DETERMINISTIC AND STOCHASTIC SIMULATIONS OF INFECTIOUS DISEASES

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DETERMINISTIC AND STOCHASTIC SIMULATIONS OF INFECTIOUS DISEASES

by

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ABSTRAK

Pemodelan dinamik untuk transmisi penyakit berjangkit di dalam satu kawasan tertentu ialah fokus utama tesis ini. Pergerakan individu yang telah dijangkit dari satu kawasan ke kawasan lain menggalakkan penyebaran penyakit berjangkit, contohnya sindrom pernafasan akut teruk (SARS) and influenza A (H1N1). Objektif utama kajian ini adalah untuk mengembangkan keupayaan pihak berkuasa kesihatan awam di Malaysia bagi merancang and melaksanakan strategi intervensi yang efektif untuk mengurangkan wabak epidemik pada masa depan. Kerjasama antara pihak berkuasa kesihatan dan masyarakat tempatan adalah penting untuk melaksanakan langkah-langkah mitigasi bagi mengurangkan jangkitan tempatan. Bagi tujuan ini, model influenza simulasi berdasarkan formulasi SIR dan nama kodnya FluSiM telah dikembangkan untuk menyiasat dinamik transmisi penyakit berjangkit dan untuk mencadangkan strategi intervensi yang sesuai bagi mengawal wabak epidemik. FluSiM asas Window yang mesra pengguna telah dikembangkan untuk membantu pelajar-pelajar siswazah universiti sertai penyelidik akademik menjalankan penyelidikan epidemiologi. Versi FluSiM ini juga digunakan untuk mensimulasikan influenza pandemik 1918 di Switzerland, H1N1 2009 in Amerika Syarikat (AS) and Furunculosis in populasi salmon. FluSiM deterministik ini kemudiannya dipertingkatkan ke model stokastik dengan merangkumi ciri-ciri stokastik di dalam transmisi penyakit. FluSiM stokastik ini digunakan untuk menyiasat ketidaktentuan semasa wabak epidemik. Simulasi FluSiM stokastik menunjukkan bahawa keheterogenan ketara dalam satu populasi mungkin menjadi penghalang kepada pelaksanaan intervensi yang efektif. FluSiM juga dipertingkatkan ke model meta-populasi untuk mengkaji penyebaran SARS dari Hong Kong ke Singapura pada

tahun 2003. Simulasi menunjukkan bahawa strategi intervensi seperti kempen vaksinasi dan pejarakan sosial perlu dilaksanakan apabila wabak epidemik disahkan. Kefahaman yang diperolehi daripada penyelidikan ini pada subjek transmisi penyakit and strategi intervensi akan berguna untuk mengawal wabak epidemik pada masa depan di Malaysia.

DETERMINISTIC AND STOCHASTIC SIMULATIONS OF INFECTIOUS DISEASES

ABSTRACT

Modeling the dynamics of infectious disease transmission in a specific region is the main focus of this thesis. Movements of infective individuals from one region to another promote the spread of infectious diseases, such as severe acute respiratory syndrome (SARS) and influenza A (H1N1). The primary objective of this research is to develop the capability within Malaysian public health authorities to plan and implement intervention strategies that is effective for mitigating future epidemic outbreaks. The collaboration between health authorities and local community is essential in implementing mitigation measures to reduce local infection. For this purpose, an influenza simulation models-based upon the SIR formulation and codenamed FluSiM is developed to investigate the dynamics of infectious disease transmission and to suggest appropriate intervention strategies to control the epidemic outbreak. The user-friendly Window-based FluSiM is developed to aid university graduate students as well as academic researchers in conducting epidemiology related research. This version of FluSiM is also used to simulate the 1918 influenza pandemic in Switzerland, the H1N1 2009 in United States of America (USA) and Furunculosis in salmon population. This deterministic FluSiM is later enhanced into a stochastic model by incorporating stochasticity in disease transmission characteristics. This stochastic FluSiM is utilized to investigate the uncertainties during an epidemic outbreak. Simulations of stochastic FluSiM indicate that significant heterogeneity in population may be a hindrance to implementation of effective interventions. FluSiM is also enhanced into a meta-population model to study the spread of SARS in 2003 from Hong Kong to Singapore. Simulations indicate that intervention strategies such as vaccination campaign and social

distancing should be implemented once an epidemic outbreak is confirmed. The insights gained from this research on disease transmission and intervention strategies would be useful for control of future epidemic outbreaks in Malaysia.

CHAPTER 1

INTRODUCTION

1.1 Introduction to Infectious Disease

Infectious diseases are viral or bacterial diseases that are transmitted from human to human and have the potential to develop into an epidemic outbreak. Infectious diseases have severely afflicted humankind in the past, and despite improved medication and extensive vaccination program, they continue to be a major cause of suffering and mortality in the present world. Infectious disease viruses undergo continuous evolution or mutation, leading to emergence of novel infectious diseases that causes epidemic outbreaks. The viruses also have a strong adapting ability which allows them to circulate in a human population. This in turn results in the existing infectious disease persisting and continuing to spread within the population.

In recent past, the most remarkable epidemic outbreaks are Severe Acute Respiratory syndrome (SARS) in 2003 and influenza A (H1N1) in 2009 which first emerged in China and Mexico respectively. SARS is a disease that originated from a mutation of a wild animal coronavirus; while H1N1 is a disease that combines a swine and a human influenza strains. During these disease outbreaks, public health authorities implemented several control measures to minimize the infection but some control measures were not as effective as expected. Thus these infectious diseases were able to cause severe mortalities and economic hardships. Humankind will undoubtedly face more novel and lethal infectious disease challenges in future. Therefore this has increased the urgency to be on alert and has promoted the need to develop an early

warning system in order to allow community to take adequate control measures to mitigate infectious disease transmissions with advance notice.

