KWAME NKRUMAH UNIVERSITY OF SCIENCE AND TECHNOLOGY

EPIDEMIOLOGICAL MODEL OF INFLUENZA A (H1N1) TRANSMISSION IN ASHANTI REGION OF GHANA

By

Samuel Okyere, B.Sc. (Mathematics and Economics)

A thesis submitted to the Department of Mathematics

In partial fulfillment of the requirement for the award of the degree

of

Master of Philosophy in Mathematics

College of Science

June, 2012

DECLARATION

I hereby declare that this submission is my own work towards the MPhil., and that, to the best of my knowledge, it contains no material previously published by another person nor material which has been accepted for the award of any other degree of the University, except where due acknowledgement has been made in the text.

Samuel Okyere (PG5071310) …….. ……

(**Student Name and ID**) Signature Date

Certified by:

F. T. Oduro (PhD) …… ……

(**Supervisor**) Signature Date

Certified by:

Kwaku Darkwah (Mr.) …… ……

(**Head of Department**) Signature Date

ACKNOWLEDGEMENT

I wish to express my profound gratitude to the Almighty God who in his wisdom made it possible for me to write this thesis.

This work was carried out at the department of Mathematics, KNUST. My MPhil. Programme is funded by Ghana Educational Trust Fund (GETFund) for which I am extremely grateful.

Special thanks go to my supervisor, Dr. F. T. Oduro for always being there for me and providing many relevant suggestions and worthy opinions through all stages of this thesis. I am indeed most grateful to him.

To Dr. Osei Bonsu of Eastern Connecticut State University, I owe a special debt of gratitude not only for his inspiration, also for his direct support in terms of providing materials through the internet and constructive critism for the success of the research, may God richly bless you.

I am also grateful to the staff of Dean of students, especially Mr. Gyau and Mr. Yamoah and the staff of Mathematics Department for their encouragement and support throughout the entire duration of the programme.

Lastly I would like to thank my family and friends for their support in all forms, which had led to the success of the programme.

ABSTRACT

The pandemic potential of influenza A (H1N1) has required decision makers to act in the face of uncertainties. In this thesis we develop a deterministic Susceptible – Exposed – Infectious – Recovered (SEIR) model to study the spread of H1N1 using data from the Ashanti region of Ghana. The study is based on the assumption that the population is constant with birth rate equals death rate. It is also assumed that the population interacts freely (homogeneous mixing). The model has two equilibrium states. The stability of each equilibrium point namely, the disease – free and the endemic equilibrium points are discussed. The basic reproduction number (R_O) was estimated to be 1.0064 and was found to persist with $R_O > 1$ whenever the transmission rate was increased or the recovery rate reduced but turned to $R_O < 1$, whenever the transmission rate was reduced or the recovery rate increased. A simulation was run for five months and extended to sixteen months in the neighbourhoods of the disease – free and endemic states and showed that near the disease – free state, the proportion of infectives had no effect on the susceptible population. However, as the number of infectives was increased in the neighborhood of the endemic equilibrium point, the susceptible population declined gradually reaching a minimum value at the last month. The recovered proportion of the population on the other hand, increased exponentially with time reaching a maximum value at the last month of the simulation. It is concluded that rapid vaccination is the most important factor to control the spread of H1N1 in case of an outbreak and that 0.64% of the susceptible population needs to be vaccinated in order to bring the disease under control.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER 1

INTRODUCTION

1.1 BACKGROUND OF THE STUDY

Influenza is an acute viral infection of the respiratory tract that is marked by fever, chills, and a generalized feeling of weakness and pain in the muscles, together with varying degrees of soreness in the head and abdomen (Encyclopaedia Britannica, 2012). Influenza is caused by Ribonucleic acid (RNA) virus in the family Orthomyxoviridae. The virus is divided into three main types (A, B, and C), which are distinguished by differences in two major internal proteins; hemagglutinin (HA) and neuraminidase (NA). Influenza Type B infects humans and birds, producing a milder disease that can cause epidemics. Type C apparently infects only humans. It typically produces either a very mild illness indistinguishable from a common cold or no symptoms at all. Type C does not cause epidemics. Influenza type A is the most dangerous; it infects a wide variety of mammals and birds. It causes the most cases of the disease in humans and is the type most likely to become epidemic. Influenza A is further divided into subtypes based on differences in the membrane protein hemagglutinin (HA) and neuraminidase (NA), which are the most important targets for the immune system. Influenza type A has 16 hemagglutinin subtypes (H1 – H16) and 9 neuraminidase subtypes (N1 – N9) known in birds. Only H 1, 2, and 3 and N 1, 2, are commonly found in humans. There are currently two subtypes circulating in humans: H1N1 and H3N2. Subtypes are further divided into strains; each genetically distinct virus isolate is usually considered to be a separate strain. An antigenic shift in the

influenza A virus can produce a pandemic affecting most of the world within a matter of months.

Evidence suggests that all influenza viruses in mammals, including humans, derived from viruses in wild ducks and other waterfowl. Some of these viruses could have been acquired by humans thousands of years ago. But medical historians know of no clearly identifiable influenza epidemics until large – scale outbreak occurred in Europe in 1510, 1557, and 1580. The 1580 outbreak also spread to Africa and Asia, making it the first known pandemic. Major pandemic took place in 1729 – 1730, 1732 – 1733, 1781 – 1782, 1830 – 1831, 1833, and 1889 – 1890 (Sibu, 2010). Influenza is transmitted from person to person through large respiratory droplets; expelled directly through coughing or sneezing, indirectly through contact with respiratory droplets or secretions, followed by touching the nose or the mouth and one needs not to be more than one meter to be infected. Preventing transmission requires removing one or more of the conditions necessary for transmission: e.g. blocking and or minimizing the ways by which the virus can get to a susceptible host, inhibiting or killing the virus. People infected with H1N1 first pass through latent and incubation period where they are not infectious and do not have the symptoms. The period of incubation for H1N1 is 1 – 4 days and the infectious period for a confirmed case is defined as 1 day prior to the onset of symptoms to 7 days after onset (Gu et al., 2011). The symptoms of influenza are: cough, nausea, diarrhea, fever, headache, sore throat, muscle aches, runny nose, shortness of breath, joint pains etc. (Wikipedia). Influenza occurs as an annual outbreak. An outbreak can occur if a new strain of influenza virus emerges against which the population has no immunity. The disease can become a pandemic when a particular strain of the virus spreads rapidly amongst human and causes intermittent

worldwide outbreaks. Major pandemics have caused the loss of millions of lives, for example the influenza pandemic of the 20th century: 1918 – 1919 (Spanish flu); the most destructive influenza outbreak in history and one of the most severe disease epidemic which has ever been encountered was caused by a subtype of influenza A known as H1N1, claimed 50 to 100 million lives worldwide, while the 1957 to 1958 Asian flu (H2N2) led to nearly one million deaths and the Hong Flu (H3N2) from 1968 to 1970, responsible for approximately 700,000 deaths (Wikipedia)

The recent outbreak of disease in people in 2009 globally was caused by a new influenza type A (H1N1) virus. Unlike H5N1 or avian influenza, which is slow spreading but a much more deadly strain, the 2009 H1N1 Influenza became a pandemic within a matter of two months raising health and economic fears from campuses to governments. On June 11, 2009, the World Health Organisation (WHO) announced the first influenza pandemic of the 21st century, following its rapid worldwide spread. By March 2010, most countries had experienced a season of pandemic influenza H1N1, with one or occasionally two peaks. Surveillance reports showed that the burden of illness during this first season did not differ much from that of the recent seasonal influenza epidemics. People of all age groups are susceptible to this new virus. In addition considering the virus high contagiousity, it is transmitted rapidly from an infected to a susceptible person.

Worldwide, as of 1st August 2010, more than 214 countries and overseas territories or communities have reported laboratory confirmed cases of pandemic influenza H1N1 2009, including over 18,449 deaths (WHO Global Alert and Response). In Ghana, the first laboratory – confirmed case was reported on 5th August 2009; a 25 year – old

woman who had contact with her brother who returned from United Kingdom (UK) and confirmed positive and had stayed with. Since then 1036 cases have been confirmed out of 8066 people screened to date (Noguchi Memorial Institute for Medical Research), the national influenza Centre in Ghana. For many years the world health organizations and other global bodies concerned had seeked solutions to various pandemics in the world among these are mass vaccination and mathematical modeling. In the next section we introduce mathematical epidemic modeling.

1.1.1 MATHEMATICAL EPIDEMIC MODELLING

Mathematical modeling plays an important role in understanding the complexities of an infectious diseases and their control. It can be beneficial for studying the mechanism underlying observed epidemiological patterns assessing the effectiveness of control strategies, and predicting epidemiological trends.

Mathematical modeling of human disease has a long history. The first mathematical model in epidemiology was the work of Daniel Bernoulli the Swiss Mathematician on the effect of variolation against smallpox in increasing life expectancy (Bernoulli 1766). His work contained the idea of differential mortality to estimate the rate of deaths attributable to a given disease, a method which has been used to estimate disease death – rates of past epidemics, such as the 1918 influenza pandemic. This was followed by the work of R. A. Ross (1897) on malaria transmission. Ross (1897) showed that malaria was transmitted through mosquitoes and developed a model to describe the spread of malaria. He then deduced from his model that reducing the mosquito population could control malaria in a given region. Then W. O. Kermack and A. G. Mckendrick (1927), whose paper a contribution to the mathematical theory of

epidemic was published in 1927. A simple deterministic (compartmental) model; susceptible – infectious – recovered (SIR) model was first to be used for explaining the behavior of the plague and cholera (London 1865) epidemics.

Two important concepts in modeling outbreaks of infectious diseases are the basic reproductive number, universally denoted by R_O, and the generation time (the average time from symptom onset in a primary case to symptom onset in a secondary case), which jointly determine the likelihood and speed of epidemic outbreaks (Anderson and May 1991; Diekman and Heesterbeek 2000; Wallinga and Teunis 2004).

R_O is defined by epidemiologist as "the average number of secondary cases produced by a typically primary case in an entirely susceptible population". It is a basic concept in mathematical epidemiology, derived originally from theoretical modeling considerations and then verified in observations. Its calculation for a given model and its estimation from observations are central in the analysis of models and the interpretation of data. When $R_O > 1$, the disease can enter a totally susceptible population and the number of cases will increase, whereas when $R_O < 1$, the disease will always fail to spread. Therefore in its simplest form R_O tells us whether a population is at risk from a given disease. Nowadays, the results of many epidemiological researches are presented in terms of basic reproduction number.

1.1.2 PROFILE OF STUDY AREA

Ghana, a country of western Africa, situated on the coast of the Gulf of Guinea, has a population of 24,233,431 of which 11,801,661(48.7%) are males and 12,421,770 (51.3%) are females. The population is predominantly of African origin, with the Akan

tribe comprising 44 percent of the population, the Moshi – Dagomba 16 percent, the Ewe 13 percent, the Ga – Adangbe 8 percent, the Yoruba 1.3 percent, and European and other nationalities less than 1 percent (www.nationsencyclopedia.com). It has an area of 239,540 square kilometers (92,486 square miles). Water occupies 8520 square kilometers (3,290 square miles) of the country, primary Lake Volta.

Ghana has ten regions: the Northern, Upper West, Upper East, Volta, Ashanti, Brong Ahafo, Eastern, Central, Western and Greater Accra. Also it has 170 districts (9 – 27 per region), 800 sub – districts and 25,672 communities, its capital is Accra. English is the official language with the other main languages being Akan, Moshi – Dagomba, Ewe, and Ga. The country comprises of Christians, Muslims and Traditionalist.

Ghana had not been spared with an outbreak of diseases since 1906 to date. From chronic, communicable to infectious diseases, epidemics tended to hit in three main periods, 1906 – 1908, 1918 – 1924 and 1940 – 1950. The major diseases included trypanosomiasis, cerebro – spinal meningitis, influenza, smallpox and onchocerciasis. Influenza A (H1N1) virus is our main concern for this thesis.

The country was first hit by the influenza A (H1N1) pandemic on August 31, 1918, on a ship arriving from Freetown, Sierra Leone and it spread across the country along the main lines of communication. The disease hit during the dry season, when respiratory diseases were worst, and it affected so many people resulting in so many deaths; because the colonial administrators could do little to combat influenza and in any case they were almost completely unprepared for the pandemic. No one knew what cause the disease and how to stop it from spreading, or how to treat the victims, and to make

matters worse the demands of world war 1 has reduce the Gold Coast medical staff to almost skeleton level. The 1918 – 1919 pandemic killed at least 100,000 people.

This has been followed by so many influenza outbreaks, for instance the 1957 – 1958 Asian Flu (H2N2) and 1968 – 1970 Hong Flu (H3N2). In April 2005, outbreak of influenza A H5N1 and August 2009, confirmed first case of pandemic Influenza A (H1N1) 2009 and to date 1036 confirmed cases out of 8066 people screened.

