USING MODELING AND SIMULATION TO EVALUATE DISEASE CONTROL MEASURES

by

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ABSTRACT

This dissertation introduced several issues concerning the analysis of diseases by showing how modeling and simulation could be used to assist in creating health policy by estimating the effects of such policies.

The first question posed was how would education, vaccination and a combination of these two programs effect the possible outbreak of meningitis on a college campus. After creating a model representative of the transmission dynamics of meningitis and establishing parameter values characteristic of the University of Central Florida main campus, the results of a deterministic model were presented in several forms. The result of this model was the combination of education and vaccination would eliminate the possibility of an epidemic on our campus.

Next, we used simulation to evaluate how quarantine and treatment would affect an outbreak of influenza on the same population. A mathematical model was created specific to influenza on the UCF campus. Numerical results from this model were then presented in tabular and graphical form. The results comparing the simulations for quarantine and treatment show the best course of action would be to enact a quarantine policy on the campus thus reducing the maximum number of infected while increasing the time to reach this peak.

Finally, we addressed the issue of performing the analysis stochastically versus deterministically. Additional models were created with the progression of the disease occurring by chance. Statistical analysis was done on the mean of 100 stochastic simulation runs comparing that value to the one deterministic outcome. The results for this analysis were

inconclusive, as the results for meningitis were comparable while those for influenza appeared to be different.

To my wonderful family and my great friends.

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TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

CHAPTER ONE: INTRODUCTION

Introduction

We truly live in a small world. The ease of world travel makes everyone a neighbor. This interconnectedness has created a need to understand and be able to predict infectious diseases. Mathematical modeling has provided an economical means to comprehending the transmission dynamics of diseases as well as the ability to choose the most effective and economical interventions aimed at preventing and treating disease. In this dissertation we will attempt to answer policy questions using the simulation results from several mathematical models.

Research Problem Statement

The modeling of infectious diseases is a tool which has been used to study the means by which diseases spread, to forecast the future course of an outbreak and to evaluate strategies to control an epidemic (Daley and Gani, 2005) and even though mathematical models may not offer comprehensive descriptions of how to control diseases, they are elegant methods for evaluating the possible influence of different strategies offered in public health intervention programs (Moghadas, 2006). Due to the recent influenza A, H1N1 (Swine Flu) pandemic the use of such modeling to investigate interventions, both social and medical, has entered the spot-light. This dissertation will consider the effects of such disease control measures on a Meningococcal Disease (meningitis) outbreak on a college campus as well as a broader look at their effects on the current influenza pandemic in the same defined population in order to show the value of

using such data to help inform decision makers about clinical practices and health-care resource allocations (Weinstein et al., 2003).

Research Goal

The modeling of disease transmission behavior takes a practical approach to the area of modeling and simulation. This research will give a novel look into the basic science of epidemic modeling as well as present potentially valuable insight, for health policy makers, into disease intervention, particularly meningitis and the newest strain of influenza, H1N1. This dissertation will present a new model for meningitis which will be used to evaluate potential university policy. Combining this new model with influenza models from the literature, a representation of the new strain of influenza A (H1N1) will be created which will allow for evaluation of quarantine practices in an effort to assist in policy development.

Three main goals of this research have been identified. They are summarized as follows:

- Assess the potential results of a mandatory vaccination program versus a program aimed at educating individuals on behaviors consistent with reducing the risk of contracting the disease by creating a deterministic mathematical model with valid parameter values corresponding to meningitis on the main University of Central Florida (UCF) campus.
- Show that results obtained from a stochastic epidemic model are comparable to those of a deterministic model by creating stochastic mathematical models analogous to the deterministic meningitis and influenza models.

- Evaluate the potential results of quarantine and treatment on the spread of the disease by creating a deterministic mathematical model with valid parameter values corresponding to H1N1 on the main campus of UCF.

CHAPTER TWO: LITERATURE REVIEW

Mathematical Epidemiology

From the beginning of recorded history communicable diseases have drastically affected the course of development of our planet. The Bible talks about the plagues, such as that mentioned in the book of Numbers 16:46-49. "*46Then Moses said to Aaron, "Take your censer and put incense in it, along with fire from the altar, and hurry to the assembly to make atonement for them. Wrath has come out from the LORD; the plague has started." 47So Aaron did as Moses said, and ran into the midst of the assembly. The plague had already started among the people, but Aaron offered the incense and made atonement for them. 48He stood between the living and the dead, and the plague stopped. 49But 14,700 people died from the plague, in addition to those who had died because of Korah*." From 1346 to 1350 the Black Death (bubonic plague) is blamed for reducing the population of Europe by one third. Between 1519 and 1530 the Indian population of Mexico declined from thirty million to three million due to outbreaks of various diseases brought from Europe, such as smallpox, measles and diphtheria. During the time span of 1720 to 1722 the plague shrunk the population of some regions of France by as much as sixty percent (Brauer and Castillo-Chávez, 2001). These and other drastic reductions in population have perplexed scientists for many years.

The first scientist who systematically tried to quantify causes of death was John Graunt in his book *Natural and Political Observations made upon the Bills of Mortality*, in 1662. The bills he studied were listings of numbers and causes of deaths published weekly. Graunt's analysis of causes of death is considered the beginning of the "theory of competing risks" which

according to Daley and Gani (2005, p. 2) is "a theory that is now well established among modern epidemiologists". The theory of competing risks looks at events which remove an individual from being at risk for the outcome under investigation (Last, 2001).

The earliest account of the mathematical modeling of the spread of a disease was carried out in 1766 by Daniel Bernoulli. Trained as a physician, Bernoulli created a mathematical model to defend the practice of inoculating against smallpox (Hethcote, 2000). The calculations from this model showed that universal inoculation against smallpox would increase the life expectancy from 26 years 7 months to 29 years 9 months (Bernoulli and Blower, 2004).

Following Bernoulli, other physicians contributed to modern mathematical epidemiology. Among the most acclaimed of these were A. G. McKendrick and W. O. Kermack, whose paper *A contribution to the Mathematical Theory of Epidemics* was published in 1927. A simple deterministic (compartmental) model was formulated in this paper and was successful in predicting the behavior of an epidemic very similar to that observed in many recorded epidemics (Brauer and Castillo-Chávez, 2001).

In the years since, mathematicians, biologists, physicians, epidemiologists, and others have contributed to the maturing discipline of mathematical epidemiology. Several books have played a significant role in the development of theory. In 1975, Bailey published a book on the mathematical theory of infectious diseases followed in 1991 by *Infectious Diseases of Humans Dynamics and Control* by Anderson and May, *Epidemic Modeling* (1999) by Daley and Gani, *Mathematical Epidemiology of Infectious Diseases Model Building, Analysis and Interpretation* (2000) by Diekmann and Heesterbeek and *Mathematical Models in Population Biology and Epidemiology* (2001) by Brauer and Castillo-Chávez.

Variations to the Susceptible-Infectious-Recovered (SIR) model have been used to analyze and evaluate diseases; from adding demographics to spatial-temporal models to insights into past epidemics. Most importantly for this work, however, is using a mathematical model to outline prospective behavioral and biomedical interventions and their potential impact on a disease.

Meningococcal Disease Control Measures and Modeling

A review of the published literature covering the topic of mathematical modeling of meningococcal disease (meningitis) turned up very few results. The first research found used a system of equations solved simultaneously to estimate the weekly attack rates of both the vaccinated and non-vaccinated populations during an epidemic in Nairobi Kenya in 1989 (Pinner et al., 1992). In 1999, Coen, Cartwright and Stuart utilized deterministic compartmental models to fit age-structured data to test theories on the methods that determine the transmission of meningitis. Another age-structured model was created by Martcheva and Crispino-O'connell (2003), again to better understand the transmission dynamics of the meningococcal infection. Next, the progression of a system towards criticality was studied using an epidemiological model for meningitis by Stollenwerk and Jansen (2003).

Until now the mathematical modeling of Meningococcal Disease on college campuses has been nonexistent but studies on the risk factors contributing to the transmission of the disease and the analysis of prevention programs in that environment are prolific. It has been shown that college students (particularly first year students living in residence halls) are at increased risk of developing meningitis (Bruce et al., 2001; Froeschle, 1999; Harrison et al., 1999). Further studies show that certain lifestyle choices contribute to this increased risk; activities such as bar

patronage, binge drinking, cigarette smoking and cigarette sharing are such behaviors typical of much of the college population (Imrey et al., 1996; Stanwell-Smith et al., 1994). Health professionals from over 25 states have acknowledged these risks and passed varying types of legislation concerning the vaccination against meningitis or requiring universities to enact education programs designed to alert students and their parents to these increased risks (Castel, Reed, Davenport, Harrison & Blythe, 2007). The cost of these measures has been examined. Jackson, Schuchat, Gorsky and Wenger (1995) determined the cost for purchase and administration of the vaccine to be $56 million per year and suggest more "cost-effective" prevention strategies. Another study performed by Scott, Meltzer, Erickson, De Wals, and Rosenstein (2002) produced similar results, showing that a vaccination program was not cost-saving.

Influenza Control Measure Modeling

The transmission dynamics of influenza (flu) have been examined using mathematical models. Such models have been used as tools to create healthcare policies and to forecast the effects on the disease resulting from behavioral and biomedical interventions.

Social distancing is one approach utilized to lessen the number of cases of a disease. Sattenspiel and Herring (2003) used a compartmental model and data from the 1918-19 central Canadian flu to simulate the geographic spread of influenza and address the prospective effectiveness of human quarantine. In 2007, a stochastic, equation-based model was developed by Epstein, Geodecke, Yu, Morris, Wagener and Bobashev to study global transmission of pandemic flu. Their simulation included the effects of travel restriction on the global spread of a pandemic. The effect of school closures has also been modeled; Cauchemez, Valleron, Boëlle,

Flahault and Ferguson (2008) used surveillance data from France to assess the role of schools in epidemics and to predict the effect of their closure during a pandemic.

Inoculating against the flu and treating individuals with antiviral agents are additional interventions studied using modeling and simulation. Longini, Halloran, Nizam and Yang (2004) used stochastic epidemic simulations to compare targeted antiviral prophylaxis with vaccination strategies. Arino, Brauer, van den Driessche, Watmough and Wu (2006, 2008) use the parameters developed by Longini et al. (2004) to examine the results antiviral treatment and/or vaccination would have on a developing pandemic using a compartmental model. Thus, showing the benefits of this simpler model which allows for sensitivity analysis in the case of mixed strategies. In 2005, Ferguson et al. modeled influenza transmission in Southeast Asia to investigate potential results of targeted mass prophylactic use of antiviral drugs as a control strategy. A model which incorporated both an individual's response to vaccination at different doses and the process of person-to-person transmission of pandemic influenza was created by Riley, Wu and Leung (2007) with the goal of optimizing the dose of vaccines in order to reduce the infection rate. Medlock and Galvani (2009) created a deterministic model which they used to evaluate the optimum vaccine distribution based on five outcome measures: deaths, infections, years of life lost, contingent valuation and economic costs. Their results indicated that consideration of the age-specific transmission dynamics is vital when calculating the most advantageous allocation for the influenza vaccine.

