MEASURING THE EFFECTS OF DIFFERENT CONTROL POLICIES FOR SMALLPOX EPIDEMIC AND AN OPTIMAL INVENTORY MODEL

A THESIS SUBMITTED TO

THE GRADUATE SCHOOL OF SOCIAL SCIENCES

OF

IZMIR UNIVERSITY OF ECONOMICS

BY

EBRU SELİN SELEN

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF SCIENCE
IN
THE GRADUATE SCHOOL OF SOCIAL SCIENCES

JULY 2010

Approval of the Graduate School of Social Sciences

_____

Prof. Dr. Cengiz Erol
Director

I certify that this thesis satisfies all the requirements as a thesis for the degree of Master of Science/Doctor of Philosophy.

_____

Asst. Prof. Dr. Muhittin H. Demir
Head of Department

This is to certify that we have read this thesis and that in our opinion it is fully adequate, in scope and quality, as a thesis for the degree of Master of Science/Doctor of Philosophy.

_____

Asst. Prof. Dr. Burcu Adıvar
Supervisor

Examining Committee Members

Asst. Prof. Dr. Burcu Adıvar _____

Assoc. Prof. Dr. Şafak Taner Gürsoy _____

Asst. Prof. Dr. Ebru Özbilge _____

ABSTRACT

MEASURING THE EFFECTS OF DIFFERENT CONTROL POLICIES FOR SMALLPOX EPIDEMIC AND AN OPTIMAL INVENTORY MODEL

Selen, Ebru Selin

Master of Science in Logistics Management, Institute of Social Sciences

Supervisor: Asst.Prof. Dr. Burcu Adıvar

July 2010, 183 pages

Logistics can be explained by planning, managing and controlling of all the process beginning with 'demand' or 'need' and ending with satisfying or meeting the demand(s) or need(s). Success of managing an operation, a business or an event, comes with the implementation of good decisions. Today's successful business organizations pay more attention to their logistics processes in order to not to lose their competitive advantage. Governments make surveillance plans which also include distribution of logistics systems in order to respond more effectively to disasters.

In this thesis, we focus on epidemic disasters and the humanitarian aspects of logistics. We analyze smallpox disease dispersion by using epidemiological modeling to provide insights for logistical decision making

process. We examine the disaster management concept, more precisely epidemic disasters. We focus on the concept of epidemiological modeling and provide a literature review, present our research question and proposed models for smallpox epidemic. We provide an optimal order policy for vaccine requirements in three different scenarios. Model data and numerical results corresponding to epidemic models and an optimal inventory model are provided. Finally, we finalize the thesis with conclusions and future research directions

Keywords: Epidemiological modeling, smallpox, logistics, disaster management

ÖZET

ÇİÇEK HASTALIĞI SALGINI İÇİN FARKLI KONTROL POLİTİKALARININ DEĞERLENDİRİLMESİ VE OPTİMAL ENVANTER MODELİ

Selen, Ebru Selin

Lojistik Yönetimi Yüksek Lisansı, Lojistik Yönetimi Bölümü

Tez Yoneticisi: Yrd. Doç. Dr. Burcu Adıvar

Temmuz 2010, 183 sayfa

Lojistik talep veya ihtiyaç ile başlayan, talebin tatmin edilmesi veya ihtiyacın karşılanmasına kadar olan süreçlerin planlanması, yürültülmesi ve kontrol edilmesi olarak tanımlananır. Bir operasyonun, işin veya bir olayın yönetiminde başarı, öncesinde alınan kararların kalitesi ile doğru orantılıdır. Günümüz organizasyonları, kurum ve kuruluşları elde ettikleri rekabetçi avantajı kaybetmemek adına lojistik süreçlerine daha çok önem vermektedirler. Benzer bir şekilde devlet kurum ve kuruluşları da istenmeyen bir durum karşısında kalınması halinde en etkili şekilde cevap verebilmek için, acil durum planlarında lojistik sistemlerine önem vermektedir.