1.2 PROBLEM STATEMENT

The H1N1 virus had infected more than one million people worldwide (World Health Organisation). Policy makers face the difficult task of making appropriate and timely decisions to mitigate the serious adverse effects over a short period of time. While prediction of the features of influenza pandemic is difficult, preparedness against such pandemics is highly recommended by the World Health Organisation, and many countries have pandemic preparedness plans.

Infectious disease surveillance has traditionally played an important sentinel role in the public health pandemic preparedness. Detection of unusually high activity is the first step in any response strategy from bioterrorism to emerging diseases. World Health Organisation (WHO) has been tracking infectious diseases throughout the world and in the United States; the Centre for Disease Control is responsible for tracking infectious diseases. Besides detection, also essential for public health preparedness are timely estimates and predictions of disease activities based on surveillance data. Such estimates can enable policy makers to evaluate different disease containments and medical response plans. Based on the above information, it is very important for health

policy makers to have access to outbreak models in different scenarios to predict the speed of expansion under different circumstances.

Mathematical models have become a viable approach to evaluate the impact of public health intervention strategies and suggest the optimal course of action in the ongoing fight against persistent and emerging infectious diseases.

Ghana is no exception to the menace of the influenza virus H1N1. The country like any other African countries faces influenza epidemics and this poses public health and developmental challenges similar to challenges posed by communicable and chronic diseases. This has required decision – makers to act in the face of substantial uncertainties. Even though vaccines are available for many infectious diseases, these diseases still cause suffering and mortality in Ghana and Ashanti region in particular. It is against this backdrop that this research is called for to ascertain the wide spread of the influenza A (H1N1) virus.

1.3 OBJECTIVES OF THE STUDY

The objectives of the study are;

- To develop a mathematical model for H1N1 (a subtype of influenza A) in Ghana.
- To predict the future of H1N1 virus infection and the impact of vaccination strategies in Ghana, and help prevent future pandemics and epidemiology of infectious diseases in the country.
- To adapt and interpret experiences from developed countries so that they may be applied to low resource settings like Ghana.

1.4 METHODOLOGY

We present mathematical models that capture salient aspects of epidemiology of H1N1 in Ashanti region of Ghana. This thesis employs a model based on biological information and from previous works. The model we decided to use in studying the H1N1 virus is the Susceptible – Exposed – Infectious – Recovered compartmental model, or more commonly the SEIR model (Anderson and May 1991). This model is the same as the SIR model, except that before the individual becomes infectious, of course he/she will be exposed to the environment. We assumed the host population to be constant through time, with birth rate equals death rate. Once a model is formulated, we looked at the dynamics of a deterministic ordinary differential equation model which is derived and analyzed both analytically and numerically using matlab. Simulation and sensitivity analysis are then performed on the model equations to determine the effect of the parameter values on the spread of the disease. We attempt to use 2010 H1N1 data of Ashanti region of Ghana.

1.5 JUSTIFICATION

This thesis intends to justify why citizens of Ghana should make every effort to prevent the spread of H1N1 in the country and to encourage their family and friends to take part in H1N1 vaccination programme.

The H1N1 pandemic is a threat to socio – economic development and could affect the survival of the entire population. The occurrence of death from the disease generally affects the country's productivity and hence gross domestic product.

1.6 THESIS ORGANIZATION

This thesis is organized into five main chapters. Chapter 1 presents the introduction of the thesis. This consists of the background of the study, the research problem statement, objectives of the research, methodology, thesis justification and organization of the thesis. Chapter 2 is the literature review, which looks at briefly work done by other researchers on the topic. Chapter 3 is the formulation of the mathematical model. Chapter 4 contains the data collection and analysis. Chapter 5 looks at Summary, Conclusions and Recommendation of the analyzed data.

CHAPTER 2

LITERATURE REVIEW

This chapter looks into the review of related works on past influenza pandemics and 2009 influenza A (H1N1) modeling.

2.1 MODELLING THE PAST INFLUENZA PANDEMICS

Modeling studies have provided interesting insights into the severity of past influenza pandemics. For instance using R_O ranged between 1.3 and 1.9, Chowell et al. (2007) explored the association between influenza death rates, transmissibility and geographical and demographic indicators for the autumn and winter wave of the 1918 – 1919 pandemic in towns and rural areas of England and Wales. Their results showed spatial variation. Death rates varied markedly with urbanization, with 30 – 40% higher rates in cities and towns compared with rural areas. Also death rates varied with population size across rural settings. By contrast they found no association between transmissibility, death rates and indicators of population density and residential crowding. They concluded that further studies into the geographical mortality patterns associated with the 1918 – 1919 influenza pandemic may be useful for pandemic planning.

Germann et al. (2006) used stochastic simulation model to study the impact that a variety of levels and combinations of influenza antiviral agents, vaccines, and modified social mobility (including school closure and travel restrictions) have on the timing and magnitude of the spread of the 1917 – 1918 avian influenza in the US population of 281

million. For Ro range from 1.6 to 2.4, the results of their simulations demonstrate that, in a highly mobile population, restricting travel after an outbreak is detected, is likely to delay slightly the time course of the outbreak without impacting the eventual number ill. For $R_o < 1.9$, the model suggests that the rapid production and distribution of vaccines, even if poorly matched to circulating strains, could significantly slow disease spread and limit the number ill to less than 10% of the population, particularly if children are preferentially vaccinated.

Many modeling studies have investigated the three historical pandemics of the 20th century: the Spanish Flu 1918 – 1919 (H1N1), Asian Flu 1957 - 1958 (H2N2), and Hong Kong Flu 1968 (H3N2). Mills et al. (December, 2004),using pneumonia and influenza mortality data collected in 45 cities in the USA, estimated that the value of R_o for the 1918-1919 pandemic was between 2 and 3 by fitting Susceptible – Exposed – Infected – Recovered (SEIR) model. The results of their estimation showed that the proportion of the population with influenza A (H1N1) immunity before September 1918 was less than four. They concluded that the R_o for 1918 pandemic influenza is not large relative to many infectious diseases and also due to dearth of global antiviral and vaccine stores, aggressive transmission reducing measures will probably be required.

Yoneyama and Krishnamoothy (2010) used SEIR and social network model to study the spread of the 1918 - 1919 pandemic in twelve countries taken into consideration data on both civil and military traffic. They then simulated another scenario where there was no military traffic during the pandemic to determine the influence of the war on the pandemic. The results of their simulation showed that in countries which were deeply

involved in the war the infections were much influenced by the war whiles countries which were not much engage in the war, the infections were not influenced by the war.

Chowell et al. (2007) estimated Ro using the daily case notification during the autumn wave of the 1918 – 1919 influenza pandemic in the city of San Francisco, California. In order to elucidate the effects from adopting different estimations, they used four different methods; early exponential – growth rate, a simple SEIR model, a more complex SEIR – type model that accounts for asymptomatic and hospitalized cases and lastly a stochastic SIR with Bayesian estimation that determines the effective R_o at a given time. The first three methods fitted initial – growth phase of the epidemic, which was explicitly determined by goodness – of – fit test. The first three methods yielded R_o of 2.98 (95% confidence interval (CI): 2.73, 3.25), 2.38 (2.16, 2.60) and 2.20 (1.55, 2.84). Method four provided a maximum likelihood effective R_o of 2.10 (1.21, 2.95) for the first 17 days of the epidemic and 2.36 (2.07, 2.65) for the entire autumn wave. They concluded that the R_o for the pandemic at the city level can robustly assessed to lie in the range of 2.0 – 3.0 in broad agreement with previous data using distinct data.

Yoneyama and Krishnamoothy (2010) modeled the spread of the 1957 – 1958 influenza pandemic considering the effect of the cold war in nineteen countries using the SEIR and network model. The SEIR model for local areas and the network model for global connection between countries. Their simulation took into consideration international relationship among countries in different years. The results of their simulation showed that the impact of the pandemic in each country was much influenced by international relations. They concluded that if there was less effect of the cold war, western nations

would have larger number of death cases, Eastern nations would have smaller number of death cases and the world impact would increase somewhat.

Modeling has also been applied to assess the effect that interventions may have had in mitigating the past pandemic. Wu et al. (2006) estimated that the combination of household – based quarantine, isolation of cases outside the household and targeted prophylactic use of anti – viral would be highly effective in reducing the attack rates. The results of their estimation showed that with a given R_o of 1.8 assuming only 50% compliance, this combination could reduce the infection (symptomatic) attack rate from 74% (49%) to 40% (27%), requiring peak quarantine and isolation levels of 6.2%and 0.8% of the population and an overall anti – viral stockpile of 3.9 doses member of the population. They concluded that additional benefits and resource requirements of household – based interventions in reducing average levels of transmission should also be considered, even when expected levels of compliance are only moderate.

Bootsma and Ferguson (2007) estimated that public health measures, based on social distancing, reduced mortality by 10 to 30% in 16 cities in the US. They concluded that the timing of public health interventions strongly influenced the magnitude of the autumn wave of influenza. Their analysis also suggests that individuals reactively reduced their contact rates in response to high levels of mortality during the 1918 pandemic.

Halloran et al. (2008) used three different individual – based stochastic models to examined the consequences of intervention strategies chosen in consultation with the U.S. public health workers. Their first goal was to simulate the effectiveness of a set of

potentially feasible intervention strategies combinations called layered containment (TLC) of influenza antiviral treatment and prophylaxis and nonpharmaceutical interventions of quarantine, isolation, school closure, community and workplace social distancing are considered. Their second goal was to examine the robustness of the result to model assumptions. Their simulation suggested that at the expected transmissibility of a pandemic strain, timely implementation of a combination of targeted household antiviral prophylaxis and social distancing could substantially lowered the illness attack rate before a highly efficacious vaccine could become available. They concluded that timely initiation of measures and school closure could also play an important role in lowering the illness attack rate.

Longini et al. (2004) used stochastic epidemic simulations to investigate the effectiveness of targeted antiviral prophylaxis to containing influenza in the USA. In the absence of intervention, their model predicts an influenza illness attack rate of 33% of the population (95% confidence interval (CI): 30, 37) and an influenza death rate of 0.58 deaths/1,000 persons (95% Cl: 0.4, 0.8). With the use of targeted antiviral prophylaxis, if 80% of the exposed persons maintained prophylaxis for up to 8 weeks, the epidemic would be contained, and the model predicts a reduction to an illness attack rate of 2% (95% Cl: 0.2, 16) and a death rate of 0.04 deaths/1,000 persons (95% CI: 0.0003, 0.25). They concluded that vaccinating 80% of the children aged less than 19 years are almost as effective as vaccinating 80% of the population and targeted antiviral prophylaxis has potential as an effective measure, for containing influenza until adequate quantities of vaccine are available.

2. 2 MODELLING 2009 INFLUENZA A (H1N1)

While modeling of infectious diseases has been going on for some time, the first study done on the 2009 influenza A (H1N1) disease was performed by Böelle et al. (2009); the main focus of their work being the preliminary estimation of the basic reproduction ratio (R_o). They used methods of intrinsic growth rate and real time estimation to 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 et al.(2008)]) of 3.1 days and concluded that the estimates were decidedly dependent on the assumptions made concerning the generation interval.

The second study of the new strain of influenza A (H1N1) was done by Fraser et al. (2009). They used several epidemiological analyses leading to an estimation of the basic reproduction number (R_o) in the range 1.4 to 1.6 by analyzing the outbreak in Mexico, and earlier data of the global spread and concluded that this range of values is consistent with the fourteen to seventy – three instances of human – to – human transmission having occurred in Mexico to late April.

Flahault et al. (2009) used several values of the reproduction ratio and generation interval to model the potential spread of the pandemic influenza A (H1N1) across a network of 52 major cities using a simulation from stochastic Susceptible – Exposed – Infected – Recovered (SEIR) model, whiles also attempting to predict the effect of vaccination against the pandemic. The result of their simulation showed that in the absence of vaccination an attack rate (cumulative incidence of infection in a group of people observed over a period of time during an epidemic) of influenza A (H1N1) may

reach 46 percent (%) when considering a completely susceptible population with an R_o of 1.5 and a generation interval of 2 days, however a higher R_o of 2.2 and a generation interval of 3.1 days may yield 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 R_o = 2.2. Also a multi wave pandemic is possible and may be curtailed using different immunization strategies.

Boni et al. (2009) developed an age- and spatially-structured mathematical model to simulate the progression of H1N1 in Vietnam. Their research also considered the opportunities for reassortment with animal influenza viruses, a concern in this region where much of the world's poultry population lives. In the absence of effective intervention, the results of the model predicts introduction of H1N1 will result in an epidemic that will spreads to half of Vietnam in 57 days (interquatile range (IQR): 45 – 86.5) and peaks 81 days after introduction (IQR: 62.5 – 121 days).

Using the data from 216 households, Cauchemez et al. (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.