Finally, the idea of multiple interventions has also been simulated using mathematical models. Longini et al. (2005) utilized a stochastic simulation of Southeast Asia to evaluate the effectiveness of targeted antiviral prophylaxis, quarantine, and pre-vaccination to control the

pandemic at the source. The following year (2006), Ferguson et al. studied the same strategies and added school and workplace closure and restrictions on travel in attempts to mitigate a flu pandemic. Most recently (2008), Halloran et al. looked at a combination of interventions called targeted layered containment (TLC) on an influenza pandemic in the United States.

Influenza A (H1N1) Modeling

While modeling of the disease known as influenza has been going on for some time, the first case of influenza A (H1N1) was reported in Mexico in mid-April of 2009, allowing scientists less than one year, not to mention limited data, to study the transmission dynamics of this new virus. The first study done on the disease was performed by Boëlle, Bernillon and Desenclos (May, 2009); the main focus of their work being the preliminary estimation of the basic reproduction ratio ($\mathcal{R}_0$); which can be defined as the number of secondary infections caused by a single infective introduced into a population made up entirely of susceptible individuals over the course of the infection of this single infective. Using the methods of intrinsic growth rate and real time estimation they assessed the reproduction ratio to be a number less than 2.2 days to a generation interval (the period between the infection time of an infected individual and the infection time of his or her infector [Kenah, Lipsitch & Robins, 2008]) of 3.1 days and concluded that the estimates were decidedly dependent on the assumptions made concerning the generation interval.

June of 2009 brought the second study of the new strain of influenza. This study performed by Fraser et al. used several epidemiological analyses leading to an estimation of the basic reproduction ratio ($\mathcal{R}_0$) in the range of 1.4 to 1.6, and concluded that this range of values is

consistent with the fourteen to seventy-three instances of human-to-human transmission reported in Mexico to late April. Implementing a stochastic SEIR model, Flahault, Vergu and Boëlle (August, 2009) used several values of the reproduction ratio and generation interval to model the potential spread of the disease across a network of 52 cities, while also attempting to predict the effect of vaccination. The results of their simulation showed an attack rate (cumulative incidence of infection in a population over a specific time interval [Last, 2001]) of influenza A (H1N1) of 46% (considering an entirely susceptible population) with a reproduction ratio of 1.5 and a generation interval of 2 days. Higher $\mathcal{R}_0$ values (2.2) and generation intervals (3.1 days) resulted in an attack rate of 77%. They then concluded that a mass vaccination program of a disease with a basic reproduction ratio of 1.5, resulting in 50% of the population being vaccinated, begun 6 months after the start of the pandemic could possibly reduce the total number of cases by 91%, while resulting in a reduction of approximately 44% for a virus with $\mathcal{R}_0 = 2.2$.

Boni et al. (September, 2009) developed an age- and spatially-specific mathematical model to simulate the progression of H1N1 in Vietnam. Their research also considered the opportunities for reassortment with other influenza viruses, a concern in this region where much of the world's poultry population lives and where avian influenza (H5N1) is still prevalent. Later that month, (September, 2009) a study was done using a global structured metapopulation model which incorporated worldwide mobility and transportation data. Balcan et al. created stochastic realizations of the developing epidemic worldwide generating from this data prevalence, morbidity, number of secondary cases and number and date of imported cases for each subpopulation. Vaccination campaigns were modeled in November, 2009 by Vespignani et

al. These researchers used a structured global epidemic and mobility metapopulation model to explore the efficiency of vast vaccination programs for the fall and winter of 2009. Their results showed that additional interventions would be necessary to considerably reduce the cumulative number of cases and that prioritized vaccination would be vital in slowing the advancement of the pandemic. Using the data from 216 households, Cauchemez et al. (December 2009) evaluated the transmission of the influenza A (H1N1) virus in the United States. The results of their analyses showed the transmissibility of the H1N1 virus in households is lower than that calculated for historical pandemics and also provided new information on how susceptibility to infection differs with age.

Deterministic vs. Stochastic Models

A deterministic model is one that given the same initial conditions, the same results are always observed. Stochastic models, on the other hand, include an element of randomness indicative of the real world. An example of this is the extinction behavior which is seen in stochastic models that is not represented in deterministic ones (Allen & Burgin, 2000). According to Fred Brauer and Carlos Castillo-Chávez, in their book *Mathematical Models in Population Biology and Epidemiology* (2000), a deterministic model offers a functional means of obtaining adequate knowledge of the dynamics of a population when the population is sufficiently large. Arino et al. (2006) advocate the use of deterministic models in the preparation for an outbreak of a disease whose parameters are unknown. Their development and subsequential analysis of a compartmental model for influenza proved comparable to the stochastic models presented by Longini et al. (2004) and Ferguson et al. (2005). For small populations, a stochastic model may be more appropriate. In this case the stochastic model,

which is concerned with mimicking the random or probabilistic event, would be more suitable (Keeling & Rohani, 2008). Allen and Burgin (2000) conducted a study in which they compared the dynamics of deterministic and stochastic *SIS* and *SIR* epidemic models. The main finding in this analysis was the ultimate disease extinction with the stochastic model regardless of the value for the basic reproduction ratio ($\mathcal{R}_0$). However, in the case of a very long time period to extinction, they concluded that there exists a quasi-stationary probability distribution whose mean agrees with the deterministic endemic equilibrium (when $\mathcal{R}_0 > 1$).

In 2009, Fierro conducted a study designed to show similarities between stochastic and deterministic model results. In this paper he showed results for the stochastic model to be quite different from its deterministic counterpart for small populations (i.e. 10 individuals). However, for large populations (i.e. 1000 individuals) the results were quite close.

The intent of this section is to show the validity of the deterministic model used for our population of 50,000 UCF students.

CHAPTER THREE: RESEARCH METHODOLOGY

Meningitis Base Model

This model began with the compartmental model developed for meningitis by Stollenwerk and Jansen (2003). Their model, however, did not account for the findings of Caugant, et al. (1994), i.e. the infection of meningitis can result in two possibilities: those infected who show symptoms and those who do not show symptoms. Due to this characteristic of the disease, the model was modified by the inclusion of a non-symptomatic compartment to become an SI_SI_NR model. As in the *SIR* model, the population (whose size we represent with the variable *N*) is partitioned into the classes susceptible $S(t)$, infected showing symptoms $I_S(t)$, infected asymptomatic $I_N(t)$, and removed $R(t)$, where $S + I_S + I_N + R = N$.

Table 1: Description of the SI_SI_NR Variables

Variables at Population Level	Description
$S(t)$	Susceptible Individuals at time t
$I_S(t)$	Infected Individuals (With Symptoms) at time t
$I_N(t)$	Infected Individuals (Without Symptoms) at time t
$R(t)$	Removed Individuals at time t

Individuals in the susceptible compartment are subjected to an infected host with a contact rate of β. Those contracting the disease enter the infected classes at a rate of p into the symptomatic class, or $(1 - p)$ entering the asymptomatic class. Individuals with the symptomatic form of the disease can recover from the infection and enter the removed compartment at a rate of γ (the mean recovery rate for meningitis) or die from the disease with a rate of μ (the death rate due to

the disease). Those within the asymptomatic compartment exit into the removed category at the rate of γ. Individuals enter the removed category resistant to the disease for a period of time, α, then become susceptible again. The following system of ordinary differential equations (ODEs) is used to represent this model:

$$\frac{dS}{dt} = -\beta S(I_S + I_N) \tag{1}$$

$$\frac{dI_S}{dt} = p\beta S(I_S + I_N) - I_S(\mu + \gamma) \tag{2}$$

$$\frac{dI_N}{dt} = (1-p)\beta S(I_S + I_N) - \gamma I_N \tag{3}$$

$$\frac{dR}{dt} = \gamma(I_S + I_N) \tag{4}$$

These ODEs give continuous average rates for each of the population compartments, susceptible, infected – symptomatic, infected – asymptomatic, and removed. A summary of the notation can be seen in Table 2.

Table 2: Meningitis Summary of Notation

Symbol	Meaning	Value
β	Contact Rate	varies with scenario
γ	Average Recovery Rate	0.1
μ	Average Death Rate due to Meningitis	5% - 15%

The SI_SI_NR system parameters were determined using several methods. These methods require the formulation of several assumptions. Firstly, since the simulation is to take place on the UCF main campus, the host population is taken to be constant, i.e. no births (incoming students) or deaths due to causes other than meningitis were considered. Secondly, the model considers

homogeneous mixing of the campus population resulting in all individuals having an equal opportunity to contract the disease. Finally, this representation of meningitis assumes a recovery from the asymptomatic disease with no lasting immunity. The flow diagram for this model can be seen in Figure 1.

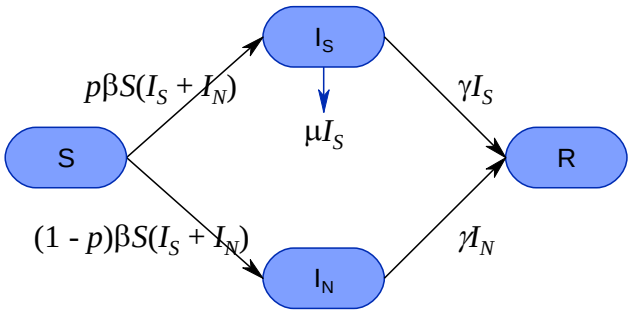

Figure 1: Flow Diagram for Meningitis

Contact rate, β, was determined for the specified campus area using the equation (5) derived by Rhodes and Anderson (2008).

$$\beta = \frac{8Rq\bar{v}\rho}{\pi} \tag{5}$$

This formula considers a moving population where the transmission rate of the disease is a factor of the density of the individuals within the specified area. Here ρ is $\frac{N}{A}$; where A is the area in which the population is constrained and N is the previously defined total population size. The value used here is the area of UCF's main campus, 1,415 acres (5.726 km^2). The parameter R is the radius within which an infected individual must encounter a susceptible person in order to transmit the disease. One centimeter was used as the value for this parameter. This distance was assumed, as transmission of meningitis is a result of touching or sharing very close spaces. In accordance with the U. S. Department of Transportation (DOT), 4 ft/sec (4.39 km/hr) was

utilized as the population average speed, $\bar{v}$ (DOT, 2003). The value for the probability of an infective transmitting the infection, *q*, was changed within each scenario to be considered, allowing the creation of different levels of meningitis education within the population.

Table 1 also lists other parameter values specific to meningitis found through our research, they include:

- Death rate due to the disease (μ = 5 to 15%) was found in the article by Paneth, et al. (2000).
- Proportion of infectives developing the symptomatic form of meningitis (p = 11%) was derived by Caugant, et al. (1994).

Meningitis Alternative Models

Three different alternative scenarios were considered in an effort to relate education and vaccination rates to a potential outbreak of meningitis in this defined population of a college campus. These scenarios are presented in Table 3. (See Appendix E for calculation of parameters.)

Table 3: Meningitis Parameter Values

Parameter	Variable	Base Model	Education	Vaccination	Education & Vaccination
Probability of Transmitting Infection	q	0.1	0.05	0.1	0.05
Number Vaccinated	v_0	0	10%	51%	61%
Calculated Contact Rate	β	2.34	1.05	1.15	0.46
Basic Reproduction Ratio	$\mathcal{R}_0$	7.8	3.5	3.8	1.5

Three assumptions were made in the formulation of these alternate scenarios. First, a program including education would reduce the probability of transmitting an infection by half through increasing the awareness of students with respect to the sharing of personal items and improved hygiene. This educational program, while not requiring vaccination, would however, increase the rate of vaccination within the student population by 10% due to an increased awareness of the risks associated with contracting meningitis. Secondly, due to the fact that the actual statistics for vaccinations at UCF were not available, the student vaccination rates determined by Paneth et al. (2000) were used. Paneth and his colleagues (2002) determined that a vaccination program similar to that already in place at UCF would result in 51% of the student population under the age of 30 being inoculated for the disease. Finally, that an educational awareness program coupled with a vaccination program would boost vaccination rates to equal 61% for use in this alternative model.