1.2 Influenza A (H1N1) in 2009

In early April of 2009, a novel influenza A (H1N1) emerged in Veracruz, Mexico and spread rapidly throughout the world, causing the influenza pandemic. On 29 April, 2009 The World Health Organization (WHO) declared the global pandemic alert level to Phase 5, indicating sustained human-to-human transmission. During the early stage of H1N1 pandemic, there were uncertainties about all aspects of this outbreak, including virulence, transmissibility and origin of the virus. Many feared that this outbreak is uncontrollable and will cause significant mortality and economic loss.

Promoted by international travel pattern, the H1N1 virus spread rapidly via air traveling, infecting 74 countries within five weeks from the initial outbreak in Mexico. During the initial outbreak period, more than 300,000 people traveled internationally from Mexico each week. This in turn results in difficulties in disease containment as hundreds of infected individuals had traveled aboard before the virus was identified. In the first week of May, 3,000 new infections were identified in United States (US), Canada and Europe.

There were several control measures taken to minimize the infection of H1N1 during its outbreaks. In Mexico, the government implemented a period of national quarantine starting in May by closing restaurant and schools. In the US, the Center of Disease Control and Prevention (CDC) developed a vaccine for H1N1 during the

second wave in the fall season. In Canada and Europe, the public health authorities focused on quarantine of infective individuals and limited their mobility. In April 2010, WHO lifted the global pandemic alert but declared that there is a possibility of H1N1 recurrence. The H1N1 outbreaks in 2009 has caused severe mortality and great losses in global economic.

1.3 Epidemiology Modeling

Epidemiology is the study of the distribution and determinants of disease prevalence in a host population. The main objective of epidemiologists is to identify the causes and risk factors for diseases. This in turn aids the public health authorities to plan, implement and evaluate control and prevention measures during a disease outbreak. Thus epidemiology modeling refers to dynamic modeling where the host population is divided into compartments based on their epidemiological status. The movements between compartments by infected, recovered or migrated individuals are specifically defined by a system of differential equations or other types of formulations.

The first structured mathematical model in epidemiology is Susceptible-Infected-Recovered (SIR) model which was initially developed by Kermack and McKendrick in 1927. In the development of the SIR model, the most outstanding result obtained was the Threshold Theorem which is used to determine if an infectious disease can evolve to an epidemic outbreak. If the susceptible population exceeds a certain critical value, then there is a possibility that the infectious disease may cause a local epidemic. Later in the middle of twentieth century, many epidemiologists and modelers developed a variety of models using SIR model as a prototype to

investigate the dynamics of a specific infectious disease transmission, and thus epidemiology modeling started to grow exponentially. Recent approaches in epidemiology modeling including deterministic and stochastic models are often implemented using computer simulation to fit the observed data in order to have better insights of infectious disease transmissions. In recent years, epidemiology modeling has an increasing influence on the theory and practice of disease management and control, and becomes very important for decision making of infectious disease intervention strategies in many countries.

1.4 Objectives of Thesis

The objectives of this thesis research include:

1. To develop the influenza simulation model FluSiM;
2. To use the in-house deterministic FluSiM for simulating the 1918 influenza pandemic, the 2009 influenza A (H1N1) and Furunculosis in Chinook salmon;
3. To investigate the uncertainties during an epidemic outbreak by means of the in-house stochastic FluSiM;
4. To use the meta-population FluSiM for simulating the 2003 severe acute respiratory syndrome (SARS) spread from Hong Kong to Singapore;
5. To assess the effectiveness of intervention strategies including vaccination campaign and social distancing by means of FluSiM simulations.

1.5 Scope and Organization of Thesis

This thesis begins with a brief introduction to infectious disease and its impact on human population, drawing insights from past epidemic outbreaks such as severe acute respiratory syndrome (SARS) and influenza A (H1N1). The need of

incorporating epidemiology modeling in epidemic management is then explored, leading to the main focus of this thesis. The objectives, scope and organization of this thesis are then described.

Chapter 2 presents a review of related literature, beginning with an introduction to epidemiology modeling that includes mechanism of disease transmission, applications and limitations of epidemiology modeling. SIR and SEIR models are introduced in this chapter by describing their model equations and basic reproduction number R_0. These insights stimulate our interest in developing an in-house influenza simulation model codenamed FluSiM. This is followed by a brief exploration of unique epidemic phenomenon that includes global influenza transmission and multiple infection waves. A discussion on intervention strategies of influenza transmission is presented in the last section in this chapter.

A detailed discussion on the SIR model forms the main focus for Chapter 3, which stimulates the interest in developing a user-friendly Window-based FluSiM that displays suggestive icons representing the key disease transmission parameters. A simple guidebook is included in this chapter to aid FluSiM users for utilizing this simulation model in conducting epidemiology related research. Three different epidemic outbreaks cases are studied and revised using this FluSiM in the subsequent sections. Simulations of FluSiM that incorporate intervention strategies such as vaccination campaign and social distancing will round up this chapter.