Gojovic et al. (2009) developed a simulation model of the pandemic (H1N1) using demographic and epidemiologic influenza data of the city Ontario. They projected the

attack rate under different combinations of school closure and antiviral drug strategies. They used combinatorial analysis to assess the impact of epidemiologic and program uncertainties. The results of their simulation showed that, school closure was effective in reducing the attack rate especially if applied early in the outbreak but this is not necessary if the vaccine is available early or pre – existing immunity is strong. They concluded that early action especially rapid deployment is disproportionately effective in reducing the attack rate.

Cruz – Pacheco et al. (2009) used time dependent modification of a classical Kermack and McKendrick model to study the evolution of the influenza outbreak reported in Mexico City using only the preliminary estimates of the lifetime of the virus and initial growth of the incidence curve at the onset of the outbreak. The effect of the sanitary measures was studied modeling the decrease and increase of the contact rate using linear functions of time. The results of the model illustrate how the sanitary measures postponed the peak of the epidemic and decrease its intensity. It provided quantitative prediction on the effect of relaxing the sanitary measures after a period of control. They showed how the sanitary measures reduced the maximal prevalence of the infected population from 10% to less than 6% of the total population.

Other researchers have used network models to study the spread of influenza A (H1N1) in other parts of the world, for instance, Mei et al. (2010) modeled the pandemic influenza A (H1N1) transmission through china campus contacts and forecast the effectiveness of interventions based on Complex Agent Network model for simulating infectious diseases. The results of the simulation show that the pandemic will die out even with no intervention taken; the most effective intervention is still quarantining

confirmed cases as early as possible and in addition vaccinating susceptible people can further decrease the maximum daily number of the infected. They concluded that the study can support quantitative experimentation and prediction of infectious disease within predefined areas and assessment of intervention strategies.

Jin et al. (2011) also used network modeling to study the transmission of the virus in China and also considered the effects of various immunization schemes in their study. They calculated the reproduction number to be 1.6809 for China and estimated the model parameters via least squares fitting of the model solution to the observed data in China. Results of the network model showed that disease free equilibrium is globally asymptotically stable when the Ro is less than one. They concluded that the network model is very useful in studying the transmission of H1N1 in China and a targeted immunization focusing on specific groups with giving connectivity may better control the endemic.

Towers and Feng,(2009) used data on confirmed cases of H1N1 pandemic disseminated by US CDC to fit the parameters of SIR model and assessed the efficacy of planned CDC H1N1 vaccination campaign. They used the resulting model to predict the course of H1N1 pandemic in autumn, 2009. The results of the model predicts that there will be a significant wave in autumn with 63% of the population being infected, and that this wave will peak so early that the planned CDC vaccination will likely not have a large effect on the total number of people ultimately infected by the pandemic H1N1 influenza virus.

Massad et al. (2010) used an SIR model to calculate the risk (probability) of acquiring the new influenza A (H1N1) for Brazilian travelers to Chile, Argentina and USA. The results of their model revealed that the maximum estimated risk reached 7.5 cases per 10,000 visitors to Chile, 17 cases per 10,000 travelers to Argentina and 23 cases per 10,000travelers to USA. The estimated number of imported cases until 27th July is 57 ± 9 from Chile, 136 ± 27 from USA and 301 ± 21 from Argentina. They concluded that the estimate from the imported cases was important for the moment of the disease introduction into the country.

Lee et al. (2010) employed an agent – based computer simulation model of the Washington DC metropolitan region, USA to delineate what mechanisms could generate a "third pandemic wave" and explored whether vaccinating the population at different rates and times would mitigate the wave. They took into consideration explicit representation of the region's individuals, school systems, workplaces / commutes, households and communities. Results: they identified three mechanisms that could cause a third pandemic wave; substantially increased viral transmissibility from seasonal forcing (changing influenza transmission with changing environmental conditions i.e. seasons) and progressive viral adaptation; an immune escape variant and changes in social mixing from holiday school closures. They concluded that implementing vaccination for these mechanisms significantly mitigated the wave and additional waves in an epidemic can be mitigated by vaccination even when an epidemic appears to be waning.

Suh et al. (2010) developed a deterministic model of a pandemic (H1N1), 2009 in a structured population using the demographic data from the Korean population and the

epidemiological feature of the pandemic. The model takes into account the response strategies of the Republic of Korea for novel influenza A (H1N1) such as school closure, mass vaccination,(70% of the population in 30 days), and a policy for anti – viral drug (treatment or prophylaxis). The results of the model showed that the effect of two – week school closure on the attack rate was low regardless of the timing of the intervention. The earlier vaccination showed the effect of greater delays in reaching the peak of outbreaks. When it was no vaccination, vaccination at initiation of outbreak, vaccination 90 days after initiation of outbreak and vaccination at the epidemic peak point, the total number of clinical cases for 400 days was 20.8 million, 4.4 million, 4.7 million, and 12.6 million respectively. They concluded that rapid vaccination was the most important factor to control the spread of pandemic influenza and the response strategies of the Republic of Korea were shown to delay the spread of pandemic influenza in their deterministic model.

Hsieh (2010), used age dependent compartmental model with pre – asymptomatic and asymptomatic which incorporates intervention measures such as age vaccination to study the spread of influenza A (H1N1) in Taiwan community. He estimated the reproduction number slightly above one (≈ 1.001) using Pneumonia and Influenza mortality and vaccination data of 2004/2005 Taiwan winter season. The results of the simulation showed that more active group was transmitting the influenza to the other age groups as compared to the very old. Also asymptomatic infective has more pronounced impact on the model fit for the elderly mortality than the pre – asymptomatic. He concluded that the impact of the vaccination on the disease incidence might not be fully reveled in the change (or the lack thereof) in the effective reproduction number with interventions but could still be substantial.

Shil et al. (2011) used Susceptible – Exposed – Infectious – Asymptomatic – Recovered (SEIAR) model to study the transmission dynamics of an outbreak of influenza A (H1N1) in June – July , 2009 in a residential school in Panchgani western part of Maharashtra, India. Analyses of their epidemiological data revealed that close clustering within population resulted in high transmissibility with basic reproduction number Ro = 2.61 and transmission rate being 0.001566. They concluded that the SEIAR model has successfully describe the dynamics of transmission in a residential school setting and helped in ascertaining the epidemiological parameters for asymptomatic cases and effectiveness of the control measures.

Li et al. (2011) used the gravity model to predict the spread of influenza A (H1N1) worldwide and its relationship with socio – economic indicators such as population size, per capita gross domestic production (GDP), and distance between countries and states through the estimation of parameters of a generalized linear model. The Gravity model considers the effect of distance and the size of the donor and recipient communities. They concluded that the gravity model is valid if the spread period is long enough for estimating the model parameters.

Poletti et al. (2010) analyzed the 2009 influenza epidemic in Italy by using cost / benefit analysis to understand whether spontaneous behavioral changes in the population could be responsible for the epidemic spread. The performed investigation revealed that an initial overestimation of the risk of infection in the general population possibly induced by the high concerned for the emergence of a new influenza pandemic results in a pattern of spread compliant with the observed one. By assuming a

generation time of 2.5 days, the initial diffuse misperception of the risk of infection led to a relatively low value of the reproductive number 1.24 which increased to 1.48 in the subsequent phase of the pandemic. They concluded that spontaneous behavioral changes in the population not accounted by the large majority of influenza transmission model cannot be neglected to correctly informed public health decisions. Individual choices can drastically affect the epidemic spread, by altering timing, dynamics and overall number of cases.

Jumpen et al. (2011) proposed an algorithm to generate adaptive social network for studying the Susceptible – Infected – Susceptible (SIS) – Susceptible – Exposed – Infected – Quarantine – Recovered (SEIQR) pandemic influenza. They simulated the pandemic influenza on the SIS – SEIQR adaptive network with nine hub nodes to capture the disease transmission in a human community. Effects of visiting probability on the spread of the disease were investigated. The results of their simulation indicated that high visiting probability increased the transmission rate of the disease. They concluded that, to control the spread of the disease when the pandemic influenza occurs, public places such as theater and school would be closed or the risk people avoiding visiting the public places.

Using data relevant to the province of Manitoba, Canada, Sharomi et al. (2010) developed a compartmental model for the transmission dynamics of swine influenza (H1N1) pandemic in a population in the presence of imperfect vaccine and use of drug therapy for confirmed cases. Rigorous analysis of their model, which stratifies the infected population in terms of their risk of developing severe illness, reveals that it exhibits a vaccine induced backward bifurcation when the associated $R_O < 1$. The

epidemiological consequence of this result is that the effective control of H1N1, when $R_O < 1$, in the population would then be dependent on the initial sizes of the subpopulations of the model. From the case where the vaccine is perfect, their results shows that having $R_O < 1$ is necessary and sufficient for effective control of H1N1 in the population. The numerical simulations of their model also showed that it mimics the observed H1N1 pandemic data for Manitoba during the first (spring) wave of the pandemic. They concluded that, timely implementation of a mass vaccination program together with the size of the Manitoban population that have preexisting infection-acquired immunity (from the first wave) are crucial to the magnitude of the expected burden of disease associated with the second wave of the H1N1 pandemic, and with an estimated vaccine efficacy of approximately 80%, they have projected that at least 60% of Manitobans need to be vaccinated in order for the effective control or elimination of the H1N1 pandemic in the province to be feasible. Finally, the burden of the second wave of H1N1 is expected to be at least three times that of the first wave, and that the second wave would last until the end of January or early February, 2010.

CHAPTER 3

METHODOLOGY

3.1 INTRODUCTION

This chapter looks into the methodology used to model the H1N1 disease. There are two types of epidemiological modeling technique: stochastic (probabilistic) and deterministic (compartmental models, non probabilistic). In this thesis, we employ a deterministic model approach to derive different models and propose an appropriate model for H1N1 disease. There are several compartmental models of which the most notable are: Susceptible – infective (SI), Susceptible – Infective – Susceptible (SIS), Susceptible – Infective – Recovered (SIR), Susceptible – Infective – Quarantine - Recovered (SIQR), Maternally – derived immunity – Susceptible – Infective – Recovered (MSIR), Susceptible – Exposed – Infective – Recovered (SEIR) and Carrier State Model. The choice of which compartments to use in a model depends on the characteristics of the disease and the purpose of the model. We will define and explain some of these models, then choose the appropriate model for the disease under study. In the rest of this chapter, we define the important terms relevant to this thesis.

3.2 PRELIMINARIES

Deterministic models of epidemiology are usually described by differential equations of which there are 2 types; ordinary differential equations (ODE's) and partial differential equations (PDE's). In this thesis, our models will be derived from ODE's. They will be analyzed by classifying their steady states. We now define and give a few theorems that are relevant to the thesis.

Definition 3.1 (Ordinary differential equations)

A differential equation of order n is an equation of the form

$$f\left(y, \frac{dy}{dt}, \frac{d^2y}{dt}, \ldots., \frac{d^ny}{dt^n}, t\right) = 0. \qquad (3.10)$$

A typical n^{th} order linear differential equation is given by

$$\frac{d^ny}{dt^n} + a_1(t)\frac{d^{n-1}}{dt^{n-1}} + \cdots + a_{n-1}(t)\frac{dy}{dt} + a_n(t)y = g(t) \qquad (3.11)$$

Definition 3.2 (System of ordinary differential equations)

A system of n differential equations is defined as

$$\frac{dx}{dt} = F(x(t), t) \qquad (3.12)$$

Where

$$X(t) = \left(x_1(t), x_2(t), \ldots\ldots\ldots, x_n(t)\right)^T, F = (f_1, f_2, \ldots\ldots., f_n)^T \qquad (3.13)$$

And

$$f_i = f_i(x_1(t), x_2(t), \ldots, x_n(t), t) \qquad (3.14)$$

3.3 STEADY STATES / EQUILIBRIUM POINTS

The equilibrium solutions (points) to a system of first order differential equations are the points at which the first derivatives are equal to zero. That is, for the system

$$\frac{dx}{dt} = f(x, y) \qquad (3.15)$$

$$\frac{dy}{dt} = g(x, y) \qquad (3.16)$$

The equilibrium points are the solution to the algebraic equation

$f(x, y) = 0$

$g(x, y) = 0$

In this thesis, we are going to have two equilibrium points in each of the models: the disease – free equilibrium (where there is no infection in the population) and the endemic equilibrium (where all the compartments of the population coexist) for the differential equation. This is only for peculiar cases for first order nonlinear differential equations. Sometimes the systems can give you more than one equilibrium points.

3.4 STABILITY OF THE STEADY STATES

3.4.1 STABILITY BY LINEARIZATION

For most dynamical systems the equilibrium point (fixed point) of a system of nonlinear differential equations plays an important role in the analysis of the models, we therefore give the definition of a fixed point and describe the analysis of the fixed point below.

Let $f: R^n \rightarrow R^n$ be a C^1 map and suppose that p is a point such that $f(p) = 0$, i.e., p is a fixed point for the differential equation $y'(t) = f\big(y(t)\big)$.