Influenza A (H1N1) Base Model

While the SIR model takes into account only those diseases which cause an individual to be able to infect susceptibles upon encounter, many diseases have what is termed a *latent* or *exposed* phase, during which the individual is said to be *infected* but not *infectious*. Influenza is one such disease. Because of this aspect of its epidemiology the model used above needed to be adapted to include a compartment for these exposed individuals. The basic *SEIR* epidemic model created by Arino, Brauer, van den Driessche, Watmough and Wu (2006) was modified to include deaths from the symptomatic infectious compartment due to the disease. An SEI_SI_NR model is used here; the following ODEs represent this model:

$$\frac{dS}{dt} = -S\beta(I_S + \delta I_N) \tag{6}$$

$$\frac{dE}{dt} = S\beta(I_S + \delta I_N) - \kappa E \tag{7}$$

$$\frac{dI_S}{dt} = p\kappa E - \gamma I_S - \mu I_S \tag{8}$$

$$\frac{dI_N}{dt} = (1-p)\kappa E - \eta I_N \tag{9}$$

$$\frac{dR}{dt} = \gamma I_S + \eta I_N \tag{10}$$

As in the meningitis model, individuals in the susceptible compartment are subjected to an infected host with a contact rate of β. Once infected with the disease, they then enter the exposed phase where the virus multiplies for a period of time equal to κ, it is important to note here that for this model we do not consider the mutation of the pathogens. From the exposed compartment a portion, p, of individuals enter the infected with symptoms (I_S) phase while the remainder, $(1 - p)$, of the individuals develop the asymptomatic form of the disease and enter the infected without symptoms (I_N) phase. Recovery from the infected with symptoms (I_S) phase is achieved at a rate of γ, at which time the individual enters the removed (R) stage. Another possibility is for the individual to die from the influenza. This results in a decrease from the I_S compartment by a rate of μ. One recovers from the I_N stage of the disease at a rate of η and subsequently enters the removed (R) stage.

Table 4: Description of the SEI_SI_NR Variables

Variables at Population Level	Description
$S(t)$	Susceptible Individuals at time t
$E(t)$	Exposed Individuals at time t
$I_S(t)$	Infected Individuals (With Symptoms) at time t
$I_N(t)$	Infected Individuals (Without Symptoms) at time t
$R(t)$	Removed Individuals at time t

Again, in this model the total population size (N) is equal to the sum of these compartments: $N = S + E + I_S + I_N + R$. The flow diagram for this model can be seen in Figure 2.

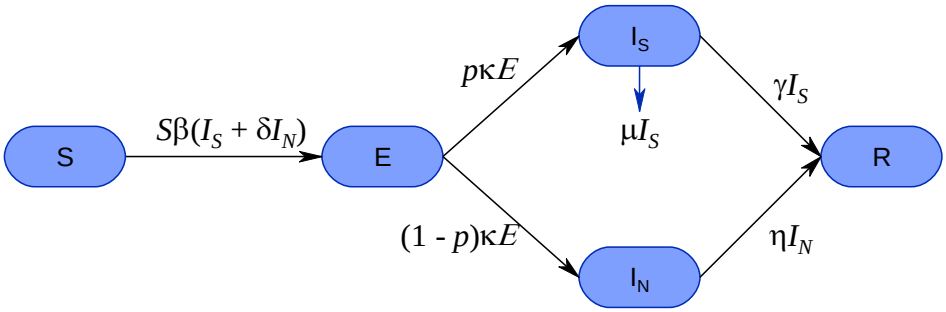

Figure 2: Flow Diagram for Influenza

The contact rate, β, was determined for the specified campus area using equation (5) derived by Rhodes and Anderson (2008). Since the study requires the demographics specific to UCF, the contact rate is kept consistent with that calculated for meningitis. An explanation of the parameters and the values used for H1N1 can be seen in Table 5.

Table 5: Influenza Parameter Summary

Symbol	Meaning	Value
$\mathcal{R}_0$	Basic Reproduction Ratio	4.04[a]
β	Contact Rate	2.343[a]
δ	Factor by which I_N have Reduced Infectivity	0.5[b]
κ	Latency Period	0.526[c]
p	Fraction of Exposed that Proceed to I_S	0.67[b]
γ	Average Recovery Rate	0.244[b]
η	Rate at which I_N Proceed to R	0.244[b]
μ	Average Death Rate due to Influenza A (H1N1)	0.0002[d]

[a] Calculated for the purpose of this study
[b] Longini, Halloran, Nizam, Yang (2004)
[c] Fraser et al. (2009)
[d] Centers for Disease Control and Prevention (2010)

Here, the basic reproduction ratio ($\mathcal{R}_0$) was calculated using the formula from Brauer and Castillo-Chávez (2001):

$$\mathcal{R}_0 = \frac{\beta}{\gamma + \mu + \eta} \tag{11}$$

See Appendix E for the calculation of the parameters.

Influenza A (H1N1) Quarantine Model

The first alternative model considered for the influenza A (H1N1) virus was one including a period of quarantine. The basic reproduction ratio, $\mathcal{R}_0$, quantifies the transmission potential of a disease. If the basic reproduction ratio falls below one ($\mathcal{R}_0 < 1$), i.e. the infective may not pass the infection on during the infectious period, the infection dies out. If the basic

reproduction ratio is greater than 1, $\mathcal{R}_0 > 1$, there is an epidemic in the population. In cases where $\mathcal{R}_0 = 1$, the disease becomes endemic, meaning the disease remains in the population at a consistent rate, as one infected individual transmits the disease to one susceptible (Trottier & Philippe, 2001). The idea of quarantine is to reduce the number of contacts of an infective individual therefore reducing the basic reproduction number below one, effectively negating the opportunity for an epidemic. To represent this removal of infectives an additional compartment (Q) was added to our base influenza model.

Table 6: Description of the SEI_SI_NQR Variables

Variables at Population Level	Description
$S(t)$	Susceptible Individuals at time t
$E(t)$	Exposed Individuals at time t
$I_S(t)$	Infected Individuals (With Symptoms) at time t
$I_N(t)$	Infected Individuals (Without Symptoms) at time t
$Q(t)$	Quarantined Individuals at time t
$R(t)$	Removed Individuals at time t

The flow diagram for this model can be seen in Figure 3.

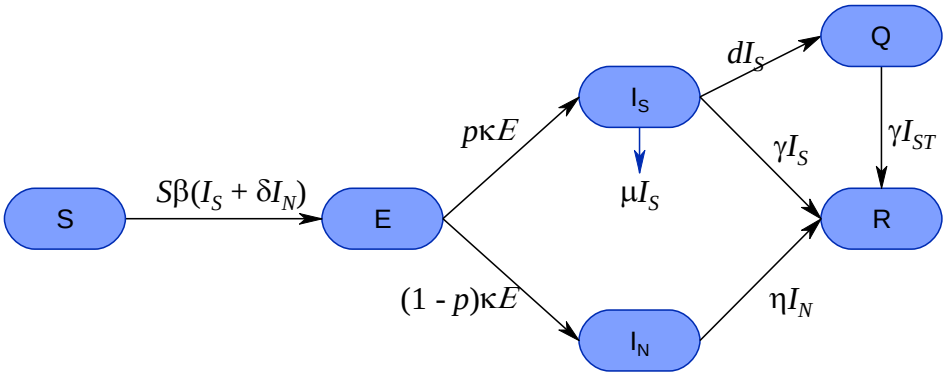

Figure 3: Flow Diagram for Influenza with Quarantine

In this modified model, infectives are removed from interacting with the population at a rate of d and placed into the quarantined (Q) compartment. They remain there for a period of τ (equivalent to the recovery period, γ) when they enter the removed (R) compartment. The model consists of a system of six ordinary differential equations:

$$\frac{dS}{dt} = -S\beta(I_S + \delta I_N) \tag{12}$$

$$\frac{dE}{dt} = S\beta(I_S + \delta I_N) - \kappa E \tag{13}$$

$$\frac{dI_S}{dt} = p\kappa E - \gamma I_S - dI_S - \mu I_S \tag{14}$$

$$\frac{dI_N}{dt} = (1-p)\kappa E - \eta I_N \tag{15}$$

$$\frac{dQ}{dt} = dI_S - \tau Q \tag{16}$$

$$\frac{dR}{dt} = \gamma I_S + \tau Q + \eta I_N \tag{17}$$

The parameter values for this model are consistent with the base influenza A (H1N1) model, with the inclusion of the time spent in isolation, τ. These can be seen in Table 7.

Table 7: Influenza Quarantine Parameters

Symbol	Meaning	Value
$\mathcal{R}_0$	Basic Reproduction Ratio	varies with scenario
β	Contact Rate	2.343[a]
δ	Factor by which I_N have Reduced Infectivity	0.5[b]
κ	Latency Period	0.526[c]
p	Fraction of Exposed that Proceed to I_S	0.67[b]
γ	Average Recovery Rate	0.244[b]
η	Rate at which I_N Proceed to R	0.244[b]
μ	Average Death Rate due to Influenza A (H1N1)	0.0002[d]
d	Rate at which Infected Individuals are Detected and Removed to Quarantine	varies with scenario
τ	Average Time Spent in Isolation	0.244

[a] Calculated for the purpose of this study (Appendix E)
[b] Longini, Halloran, Nizam, Yang (2004)
[c] Fraser et al. (2009)
[d] Centers for Disease Control and Prevention (2010)

For this model the rate at which the infected individuals are removed from the college populace is varied in order to determine the consequences of allowing the infected to remain longer in the population. It can easily be seen that if we set $d = 0$, the resulting model is that defined as the base influenza model. Here we have decided to remove individuals only after symptoms present themselves and we do not preemptively remove their contacts.

Influenza A (H1N1) Treatment Model

Another option for containing an influenza pandemic would be antiviral treatment. The second alternative influenza model we consider is that of treating the symptomatic cases of the disease. Influenza antiviral agents can be used to thwart the illness in the event of exposure,

diminish the symptoms given infection and to reduce the chance of transmitting the virus to others in the case of infection (Longini et al., 2004). Our treatment model will look at the impact antiviral treatment would have on the total number of influenza cases given varying rates of treatment. Treatment can be applied before an epidemic or during by targeting diagnosed infectives and/or exposed individuals of the populations identified by contract tracing during an epidemic. Our model considers treating only those diagnosed cases of the disease. Table 8 shows a description of the variables for this model.

Table 8: Description of the $SEI_SI_{ST}I_NR$ Variables

Variables at Population Level	Description
$S(t)$	Susceptible Individuals at time t
$E(t)$	Exposed Individuals at time t
$I_S(t)$	Infected Individuals (With Symptoms) at time t
$I_{ST}(t)$	Treated Infected Individuals at time t
$I_N(t)$	Infected Individuals (Without Symptoms) at time t
$R(t)$	Removed Individuals at time t

To represent the treated individuals we added an additional compartment, I_{ST}, to our base influenza model. The flow diagram of this model is very similar to that of the quarantine model and can be seen in Figure 4.