The limitations of deterministic SIR model as it is premised upon homogeneous mixing assumption will first be discussed in Chapter 4. This leads to the

development of stochastic FluSiM, an enhanced model that allows key disease transmission parameters to randomly change with time, following a specified normal distribution. This version of FluSiM is utilized to simulate different epidemic scenarios that have different values of basic reproduction number for investigating the uncertainties during an epidemic outbreak. This chapter will end with investigations of heterogeneity as a hindrance in reducing the effectiveness of the implemented intervention during an epidemic outbreak.

Often a disease virus will spread from a source region to another uninfected region before the end of the local epidemic outbreak. The global pandemic phenomenon is the main focus of Chapter 5. A meta-population FluSiM is proposed and developed for investigating the inter-regional disease transmission. This is followed by sensitivity analyses of two newly introduced parameters that affect the exportation of infective individuals from one subpopulation to another. Furthermore, meta-population FluSiM is applied to study and update the 2003 SARS transmission from Hong Kong to Singapore for fitting the primary and secondary collected data to FluSiM.

This thesis ends with a brief summary regarding future research direction on infectious disease transmission simulation in Chapter 6.

CHAPTER 2

LITERATURE REVIEW

2.1 Epidemiology Modeling

In recent years, modeling is widely applied to study the spread of an infectious disease in a host population for obtaining information and explanations that may be applicable to a future epidemic outbreak with similar disease characteristics. Experiments with disease transmission on human are impossible as they are unethical. Therefore the data for testing models generally originate from past documented epidemics such as the 1918 influenza pandemic, the Severe Acute Respiratory Syndrome (SARS) in 2003 and the influenza A (H1N1) in 2009.

The mathematical and public health approaches to the model developments have diverged in the past, and the communication gap between modelers and public health authorities has evolved. However, there have been strenuous efforts to connect this gap during the SARS epidemic outbreaks in 2003. The importance of these efforts is highlighted in the development of mathematical models for evaluating the disease intervention strategies. Participants at a Canadian pandemic preparedness workshop held in 2008 noted that models are most useful when they are developed in synergistic cooperation between modelers and public health authorities (Arino et al., 2011).

Modeler and public health authorities may have different viewpoints or perspectives. Modelers are more interested in solving epidemiology models to hopefully obtain better insights of the mechanisms of disease transmission; while public health

authorities would need detailed analysis for specific circumstances in order to answer policy questions. The decisions made by public health authorities are usually influenced by political considerations. Thus they need to take into account scientific information into their decision making, keeping the political perspectives in close focus. Collaboration between modelers and public health authorities is needed in model development in order to support complex decision makings.

This section of literature review attempts to provide a summary of epidemiology modeling with application to epidemic outbreak scenarios. This is divided into several sections, such as the mechanism of disease transmission, advantages and disadvantages of certain models, applications and limitations of epidemiology modeling.

2.1.1 Mechanism of Disease Transmission

Over the years viruses have infected human population, transmitted from one population to another by some forms of contact, spread through a part of the population and later disappeared without infecting the entire population. The first epidemic model, namely the SIR model, developed by Kermack and McKendrick in 1927 exhibits this mechanism of disease transmissions (Bailey, 1975; Brauer et al., 2008; Frauenthal, 1980). The SIR model is a compartmental model which divides the population N into three disjoint compartments consisting of the Susceptible S, Infective I and Recovered R. The Susceptible is an individual who has no immunity to the infectious disease, while the Infective is an individual who transmits the infection and the Recovered is an individual who recovers with immunity against re-infection. The infectious disease is assumed to be transmitted to a susceptible

individual by an infective individual through contact during his infectious period. This model consists of rates at which individuals move from a compartment to another, and these rates lead to a system of differential equations that expresses the mechanism of disease transmission mathematically as shown in Equations (2.1) (Bailey, 1975; Frauenthal, 1980; Thieme, 2003). Detailed description and discussion of SIR model is later presented in Chapter 3.

$$\frac{ds}{dt} = -\beta SI \; ; \qquad \frac{dI}{dt} = \beta SI - \gamma I \; ; \qquad \frac{dR}{dt} = \gamma I \; . \tag{2.1}$$

During the course of an epidemic, the number of new infection increases initially to an epidemic peak, and then as the number of susceptible individual decreases, the number of new infection decreases, slowing the disease transmission and ultimately ending the epidemic. Hence all epidemiology models should exhibit this general pattern of epidemic evolution as displayed in Figure 2.1.