Bu tezde, beklenmeyen bir çiçek salgınında lojistiğin insani operasyon boyutu incelenecektir. Çiçek hastalığının popülasyon içerisindeki dağılımı matematiksel modelleme yardımı ile incelenecek ve sonuçların lojistik planlama

sürecine nasıl bir girdi sağlayacağının üstünde durulacaktır. Afet yönetimi konusu çalışılarak, salgın hastalıkların neden olduğu afetlerin yönetimsel süreçleri incelenmiştir. Epidemiyolojik modelleme konusu işlenmiş ve ilgili yazın taraması sunulmuştur. Aynı zamanda epidemiyolojik modellemenin lojistik ile ilgisi vurgulanacaktır. Araştırma problemi tanıtılacak ve modellenecektir. Epidemiyolojik modellemeden elde edinilen bilgi ile envanter planlama modeli sunulacaktır. Probleme dair nümerik çözümler yapılacak ve problem sonuçlandırılacaktır. İleride irdelenecek problemler üzerinde durulacak ve tez sonlandırılacaktır.

Anahtar Kelimeler: Epidemiolojik modelleme, çiçek hastalığı, lojistik, afet yönetimi

DEDICATION

To my parents

ACKNOWLEDGEMENTS

I would like to thank my supervisor Asst. Prof. Dr. Burcu Adıvar for becoming my thesis advisor. Her support, guidance and instruction in this work and throughout my graduate study have been invaluable. I would also like to thank committee members Assoc. Prof. Dr. Şafak Taner Gürsoy and Asst. Prof. Dr. Ebru Özbilge for being part of this thesis and also for their major contributions. I am grateful to the other faculty members in the Department of Logistics Management, Prof. Dr. Tunçdan Baltacıoğlu, Asst. Prof. Dr. Muhittin Demir, Asst. Prof. Dr. Öznur Yurt and Asst. Prof. Dr. Özgür Özpeynirci for always being there for me and their constructive suggestions and comments. I would also like to thank Assoc. Prof. Dr. Murat Adıvar for helping me with models and providing insights. Finally, I would like to thank my family especially, my sister, Dr. Eser Selen and my friends.

LIST OF TABLES

LIST OF FIGURES

TABLE OF CONTENTS

CHAPTER 1

INTRODUCTION

The concept of logistics involves broad range of activities including business activities such as satisfying the demands of customers and also humanitarian activities such as meeting the needs of disaster victims. In business logistics, while decreasing costs and maximizing the profits are essential, in humanitarian logistics minimizing the total number of deaths is the main consideration. All the operations with the aim of preserving the remaining life after the disaster can be considered as relief operations in the context of humanitarian logistics. As Kovacs and Spens (2007) report, logistics is responsible from 80% of the success in relief operations. Most of the relief operations are included in the field of logistics, with an aim of delivering the right service or product to the right place at the right time in order to minimize the total number of disaster induced deaths.

In this thesis, we focus on epidemic disasters. Altay and Green (2006) provide a general description of relief operations corresponding to the disaster management stages, which are mitigation, preparedness, response and recovery. In this context, we provide a detailed list of activities that might be considered in managing epidemic disasters. Based on the likelihood of a possible bioterrorist attack, we consider smallpox disease and use epidemiological modeling to

examine the logistical concerns and decisions that are related to epidemic disasters.

The outline of the Thesis is as follows. Concepts and terminology regarding epidemiology, epidemiologic modeling and their relationship with logistics are introduced in this Chapter. Chapter 2 presents the literature on epidemiologic modeling and smallpox studies. Chapter 3 includes four alternative biological attack scenarios and corresponding epidemiological models. Based on the control policies and preventive measurements presented in Chapter 3, Chapter 4 includes the optimal inventory model for vaccine order decision. Relevant scenario data, numerical results and comparative analysis for the proposed models are provided in Chapter 5. Thesis is concluded with the discussion and future research directions presented in Chapter 6.