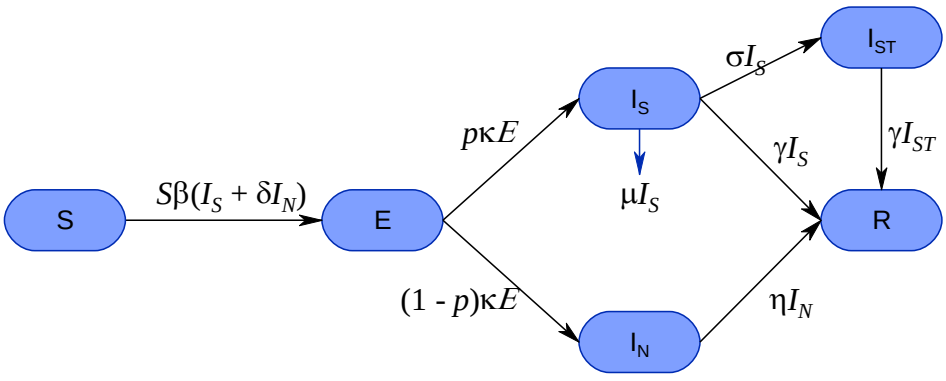

Figure 4: Flow Diagram for Influenza with Treatment

In this model we have symptomatic infected individuals being treated at a rate of σ, with a reduced infectivity of φ. The ODE's for this model are mentioned below:

$$\frac{dS}{dt} = -S\beta(I_S + \delta I_N + \phi I_{ST}) \tag{18}$$

$$\frac{dE}{dt} = S\beta(I_S + \delta I_N + \phi I_{ST}) - \kappa E \tag{19}$$

$$\frac{dI_S}{dt} = p\kappa E - \sigma I_S - \gamma I_S - \mu I_S \tag{20}$$

$$\frac{dI_{ST}}{dt} = \sigma I_S - \theta I_{ST} \tag{21}$$

$$\frac{dI_N}{dt} = (1-p)\kappa E - \eta I_N \tag{22}$$

$$\frac{dR}{dt} = \gamma I_S + \eta I_N + \theta I_{ST} \tag{23}$$

As can be seen from the flow diagram and the defining ordinary differential equations, additional parameters need to be defined. For this model we also make the assumption that an antiviral agent will lessen the length of the infectious period by one day (Longini et al., 2004). Table 9 shows the meanings and values for these parameters.

Table 9: Influenza Treatment Parameters

Symbol	Meaning	Value
β	Contact Rate	2.343[a]
δ	Factor by which I_N have Reduced Infectivity	0.5[b]
κ	Latency Period	0.526[c]
p	Fraction of Exposed that Proceed to I_S	0.67[b]
γ	Average Recovery Rate	0.244[b]
η	Rate at which I_N Proceed to R	0.244[b]
θ	Rate at which I_{ST} Proceed to R	0.323[b]
μ	Average Death Rate due to Influenza A (H1N1)	0.0002[d]
σ	Rate at which Treatment is Administered	varies with scenario
ϕ	Reduced Infectivity of Treated Individuals	0.8[b]

[a] Calculated for the purpose of this study (Appendix E)
[b] Longini, Halloran, Nizam, Yang (2004)
[c] Fraser et al. (2009)
[d] Centers for Disease Control and Prevention (2010)

Mathematical Methods

The solutions to the mathematical models were obtained with the help of the computer program MATLAB. To obtain the numerical solutions, the ordinary differential equations for this study were programmed into MATLAB and solved using the ODE45 solver. This solver is an explicit one-step Runge Kutta medium order (4^{th} to 5^{th}-order) solver (Hanselman & Littlefield, 2005).

CHAPTER FOUR: MENINGITIS RESULTS

Deterministic Meningitis Model

A summary of the maximum number of infected individuals and the number of days to reach that level can be seen in Table 10. These numbers reflect the results of the simulation of the base model and the three alternative SI_SI_NR models. (The MATLAB code for the SI_SI_NR model for meningitis can be found in Appendix A.)

Table 10: Numerical Meningitis Simulation Results (Deterministic)

	Base Model	**Education**	**Vaccination**	**Education & Vaccination**
Number Infected	3438	1803	540	1
Number of Days	6	16	30	Initial Condition

It is important to note that these values assume that from the onset of the disease, no action is taken to prevent further cases of the disease. In other words, mitigating actions (such as closing the campus or inoculations) by health officials do not occur. In the base model there are less than six days to recognize that an outbreak is occurring and take appropriate measures before more than 3,400 people are infected. Figure 5 graphically presents the results of the simulations.

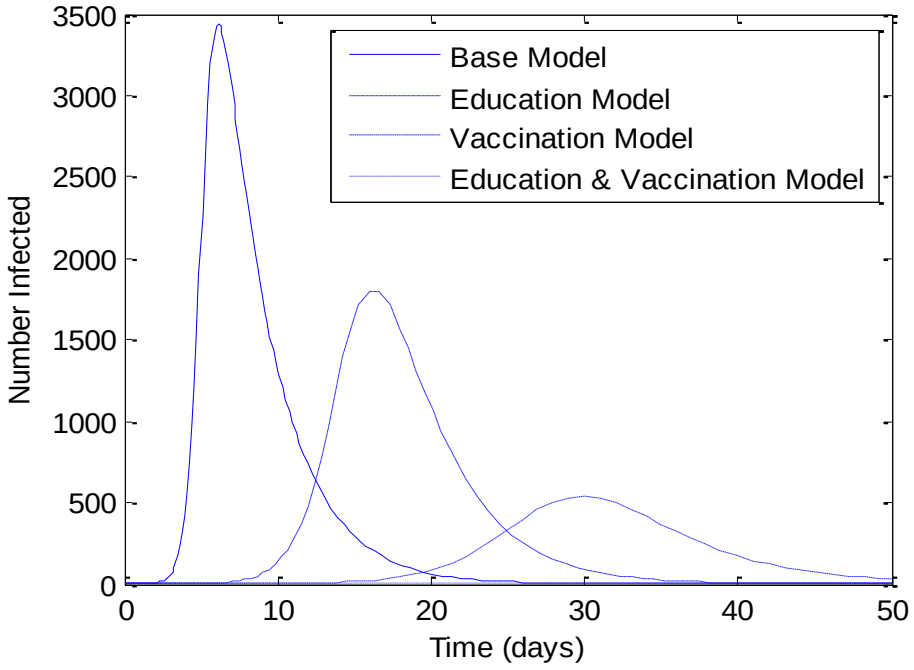

Figure 5: Graphical Meningitis Simulation Results (Deterministic) Base Model vs. Education, Vaccination and Both

Table 11 presents the effects of the three alternative designs from the baseline established by the base model. These effects are presented by decreases in the number of infected individuals and the increased amount of time available before this maximum occurs. Examination of the table reveals that the combination of the education and vaccination programs mitigates the chance of an outbreak.

Table 11: Effect of Meningitis Programs

	Education	**Vaccination**	**Education & Vaccination**
Effect on Number Infected	-1635 (47% less)	-2898 (84% less)	-3438 (100% less)
Effect on Time to Maximum	+10 days	+14 days	N/A

Stochastic Meningitis Model

The intent of this section is to show the deterministic model used is suitable for our population of 50,000 UCF students. Here the model presented in the previous section is modified with the inclusion of demographic stochasticity and the results of this stochastic model compared to those presented previously for the deterministic model. Demographic stochasticity is defined by Keeling and Rohani (p. 201, 2008) as "fluctuations in population processes that arise from the random nature of events at the level of the individual". In this instance, though the probability of each event is fixed, individuals undergo differing outcomes due to chance. For the SI_SI_NR model considered here we needed to consider five events that can occur, each causing the numbers in the relative classes to increase or decrease by one:

- Transmission occurs at rate $\beta Sp(I_S+I_N)/N$. Result $S \rightarrow S - 1$ and $I_S \rightarrow I_S + 1$.
- Transmission occurs at rate $\beta S(1-p)(I_S+I_N)/N$. Result $S \rightarrow S - 1$ and $I_N \rightarrow I_N + 1$.
- Recovery occurs at rate γI_S. Result $I_S \rightarrow I_S - 1$ and $R \rightarrow R + 1$.
- Death occurs at rate μI_S. Result $I_S \rightarrow I_S - 1$.
- Recovery occurs at rate γI_N. Result $I_N \rightarrow I_N - 1$ and $R \rightarrow R + 1$.

This program was implemented using Gillespie's Direct Method (Gillespie, 1977). (Matlab code for this model can be found in Appendix B.) A comparison of the graphical results from one run of the stochastic model against the deterministic results can be seen in Figure 6, showing the two types of simulations to be very similar in nature.

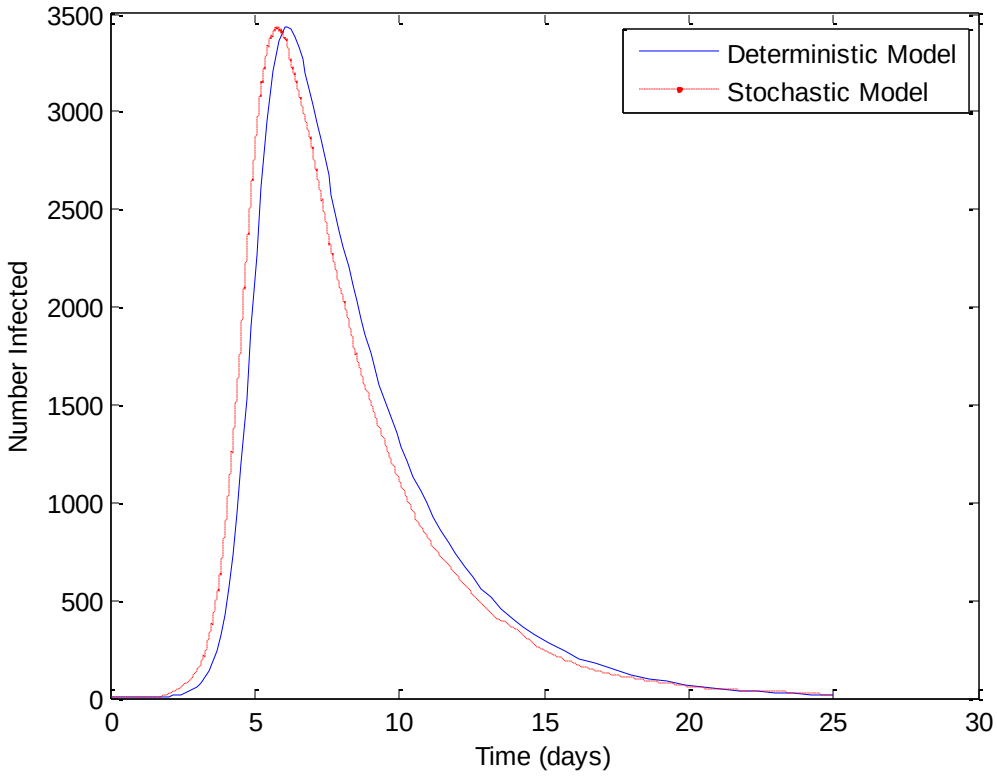

Figure 6: Graphical Meningitis Results of Stochastic vs. Deterministic Simulations

Further statistical analysis was done on a set of 100 stochastic simulation runs. The maximum infected and the time to that peak for each of these runs and the deterministic result can be seen in Figure 7.