The linear part of f at p, denoted $Df(p)$, is the matrix of partial derivatives at p. For $y \epsilon R^n$, we write

$$f(y) = \begin{pmatrix} f_1(y) \\ f_2(y) \\ \vdots \\ f_n(y) \end{pmatrix} \tag{3.17}$$

The functions f_i are called the component functions of f. we define

$$Df(p) = \begin{pmatrix} \frac{\partial f_1}{\partial y_1}(p) & \frac{\partial f_1}{\partial y_2}(p) & \dots & \frac{\partial f_1}{\partial y_1}(p) \\ \vdots & \vdots & \vdots & \vdots \\ \frac{\partial f_n}{\partial y_1}(p) & \frac{\partial f_n}{\partial y_2}(p) & \dots & \frac{\partial f_n}{\partial y_n}(p) \end{pmatrix} \tag{3.18}$$

Called Jacobian matrix, Since $f \in C^1$, Taylor's theorem for functions of several variables says that $f(y) = Df(p)(y-p) + h(y)$. We use $f(p) = 0$ where $h(y)$ is a function. The stability of a flow of a nonlinear system can be studied using different approaches. In this thesis we restrict ourself to Routh – Hurwitz stability criterion

3.5 STABILITY ANALYSIS

3.5.1 Routh – Hurwitz stability criterion

The Routh – Hurwitz criterion is a method for determining whether a linear system is stable or not by examining the locations of the roots of the characteristic equation of the system. It is an important criteria that give necessary and sufficient conditions for all of the roots of characteristic polynomial (with real coefficients) to lie in the left half of the complex plane (Gantmacher, 1964). The Routh – Hurtwitz criteria are stated in the theorem below.

Theorem 3.1 (Routh – Hurwitz criteria)

Given the polynomial,

$$p(\lambda) = \lambda^n + a_1\lambda^{n-1} + \cdots + a_{n-1}\lambda + a_n, \qquad (3.19)$$

where the coefficients a_i are all constants, $i = 1, \ldots\ldots, n$. Define the n Hurwitz matrices using the coefficients a_i of the characteristic polynomial as;

$$H_1 = (a_1), \quad H_2 = \begin{pmatrix} a_1 & 1 \\ a_3 & a_2 \end{pmatrix}, H_3 = \begin{pmatrix} a_1 & 1 & 0 \\ a_3 & a_2 & a_1 \\ a_5 & a_4 & a_3 \end{pmatrix} \quad and$$

$$H_n = \begin{pmatrix} a_1 & 1 & 0 & 0 & \cdots & 0 \\ a_3 & a_2 & a_1 & 1 & \cdots & 0 \\ a_5 & a_4 & a_3 & a_2 & \cdots & 0 \\ \vdots & \vdots & \vdots & \vdots & \cdots & \vdots \\ 0 & 0 & 0 & 0 & \cdots & a_n \end{pmatrix} \qquad (3.20)$$

where $a_j = 0 \; if \; j > n.$ All the roots of the polynomial $p(\lambda)$ are negative or have negative real part iff the determinants of all Hurwitz matrices are positive:

$$\det H_j > 0, j = 1,2, \dots, n.$$

For polynomials of degree $n = 2,$ the Routh – Hurwitz criteria simplify to

$$\det H_1 = a_1 > 0 \; and \; \det H_2 = \det \begin{pmatrix} a_1 & 1 \\ a_3 & a_2 \end{pmatrix} = a_1 a_2 > 0 \text{ or } a_1 > 0 \; and \; a_2 > 0.$$

For polynomials of degree $n = 2, 3, 4 \; and \; 5$ the Routh – Hurwitz criteria are summarized below;

$$\begin{aligned} &n = 2: a_1 > 0 \; and \; a_2 > 0 \\ &n = 3: a_1 > 0, a_3 > 0, and \; a_1 a_2 > a_3. \\ &n = 4: a_1 > 0, a_3 > 0, a_4 > 0, and \; a_1 a_2 a_3 > {a_3}^2 + {a_1}^2 a_4 \\ &n = 5: a_i > 0, i = 1,2,3,4,5, a_1 a_2 a_3 > {a_3}^2 + {a_1}^2 a_4, and \\ &(a_1 a_4 - a_5)(a_1 a_2 a_3 - {a_3}^2 - {a_1}^2 a_4) > a_5 (a_1 a_2 - a_3)^2 + a_1 {a_5}^2. \end{aligned} \qquad (3.21)$$

For a proof of the Routh – Hurtwitz criteria see Gantmacher (1964).

Proof of Theorem 3.1 (For $n = 2$)

For $n = 2$, the Routh – Hurwitz criteria are just $a_1 > 0$ and $a_2 > 0$. The characteristic polynomial in the case $n = 2$ is

$$p(\lambda) = \lambda^2 + a_1\lambda + a_2 = 0 \qquad (3.22)$$

The eigenvalues satisfy

$$\lambda_{1,2} = \frac{-a_1 \pm \sqrt{{a_1}^2 - 4a_2}}{2} \qquad (3.23)$$

Suppose a_1 and a_2 are positive. It is easy to see that if the roots are real, they are both negative, and if they are complex conjugates, they have negative real part.

Next, to prove the converse, suppose the roots are either negative or have negative real part. Then it follows that $a_1 > 0$. If the roots are complex conjugates, $0 < {a_1}^2 < 4a_2$, which implies that a_2 is also positive. If the roots are real, then since both of the roots are negative it follows that $a_2 > 0$.

In the next section we describe some epidemiological models and emphasized the model/s that will be used for this work.

3.6 EPIDEMIOLOGICAL MODELS

The simplest epidemiological model in which recovery does not give immunity is the SIS model. In this model, the population is divided into two groups of people (see figure 3.1), those that have been infected by the disease and are infectious, and those that are susceptible to being infected by the disease. This model assumes the population to be homogeneous, well – mixed and divided into these two groups. It also assumes the population become infectious once is infected. It assumes that each infected person

was fully recovered after one time period. Moreover, it assumes people who have been infected before do not have immunity of the disease, and can be infected again in the future. The SIS models are appropriate for some bacterial agent diseases such as meningitis, plague, and sexually transmitted diseases and for protozoan agent diseases such as malaria and sleeping sickness.

Figure 3.1: SIS model

Another epidemiological model is the SIR model (see figure 3.2). This model is the same as the SIS model except that once a person has recovered from the disease, they would receive lifelong immunity. The first SIR model, which computes the theoretical number of individuals infected with a contagious illness in a closed population over time, was proposed by Kermack and McKendrick (1927). The SIR model is appropriate for viral diseases such as measles, mumps and rubella.

Figure 3.2: SIR Model

An extension of the SIR model is the SIRS model (see figure 3.3). This model was introduced in 1933 by Kermack and McKendrick to describe endemic infections. The only difference between the SIR and the SIRS is that the SIRS model allows members of the recovered class to be free of infection and rejoin the susceptible class. Thus the infected population can acquire immunity for a period before they become susceptible

again, obviously inapplicable to fatal diseases. The S, I and R carry the same meaning as the SIR model giving above.

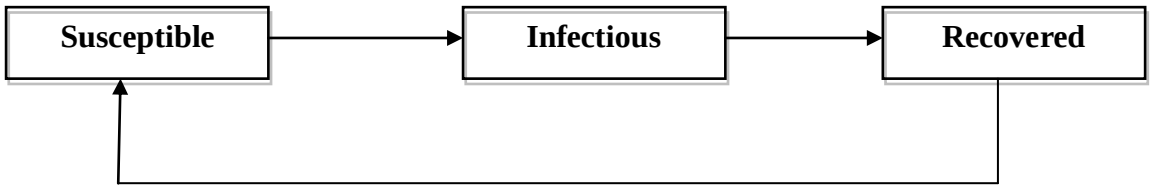

Figure 3.3: SIRS epidemiological model

Another extension of the SIR model is the MSIR model (see figure 3.4). For many infections, including measles, babies are not born into the susceptible compartment but are immune to the disease for the first few months of life due to protection from maternal antibodies (passed across the placenta or through colostrum). An infected or vaccinated mother transfers some IgG antibodies (antibody molecules) across the placenta to her fetus, so that her newborn infant has temporary passive immunity to an infection. When these passive antibodies are gone (no new antibodies are produced by the infant), the infant moves from the passively immune state M to the susceptible state. Infants, who do not have any passive immunity, because their mothers were neither infected nor vaccinated, also enter the susceptible class and can become infected. As they age from then on, they may become infected and infectious to others. After infection, they recover and acquire lifelong immunity.

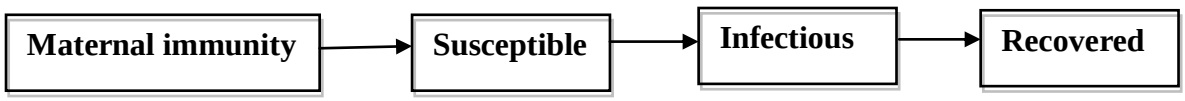

Figure 3.4: MSIR epidemiological model

Whilst the SIR model takes into account only those diseases which cause an individual to infect a susceptible individual 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 (one of such diseases is measles), in this case we introduce an addition compartment to the SIR model to cater for the exposed individuals. This model is called the SEIR model (see figure 3.5). The exposed phase or latency period is where the person is infected but not infectious (thus, symptoms of the disease have not been shown and the person cannot communicate the disease either).

Figure 3.5: SEIR epidemiological model

Whereas most of the models mentioned in this chapter have been effective in describing the dynamics of other diseases, they cannot be used to model influenza because there is some form of latency or exposed phase of the Influenza virus (Uhavax, 2001). For this reason, Influenza will have to be modeled with an additional compartment (Exposed). We therefore adopt the SEIR model (see figure 3.5) to model the spread of H1N1 disease.

3.7 SEIR MODEL

3.7.1 MODEL ASSUMPTIONS

- The population has constant size N, which is sufficiently large so that the sizes in each class can be considered as continuous variables.
- Births and deaths occur at equal rates and that all newborns are susceptible (no inherited immunity).

- The population is homogeneously mixing, with no restriction of age, mobility or other social factors.
- We assume once infected you become exposed to the environment before becoming infectious.
- The transmission coefficient $\beta > 0$, the latency coefficient $\alpha > 0$, the recovery coefficient $\gamma > 0$ and the capital death rate $\mu > 0$. (see figure 3.6)

The flow diagram for this model is given in figure 3.6.

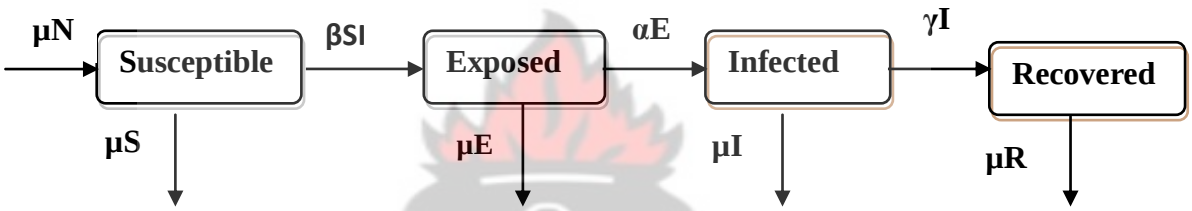

Figure 3.6: Flowchart for SEIR model

The following system of ordinary differential equations (ODE's) is used to represent this model:

$$\frac{dS}{dt} = \mu N - \mu S - \beta IS \quad (3.24)$$

$$\frac{dE}{dt} = \beta IS - (\mu + \alpha)E, \quad (3.25)$$

$$\frac{dI}{dt} = \alpha E - (\gamma + \mu)I, \quad (3.26)$$

$$\frac{dR}{dt} = \gamma I - \mu R, \quad (3.27)$$

The nonlinear system of differential equations formulated above has initial conditions

$S(0) = S_0 > 0, E(0) = E_0 > 0, I(0) = I_0 > 0, R(0) = R_0 > 0$

Where $S(t)$ denotes the number of susceptible at time t, $I(t)$ denote the number of infective at time t, $E(t)$ denote the number of exposed individuals at time t, $R(t)$

denotes the number of recovered individuals at time t. The average birth and death rate is μ. The rate at which individuals are born into the susceptible class with no passive immunity is μN and the rate at which they leave it via death is μS. Also βSI is the rate at which susceptible enters the Exposed class without been infectious and αE is the rate at which an exposed person becomes infectious. γI is the rate at which an infected individual may recover, where they will remain until death. Denoting with N the total population, that is $N = \mathrm{S(t)} + \mathrm{E(t)} + \mathrm{I(t)} + \mathrm{R(t)}$ then

$$\frac{\mathrm{dS}}{\mathrm{dt}} + \frac{\mathrm{dE}}{\mathrm{dt}} + \frac{\mathrm{dI}}{\mathrm{dt}} + \frac{\mathrm{dR}}{\mathrm{dt}} = 0 \qquad (3.28)$$

Expressing equations $3.24 - 3.27$ as a proportion of the population we obtain

$$s(t) = \frac{S(t)}{N}, e(t) = \frac{E(t)}{N}, i(t) = \frac{I(t)}{N}, r(t) = \frac{R(t)}{N} \qquad (3.29)$$

thus,

$$s(t) + e(t) + i(t) + r(t) = 1$$

Substituting equation (3.29) into equations $(3.24) - (3.27)$ we obtain the following

$$\frac{ds}{dt} = \mu - (\mu + \beta i)s \qquad (3.30)$$

$$\frac{de}{dt} = \beta si - (\mu + \alpha)e \qquad (3.31)$$

$$\frac{di}{dt} = \alpha e - (\gamma + \mu)i \qquad (3.32)$$

$$\frac{dr}{dt} = \gamma i + \mu r \qquad (3.33)$$

With $r(t) = 1 - s(t) - e(t) - i(t)$, we have equations $(3.30) - (3.33)$ as a reduced three dimensional system. The probability to survive the latency and to enter the

infectious period equals to $\frac{\alpha}{\alpha+\mu}$ (Bjørnstad, 2005), therefore the basic reproduction number in this case is

$$R_o = \frac{\beta\alpha}{(\mu + \gamma)(\mu + \alpha)} \tag{3.34}$$

(Bjørnstad, 2005)

The number of contacts between susceptible and infective is given by

$$\sigma = \frac{\beta}{\gamma} \tag{3.35}$$

Studying the global stability of the system $(3.30) - (3.32)$ in the region $\{(s(t) + e(t) + i(t)): 0 \leq s(t), e(t), i(t) \leq 1,\ s + e + i \leq 1\}$ is highly nontrivial, because to prove the global stability of such a high dimensional system is not usually possible. The parameters and variables used in the model are summarized in table 3.1.