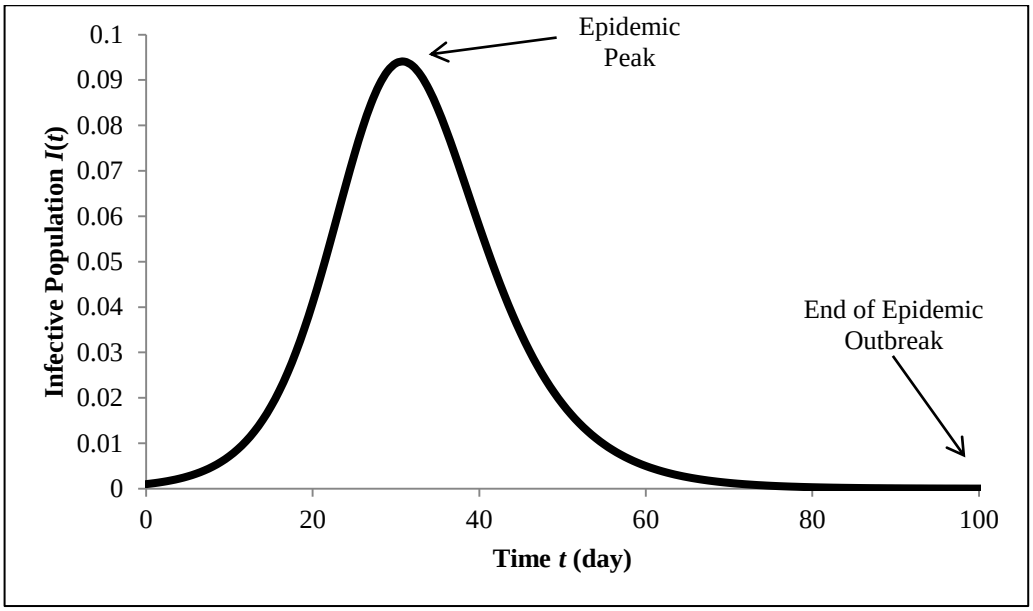

Figure 2.1: Epidemic evolution

2.1.2 Applications of Epidemiology Modeling

The first advantage of epidemiology modeling is the clarification of assumptions about the biological and social mechanisms which affect disease transmissions (Frauenthal, 1980, Hethcote 2008). The model development process is essential to modelers as they have to be precise in the mechanism of disease transmission. Parameters which have well-understood epidemiological interpretation, such as contact rate β and infectious period $1/\gamma$, are used in the SIR model development. A model using differential or difference equations (Kapur and Khan, 1981; Roeger and Barnard, 2007) is neither ambiguous nor vague if the parameters are precisely defined and each term in the equations is mechanistically explained. Equations (2.2) show the difference equations of SIR model.

$$\begin{aligned} S(t+1) &= S(t) - \beta S(t) I(t); \\ I(t+1) &= I(t) + \beta S(t) I(t) - \gamma I(t); \\ R(t+1) &= R(t) + \gamma I(t). \end{aligned} \tag{2.2}$$

In order to utilize modeling effectively in epidemiology, one must understand the transmission of a specific disease, so that he can decide which necessary factors should be included in a model development for the disease. This option often depends on the particular questions that are to be answered. Simple models have small number of parameters as their advantage but they may be oversimplified. For example, SIR model has two parameters named contact rate β and recovery rate γ. In contrast, complex models may be more realistic, but they contain more parameters whose estimation value may not be readily obtained. For example, SEIR model which includes an Exposed compartment has one extra parameter named the average

latent period $1/\alpha$ (Brauer et al., 2008, Hethcote, 2008). Equations (2.3) give the system of differential equations of SEIR model.

$$\frac{ds}{dt} = -\beta SI\ ; \qquad \frac{dE}{dt} = \beta SI - \alpha E\ ;$$

$$\frac{dI}{dt} = \alpha E - \gamma I\ ; \qquad \frac{dR}{dt} = \gamma I\ . \tag{2.3}$$

The art of modeling is to make suitable options in model development so that the model is as simple as possible and yet it is adequate to answer the questions being considered. One of the applications of modeling is to allow explorations of the effect of different assumptions or various options available for the modeler to choose. For example, modelers can examine the effect of heterogeneous mixing between susceptible and infective individuals instead of homogeneous mixing. They can also examine the behavior of solution by including an exposed compartment for individuals in the latent period into the model (Brauer et al., 2008; Ng et al., 2003). The advantage of exploring different assumptions is to guide modelers in choosing a suitable model for a specific disease and to provide better insights for epidemiologists and public health authorities in planning intervention strategies to control the disease.

After completing the model development, there are several mathematical methods available for solving and analyzing the model to determine the threshold relevant to the disease, to project the disease evolution, or to suggest control measures. Where analytical solutions are not possible, the behavior of solution can also be obtained using numerical methods in computer simulations. This stimulates the interest to

develop a flu transmission simulation model codenamed FluSiM for this research as later presented in Chapter 3. If the results of mathematical analysis and numerical simulation are in agreement, then these methods can be used in identifying important combination of parameters that are critical to the disease transmission. Key parameters, such as contact rate β and infectious period $1/\gamma$, can be estimated via fitting the output from a model to the data collected. In addition, if parameters have been estimated from the literature, then these estimations can be checked using models. Thus modeling can be applied to check if the parameters and data actually fit into a consistent framework (Poletti et al., 2011). Comparisons in modeling can provide better understanding of the disease transmission. They are usually performed to estimate parameter values for a specific disease and then compare the parameter values. Outputs of a model are said to be sensitive to a parameter if a slight change in the parameter values causes a significant change in the output. On the other hand, a model is insensitive to a parameter if the outputs are almost the same for a broad range of parameter values. The determination of the parameter sensitivity and insensitivity are crucial as this provides insight into the disease transmission sensitivity (Hethcote, 2008). Efforts for collecting data to obtain better parameter estimations can be made if the parameter sensitivity is identified. Therefore modeling can help to identify important data that should be collected.