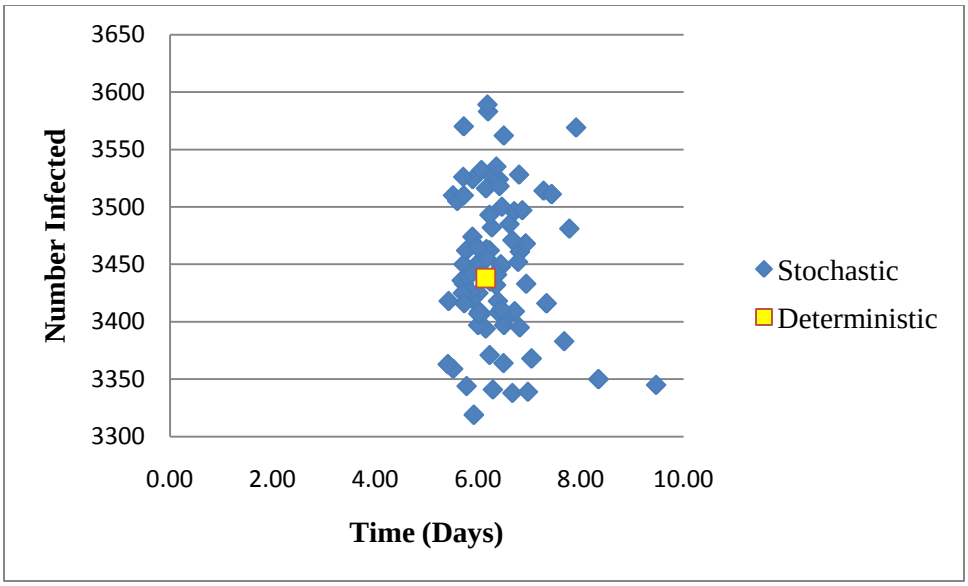

Figure 7: Scatter Plot of 100 Stochastic Meningitis Results vs. Deterministic Meningitis Result

The descriptive statistics (calculated in Excel) for the 100 stochastic runs can be seen in Table 12.

Table 12: Stochastic Meningitis Statistics

Mean	3445.82
Standard Deviation	61.78774028
Sample Variance	3817.724848
Count	100

Next, a large-sample test was performed on the data to test the following null and alternative hypotheses:

H_0: $\mu = 3438$

H_a: $\mu \neq 3438$

The test statistic, t, was calculated to be 1.29 which falls within the acceptance region for $\alpha = 0.05$. Therefore, we do not have enough evidence to reject the null hypothesis and can assume

that the two means are the same. Showing that for our large population of 50,000 students, the deterministic simulation is acceptable.

CHAPTER FIVE: INFLUENZA A (H1N1) RESULTS

Base vs. Quarantine Model

Figure 8 gives the graphical baseline results (with no intervention) and the quarantine results with quarantine time ranging from ten days to one day. These simulation results show the practice of quarantining infected individuals to be quite effective on the peak number infected at the university as well as the time to that peak, with our lowest number of infected being less than 2000 if individuals are identified and isolated within one day of showing symptoms and becoming infectious. Without knowledge of the model itself, policy makers would be able to glance at the results and make a decision.

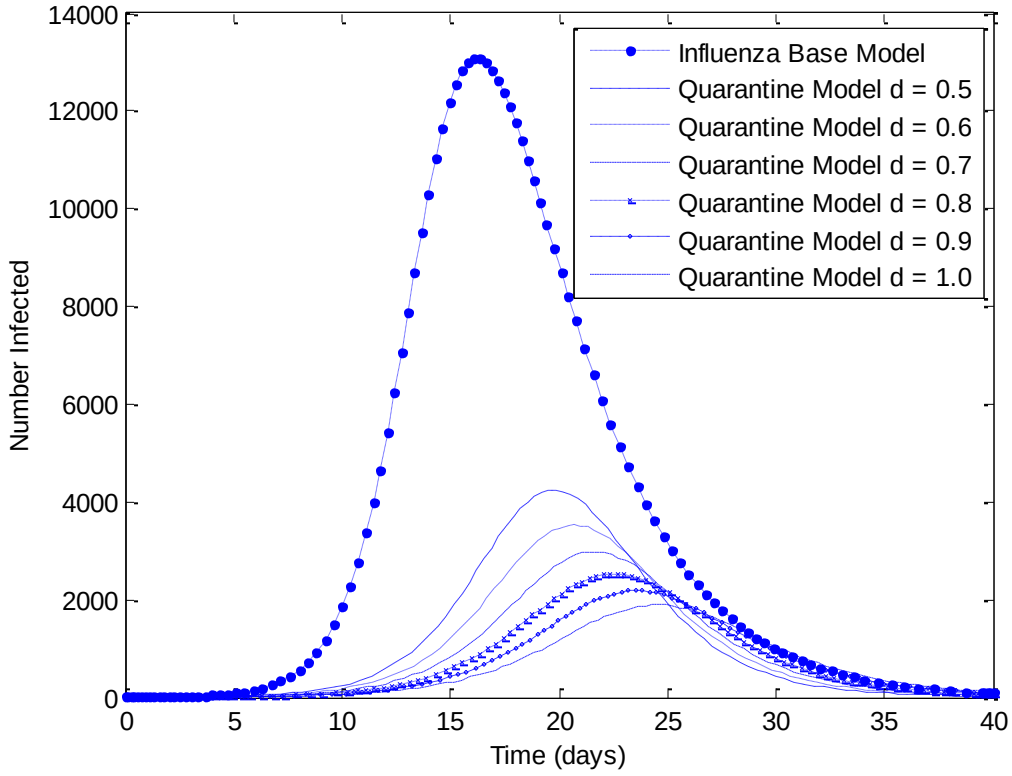

Figure 8: Graphical Flu Results (Base vs. Quarantine, with Varying *d* Values)

The populations over time in the susceptible, infectious (I_S) and quarantined (Q) compartments with varying values of the quarantine rate can be seen in Figure 9. (The MATLAB code for the SI_SI_NQR model for influenza can be found in Appendix C.)

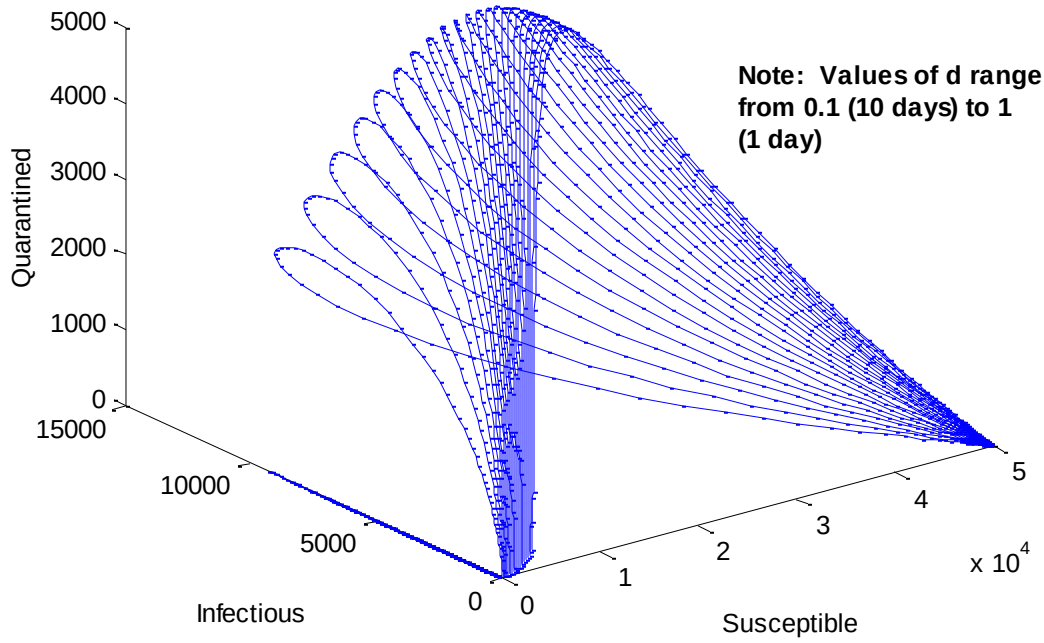

Figure 9: Susceptible vs. Infectious vs. Quarantined Populations in Influenza Model with Varying *d* Values

Table 13 contains a summary of the influenza simulations, including the value for the parameter *d*, the rate at which infected individuals are detected and removed to quarantine, the basic reproduction ratio and the total number infected.

Table 13: Numerical Flu Results (Base vs. Quarantine)

Rate of Quarantine	Equivalent of *d* in Days	Basic Reproduction Ratio, $\mathcal{R}_0$	Number Infected
$d = 0.10$	10	3.8	10060
$d = 0.25$	4	3.6	7058
$d = 0.50$	2	3.5	4226
$d = 0.55$	1.8	3.5	3854
$d = 0.60$	1.7	3.5	3526
$d = 0.65$	1.5	3.5	3230
$d = 0.70$	1.4	3.5	2973
$d = 0.75$	1.3	3.5	2726
$d = 0.80$	1.25	3.5	2532
$d = 0.85$	1.2	3.5	2346
$d = 0.90$	1.1	3.5	2180
$d = 0.95$	1.05	3.5	2029
$d = 1.00$	1	3.5	1893

Table 13 also reveals an interesting phenomenon. That is the relationship the rate of quarantine (d) has with the basic reproduction ratio ($\mathcal{R}_0$). Figure 10 shows graphically the correspondence between the value of the parameter d and $\mathcal{R}_0$, showing an obvious fixed point at $\mathcal{R}_0 = 3.5$.

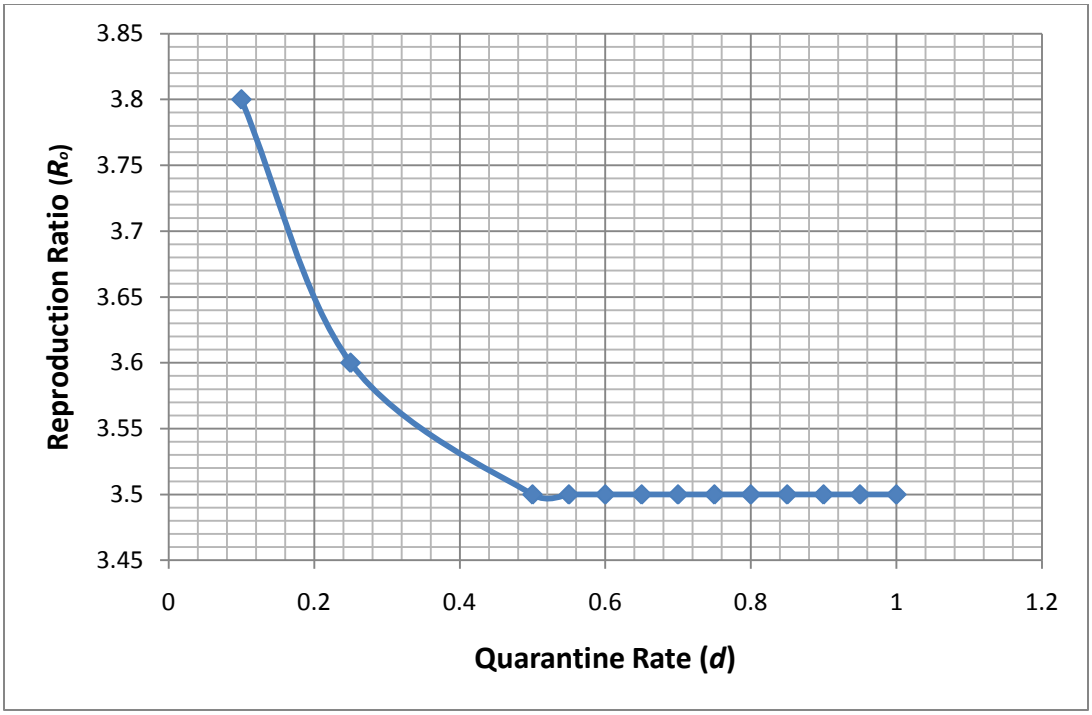

Figure 10: Basic Reproduction Ratio vs. Quarantine Rate for Influenza

From this we are able to surmise that the intercession of an influenza outbreak solely with isolation of infected individuals can reduce the basic reproduction ratio only so far. Additional interventions such as vaccination and antiviral agents would be necessary to eliminate the possibility of a pandemic.