Table 3.1: Summary of the notations used in the SEIR model

VARIABLES	DESCRIPTION
$S(t), s$	Susceptible individuals at time t, (fraction of S)
$E(t), e$	Exposed individuals at time t, (fraction of E)
$I(t), i$	Infective individuals at time t, (fraction of I)
$R(t), r$	Recovered individuals at time t, (fraction of R)
$N(t)$	The total population which is constant at time t

PARAMETERS	DESCRIPTION
β	Reflecting the rate at which disease spreads
α	Duration of the latency of the disease
γ	Reflecting the rate which people recover from the disease
μ	Reflecting the birth rate and death rate.
R_O	The basic reproduction number

3.7.2 THE STEADY STATES

In order to determine the stability of the model we need to evaluate the steady state of the system $(3.30) - (3.32)$. In solving equations $(3.30) - (3.32)$ we consider 2 states i.e. infection – free state ($i = 0$) and endemic state ($i \neq 0$).

That is,

$$\frac{ds}{dt} = 0, \qquad \frac{de}{dt} = 0, \qquad and \quad \frac{di}{dt} = 0$$

This gives

$$\mu - (\mu + \beta i)s = 0 \qquad (3.36)$$

$$\beta is - (\mu + \alpha)e = 0 \qquad (3.37)$$

$$\alpha e - (\gamma + \mu)i = 0 \qquad (3.38)$$

Solving equation $(3.36) - (3.38)$ at $i = 0$, we have $s = 1$, and $e = 0$, hence the first equilibrium point is

$$(s, e, i) = (1, 0, 0) \qquad (3.39)$$

which is the disease – free equilibrium.

To determine the endemic state we set $e = \frac{\gamma + \mu}{\alpha} i$ using equation (3.38). We, then substitute the value of e into equation (3.37) to obtain $s = \frac{1}{\beta\alpha}(\mu + \alpha)(\gamma + \mu) = \frac{1}{R_O}$.

Putting the value of s into equation (3.36), we have $i = \frac{\mu}{\beta}(R_O - 1)$. We substitute i back into $e = \frac{\gamma+\mu}{\alpha} i$ to obtain $e = \frac{\mu(R_o-1)}{R_o(\mu+\alpha)}$. Thus the endemic equilibrium point is given by

$$(s^*, e^*, i^*) = \left(\frac{1}{R_o}, \frac{\mu(R_o - 1)}{R_o(\mu + \alpha)}, \frac{\mu(R_o - 1)}{\beta} \right) \quad (3.40)$$

3.7.3. STABILITY OF THE STEADY STATES / EQUILIBRIUM POINTS

In this section we calculate the local stability of these steady states by linearizing the system (3.30) – (3.32). The Jacobian matrix is found to be

$$J = \begin{bmatrix} -\mu - \beta i & 0 & -\beta s \\ \beta i & -(\mu + \gamma) & \beta s \\ 0 & \alpha & -(\gamma + \mu) \end{bmatrix} \quad (3.41)$$

3.7.3.1. DISEASE FREE – EQUILIBRIUM

Since the disease free equilibrium is $(s, e, i) = (1, 0, 0)$, we evaluate the Jacobian matrix at this equilibrium point to obtain

$$J_{infection-free} = \begin{bmatrix} -\mu & 0 & -\beta \\ 0 & -(\mu + \alpha) & \beta \\ 0 & \alpha & -(\gamma + \mu) \end{bmatrix} \quad (3.42)$$

This leads to the characteristic equation $\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0$ where

$$\left.\begin{aligned} a_1 &= (3\mu + \gamma + \alpha) \\ a_2 &= [(\mu + \gamma)(\mu + \alpha) - \beta\alpha + \mu(2\mu + \gamma + \alpha)] \\ a_3 &= \mu[(\mu + \alpha)(\mu + \gamma) - \beta\alpha] \end{aligned}\right\} \quad (3.43)$$

From Routh – Hurwitz stability criterion if the conditions $a_1 > 0,\ a_3 > 0\ and\ a_1a_2 - a_3 > 0$ are true, then all the roots of the characteristic equation have negative real part which means stable equilibrium. We now consider the stability of the endemic steady state.

3.7.3.2. ENDEMIC STEADY STATE

Since the endemic steady state is $(s^*, e^*, i^*) = \left(\frac{1}{Ro}, \frac{\mu(Ro-1)}{Ro(\mu+\alpha)}, \frac{\mu(Ro-1)}{\beta}\right)$. We evaluate the Jacobian matrix at this equilibrium point to obtain

$$J_{endemic} = \begin{bmatrix} -\mu R_o & 0 & \frac{-(\mu+\alpha)(\mu+\gamma)}{\alpha} \\ \mu(R_o-1) & -(\mu+\alpha) & \frac{(\mu+\alpha)(\mu+\gamma)}{\alpha} \\ 0 & \alpha & -(\gamma+\mu) \end{bmatrix} \tag{3.44}$$

This leads to the characteristic equation $\omega^3 + b_1\omega^2 + b_2\omega + b_3 = 0$. Where

$$\left.\begin{aligned} b_1 &= \alpha + \gamma + (2 + R_o)\mu, \\ b_2 &= \mu R_o(2\mu + \alpha + \gamma), \\ b3 &= \mu(R_o - 1)[\mu^2 + \mu(\alpha+\gamma) + \alpha\gamma] \end{aligned}\right\} \tag{3.45}$$

We then use Routh – Hurwitz stability criterion to determine the stability of the characteristic equation above. From Routh – Hurwitz stability criterion, if the conditions $b_1 > 0, b_3 > 0$ and $b_1b_2 - b_3 > 0$ are true, then all the roots of the characteristic equation have negative real parts which means a stable equilibrium. From equation (3.45), the first two conditions are true for $R_0 > 1$ as $b_1 and\ b_3$ are both positive quantities. Since $b_1b_2 - b_3 > 0$, the third condition which is given by

$$\mu[R_o\{(3\mu + \alpha + \mu R_o)(\alpha+\gamma) + \mu^2(3 + 2R_o) + \gamma^2\} + \mu^2 + \mu(\alpha+\gamma) + \alpha\gamma]$$

is greater than zero (for all parameter values and $R_O > 1$), hence it is also true. Thus the endemic steady state is stable when $R_o > 1$ by the Routh – Hurwitz criteria. Further analysis of the models will be done in chapter 4

3.8 THE HERD IMMUNITY THRESHOLD

The endemicity depends on the basic reproduction number R_O. This threshold value can tell us, whether the disease will invade in the population and spread out or not. If $R_O > 1$, a single infective introduced in the completely susceptible population can establish the disease. If this infective has replaced himself with more than one infective at the end of his disease, then an epidemic outbreak is produced which drives the population to the globally attractive endemic state.

The outbreak does not have to occur necessarily. There can be certain number of immunes in the population and therefore the number of susceptible can be too low. Although, this situation will not remain, because there is a constant inflow of susceptible newborns who replaces the immunes. So it seems that if we can keep the level of immunes at certain level, then the probability of an epidemic outbreak is very low. This number of immunes can be kept at a constant level artificially by vaccination or also by natural infection. This is so called herd immunity. The herd immunity threshold (H_1) is the percentage of the population that needs to be immune to control transmission of the disease. It protects directly the immune individuals from reinfection but also provides an indirect protection to susceptible population. The equation (given by Diekmann and Heesterbeek, 2000) for estimating the herd immunity threshold is

$$H_1 = 1 - \frac{1}{R_O} \tag{3.46}$$

As the amount of vaccination increases, the herd immunity threshold also increases.

CHAPTER 4

MODEL APPLICATION

4.1 INTRODUCTION

In this chapter we model the epidemiology of influenza A (H1N1) using data from the Ashanti Region of Ghana. Analysis of the data indicates that in March - August 2010 a total of 252 people attended hospitals in Ashanti region for flu screening and 76 people were found to be infected with influenza A (H1N1). Of these confirmed cases all the patients recovered (see Figure4.1, the data is also displayed in the appendix B). The data gives the following values; $S_0 = 4725042, E_0 = 2, I_0 = 2$ and $R_0 = 0$ as the initial susceptible, exposed, infective and recovered respectively. The number of susceptible at the end of the epidemic is given by $S_\infty = 4724794$. Dividing through by the total population of Ashanti region which is 4725046, we have $s_\infty = 0.999947$ as proportion of the susceptible at the end of the epidemic and $s_0 = 0.999999915$, $e_0 = 4.232763025 \times 10^{-7}$, $i_0 = 4.232763025 \times 10^{-7}$ and $r_0 = 0.0$ as initial proportion of susceptible, exposed, infectious and recovered respectively. The solutions to the H1N1 model equations are obtained with the Matlab ODE45 solver Runge Kutta method. We will also determine the stability of the equilibrium points of the H1N1 model and perform sensitivity analysis on the parameter values to determine the effect on the spread of H1N1 in Ghana.

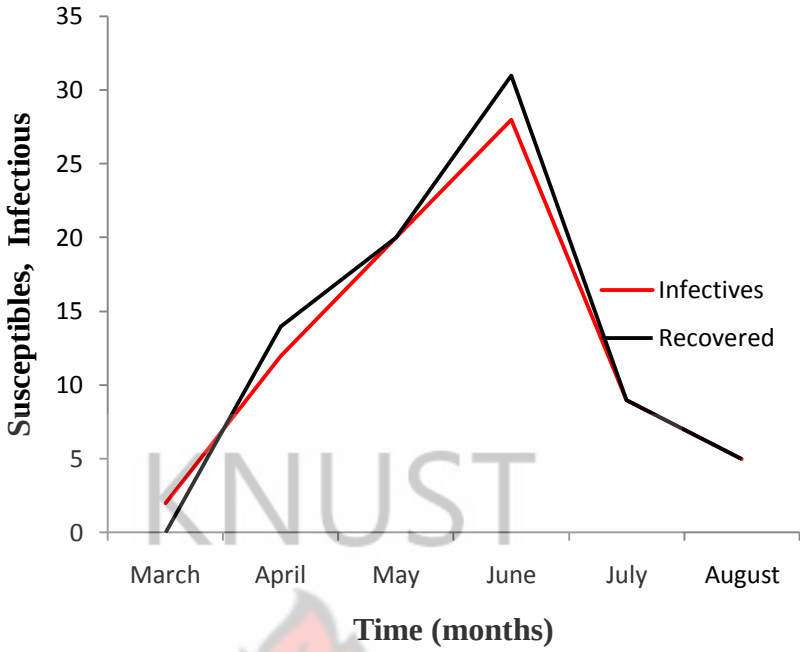

Figure 4.1: Time series plot of influenza A (H1N1) infection in Ashanti Region

From Figure 4.1 the epidemic started during the month of March and ended in August. The peak of the infection was on month of June for both recovered and infectious populations.

We now developed a model for H1N1 in Ghana, but before we do so we need to make some assumptions based on the features of H1N1 discussed in Chapter 1 Section 1.1.

4.2 MODEL ASSUMPTIONS

The assumptions of the model are as follows

- The population of Ghana has a constant size N, where birth and death occur at equal rates and that newborns are susceptible (no inherited immunity).
- The population is homogeneously mixing, with no restriction of age, mobility or other social factors.

- We assume once infected with H1N1 virus you become exposed to the environment before becoming infectious
- The transmission, latency and recovery coefficients are positive and constant.