Models in epidemiology can provide the concept of threshold, namely the basic reproduction number R_0, which is used to determine if the disease can cause an epidemic outbreak (Brauer et al., 2008). Equations (2.4) and (2.5) show the R_0 of SIR and SEIR models respectively. A detailed discussion of calculating this threshold in SIR model is presented in Chapter 3.

$$R_0 = \frac{\beta S_0}{\gamma} \tag{2.4}$$

$$R_0 = \frac{\beta S_0}{\alpha + \gamma} \tag{2.5}$$

S_0 is the number of susceptible individual at the beginning of the epidemic (time t = 0). As observed in Equations (2.4) and (2.5), R_0 is a combination of parameters from the model which gives the average number of new infections caused by an infective individual introduced into a completely susceptible population during his infectious period (Brauer et al., 2008; Thieme, 2003). This is the most valuable contribution of modeling to epidemiology as one can know the potential of an infectious disease to evolve into an epidemic outbreak, and later use it to plan intervention strategies in order to control the outbreak. Attack ratio A is another useful parameter to describe the severity of an epidemic outbreak (Arino et al., 2011). A is defined as the fraction of the susceptible population infected during the entire course of an epidemic and can be expressed in Equation (2.6).

$$A = 1 - \frac{S_f}{N} \tag{2.6}$$

S_f is the number of susceptible population at the end of the epidemic. There is a mathematical relationship between R_0 and A namely final size relation and is given in Equation (2.7).

$$ln \frac{S_0}{S_f} = R_0 A = R_0 \left[1 - \frac{S_f}{N} \right] \tag{2.7}$$

Figure 2.2 displays a graphical relation between R_0 and A in a population that has N = 10000 and $I(0)$ = 1. Attack ratio A is applied to evaluate the effectiveness of intervention strategies such as quarantine, social distancing and vaccination campaign as later presented in Chapter 3.

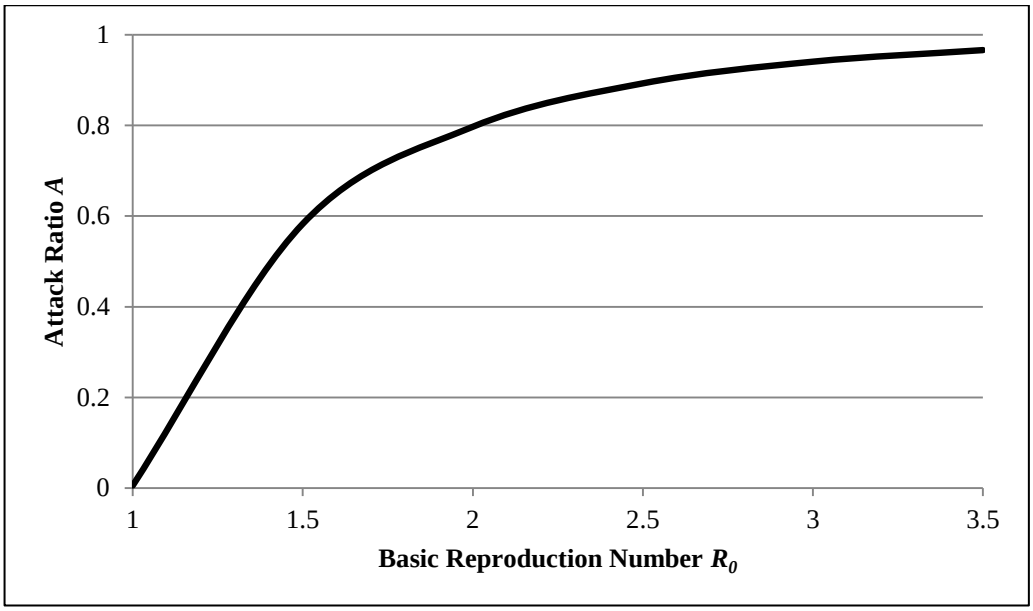

Figure 2.2: Basic reproduction number R_0 versus attack ratio A

Mathematical modeling and computer simulation are fundamental experiment tools for epidemiologist and modelers to build and test theories (Hethcote, 2008). The data usually available are from naturally occurring epidemics in the past because experiments with disease spread on human are impossible as they are unethical. Unfortunately these data are not complete nor easily available, because many cases were not reported. Since experiment and accurate data are usually not available in epidemiology, computer simulations must be used to perform necessary theoretical experiments with different parameter values and different data sets.

A very important application of modeling in epidemiology is to perform theoretical evaluations and comparisons of intervention strategies (Cruz-Pacheco et al., 2009; Towers and Feng, 2009; Gjorgjieva et al., 2005). Cruz-Pacheco and his colleagues studied the national social distancing policy implemented by the Mexican Secretariat of Health during the H1N1 outbreak in Mexico, while Gjorgjieva and her colleagues conducted a research on the role of vaccination campaign in the control of SARS. Epidemiologists and public health authorities need to understand the effects of different control measures for making the best decision to minimize the infections. Qualitative results of models are always subject to uncertainties because the models are simplified and the parameters values can only be estimated. However, quantifications of the relative advantages of several control measures are often robust in the sense that the same conclusions hold for a wide range of parameter values and various models.

The last application of modeling is to make forecasts regarding the future epidemics. People often think of forecast as the only application of modeling, but investigating the effectiveness of intervention strategies is more important. Accurate forecasts are impossible due to the simplified assumptions in model development and uncertainties in the parameter values. However, possible forecasts under different circumstances can sometimes be predicted or the general pattern can be identified if the uncertainties are reduced in future epidemic projections.

2.1.3 Limitations of Epidemiology Modeling

After discussing the applications of epidemiology modeling, it is necessary to discuss its limitations as well. Epidemiologists and modelers need to acknowledge both the

strength and weakness of modeling in epidemiology. The first limitation is that all deterministic models are simplifications of reality as they are developed based on several assumptions such as homogeneous mixing and the total population size is fixed (Brauer et al., 2008; Frauenthal, 1980). The deviation from reality of these simplifications varies with the disease and circumstances, and therefore it is difficult to be measured. For example, the SIR model is not a good description at the beginning of an epidemic outbreak because of its homogeneous mixing assumption which is not necessarily valid, if given stochasticity (Arino et al., 2011). Hence one can never be completely certain about the forecast results from deterministic models. Complex models are sometimes developed to obtain a better approximation of actual disease transmission but they require more data which are not readily available.