1.1. Concept of 'disaster'

A disaster can be examined under two main groups, natural disasters and man-made disasters (Rutherford and Boer, 1982, van Wassenhove, 2006, Altay and Green, 2006). Natural disasters include floods, avalanches, earthquakes which are not sourced directly by anthropogenic effects. On the contrary, man-made disasters include wars, industrial or chemical accidents or leakages, and bioterrorist attempts.

Table 1.1: Rutherford and Boer's (1983) disaster classification.

Man-Made Disasters		Natural Disasters
Traffic		Earthquake
Explosion		Flood
Collapse		Hurricane
Fire		Volcanic eruption
Poisonous gas		Avalanche
Civil disturbance		Meteoric collision
Panic		Drought
Nuclear accidents		Famine
Local wars ⟶	Fugitives ⟶	Epidemic

Earthquakes, landslides, floods, hurricanes, volcanic activities, avalanches, tsunamis can be listed as high energy involved natural disasters, whereas, famine, drought and epidemics can be considered as life-threatening natural disasters without any physical destructions. Man-made disasters can be sourced from accidental events such as explosions, chemical leakage or intentional attempts such as wars or terrorist attacks. Most of man-made disasters results in physical destruction and mass casualties. Rutherford and Boer's (1983) classification of disasters is listed in Table 1.1.

As a special case, epidemic disasters can be considered in both natural and man-made disasters. Naturally, an epidemic may originate from a new form of a biological agent or as a result of combined effects of other disasters. For instance, a change in climate can result in drought and cause famine and epidemic disasters. Similarly, war or a bioterrorist attack can be the reasons for an epidemic due to the release of biological agents or starvation, disruptions in health systems, and lack of sanitation due to the adverse effects of war. In contrast to a war or an earthquake, an epidemic does not cause any physical

disturbance in infrastructure (Kovacs and Spens, 2007). Due to the absence of any disturbance in infrastructure, it can take longer to assess the start, and potential impact of an epidemic on population(s). This delay in recognition of an epidemic might result in uncontrolled dispersion of the disease, and might end up with millions of causalities. Unlike an earthquake or other mass destructive weapons, intentional use of bio-weapons that is supplied by agents such as virus, bacteria, toxins, might not be easily detected and identified (Blanty,2005). There are systems available to use in order to detect any unwanted and unexpected agents in the air. The operation principle of biological point detection system is analyzed by Blanty (2005). For better understanding of epidemics and epidemic disasters, in the next Section, we present related terminology regarding epidemiology.

1.2. Related Terminology

According to International Federation of Red Cross and Red Crescent's (IFRC) official definition; 'a **disaster** is a sudden, calamitous event that seriously disrupts the functioning of a community or society and causes human, material, and economic or environmental losses that exceed the community's or society's ability to cope using its own resources.[1]

Rutherford and Boer (1982) define disasters as the release of huge amount of energy that will result in life-threatening physical destructions.

[1] International Federation fo Red Cross and Croissant (IFRC)

The term **epidemiology** is derived from the Greek words meaning study upon populations (epi- upon, demos people, -ology study) (Farmer and Lawrenson, 2004, Bhopal, 2002).

According to Porter (2008), the term **disease** is defined as the physiological dysfunction in result of the presence excessive presence or relative absence of a causative factor which can be a microorganism, chemical substance, or form of radiation.

According to WHO definition, **infectious diseases** are caused by pathogenic microorganisms, such as bacteria, viruses, parasites or fungi; the diseases can be spread, directly or indirectly, from one person to another.

Porta (2008) defines **outbreak** as an epidemic limited to localized increase in the incidence of a disease, e.g., in a village, town, or closed institution; upsurge is sometimes used as a euphemism for outbreak. Whereas Porter (2008) defines **epidemic** as "A single case of a communicable disease long absent from a population or first invasion by a disease not previously recognized in that area requires immediate reporting and full field investigation; two cases of such a disease associated in time and place may be sufficient evidence to be considered an epidemic."