Based on the assumptions above, which are also consistent with the conditions in Ghana, the H1N1 model satisfies the SEIR epidemiological model discussed in chapter three section 3.7, hence we adopt the SEIR model to study the spread of influenza A (H1N1) in Ghana by classifying the population as susceptible (S), exposed (E), infectious (I) and recovered (R). All parameters are as describe in section 3.7

4.3 PARAMETER ESTIMATION

We estimate the parameters of the model base on the following information. The latency period of H1N1 is $1-4$ days and infectious period is 1 day prior to onset of symptoms to 7 days after symptom onset (Gu et al., 2011), hence the mean latency period of H1N1 is 2 days and the mean infectious period is 3.5 days. The expected duration of infection is the inverse of the removal rate (Jones, 2007) hence

$$\gamma = \frac{1}{mean\ infectious\ period} = \frac{1}{3.5} = 0.2857$$

And

$$\alpha = \frac{1}{mean\ latency\ period} = \frac{1}{2} = 0.5$$

The transmission rate (β) given by (Wikipedia, transmission rate and risks) is

$$\beta = \frac{effective\ contacts}{total\ contacts} = \frac{76}{252} = 0.3016$$

The natural death rate of Ghana stands at 8.75 deaths per 1000 population (Index mundi, 2012) hence we have $\mu = 0.0088$. The above parameter estimates are summarized in table 4.1 below.

Table 4.1: Parameter estimates of SEIR model for H1N1

PARAMETER	DESCRIPTION	VALUE
μ	Per capita death rate	0.0088
β	Transmission rate	0.3016
α	Latency rate	0.5000
γ	Recovery rate	0.2857

4.4 MODEL EQUATION

Substituting the parameter values in Table 4.1 into SEIR model equation $(3.30) - (3.33)$, we obtain

$$\frac{ds}{dt} = 0.0088 - (0.0088 + 0.3016i)s \qquad (4.11)$$

$$\frac{de}{dt} = 0.3016si - 0.5088e \qquad (4.12)$$

$$\frac{di}{dt} = 0.5e - 0.2945i \qquad (4.13)$$

$$\frac{dr}{dt} = 0.2857i + 0.0088r \qquad (4.14)$$

If $r(t) = 1 - s(t) - e(t) - i(t)$, then equations $(4.11) - (4.14)$ reduced to a three dimension system. From equation(3.34), the basic reproduction number for the SEIR model above is given by

$$R_o = \frac{\beta\alpha}{(\mu+\alpha)(\mu+\gamma)} = \frac{0.3016 \times 0.50}{(0.0088+0.5)(0.0088+0.2857)} = 1.0064 \qquad (4.15)$$

Since $R_o > 1$ an outbreak of Influenza A (H1N1) will result in an epidemic in Ghana.

From equation (3.35) , the number of contacts between susceptible and H1N1 patient is given by

$$\sigma = \frac{\beta}{\gamma} = \frac{0.3016}{0.2857} = 1.0557 \qquad (4.16)$$

This means that on average 2857 influenza patients contacts 3016 susceptible people in the country during an infectious period.

4.5 STEADY STATES

From section (3.7), the system$(3.30) - (3.32)$ possess two steady states; infection – free $(i = 0)$ and endemic steady state $(i \neq 0)$ which were determined in section $(3.7.2)$ to be

$$(s, e, i) = (1, 0, 0) \qquad (4.17)$$

Which is the disease – free equilibrium, and

$$(s^*, e^*, i^*) = \left(\frac{1}{R_o}, \frac{\mu(R_o - 1)}{R_o(\mu + \alpha)}, \frac{\mu(R_o - 1)}{\beta}\right) = (0.994, 0.000109, 0.000187) \quad (4.18)$$

Which is the endemic equilibrium state. We now look at the stability of the steady state for the model.

4.6 STABILITY ANALYSIS

4.6.1 DISEASE – FREE EQUILIBRIUM

Since the disease – free equilibrium is $(s, e, i) = (1,0,0)$. The Jacobian matrix corresponding to this equilibrium point is given by

$$J_{Infection-free} = \begin{bmatrix} -0.0088 & 0 & -0.3016 \\ 0 & -0.5088 & 0.3016 \\ 0 & 0.5 & -0.2945 \end{bmatrix} \qquad (4.19)$$

The characteristic equation corresponding to the Jacobian matrix above is given by

$$\lambda^3 + 0.8121\lambda^2 + 0.0061\lambda - 0.0000084339 = 0$$

Since $-0.0000084339 < 0$ then by the Routh – Hurwitz stability criterion the disease – free equilibrium is an unstable steady state. This means that the presence of a person infected with H1N1 virus in a completely susceptible population will eventually result in an outbreak of the disease.

4.6.2 ENDEMIC STEADY STATE

The endemic equilibrium is given by $(s^*, e^*, i^*) = (0.9956, 0.0000758, 0.000129)$. The Jacobian matrix corresponding to the endemic equilibrium, is given by

$$J_{Endemic} = \begin{bmatrix} -0.0089 & 0 & -0.2997 \\ 0.000056320 & -0.5088 & 0.2997 \\ 0 & 0.5 & -0.2945 \end{bmatrix} \qquad (4.20)$$

The characteristic equation corresponding to the Jacobian matrix above is given by

$$\lambda^3 + 0.8122\lambda^2 + 0.0071\,\lambda + 0.0000084391 = 0$$

Since $0.8122 > 0,\ 0.0000084391 > 0,\ (0.8122)(0.0071) - (0.0000084391) = 0.0058 > 0$, Routh – Hurwitz stability criteria is satisfied therefore the endemic steady state is asymptotically stable. This means the H1N1 disease would spread.

We now consider the effects of changes in the parameter values on the spread of the disease.

4.7 SENSITIVITY ANALYSIS

4.7.1 DISEASE – FREE EQUILIBRIUM

If the value of the parameter β changes whilst α, μ and γ are maintained, and also if the value of the parameter γ changes whilst α, μ and β are held fixed, Table 4.2 summarizes the effects on the reproduction number and the stability of the disease – free equilibrium in section 3.7.3.1.

Table 4.2: Sensitivity analysis of the disease – free equilibrium

μ	β	α	γ	R_O	a_1	a_2	a_3	$a_1a_2 - a_3$	Nature of steady state
0.0088	0.400	0.5	0.2857	1.3347	0.8121	-0.043	-0.000414	-0.0346	Unstable
0.0088	0.1750	0.5	0.2857	0.5839	0.8121	0.069	0.0005486	0.0558	Stable
0.0088	0.3016	0.5	0.5000	0.5825	1.8571	0.9155	0.1333	1.5668	Stable
0.0088	0.3016	0.5	0.1050	2.6044	0.6314	-0.0874	-0.000818	-0.0544	Unstable

From Table (4.2) above, as the transmission rate increases or the recovery rate decreases the $R_O > 1$ and the disease – free equilibrium is unstable. This means that in the cause of an outbreak the disease will spread. On the other hand, as the transmission rate decreases or the recovery rate increases $R_O < 1$ and the disease – free equilibrium is stable. This means that the disease will fail to spread.

4.7.2 THE ENDEMIC EQUILIBRIUM

If the value of the parameters, β changes whilst α, μ and γ are maintained, and if the value of the parameters, γ changes whilst α, μ and β remain constant, Table 4.3 summarizes the effects on the reproduction number and the stability of the endemic equilibrium point in section 3.7.3.2.

Table 4.3: Sensitivity analysis of the endemic equilibrium point

μ	β	α	γ	R_O	b_1	b_2	b_3	$b_1 b_2 - b_3$	Nature of steady state
0.0088	0.4000	0.5	0.2857	1.3347	0.8150	0.0094	0.000441	0.0072	Stable
0.0088	0.1750	0.5	0.2857	0.5839	0.8084	0.0041	-0.00055	0.0039	Unstable
0.0088	0.3016	0.5	0.5000	0.5825	1.0227	0.0052	-0.00095	0.0063	Unstable
0.0088	0.3016	0.5	0.1050	2.6044	0.6455	0.0143	0.000818	0.0084	Stable

From Table 4.3, as the transmission rate increases and the recovery rate decreases, $R_O > 1$ and the endemic equilibrium are stable. This means that the disease will spread. On the other hand as the transmission rate decreases and the recovery rate increases, $R_O < 1$ and the endemic equilibrium is unstable. This means the disease will fail to spread.

4.8 SIMULATIONS AND RESULTS

We used the parameter values given in Table 4.1 for the SEIR model equations$(3.30) - (3.33)$. Matlab codes for the SEIR model can be found in appendix A. According to the 2010 population census, the initial population of Ghana is 24,223,431 and that of Ashanti region is 4,725,046. Since we are using data from

Ashanti region we use the population of Ashanti region. We measure time in months from March to August, 2010. From the simulation we obtain the graph in Figure 4.2.

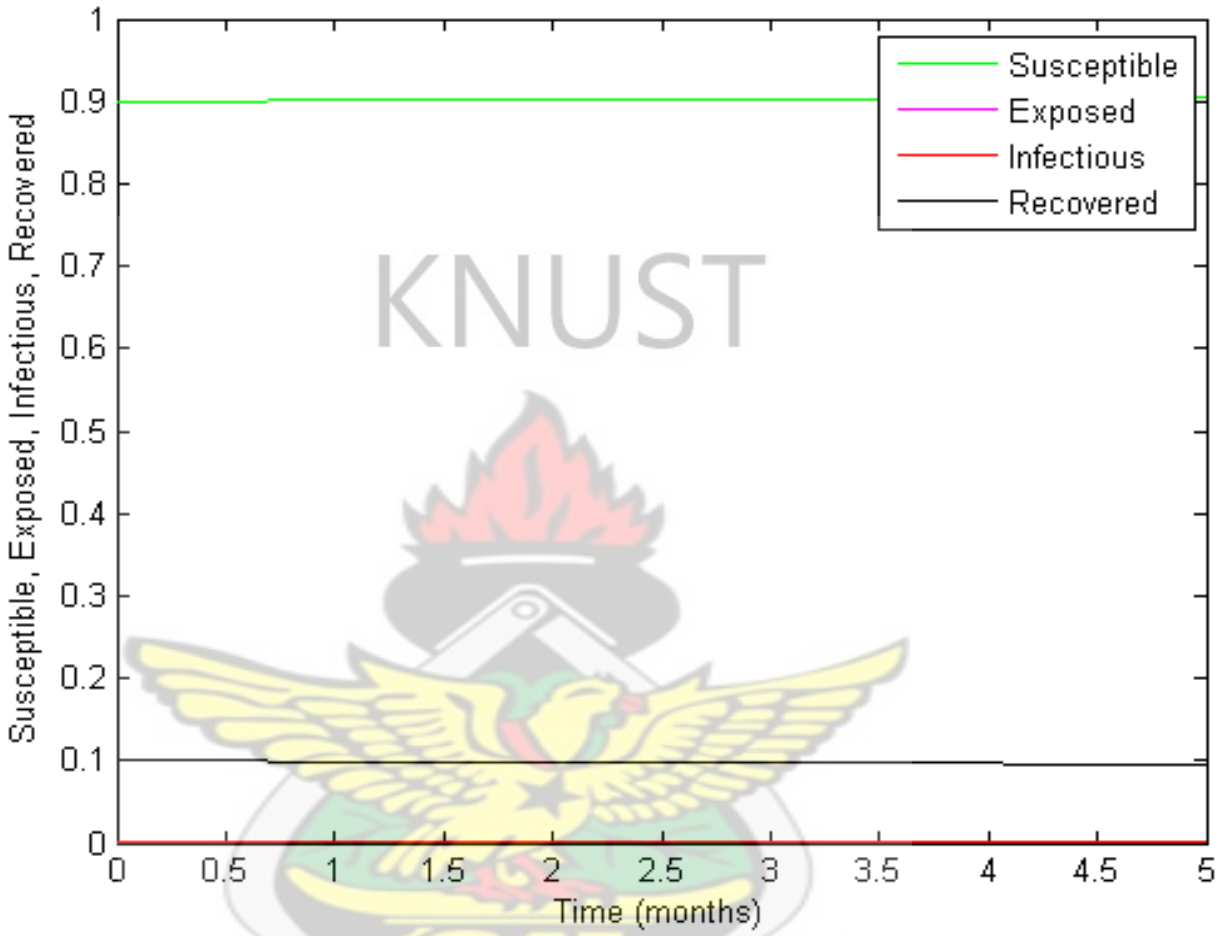

Figure 4.2: Dynamics of the various compartments at the initial outbreak of H1N1

From Figure 4.2, the initial proportion of infectious has small or no effect on the susceptible population, hence we have disease – free state.

4.8.1 EFFECTS OF A CHANGE IN THE INITIAL PROPORTION OF THE INFECTIVES ON THE VARIOUS COMPARTMENTS

We vary the proportion of infectives around the neighborhood of the endemic equilibrium point for 5 months and 16 months to see the effect on the various compartments. This is illustrated in the figure 4.3 and figure 4.4 respectively.