Deterministic models are models that use difference or differential equations to describe the size changes of disease status compartments with time. These models do not reflect the role of probability or uncertainty in disease transmission as parameter values in these models are often set equal to the mean of observed values and the variance of parameters is ignored (Hethcote, 2008; Bailey, 1975). Furthermore, a set of initial conditions leads to exactly one output in deterministic models, thus there is no information available on the confidence in the model output. When parameters such as contact rate and basic reproduction number are estimated by fitting model output to observed data, confidence intervals on these parameters are not obtained. However, sensitivity analyses may be conducted to obtain understanding of the dependence on parameter values for determining the effects of changes in parameter values on model outputs. If the variance of the observed parameter value is low and the model outputs are sensitive to that parameter, then the confidence in the model

outputs would be low. Stochastic models incorporate probability, but it is difficult to obtain analytical result for these models and it requires large number of simulations to detect the behavior of a disease transmission for obtaining quantitative results (Hethcote, 2008).

There are also some difficulties in the process of fitting models to observed data (Arino et al., 2011). Various kinds of bias may arise in the collection of observed data. Analysis of clinical data is complicated due to administrative factors such as reporting delays and inconsistencies in classification of clinical cases. This is particularly important for a disease such as influenza in which many cases are asymptomatic or very mild and therefore are not diagnosed or reported. Modelers often fit models to observed data in order to obtain a curve describing the evolution of an epidemic and to estimate key parameters, such as contact rate. However, fitting model outputs to observed data is only valid if the model produces outputs with the same meaning as the observed data, and often a model output may not give the true picture of observations. Epidemic data represents the number of reported infections, while model outputs represent the number of actual infections. Therefore a modeler should be aware when fitting the model to observed data.

2.2 Effects of International Travel on Influenza Transmission

In the past, international travels were less likely as people could only travel via land and water transports, but today's people travel internationally via air transport because it is more convenient and faster if compared to the transportations in the past. Therefore people can move far frequently and with a high rate of long distance travel (Sattenspiel and Dietz, 1995). This in turn allows the intensive exportation of

infective individuals from a known source to other regions during a local epidemic outbreak.

The international spread of influenza A (H1N1) in 2009 was more rapid than the previous global pandemics such as the 1918 influenza pandemic due to the tight connectivity of the globe through air travel. It is believed that the global spread of the 1918 influenza pandemic was greatly influenced by military traffic in the First World War (Yoneyama & Krishnamoorthy, 2010) and it took 3 years to circle the globe (Hosseini et al., 2010). In contrast, the H1N1 virus in 2009 spread quickly via international air travel, infecting 74 different countries within five weeks of the Mexico outbreak in early April (CDC, 2010). The volume of air traveler determined the dynamics of the H1N1 global spread. At the onset of outbreak in Mexico, it is estimated 300,000 individuals flew internationally every week (Fraser et al., 2009). Infection rates in Mexico approximately reached 1 in 10,000 during early April, and hundreds of infected individuals most likely had already traveled to other countries before the H1N1 virus was identified (Chang et al., 2010).

Of the 1.3 million individuals who traveled out of Mexico during April 2009, 68% of individuals traveled to United States (U.S), 16% traveled to Canada, 8% traveled to Europe and 7% traveled to Latin American. Later in the first two weeks of May, 3,000 new infections were identified in U.S, Canada and Europe with 74%, 11% and 7% of them respectively (Chang et al., 2010). These results showed an agreement with the air travels out of Mexico. In conclusion, infectious diseases especially influenza is driven by international air travel and now become a more rapidly spreading international threat than ever before.

Figure 2.3 shows the global distribution of confirmed H1N1 infection in the second week of May, 2009. As observed in Figure 2.1, the countries in Northern Hemisphere were severely infected. Recent studies suggest that data on air travel can be used to forecast the spread of novel infectious disease (Massad et al., 2010; Ruan et al., 2006), and this may buy time for the public health authorities to plan intervention strategies for controlling a local epidemic outbreak. This stimulates interest in developing meta-population models, which are collections of subpopulations with links between them, in order to investigate the international spread of an infectious disease. More complex meta-population models incorporating network and mobility of individuals are also developed to track the movements of individual and to study the effect of these movements on disease transmission between patches (Sattenspiel and Dietz, 1995).

