioral changes must be held in place until the threat of the flu is passed.

11. Modeling Behavior Changes

There has been very little progress in the field of quantitative health behavior modeling (Weinstein, 2005). One of the main deterrents for quantitative modeling of human reactionary behavior is that it is difficult and there is no obvious solution or approach. This does not justify avoiding these models; behavior is a first order affect and has a strong impact on transmission dynamics. We have proposed several different methods for modeling human behavior changes. While it is almost impossible to verify

[14] This may be corrected in a more sophisticated analysis, as we adjust for the reduced population because some are either sick in bed or may have died. With a reduced population, we may wish to model the number of face-to-face daily contacts as reduced in accordance with the reduced circulating population.

their quantitative accuracy the principles are intuitive and qualitative results are insightful. In this section we will present one of our approaches to modeling behavior and its impact on transmission, for more of these models refer to Nigmatulina & Larson, 2009 or Nigmatulina, 2009.

There are several qualitative social behavior models that predict people altering 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). This type of reactionary coping behavior was observed when HIV became more prevalent; people's sexual behavior became much more cautious. Similarly, with genetic diseases such as diabetes or heart disease, individuals with heightened risks alter their behavior.

For the development of the model, 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. In the case of SARS in Hong Kong, it was clear that people reacted to the news of infection spread by altering their daily routines depending on the severity of the news as well as the number of earlier deaths and infections. Furthermore, the survey study of Singapore found that people who were more anxious about becoming sick, practiced more precautionary measures (Quah, 2004). Within the context of the model presented in Section 5 the death rate for the disease is not specified, thus the number of infected individuals is the best gauge reflecting the community members' vulnerability and severity of the threat.

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. Here are a few examples of what the population could use to gauge their risk levels, to define their $\pi_X(t)$ and consequently alter their behavior. [15]

1. Initially, the only information available to people will be the experience of their own community. People may use the number of yesterday's new infections ignoring everything that happened before yesterday as a measure of their risk. We quantify this "memoryless" approach of evaluating the risk factor as:

[15] 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. Throughout this section when we use the term "day", we are referring to one generation of the flu, which corresponds to 2-3 actual days.

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

C_1 is an input representing the importance of yesterday's information. 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.[16]

2. The news media are 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 $\pi^2_X(t)$:

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

C_2 is another input which represents the strength of impact of this cumulative information. Note that C_1 will have a smaller impact than C_2.[17]

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. We will not include this in the following model, but refer the reader to the previously mentioned works for incorporating this factor.

In reality each individual is likely to change his or her behavior using a combination of all three described approaches. Yesterday's information is likely to be the most prevalent in the mind of the community, but community resients 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

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

as the overall feedback parameter for behavior change. The parameters that will reflect this concern level through altered behavior are λ and p.

Let us focus on λ. People in all activity levels are likely to decrease the number of contacts that they have on a daily level. It is likely 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

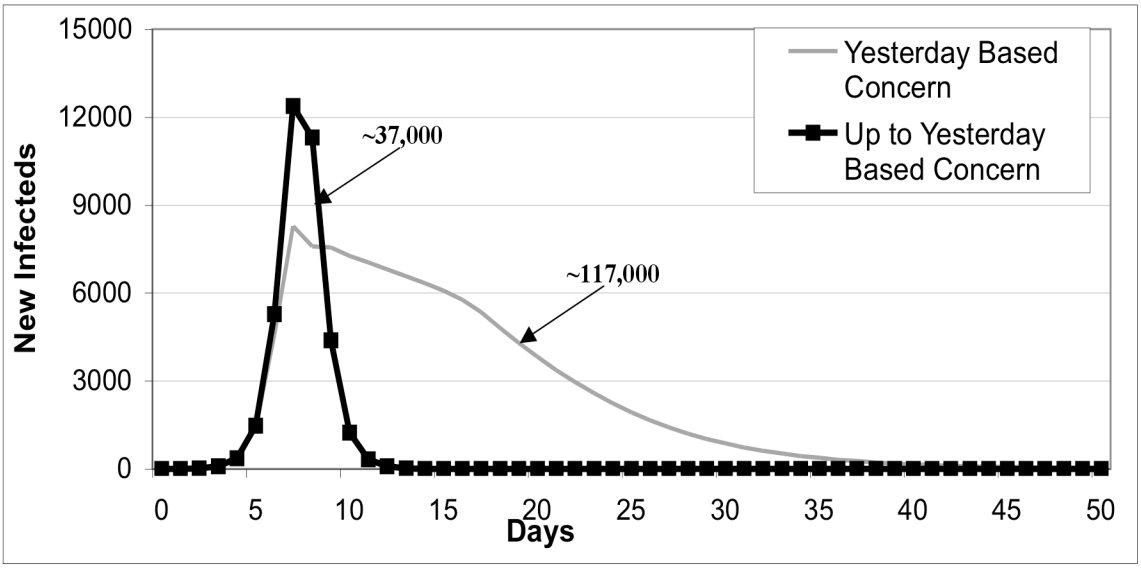
[16] The authors have not been able to find the application of the behavior forecasting models to predict general behavior changes in the case of pandemic flu, but we have found numerous examples of HBM used to estimate altered human interactions to reduce their risk for HIV infection. Studies in this 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).