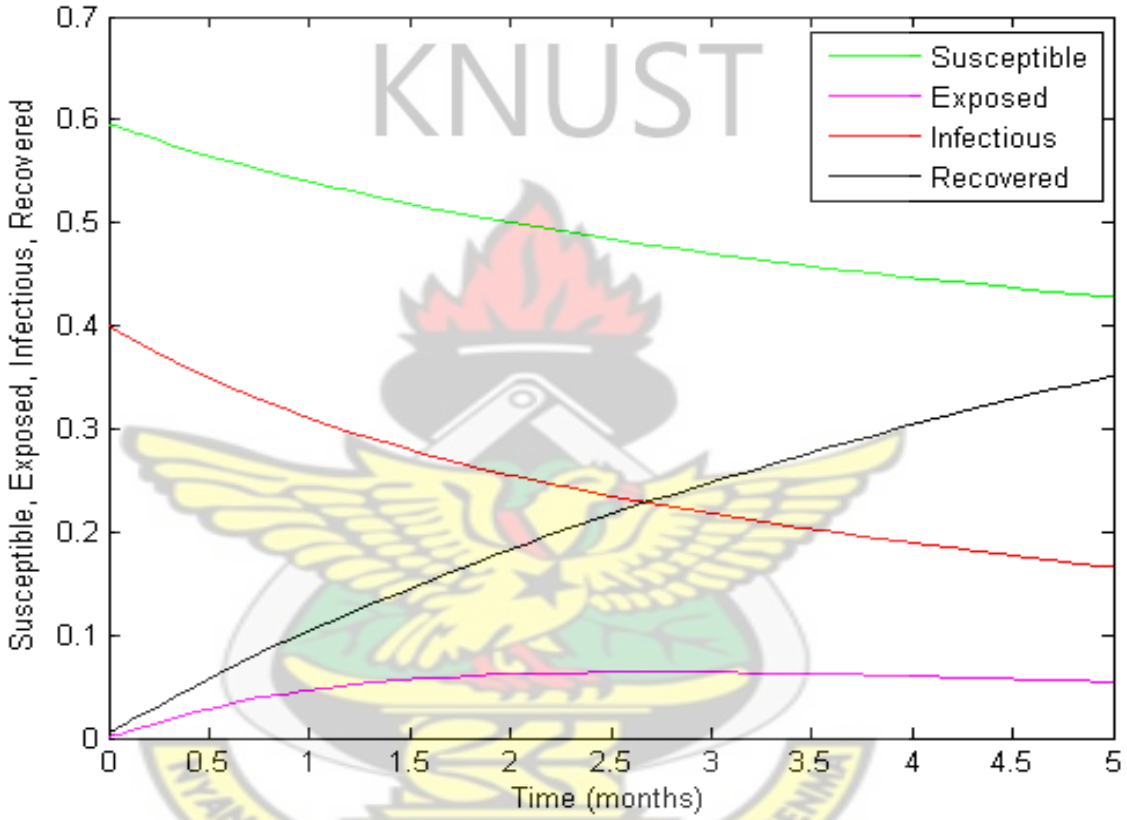

Figure 4.3: Graph of an increased in the proportion of infectives (5 months period) on various compartments

From Figure 4.3 above when the proportion of infectives increases 0.4 around the neighborhood of the endemic equilibrium, the proportion of exposed individuals initially increases from zero, reaches a peak of 0.06 in the second month then declines gradually to a minimum value of 0.05 by the fifth month. The proportion of susceptible on the other hand, declines from a value of 0.6 during the first month to a minimum

value of 0.44 by the fifth month. The proportion of recovered on the other hand increases exponentially with time and reaches a maximum value of 0.35 by the fifth month. Also the recovered population equals the infective around the third month of the outbreak.

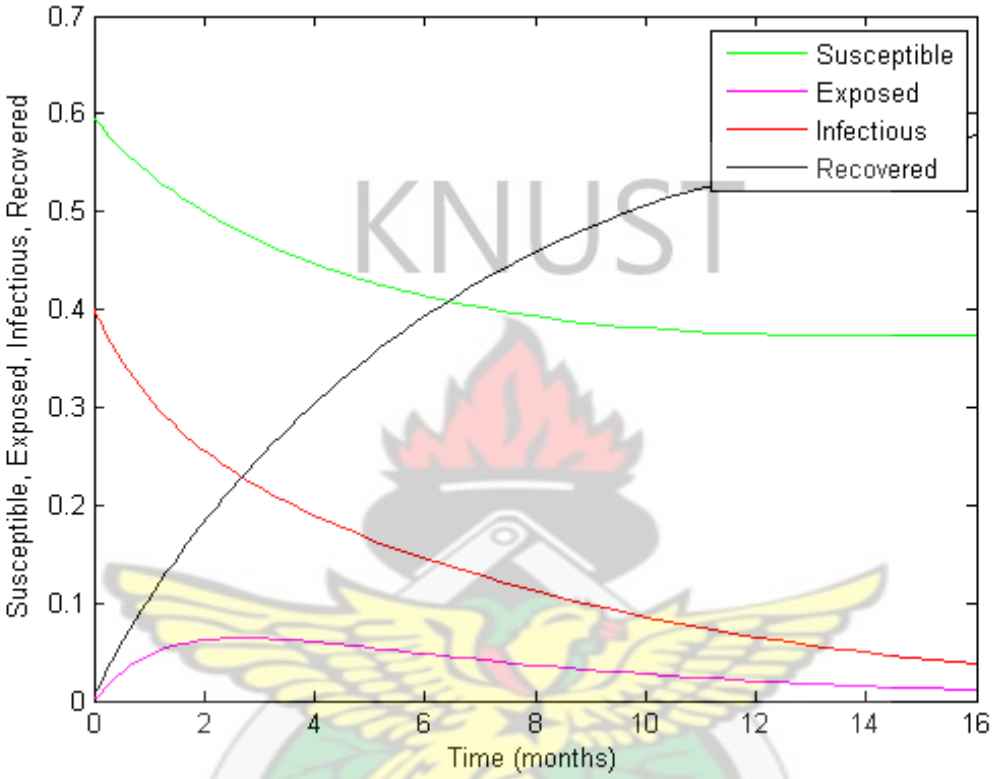

Figure 4.4: Graph in respect of an increased proportion of infectives (16 months period) on various compartments.

From Figure 4.4 above when the proportion of infectives increases to 0.4 around the neighborhood of the endemic equilibrium, the proportion of exposed individuals initially increases from zero, reaches a peak of 0.06 in the second month then declines gradually to a minimum value of 0.01 by the sixteenth month. The proportion of susceptible on the other hand, declines from a value of 0.6 during the first month to a minimum value of 0.38 by the sixteenth month. The proportion of recovered on the other hand increases exponentially with time and reaches a maximum value of 0.58 by the sixteenth month. Also the recovered population equals the infective around the third

month of the outbreak at a value of 0.23 and the susceptible around the seventh month at a value of 0.41.

4.9 THE HERD IMMUNITY THRESHOLD

From equation (3.46) the herd immunity threshold is given by

$$H_1 = 1 - \frac{1}{R_O} = 1 - \frac{1}{1.0064} = 0.0064 \qquad (4.21)$$

This means about 0.64% of the population has to be vaccinated in other to bring the disease under control in case of an outbreak.

CHAPTER 5

CONCLUSION AND RECOMMENDATIONS

5.1 INTRODUCTION

In this chapter we discuss the results obtained from the analysis of the SEIR epidemiological model in chapter four, we conclude based on the results and make recommendation for further studies.

5.2 SUMMARY OF RESULTS

From the analysis of the model we obtained the following results. The basic reproduction number, $R_O = 1.0064$, the number of contacts between H1N1 patient and susceptible, $\sigma = 1.0557$. The disease – free equilibrium $(s, e, i) = (1,0,0)$ which was found to be a saddle point (unstable) and the endemic equilibrium $(s^*, e^*, i^*) = (0.9936,0.00010999,0.00018674)$ was also found to be asymptotically stable. The sensitivity analysis shows that $R_O < 1$ when the transmission rate (β) decreases or the recovery rate (γ) increases and the equilibrium point is stable for the disease – free and unstable for the endemic state. Also $R_O > 1$ when the transmissions rate β increases or the recovery rate γ decreases and the equilibrium point is unstable for the disease – free and stable for the endemic state. From the simulation, in Figure 4.3, as the proportion of infectives is increased to 0.4 around the neighborhood of the endemic equilibrium point, the proportion of susceptible declines from a value of 0.6 during the first month to a minimum value of 0.44 by the fifth month. The proportion of exposed individuals initially increases from zero, reaches a peak of 0.06 at the second month then declines gradually to a minimum value of 0.05 by the fifth month. The proportion

of recovered on the other hand increases exponentially with time and reaches a maximum value of 0.35 at the last month. Also the recovered population equals the infective around the third month with a value of 0.22. From Figure 4.4, as the proportion of infectives is increased to 0.4 around the neighborhood of the endemic equilibrium point, the proportion of susceptible declines from a value of 0.6 during the first month to a minimum value of 0.38 by the sixteenth month. The proportion of exposed individuals initially increases from zero, reaches a peak of 0.06 at the second month then declines gradually to a minimum value of 0.01 by the sixteenth month. The proportion of recovered on the other hand increases exponentially with time and reaches a maximum value of 0.58 at the last month. Also the recovered population equals the infective around the third month of the outbreak at a value of 0.23 and the susceptible around the seventh month at a value of 0.41. The herd immunity threshold which was the sole immunization strategy was estimated to be 0.0064.

5.3 DISCUSSION OF RESULTS

From the results, the reproduction number for the SEIR epidemiological model estimated indicated that $R_O > 1$. This means the disease will spread in the cause of an outbreak. Also on the average 2857 H1N1 patients contacts 3016 susceptible people in the country during an infectious period. The sensitivity analysis revealed that whenever the transmission rate is increased or the recovery rate is reduced, the disease would spread, but whenever the transmission rate is reduced or the recovery rate is increased, the disease will fail to spread.

From the simulation, Figure 4.2, the initial proportion of infectives had no effect on the various compartments. As the proportion of infective is increased to 0.4 as shown in

Figure 4.3 and Figure 4.4 around the neighborhood of the endemic equilibrium state, the SEIR model exhibit a decline in the proportion of susceptible. This means that as more and more people are infected with the H1N1 virus, the disease will become endemic in the country. Furthermore, the recovered proportion of the population increases exponentially with time. This is as result of a relatively high recovery rate such that even though the susceptible population is infected a high amount of them recovered quickly providing herd immunity.

The herd immunity reveals that about 0.64% of the population should be vaccinated in other to bring the disease under control in case of an outbreak.

5.4 CONCLUSION

The basic reproduction number, $R_O = 1.0064 > 1$, means that the transmission rate of H1N1 is high in Ashanti region of Ghana.

From the analysis and discussions of the model, SEIR epidemiological model is a better model to study the spread of influenza A (H1N1) in Ghana.

5.5 RECOMENDATIONS

We make the following recommendations: Vaccination programmes should be encourage in the cause of an outbreak and should target 0.64% of the susceptible population. Also the government and World Health Organization (WHO) should be contacted to assist the health sector in the provision of H1N1 vaccines and equipments to ensure an effective vaccination campaign.

In this thesis we assumed the population to be constant with birth rate equals death rate. We also assumed the population interacted freely (homogeneous mixing) but in reality this is not always the case. We therefore suggest SEIR model of H1N1 in a non – constant population and a model of H1N1 in heterogeneous population using SEIR model for further research work.