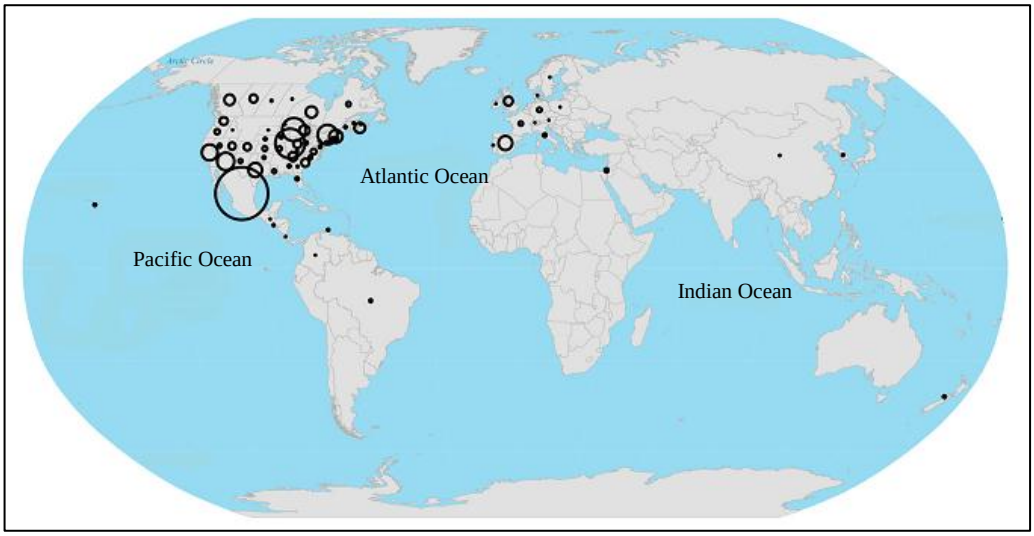

Figure 2.3: Global distribution of confirmed influenza A (H1N1) infection on May 8th, 2009 (Hosseini et al., 2010)

2.3 Multiple Infection Waves

There is scientific evidence shows that the transmissibility of influenza is significantly affected by temperature and humidity (Arino et al., 2011; Fraser et al., 2009). Therefore an epidemic begins in the spring may be less severe than in the fall, because the transmission decreases in the spring and later may recur in the fall with a more severe infection wave. In some populations, the 1918 influenza pandemic began in the spring, was essentially dormant in the summer and then reappeared in a much more severe form in the fall. As observed in Figure 2.4, the 1918 influenza pandemic in Geneva, Switzerland (Chowell et al., 2006b) exhibited this tread of infection which has higher severity in fall.

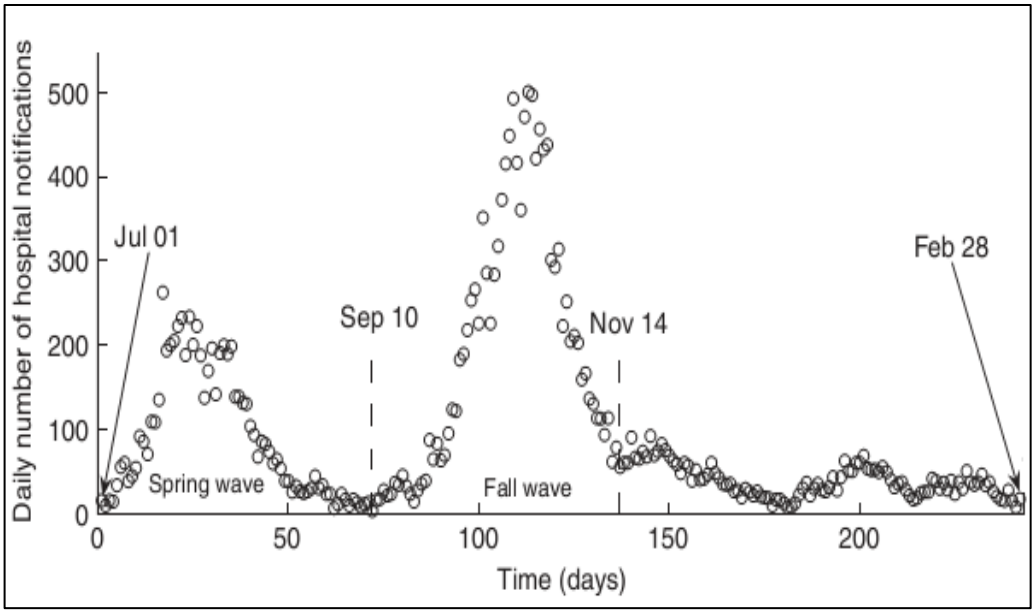

Figure 2.4: Daily number of hospital notifications of influenza cases during the 1918 influenza pandemic in the Canton of Geneva, Switzerland (Chowell et al., 2006b)

Often, the second infection wave is more severe for age groups that were not infected severely in the first wave, possibly because of partial immunity obtained via recovery during the first wave (Arino et al., 2011). During a second wave, there may be

mutation of the influenza virus to a more lethal strain or potentially severe bacterial co-infections. This suggests that after the first infection wave, even it appears not to be very severe, it is important to develop a vaccine for this strain that may provide at least partial immunity against a more lethal second wave. However, development of such a vaccine would consume some of the resources needed for the preparation of a vaccine for the next seasonal influenza, and it would be necessary to decide how to allocate these resources without knowing the relative severities of the seasonal and pandemic strains. It appears that vaccine manufacturing capacity for production both seasonal and pandemic vaccines at the same time is limited (Towers and Feng, 2009). Pandemic strains generally seem to displace the circulating seasonal strains and become the predominant strain in future influenza seasons. Seasonal variation in transmissibility is not the only suggested explanation for a second wave in a pandemic, and another possibility is co-infection with other respiratory diseases (Arino et al., 2011). This means that it is not possible to rely on a model to predict when a second wave may develop or how severe it may be. However, epidemiology models are still useful as an early warning system in order to allow public health authorities to take adequate mitigation measures with advance notice when a second infection wave occurs.