The **incubation period** is the interval between the implantation of infectious virus and the onset of the first symptoms, which in smallpox were fever and constitutional disturbances'.

1.3. Epidemiology and Epidemic Disasters

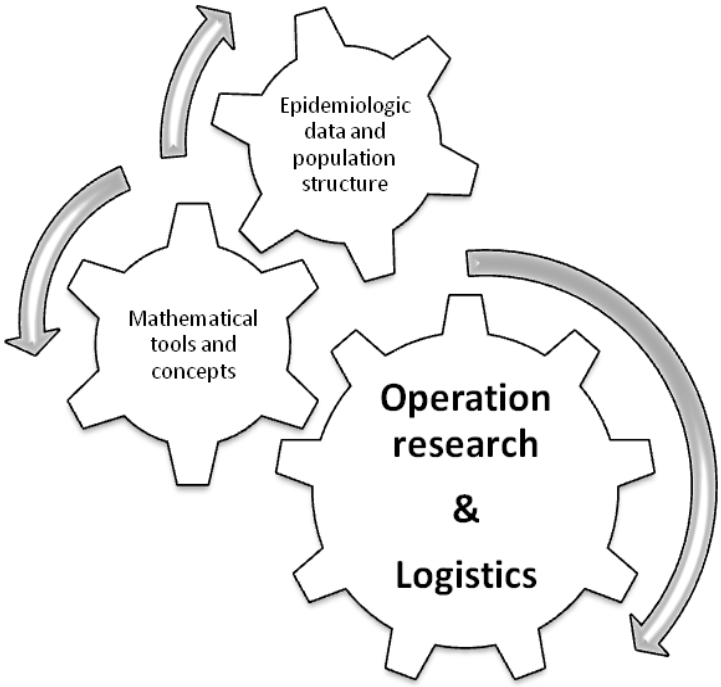


Figure 1.1. The relation between epidemiology, mathematics and logistics.

Epidemiology is an interdisciplinary area that examines the occurrence and distribution of health-related states and/or events in specified populations, including the study of the determinants influencing such states, and the application of this knowledge to control the health problems (Porta, 2008). Epidemiology heavily relies on the disciplines such as mathematics, biology, social sciences, computer science (Rothman, 2002). Figure 1.1 shows the interdependency between three fields. Although they are very different disciplines with very different considerations, we aim to emphasize the clear connection among them.