[17] 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.

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). To model this decrease in contact rate over time we propose multiplying λ^j, the contact rate for a group of activity level *j* by, $\pi_X(t, C_1, C_2, C_3)$, the perceived level of concern. So,

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

The results seen in ***Graph 3***, compare two identical populations except that one solely relies on yesterday's information and the other uses cumulative information up to and including yesterday to assess their risk. For the "memoryless" group represented by the gray curve the peak of the epidemic is lowered compared to a 'do nothing' or 'stay the course' policy. Also, the cumulative number of infections is decreased compared to 'do nothing,' but the virus maintains its presence within the community for a long period requiring sustained vigilance. Realistically, people will use more than just yesterday's information to access their risk. By "remembering" the number of people who were infected prior to yesterday, the group represented by the black curve diminishes the prevalence of the virus much faster. This shows the potential effectiveness of social distancing in reducing the cumulative burden of the infection. The main difference in the two group behaviors is the intensity of the interventions in the declining half of the outbreak. In the black curve interventions are maintained at a high level until the infection is completely depleted. For the gray curve the intensity of the interventions decreases in the later half of the outbreak. The moral of this story: Stay vigilant throughout the risk period.

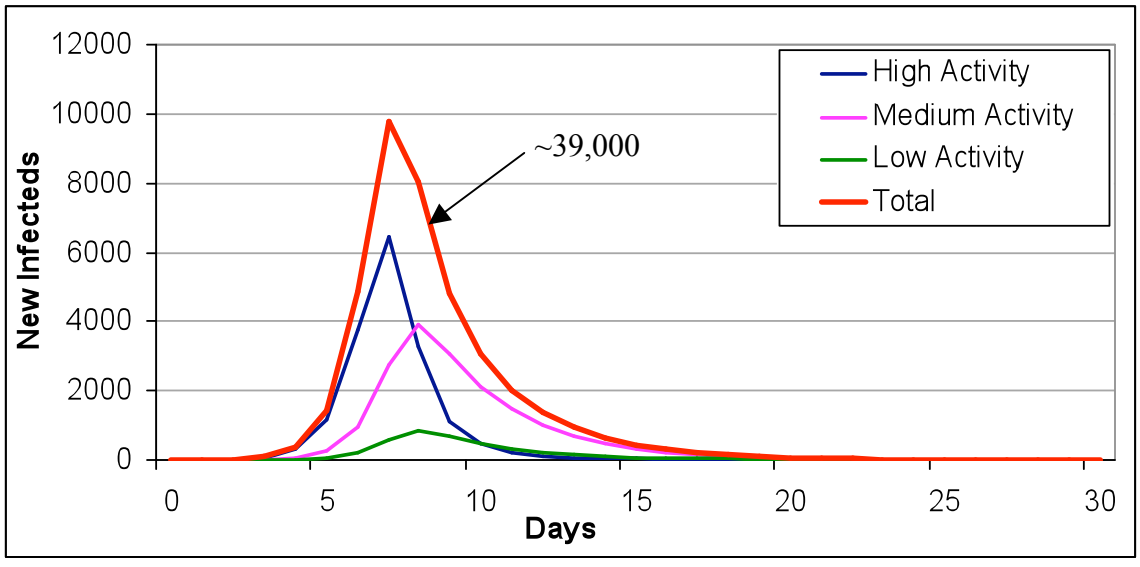


Graph 3
The impact of different types of behavior changes on the epidemic curve.

Now let's consider the human contact frequencies, the λ's, by different groups. 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 dramatically, 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. 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***. 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.

Overall, these models show the importance of including behavioral changes and their potential impact on disease transmission dynamics. From these models it becomes clear that the timing of behavioral changes and the behavior of the highly active people are some of the most important factors for transmission. Yet, the most important point is that behavioral changes such as limited social contact and improved hygiene must be included in future pandemic flu models, because they are first-order effects.