REFERENCES

Anderson, R. M. and May, R. M., (1991). Population biology of infectious diseases: Part I. nature 820, 361-367, 1979. http://mathbio.colorado.edu/mediawiki/index.php/Main_Page [Accessed: 19th Nov., 2011]

Bjørnstad, O., (2005). SEIR models. www.stat.colostate.edu/~rdavis/ey680/sir.pdf [Accessed: 13th Nov., 2011]

Boëlle, P.Y., Ansart S., Cori A., Valleron A. J.,(2011). Transmission parameters of the A/H1N1 (2009) influenza virus pandemic: a review. http://www.ncbi.nlm.nih.gov/pubmed/21668690 [Accessed: 14th Nov., 2011]

Böelle, P.Y., Bernillon P., Desenclos J.C., (2009). A preliminary estimation of the reproduction ratio for the new influenza A(H1N1) from the outbreak in Mexico http://www.ncbi.nlm.nih.gov/pubmed/19442402http://www.eurosurveillance.org/viewarticle.aspx?articleid=19205[accessed [Accessed: 20th August,2011]

Boni, M. F., Manh, B. H., Thai, P. Q., Farrar, J., Hien, T. T., Hien, N. T., Kinh, N. V., and Horby P., (2009). Modeling the progression of pandemic influenza A (H1N1) in Vietnam and the opportunities for reassortment with other influenza viruses. *BMC Medicine 2009, 7:43, doi: 10.1186/1741-7015-7-43.* http://www.biomedcentral.com/1741-7015/7/43 [Accessed: 20th Nov., 2011]

Bootsma, C. J. Martin and Ferguson M. N. The effect of public health measures on the 1918 influenza pandemic in the U.S. cities. http://www.pnas.org/content/104/18/7588.abstract [Accessed: 18th October, 2011)

Cauchemez S., Donnelly C. A., Reed C., Ghani C. A., Frazer C., Kent K. C., Finelli L., and Ferguson M. N.,(2009). Household Transmission of 2009 Pandemic Influenza A (H1N1) Virus in the United States. New England Journal of Medicine, December, 2009. http://www.nejm.org/doi/full/10.1056/NEJMoa0905498#t=article [Accessed: 3rd Sept., 2011]

Chowell G., Bettencourt M. A. L. , Johnson N., Alonso J. W. and Viboud C., The 1918 – 1919 influenza pandemic in England and Wales : spatial patterns in transmissibility and mortality impact, http://rspb.royalsocietypublishing.org/content/275/1634/501.full.pdf [Accessed: 22nd October, 2011]

Chowell G., Nishiura H., Bettencourt M. A. L.,(2007). Comparative estimation of the reproduction number for pandemic influenza from daily case notification data, http://www.springerlink.com/index/G1X0772W236N1040.pdf [Accessed: 22nd Oct., 2011]

Diekmann O. and Heesterbeek J. A. P., (2000). Mathematical epidemiology of infectious diseases: model building, analysis and interpretation

http://books.google.com.gh/books/about/Mathematical_epidemiology_of_infectious.html?hl=fr&id=5VjSaAf35pMC&redir_esc=y

Encyclopeadia Britanica, (2012). Influenza Disease. Available online http://www.britannica.com/EBchecked/topic/287790/influenza [Accessed: 1st February, 2012]

Ferguson, N. M., Cummings, D. A., Fraser, C., Cajka J. C., Cooley, P. C., Burke, D. S., (2006). Strategies for mitigating an influenza pandemic. http://www.ncbi.nlm.nih.gov/pubmed/16642006 [Accessed: 20th October, 2011]

Fraser, C., Donnelly, C. A., Cauchemez, S., Hanage, W. P., Kerkhove, M. D. V., Hollingsworth, T. D., Griffin, J., Baggaley, R. F., Jenkins, H. E., Lyons, E. J., Jombart, T., Hinsley W. R., Grassly, N. C.,Balloux, F., Ghani, A. C., Ferguson, N. M., Rambaut, A., Pybus, O. G., Lopez – Gatell, H., Alpuche – Aranda, C. M., Chapela, L. B., Zavala, E. P, Guevara, D. M. E., Checchi, F., Garcia, E., Hugonnet, S., Roth, C., and The WHO Rapid Pandemic Assessment Collaboration, (2009). Pandemic Potential of a Strain of Influenza A (H1N1): Early Findings http://www.sciencemag.org/content/324/5934/1557.full.pdf (Accessed: 13th October, 2011)

Gojovic, Z. M., Sander B., MEcDev R. N., Fisman, D., Krahn M. D., Bauch, C. T., Modeling mitigation strategies for pandemic (H1N1)

2009.http://www.cmaj.ca/content/181/10/673.abstract [Accessed: 3rd September, 2011]

Gu Y., Komiya N., Kamiya H., Yasui Y., Taniguchi K., and Okabe N., (2009). Pandemic (H1N1) 2009 transmission during presymptomatic phase, Japan. Emerg infect diseases volume 17, number 9 – September 2011. http://wwwnc.cdc.gov/eid/article/17/9/10-1411_article.htm [Accessed: 20th August, 2011]

Halloran, M. E., Ferguson, N. M., Eubank, S., Longini, I. M. Jr., Cummings, D. A. T., Lewis, B., Xu F., Fraser, C., Vullikanti, A., Germann, T. C., Wagener, D., Beckman, R., Kadau, K., Barrett C., Macken C. A., Burke D. S., and Cooley P., (2008). Modeling targeted layered containment of an influenza pandemic in the United States. http://www.pnas.org/content/105/12/4639.abstract (Accessed: 19th August, 2011)

Hsieh Y., (2010). Age groups and spread of influenza: implications for vaccination strategy. http://www.biomedcentral.com/1471-2334/10/106/abstract *(11TH October, 201*

Index mundi, (2012). http://www.indexmundi.com/ghana/death_rate.html [Accessed: 1st January, 2012]

Jumpen W., Orankitjaroen S., Boonkrong P., Wattananon B., and Wiwatanapataphee W.,(2011) SIS – SEIQR adaptive network model for pandemic influenza, http://www.wseas.us/e-library/conferences/2011/Paris/ECC/ECC-23.pd [Accessed: 21/10/2011]

Kermack, W. O. and McKendrick, A. G. (1927). Contributions to the mathematical theory of epidemics. Proceedings of the Royal Society of London. Series A, volume 115, issue 772(Aug. 1, 1927), 700-721. www.ma.utexas.edu/users/davis/375/LECTURES/L26/km.pdf [Accessed: 12th July, 2011]

Longini M. I., Halloran M. E., Nizam A, and Yang Y.,(2004), Containing pandemic influenza with antiviral agents, http://www.ncbi.nlm.nih.gov/pubmed/15033640 [Accessed: 20/10/2011]

Massad, E., Burattini, M. N., Coutinho, F. A., and Struchiner C. J., (2010). The risk of acquiring the new influenza A(H1N1) for Brazilian travelers to Chile, Argentina and the USA. *Mem Inst Oswaldo Cruz, Rio de Janeiro, vol. 105(2): pp 179-183, March 2010.* Available online: http://www.bioline.org.br/pdf?oc10031 [Accessed: 19th December, 2011]

Mei, S., van de Vijver D. A. M. C., Xuan L., Zhu Y., and Sloot P. M. A., (2010). Quantitatively evaluating interventions in the influenza A (H1N1) epidemic on China campus grounded on individual – based simulations. P.M.A. Sloot; G. D. van Albada and J. Dongarra, (Editors), *ICCS, 2010, (Procedings of*

the 10th International Conference on Computational Science, May 31- June 2, Amsterdam) in series Procedia Computer Science, volume 1, page 1669-1676. Elsevier B. V., A . Available online: http://www.dynanets.org/index.php?option=com_jombib&task=showbib&id=33&return=index.php%3Foption%3Dcom_jombib%26amp%3Bcatid%3D0%26amp%3Border%3Dryear [Accessed: 20th Nov., 2011]

Mills C. E., Robins J. M. and Lipsitch M.,(2004), Transmissibility of the 1918 pandemic influenza, http://www.ncbi.nlm.nih.gov/pubmed/15602562 [Accessed: 14/10/2011]

Sharomi O., Podder C. N., Gumel A. B., Mahmud S. M., Rubinstein E.,(2010). Modeling the transmission dynamics and control of the novel 2009 swine influenza (H1N1) pandemic. Bulletin of Mathematical biology, volume 73, number 3, 515-548, DOI: 10.1007/s11538-010-9538-z. www.ncbi.nlm.nih.gov/pubmed/20379852 [Accessed: 4th July, 2011]

Shil P., Gurav Y. K., Chadha M. S., and Mishra A. C., (2011). Transmission dynamics of novel influenza A /H1N1 2009 outbreak in a residential school in India. Current science, vol. 100, NO. 8 http://www.ias.ac.in/currsci/25apr2011/1177.pdf (Accessed: 20th Nov., 2011)

Sibu,(2010). Flu. Bukisa, http://www.bukisa.com/articles/358879_flu [Accessed: 21st November, 2011]

Suh M., Lee J., Chi H. J., Kim Y. K., Kang D. Y., Hur N. W., Ha K. H., Lee D. H., Kim C. S., (2010). Mathematical modeling of the novel influenza A (H1N1) virus and evaluation of the epidemic response strategies in the Republic of Korea. J. Prev. Med Public Health. 2010 Mar., 43(2): 109- 16. http://www.ncbi.nlm.nih.gov/pubmed/20383043 [Accessed: 23rd November 2011]

Towers S. and Feng Z., (2009). Pandemic H1N1 influenza: predicting the course of a pandemic and assessing the efficacy of the planned vaccination programme in the United States.

Uhavax, (2001). History of epidemics and plagues. http://uhavax.hartford.edu/bugl/histepi.htm [Accessed: 14th February, 2012]

Wallinga J. and Teunis P., (2004). Epidemiology. http://octavia.zoology.washington.edu/publications/others/WallingaAndTeunis04a.pdf [Accessed: 11th November, 2011]

Wikipedia the free encyclopedia. Influenza. http://en.wikipedia.org/wiki/Influenza [Accessed: 11th August, 2011]

Wikipedia, the free encyclopedia. 1918 flu pandemic. Available online http://en.**wikipedia**.org/**wiki/1918_flu_pandemic** [Accessed: 10th Oct., 2011]

Wikipedia, the free encyclopedia. Characteristic polynomial. http://en.**wikipedia**.org/**wiki/Characteristic_polynomial** [15th October, 2011]

Wikipedia, the free encyclopedia. Linearization. http://en.**wikipedia**.org/**wiki/Linearization** [Accessed: 14th October, 2011]

Wu J.T., Rileys S., Fraser C., Leung G.M., (2006), Reducing the Impact of the Next Influenza pandemic using household – based public health interventions. Plos Med 3(9): e361. doi: 10.1371/journal.pmed.0030361 http://www.plosmedicine.org/article/info:doi/10.1371/journal.pmed.0030361 [Accessed: 3rd September, 2011]

Yoneyama T., Krishnamoothy M. S., (2010). Simulating the spread of influenza pandemic of 1918 – 1919 considering the effect of the first world war. http://arxiv.org/ftp/arxiv/papers/1006/1006.0019.pdf (Accessed: 20th October, 2011)

Yoneyama T., Krishnamoothy M. S.,(2010). The influence of the cold war upon influenza pandemic of the 1957 – 1958. http://www.informatik.uni-trier.de/.../**Krishnamoorthy**:Mukkai_S=.h . [Accessed: 20th October, 2011]

APPENDIX A

Matlab code for the simulation

```
function [t,s,i,e,r]=program_2_6(beta,alpha,gamma,mu,s0,e0,i0,MaxTime)
%RISK_STRUCTURE(beta,gamma,mu,s0,i0,MaxTime)
%It is the SEIR epidemic with equal births and deaths.
%Note we no longer explicitly model the recovered class.
if nargin==0
   beta=0.3010;
   alpha=0.5;
   gamma=0.2857;
   mu=0.0088;
   s0=0.5956;
   e0=0.00007576;
   i0=0.4;
   MaxTime=5;
end
if s0<=0
   error('Initial level of susceptibles (%g)is less than or equal to zero',s0);
end
if e0<=0
   error('initial level of exposed (%g) is less than or equal to zero',e0);
end
if i0<=0
   error('initial level of infectives (%g) is less than or equal to zero',i0);
end
if beta<=0
   error('transmission rate beta (%g) is less than or equal to zero',beta);
end
if gamma<=0
    error('Recovery rate gamma (%g) is less than or equal to zero',gamma);
end
 if alpha<=0
    error('Exposed to infectious rate alpha (%g) is less than or equal to zero',alpha);
 end
if mu<=0
   error ('Birth / Death rate mu (%g) is less than or equal to zero',mu);
end
if MaxTime<=0
   error('Maximum run time (%g) is less than or equal to March',MaxTime);
end
if s0+e0+i0>1
   warning('Initial level of susceptibles+infecteds (%g+%g=%g)is greater than
one',s0,i0,s0+i0);
end
if beta*alpha<(gamma+mu)*(alpha+mu)
warning('Basic reproductive number (R_O=%g) is less than
one',beta*sigma/((gamma+mu) *(sigma+mu)));
```

```
end
s=s0; e=e0; i=i0; r=1-s-e-i;
%The main iteration
options=odeset('RelTol',1e-5);
[t,pop]=ode45(@Diff_2_6,[0 MaxTime],[s e i],options,[beta alpha gamma mu]);
s=pop(:,1); e=pop(:,2); i=pop(:,3); r=1-s-e-i;
 %plots the graphs with scaled colours
figure(1)
f=plot(t,s,'-g',t,e,'-m',t,i,'-r',t,r,'-k');
legend(f,'Susceptible','Exposed','Infectious','Recovered')
xlabel 'Time(months)'
ylabel 'Susceptible,Exposed,Infectious,Recovered'

%calculates the differential rates used in the integration.
function dpop=Diff_2_6(t,pop, parameter)
beta=parameter(1);alpha=parameter(2); gamma=parameter(3);mu=parameter(4);
s=pop(1);e=pop(2); i=pop(3);
dpop=zeros(3,1);

dpop(1)=mu-beta*s*i-mu*s;
dpop(2)=beta*s*i-alpha*e-mu*e;
dpop(3)=alpha*e-gamma*i-mu*i;
```


APPENDIX B

The table below shows the susceptible – exposed – infectious – recovered individuals of H1N1 in Ashanti region.

Month	Susceptible	Exposed	Infectious	Recovered
March	4725041	2	2	0
April	4724989	22	12	14
May	4724930	22	20	20
June	4724838	34	28	29
July	4724809	11	9	9
August	4724794	5	5	5