Base vs. Treatment Model

Graphical results of the treatment model, similar to those of the quarantine model, can be seen in Figure 11. (The MATLAB code for the $SI_SI_{ST}I_NR$ model for influenza can be found in Appendix C.)

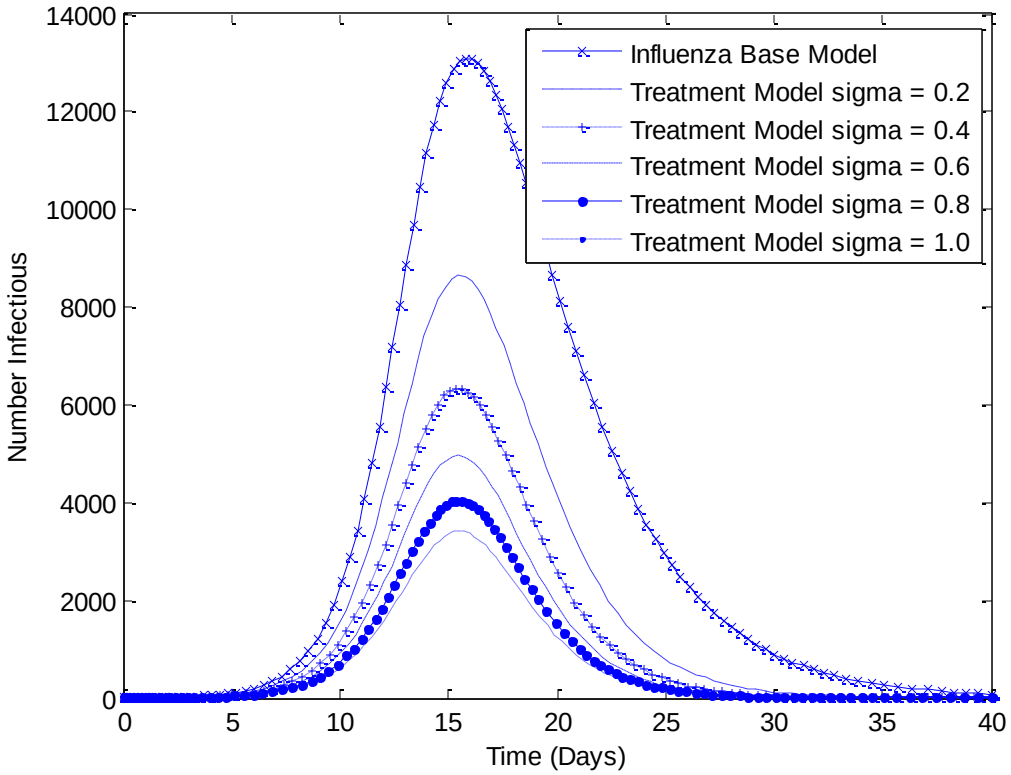

Figure 11: Graphical Flu Results (Base vs. Treatment, with Varying σ Values)

When attempting to make decisions based on simulation data, it may be advantageous to have the results in tabular form as well. Such results can be seen in Table 14.

Table 14: Numerical Flu Results (Base vs. Treatment)

Simulation Run	Days to Initiate Treatmen	Results	
		Total Number Infected	Time in Days
Base Model	NA	13000	16
σ = 0.2	5	8649	15.5
σ = 0.4	2.5	6344	15
σ = 0.6	1.7	4961	15
σ = 0.8	1.25	4049	15
σ = 1.0	1	3414	15.5

Treatment vs. Quarantine Models

In each of the intervention models we considered a range of values for the specified parameter values, i.e., for the quarantine model values of the rate of quarantine were varied from 0.10 to 1.00, with the equivalent in days being ten days to one day; for the treatment model the values of the treatment rate were varied from 0.2 to 1.0, with the equivalent being treatment with the antiviral agent beginning from five days after becoming infectious down to one day. Any combination of these parameter values can be shown in an effort to present the needed data to the health care decision maker. Figure 12 gives only one such combination; that of identifying the infectious individuals and removing them from the population (quarantine) in two days of their showing symptoms and beginning treatment of the infectious individuals with the antiviral medicine after two days of showing symptoms.

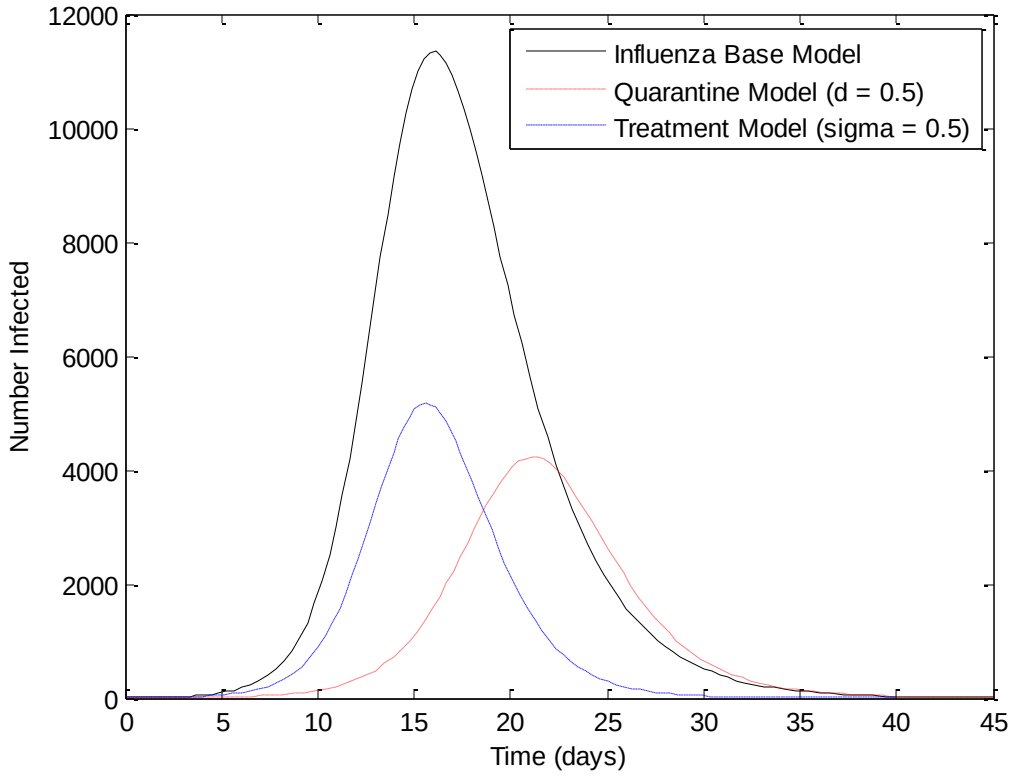

Figure 12: Graphical Flu Results, Treatment (σ = 0.5) vs. Quarantine (*d* = 0.5)

What can be seen from this graph is that the use of quarantine for this population would yield the greatest results as far as more time to the peak of the epidemic and less infectious individuals.

Stochastic Influenza Model

In Chapter 4, we showed how the standard meningitis model fitted with demographic stochasticity produced results statistically similar to those of the deterministic model. The purpose of this section is to study the influenza model with stochasticity taken into account. Here a model utilizing the parameters and rates of the deterministic influenza quarantine model

was created including demographic stochasticity. This case involves eight set rates (below) occurring by chance.

- Transmission occurs at rate $\beta S(I_S + \delta I_N)$. Result $S \rightarrow S - 1$ and $E \rightarrow E + 1$.
- The virus matures and the individual goes from exposed (E) to infected with symptoms (I_S) at a rate of $p\kappa E$. Result $E \rightarrow E - 1$ and $I_S \rightarrow I_S + 1$.
- The virus matures and the individual goes from exposed (E) to infected without symptoms (I_N) at a rate of $(1 - p)\kappa E$. Result $E \rightarrow E - 1$ and $I_N \rightarrow I_N + 1$.
- Recovery occurs at a rate γI_S. Result $I_S \rightarrow I_S - 1$ and $R \rightarrow R + 1$.
- Individuals are diagnosed and isolated at a rate dI_S. Result $I_S \rightarrow I_S - 1$ and $Q \rightarrow Q + 1$.
- Death occurs at rate μI_S. Result $I_S \rightarrow I_S - 1$.
- Recovery occurs at a rate γI_N. Result $I_N \rightarrow I_N - 1$ and $R \rightarrow R + 1$.
- Recovery and removal from isolation occurs at rate τQ. Result $Q \rightarrow Q - 1$ and $R \rightarrow R + 1$.

As in the meningitis model, Gillespie's Direct Method (Gillespie, 1977) was used to perform the iterations. (Matlab code for this model can be found in Appendix D.) A comparison of the results from 100 stochastic runs to the deterministic result can be seen in Figure 13. A value of $d = 0$ was used, resulting in a comparison of the base influenza model

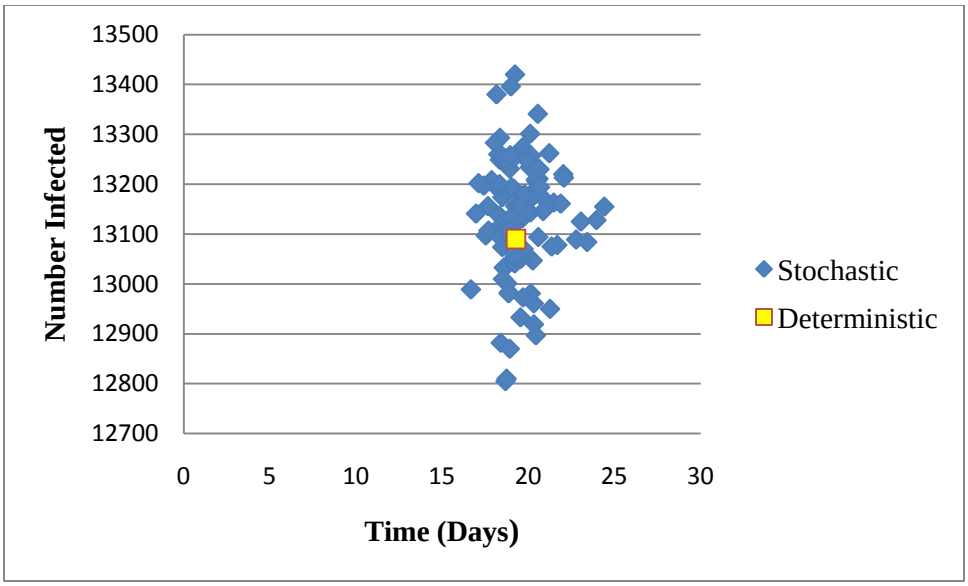

Figure 13: Scatter Plot 100 Stochastic Influenza Results vs. Deterministic Influenza Result

The descriptive statistics (calculated in Excel) for the 100 stochastic runs can be seen in Table 15.