2.4 Intervention Strategies of Influenza Transmission

There are generally two stages to control the spread of influenza (Arino et al., 2011). The first stage is containment which attempts to limit the spread of influenza from a known source region to other regions. In this stage, mobility control of infective individuals and travel restriction are usually implemented to prevent exportation of infective individual to uninfected regions. The most ideal outcome of this stage is to

contain an influenza outbreak in the source region before it has the chance to spread to other regions. An epidemic usually starts in a remote region and it is impossible to diagnose the first infection quickly. This is particular significant for a disease like influenza because majority of transmissions is from infective individuals who do not show or do not yet have symptoms. The risks are even greater if the influenza emerges in a community that has limited medical resources. This stage is a pre-pandemic scenario which has the possibility of eradicating the epidemic in the limited known sources. However, the influenza A (H1N1) in 2009 spread rapidly over the globe in the matter of few months via international air travel, and this has raised the question of whether travel restriction would slow the spread of this virus. Result from modeling, however, suggests that reduction of even more than 95% in international air travel could only delay the onset of an influenza outbreak (Arino et al., 2011). This would only buy additional time for strategizing mitigation, but this could risk pushing local epidemics forward until seasonal factors result in a more severe first wave of infection. Therefore public health authorities should be cautious on implementing travel restriction as it has pro's and con's.

If the virus spreads into many different regions and starts circulating in the local populations, then containment is no longer effective in controlling the spread of influenza. At this stage, public health authorities will move to the second stage of intervention which is the mitigation mode. There are mainly three types of mitigation strategies: behavioral measures, vaccination before or during an epidemic and treatment during an epidemic (Cruz-Pacheco et al., 2009; Towers and Feng., 2009; Bootsma and Ferguson, 2007; Gumel et al., 2004).

Behavioral measures such as increased sanitary controls, avoidance of large public gathering and closure of public facilities are mainly implemented to decrease contacts between infective and susceptible individuals that are likely to contribute to new infections. In modeling, the contact rate β can be reduced by considering the implementation of behavioral measures, resulting in decreasing the reproduction number R. Figure 2.5 displays the linear relation between β and R.

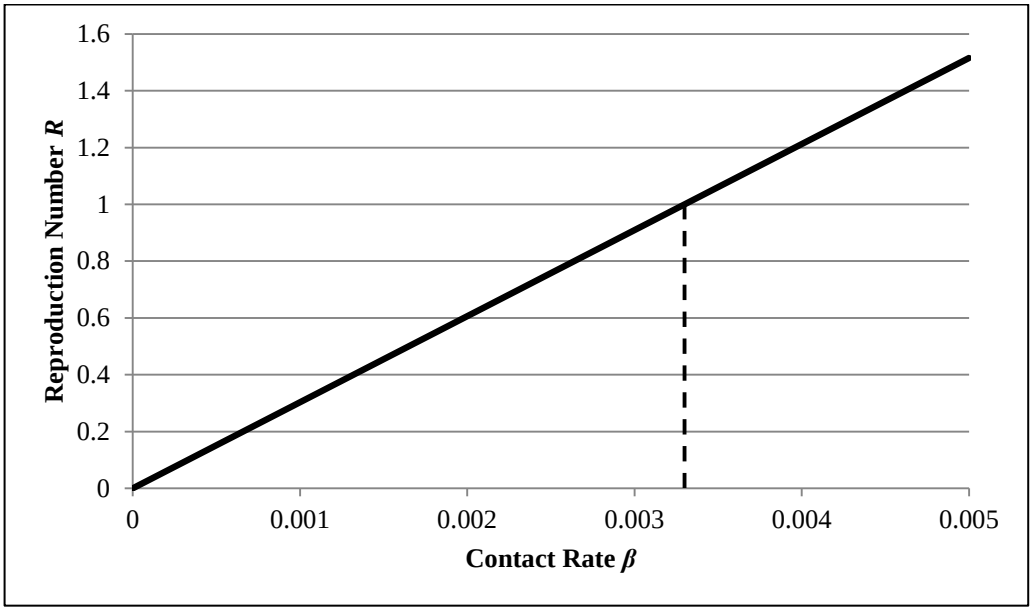

Figure 2.5: Contact rate β versus reproduction number R

If the contact rate β is reduced to a value of reproduction number R less than one, then the infection will be reduced to low level quickly, ultimately ending the epidemic. These behavioral measures are usually encouraged by public health authorities during the absent of pharmaceutical measures. In the 1918 influenza pandemic, there were no vaccines or antiviral drugs available, thus behavioral measures were the only option to decrease the infections (Arino et al., 2011). However, there are difficulties in implementing behavioral measures as individuals may be unwilling to stay at home from work during an epidemic outbreak. In

addition, closure of public facilities has economic and social costs, but school closures are more preferable to be implemented for decreasing contacts between children in order to reduce new infection in the wider community. Isolation of infective individuals and quarantine of individuals who are asymptomatic are measures that would decrease the new infections, but also have economic costs and may not be widely imposed nor accepted.

Vaccination is the second aspect of mitigation that can be implemented before or during an epidemic outbreak. It is difficult to develop a vaccine for a novel influenza such as H1N1 in 2009, resulting in impossible to implement pre-vaccination campaign. During the early stage of H1N1 outbreaks, no vaccine was available and it took nearly six months to develop one using egg-based technology (Arino et al., 2006). In SIR model, pre-vaccination campaign can be incorporated to reduce the number of susceptible individuals. This in turn decreases the basic reproduction number R_0. Figure 2.6 shows the relation between initial number of susceptible individual S_0 and R_0.

As observed in Figure 2.6, when a sufficient number of susceptible individual is vaccinated before an epidemic outbreak, the value of R_0 can be reduced to less than one, indicating the disease fails to evolve into an epidemic outbreak. Elder individuals might have some residual immunity because of previous exposure to a similar influenza that may reduce susceptibility, resulting in elder individuals may be less susceptible than others during an epidemic outbreak. When a specific vaccine is developed for a novel influenza strain, it is possibly in a limited number of doses and this causes difficulty in deciding which groups of the population should be