Graph 4.

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

12. Tipping Point Boundary

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. We demonstrated this above, reducing both λ and p by 30%, thereby reducing R_0 from 2.0 to 1.0. 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 NPI's early on in the outbreak. We believe that this can be taken a step further; NPI's, 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 chapter, 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 may be below the pandemic causing threshold of 1. We propose creating a multidimensional **"tipping point boundary"** 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 will be combinations of interventions that will lead to disease extinction, and the points above are all the bundles of measures that will lead to exponential growth in the disease. All points precisely on the boundary have $R_0 = 1$, the herd immunity value.

Let us generalize the simple numerical example we did above, a simple two-dimensional illustration of the boundary concept. Recall we know 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 constants 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 1*** one can see the two-dimensional tipping point boundary. It is the thick red line where $R_0=1$, and any points in the gray area under that boundary would cause a disease to die out in the population. Consider a flu strain that is comparable in virulence to the 1918-1919 pandemic[18] 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***

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

1. In order to stop the transmission, the combination of NPI's 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.

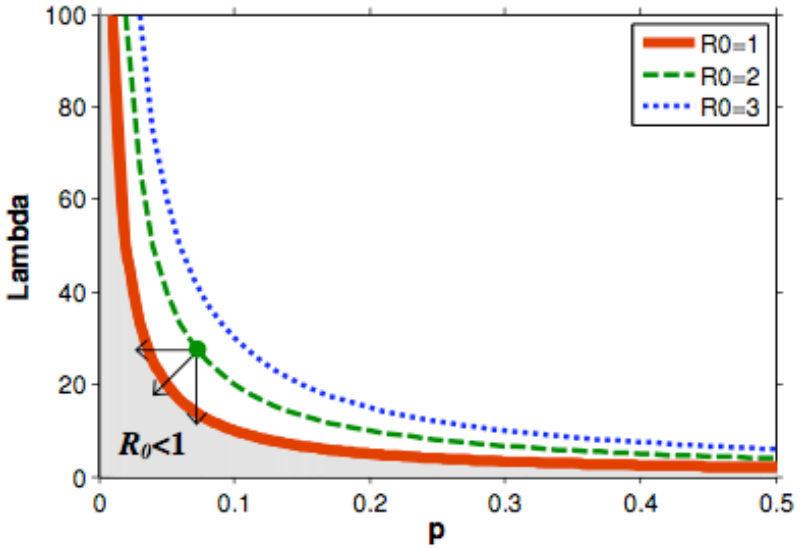


Figure 1.
The two dimensional tipping point boundary where $R_0 < 1$. To stop a pandemic, the set of interventions must decrease either λ or p or both to the gray area under the boundary.

Our simple 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 could test out their multiple intervention policies. We encourage future research in this area. Additionally, this illustration makes obvious that people, through NPI's, have the power to mitigate the outcome of the outbreak.

13. Conclusions

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. Even the normal annual 'seasonal flu" in the USA kills an average of 36,000 people each year, comparable to the number lost in auto accidents. 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.

Even without a Kirchoff's Laws or a Newtonian physics of the flu, we hope that we have shown that simple models, some axiomatically derived and some based on empirical studies, can help us engineer a system for preparing for and responding to pandemic influenza. Much is now known, especially when we compare to our almost total lack of scientific knowledge in 1918, facing the infamous "Spanish Flu." We have

emphasized human behavior as a key ingredient in mitigating the spread and effects of the flu. We took this track because the flu preparedness plans of many states treat pandemic flu as purely a medical issue. Their focus is on distribution of medicines such as anti-virals and vaccines, hospital surge capacity, coordinating a central command in emergency situations, and maintaining the health of health-care workers. While each of these is important, they are all responsive measures, all assuming that the physics of the spread of the disease is pre-ordained. We could not disagree more. We believe and hope that this chapter has shown that non-pharmaceutical interventions (NPI's), both government mandated and individually selected, may dramatically alter the course of the disease. This 'partial control' must be included, must be emphasized in any state or federal plan. This control is no less important than the flight controls that a pilot has for her aircraft or the dosage controls that an anesthesiologist has for his patient. All engineers understand the importance of controls, even partial ones, as NPI's are. But any engineered flu preparedness and response system must include them.

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, swine or any other flu pandemic is not going to demolish our world. However, there is evidence that during SARS the losses that resulted initially 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.

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