Table 15: Stochastic Influenza Statistics

Mean	13132
Standard Deviation	120
Sample Variance	14303
Count	100

Again, a large-sample test was performed on the data to test the following null and alternative hypotheses:

H_0: $\mu = 13090$

H_a: $\mu \neq 13090$

The test statistic, *t*, was calculated to be 3.5; falling outside the acceptance region for $\alpha = 0.05$. In this case, the evidence would encourage us to reject the null hypothesis and assume the two

mean values are not statistically equivalent. While forty-two cases of flu are significant to those forty-two, they are most likely not consequential in the formulation of broader policy.

CHAPTER SIX: CONCLUSION

The "purpose of a mathematical model is not to make unconditional claims about the consequences of interventions, but to reveal the relation between assumptions and outcomes" (Weinstein, 2003, p. 4). This dissertation introduced several issues concerning the analysis of diseases by showing how modeling and simulation could be used to assist in creating health policy by estimating the effects of such policies.

The first question posed was how would education, vaccination and a combination of these two programs effect the possible outbreak of meningitis on our campus. We began by developing a mathematical model for meningitis. Starting with the basic *SIR* model a new compartment was added to accommodate the existence of an infected class which does not show symptoms but is still infectious to others, an SI_SI_NR model. To make the study exclusive to UCF we used the contact rate formula created by Rhodes and Anderson (2008), utilizing demographics specific to our campus. Parameter values for meningitis within each of these programs were developed. Chapter four holds the results of the deterministic simulations performed for each scenario. Here we concluded that the combination of an education program coupled with a vaccination program would greatly reduce the number of infected individuals in the event of an outbreak. Health policy makers have the option of viewing the results in tabular or graphical form. The next step in researching this topic would be to incorporate cost issues into the modeling of each of the programs to better assist in the creation of policy.

Next, we looked at the possibility of quarantine or treatment policies implemented in the event of an influenza pandemic. Here, we began with the basic *SEIR* model again incorporating the additional compartment to represent those infectious but not showing symptoms. We arrived

at the SEI_SI_NR model. The isolation of individuals in the population required the addition of another compartment, Q, the SEI_SI_NQR model. For the analysis of this option we looked at varying the rate at which infected individuals are detected and removed to isolation (d). We examined the basic reproduction ratio ($\mathcal{R}_0$) and discovered the value of d corresponding to the lowest $\mathcal{R}_0$. Next, we modified the model to represent a class of individuals undergoing treatment for influenza. This treatment reduced the time of infectiousness as well as reduced the infectivity of the individuals. Again we present several different genres to allow the health policy decision maker the ease of perusing the findings. With assumptions made on the time to quarantine and the number of days of treatment we showed the best course of action would be to enact a quarantine policy on the UCF campus, allowing for less infecteds and additional time to reach this peak. Future work on this topic would include varying the length of isolation and treatment as well as looking at the antiviral efficacy with respect to susceptibility to infection and symptomatic disease given infection (if treatment begins before symptoms) (Longini et al., 2004).

Finally we addressed the issue of performing the simulations stochastically versus deterministically. To take up this topic, a model incorporating demographic stochasticity was created utilizing the baseline meningitis and influenza parameters. Here, rather than the simulation advancing based on a series of differential equations the progression of the disease occurs by chance. Statistical analysis was done on the mean of 100 stochastic simulation runs comparing that value to the one deterministic outcome; showing the two results to be comparable with respect to meningitis. The result of the statistical analysis of the means for influenza was not as useful as that of meningitis, in that the analysis showed the two means to be different.

This topic also has great potential for future study, including the research of all output values and additional statistical testing to determine the degree of difference of the two types of analysis.

APPENDIX A: MATLAB CODE FOR DETERMINISTIC SI_SI_NR MODEL

```
function [t,S,I,A,R] =
Meningitis_SISINR(alpha,beta,gamma,mu,p,I0,A0,V0,N,MaxTime)

% Sets up default parameters
if nargin == 0
    alpha = 0.1;
    beta = 2.34;
    gamma = 0.2;
    mu = 0.1;
    p = 0.11;
    N = 50000;
    I0 = 1;
    A0 = 0;
    V0 = 0;
    MaxTime = 25;
end


S0 = N-I0-A0-V0;

S=S0;  I=I0;   A=A0;   R=50000-S-I-A;

% The main iteration
[t, pop] = ode45(@Diff_2_1,[0 MaxTime],[S I A R],[],[alpha beta gamma mu p
N]);

S=pop(:,1);   I=pop(:,2);    A=pop(:,3);    R=pop(:,4);

%  Plots the graph
T=t;
% subplot (3,1,2);
plot(T,I,'-b');
ylabel ('Number Infected');
% axis ([0 21 0 0.09*50000]);

% subplot (3,1,1);
% plot (T,S*50000,'-b');
% ylabel ('Number Susceptible');
%
% subplot (3,1,3);
% plot (T,R*50000,'-y');
% xlabel ('Time (days)');
% ylabel ('Number Recovered');
% title ('Deterministic Meningitis Model');

hold on

% Calculates the differential rates used in the integration
function dPop=Diff_2_1(t,pop, parameter)
```

```
alpha = parameter(1); beta = parameter(2); gamma = parameter(3); mu =
parameter(4); p = parameter(5); N=parameter(6);
S=pop(1);   I=pop(2);    A = pop(3);   R=pop(4);

dPop=zeros(4,1);

% dPop(1)=alpha*R - beta*S*(I+A);
% dPop(2)=p*beta*S*(I+A) - I*(gamma + mu);
% dPop(3)=(1-p)*beta*S*(I+A)-A*gamma;
% dPop(4)=gamma*(I+A) - alpha*R;

dPop(1)= - beta*S*(I+A)/N;
dPop(2)=p*beta*S*(I+A)/N - I*(gamma + mu);
dPop(3)=(1-p)*beta*S*(I+A)/N - A*gamma;
dPop(4)=gamma*(I+A);
```

APPENDIX B: MATLAB CODE FOR STOCHASTIC SI_SI_NR MODEL

```
function [t,S,I,A,R] =
Meningitis_SISINR_stochB(alpha,beta,gamma,mu,p,I0,A0,V0,N,MaxTime);

% Sets up default parameters
if nargin == 0
    alpha = 0.1;
    beta = 2.34;
    gamma = 0.2;
    mu = 0.1;
    p = 0.11;
    N = 50000;
    I0 = 1;
    A0 = 0;
    V0 = 0;
    MaxTime = 25;
end

S0 = N-I0-A0-V0;

S=S0;  I=I0;   A=A0;   R=50000-S-I-A;

% The main iteration
[t, pop] = Stoch_Iteration([0 MaxTime],[S0 I0 A0 R],[alpha beta gamma mu p
N]);
T=t;
S=pop(:,1);   I=pop(:,2);    A=pop(:,3);    R=pop(:,4);

numRows = size(T);
%  Plots the graph
% subplot (3,1,2);
%
% plot(T,I,'-r');
% ylabel ('Number Infected');
% axis ([0 20 0 10000]);
% hold on

% subplot (3,1,1);
% plot (T,S,'-b');
% ylabel ('Number Susceptible');
% % axis ([0 20 0 50000]);

% subplot (3,1,3);
% plot (T,R,'-y');
% xlabel ('Time (days)');
% ylabel ('Number Recovered');
% title ('Stochastic Meningitis Model');
% %  axis ([0 20 0 50000]);

%  hold off
% Do the iterations using the full evnt driven stochastic methodology
% relatively general version of Gillespie's Direct Algorithm
function [T,P]=Stoch_Iteration(Time,Initial,Parameters)
```

```
S=Initial(1); I=Initial(2); A=Initial(3);  R=Initial(4);

T=0;  P(1,:)=[S I A R];
old=[S I A R];

loop=1;
while (T(loop)<Time(2))
    [step,new]=Iterate(old,Parameters);
    loop=loop+1;
    T(loop)=T(loop-1)+step;
    P(loop,:)=old;
    loop=loop+1;
    T(loop)=T(loop-1);
    P(loop,:)=new; old=new;

     if loop>=length(T)
        T(loop*2)=0;
        P(loop*2,:)=0;
    end
end

T=T(1:loop);  P=P(1:loop,:);

%  Do the actual iteration step
function[step, new_value]=Iterate(old, Parameters)

alpha=Parameters(1);  beta=Parameters(2);  gamma=Parameters(3);
mu=Parameters(4);  p=Parameters(5); N=Parameters(6);
S=old(1);  I=old(2);  A=old(3);  R=old(4);

Rate(1) = beta*S*p*(I+A)/N; Change(1,:)=[-1 +1 0 0];
Rate(2) = beta*S*(1-p)*(I+A)/N;  Change(2,:)=[-1 0 +1 0];
Rate(3) = gamma*I; Change(3,:)=[0 -1 0 +1];
Rate(4) = mu*I; Change(4,:)=[0 -1 0 0];
Rate(5) = gamma*A; Change(5,:)=[0 0 -1 +1];
% Rate(6) = alpha*R; Change(6,:)=[+1 0 0 -1];

R1=rand(1,1);
R2=rand(1,1);

if(sum(Rate) > 0)
    step = -log(R2)/(sum(Rate));
else
    return
end

% find which event to do
m=min(find(cumsum(Rate)>=R1*sum(Rate)));

      new_value=old+Change(m,:);
```

APPENDIX C: MATLAB CODE FOR DETERMINISTIC INFLUENZA MODELS

SEI$_S$I$_N$R Model

```
function [t,S,E,I,A,R] =
Flu_SEISINR(beta,delta,gamma,kappa,mu,p,I0,A0,MaxTime)

E0 = 0;

S0 = 1-I0-A0-E0;
S=S0;  I=I0;   A=A0;  E=E0;   R=1-S-I-A-E;

% The main iteration
[t, pop] = ode45(@Diff_2_1,[0 MaxTime],[S E I A R],[],[beta delta gamma kappa
mu p]);

S=pop(:,1);   E=pop(:,2);  I=pop(:,3);    A=pop(:,4);    R=pop(:,5);

%  Plots the graph
T=t;
plot(T,I*50000,'-r')
xlabel ('Time (days)');
ylabel ('Number Infected');

hold on

% Calculates the differential rates used in the integration
function dPop=Diff_2_1(t,pop, parameter)

beta=parameter(1); delta=parameter(2); gamma=parameter(3);
kappa=parameter(4); mu=parameter(5); p = parameter(6);
S=pop(1);   E=pop(2);  I=pop(3);    A = pop(4);   R=pop(5);

dPop=zeros(5,1);

dPop(1)=- beta*S*(I+delta*A);
dPop(2)=beta*S*(I+delta*A) - kappa*E;
dPop(3)=p*kappa*E - I*(gamma + mu);
dPop(4)=(1-p)*kappa*E - A*gamma;
dPop(5)=gamma*(I+A);
```

SEI$_S$I$_N$QR Model

```
function [t,S,E,I,A,Q,R] =
FluQ_SEISINR(beta,d,delta,gamma,kappa,mu,p,tau,I0,A0,MaxTime)

E0 = 0;
Q0 = 0;

S0 = 1-I0-A0-E0-Q0;
S=S0;  I=I0;   A=A0;  E=E0; Q=Q0;   R=1-S-I-A-E+Q;
```

```
% The main iteration
[t, pop] = ode45(@Diff_2_1,[0 MaxTime],[S E I A Q R],[],[beta d delta gamma
kappa mu p tau]);

S=pop(:,1);   E=pop(:,2);  I=pop(:,3);    A=pop(:,4);    Q=pop(:,5);
R=pop(:,6);

%  Plots the graph
T=t;
plot(T,I*50000)
xlabel ('Time (days)');
ylabel ('Number Infected');

hold on

% Calculates the differential rates used in the integration
function dPop=Diff_2_1(t,pop,parameter)

beta=parameter(1); d=parameter(2); delta=parameter(3); gamma=parameter(4);
kappa=parameter(5);
    mu=parameter(6); p = parameter(7); tau = parameter(8);
S=pop(1);   E=pop(2);  I=pop(3);    A = pop(4);   Q=pop(5);  R=pop(6);

dPop=zeros(6,1);

dPop(1)=- beta*S*(I+delta*A);
dPop(2)=beta*S*(I+delta*A) - kappa*E;
dPop(3)=p*kappa*E - I*(gamma + mu) - d*I;
dPop(4)=(1-p)*kappa*E - A*gamma;
dPop(5)=d*I - tau*Q;
dPop(6)=gamma*(I+A) + tau*Q;
```

SEI$_S$I$_{ST}$I$_N$R Model

```
function [t,S,E,I,A,T,R] =
Flu_SISINR_Treat(beta,delta,gamma,kappa,mu,p,sigma,phi,theta,I0,A0,E0,T0,MaxT
ime)

% Sets up default parameters
if nargin == 0
    beta = 2.34;
    delta = 0.5;
    gamma = 0.2;
    kappa = 0.526;
    mu = 0.1;
    p = 0.67;
```

```
    sigma = 0.2;
    phi = 0.80;
    theta = 0.323;
    I0 = 1e-4;
    A0 = 1e-4;
    E0 = 1e-4;
    T0=0;
    MaxTime = 40;
end

S0 = 1-I0-A0;
S=S0;  I=I0;   A=A0;  E=E0; T=T0;  R=1-S-I-A-E-T;

% The main iteration
[t, pop] = ode45(@Diff_2_1,[0 MaxTime],[S E I T A R],[],[beta delta gamma
kappa mu p sigma phi theta]);

S=pop(:,1);   E=pop(:,2);  I=pop(:,3);  T=pop(:,4);  A=pop(:,5);  R=pop(:,6);

%  Plots the graph
    plot(t,I*50000,'-.b');

% Calculates the differential rates used in the integration
function dPop=Diff_2_1(t,pop, parameter)

beta=parameter(1); delta=parameter(2); gamma=parameter(3);
kappa=parameter(4); mu=parameter(5);
p = parameter(6); sigma = parameter(7); phi = parameter(8);  theta =
parameter(9);
S=pop(1);   E=pop(2);  I=pop(3);  T=pop(4);  A = pop(5);   R=pop(6);

dPop=zeros(6,1);

dPop(1)=- beta*S*(I+delta*A+phi*T);
dPop(2)=beta*S*(I+delta*A+phi*T) - kappa*E;
dPop(3)=p*kappa*E - I*(gamma + mu + sigma);
dPop(4)=sigma*I - theta*T;
dPop(5)=(1-p)*kappa*E - A*gamma;
dPop(6)=gamma*(I+A)+theta*I;
```

APPENDIX D: MATLAB CODE FOR STOCHASTIC INFLUENZA MODEL

```
function [t,S,E,I,A,Q,R] =
Flu_SEIAQR_stoch(beta,delta,gamma,d,kappa,mu,p,tau,I0,E0,A0,Q0,N,MaxTime);

% Sets up default parameters
if nargin == 0
    beta = 2.34;
    delta = 0.5;
    gamma = 0.244;
    d = 0.5;
    kappa = 0.526;
    mu = 0.0002;
    p = 0.67;
    tau = 0.244;
    N = 50000;
    I0 = 1;
    E0 = 0;
    A0 = 0;
    Q0 = 0;
    MaxTime = 50;
end

S0 = N-I0-E0-A0-Q0;

S=S0;  I=I0;   E=E0;  A=A0; Q=Q0;   R=50000-S-E-I-A-Q;

% The main iteration
[t, pop] = Stoch_Iteration([0 MaxTime],[S0 E0 I0 A0 Q0 R],[beta delta gamma d
kappa mu p tau N]);
T=t;
S=pop(:,1);   E=pop(:,2);   I=pop(:,3);    A=pop(:,4);  Q=pop(:,5);
R=pop(:,6);

numRows = size(T);

% Do the iterations using the full evnt driven stochastic methodology
% relatively general version of Gillespie's Direct Algorithm
function [T,P]=Stoch_Iteration(Time,Initial,Parameters)

S=Initial(1);  E=Initial(2);  I=Initial(3);  A=Initial(4);  Q=Initial(5);
R=Initial(6);

T=0;  P(1,:)=[S E I A Q R];
old=[S E I A Q R];

loop=1;
while (T(loop)<Time(2))
    [step,new]=Iterate(old,Parameters);
    loop=loop+1;
    T(loop)=T(loop-1)+step;
    P(loop,:)=old;
    loop=loop+1;
    T(loop)=T(loop-1);
```

```
    P(loop,:)=new; old=new;

     if loop>=length(T)
        T(loop*2)=0;
        P(loop*2,:)=0;
    end
end

T=T(1:loop);  P=P(1:loop,:);

%  Do the actual iteration step
function[step, new_value]=Iterate(old, Parameters)

beta=Parameters(1);  delta=Parameters(2);  gamma=Parameters(3);
d=Parameters(4);  kappa=Parameters(5);  mu=Parameters(6);
    p=Parameters(7); tau=Parameters(8);  N=Parameters(9);
S=old(1);  E=old(2);  I=old(3);  A=old(4);  Q=old(5);  R=old(6);

Rate(1) = beta*S*(I+delta*A)/N; Change(1,:)=[-1 +1 0 0 0 0];
Rate(2) = p*kappa*E;  Change(2,:)=[0 -1 +1 0 0 0];
Rate(3) = (1-p)*kappa*E;  Change(3,:)=[0 -1 0 +1 0 0];
Rate(4) = gamma*I; Change(4,:)=[0 0 -1 0 0 +1];
Rate(5) = d*I;  Change(5,:)=[0 0 -1 0 +1 0];
Rate(6) = mu*I; Change(6,:)=[0 0 -1 0 0 0];
Rate(7) = gamma*A; Change(7,:)=[0 0 0 -1 0 +1];
Rate(8) = tau*Q; Change(8,:)=[0 0 0 0 -1 +1];

R1=rand(1,1);
R2=rand(1,1);

if(sum(Rate) > 0)
    step = -log(R2)/(sum(Rate));
else
    return
end

% find which event to do
m=min(find(cumsum(Rate)>=R1*sum(Rate)));

new_value=old+Change(m,:);
```

APPENDIX E: CALCULATION OF PARAMETERS

Meningitis

N = 50,000 people

A = 5.726 km^2

R = 1 cm = 0.00001 km

q = varies with scenario

$$\bar{v} = (4.39 km/hr)(24 hr/day) = 105.36 km/day$$

BASE MODEL

q = 0.1

$$\rho = \frac{50,000}{5.726} = 8732 \text{ humans per sq. km}$$

$$\beta = \frac{8Rq\bar{v}\rho}{\pi} = \frac{8(1.0\times10^{-5} km)(105.36 km/day)(8732/km^2)q}{\pi}$$
$$= 23.43q/day = (23.43/day)(0.1) = 2.343/day$$

$$\mathcal{R}_0 = \frac{\beta}{\mu+\gamma+\alpha} = \frac{(2.343/day)}{0.1+0.1+0.1} = 7.8$$

EDUCATION MODEL

q = 0.05 V_0 = 10% (N = 45,000)

$$\beta = \frac{8Rq\bar{v}\rho}{\pi} = \frac{8(1.0\times10^{-5} km)(105.36 km/day)(45,000/5.726 km^2)(0.05)}{\pi} = 1.05/day$$

$$\mathcal{R}_0 = \frac{\beta}{\mu+\gamma+\alpha} = \frac{1.05}{0.1+0.1+0.1} = 3.5$$

VACCINATION MODEL

q = 0.1 V_0 = 51% (N = 24,500)

$$\beta = \frac{8Rq\bar{v}\rho}{\pi} = \frac{8(1.0\times10^{-5}km)(105.36km/day)(24,500/5.726km^2)(0.1)}{\pi} = 1.15/day$$

$$\mathcal{R}_0 = \frac{\beta}{\mu+\gamma+\alpha} = \frac{1.15}{0.1+0.1+0.1} = 3.8$$

EDUCATION & VACCINATION MODEL

q = 0.05 V_0 = 61% (N = 19,500)

$$\beta = \frac{8Rq\bar{v}\rho}{\pi} = \frac{8(1.0\times10^{-5}km)(105.36km/day)(19,500/5.726km^2)(0.05)}{\pi} = 0.46/day$$

$$\mathcal{R}_0 = \frac{\beta}{\mu+\gamma+\alpha} = \frac{0.46}{0.1+0.1+0.1} = 1.5$$

Influenza

$$\beta = \frac{8Rq\bar{v}\rho}{\pi} = \frac{8(1.0\times10^{-5}km)(0.1)(105.36km/day)(50,000/5.726km^2)}{\pi} = 2.343/day$$

N = 50,000 people

A = 5.726 km^2

R = 1 cm = 0.00001 km = 1.0 x 10^{-5} km

q = 10% or 0.1

$\bar{v} = (4.39\,\text{km/hr})(24\text{hr/day})$ = 105.36km/day

μ = 0.0002 (CDC, 2010)

$\gamma = \eta$ = 0.244 (Longini et al., 2004)

$\mathcal{R}_0 = \frac{\beta}{\gamma+\mu+\eta}$ (Brauer & Castillo-Chávez, 2001)

$$\mathcal{R}_0 = \frac{2.343}{0.244+0.244+0.02} = \frac{2.343}{0.508} = 4.6$$

Quarantine Calculations of $\mathcal{R}_0$

$$\beta = \frac{8Rq\bar{v}\rho}{\pi} = \frac{8(1.0\times10^{-5}\,km)(0.1)(105.36km/day)}{(5.726km^2)(\pi)}N = 4.69\times10^{-5}N$$

$$\mathcal{R}_0 = \frac{\beta}{\mu+\gamma+\eta} = \frac{\beta}{0.02+0.244+0.244} = \frac{\beta}{0.508}$$

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