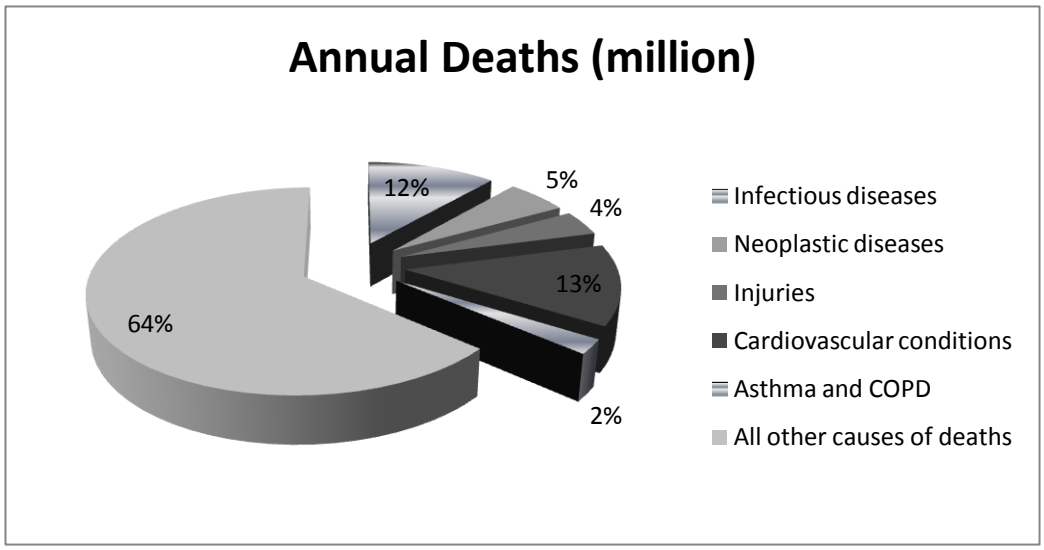


Figure 1.2. Cause of deaths declared by WHO, 2004.

There are many different types of epidemiology, which can be classified by disease type and physiology. *Infectious disease epidemiology* can be defined as the study which examines communicable disease such as, smallpox, influenza, HIV/AIDS, and hepatitis. *Cancer epidemiology* investigates the study design, data collection and developing models upon determined hypothesis of cancer illness and related deaths among the population. *Chronic disease epidemiology* examines the effects of diseases in the population that has slow onset and progress. *Renal epidemiology* can be defined as the study of kidney diseases and illness, and investigates effects on population. Among all other causes of death and illness, we focus on infectious disease epidemiology which has an important role in the field of public health and preventive medicine. Figure 1.2 shows the percentage of worldwide infectious disease induced deaths (Morens *et al.*, 2004).

Infectious (communicable diseases) are caused by an agent and spread through different ways including inhalation of the contaminated air (e.g.

influenza viruses, variola major, and *varicella* viruses), digestion of contagious food or water (*salmonella* species), being in close physical contact with an infected individual, being in an interaction with an infected vector e.g. infected rodents or carrier mosquitoes. Some diseases can spread by combined ways. Smallpox disease can be acquired by respiration and skin contact.

An infectious disease can have potential to create mass destructions in the population if there are enough numbers of susceptible and non-immune individuals. In case of SARS, immunity did not exist in the population therefore susceptibility to the agent was high. This resulted in high numbers of death including the microbiologist who identified the virus. In managing epidemic disasters, it is crucial to be prepared and if not, it is essential to detect the potential threat as soon as possible.

Morens *et al*.. (2004) suggest a classification for emerging diseases. They consider the differences among infections based on their dynamics, treatment and prevention point of views. Based on this classification, emerging infections can be examined in three classes. Newly emerging infectious diseases correspond to diseases that are not identified before e.g., SARS, Nipah, Hendra, avian flu (Blanty, 2005). Re-emerging infectious diseases such as West Nile, human monkeypox, multidrug- resistant *Mycobacterium tuberculosis* correspond to diseases that existed in past and now rapidly increasing either in incidence or in geographical or human host range (Blanty, 2005; Morens *et al.*, 2004). Deliberately emerging infectious diseases cover the infections of agents that can be found in nature and cause diseases in natural ways, and agents that are

genetically modified in order to enhance their hazard potential (Morens *et al*., 2004) .

1.3.1. Epidemics

As a disaster, an epidemic can result in suffering people and might be responsible for millions of death. With globalization, the mobility of individuals is increased, dispersion occurs more easily and the agent can reach every part of the world through transportation of products, people and livestock. Mangili and Gendreau (2005) consider transmission through air travel for several diseases. They emphasize the importance of early detection and appropriate infection control systems. Note that infectious diseases exist in nature while some are developed for a nefarious usage. This intentional usage of some agents can be examined in the context of bioterrorism.

Throughout the history, the lethal impacts of chemical and biological agents have been well known. These biological agents which can cause infectious diseases can be used intentionally, as a part of war or for causing panic and anxiety which would end up with serious psychological impacts instead of high numbers of casualties (Blanty, 2005).

A summary of some bioterrorist attempts or nefarious usage of agents is provided in Table 1.2. The Center for Disease Control (CDC) of United States defines a bioterrorist attack as the ‘deliberate release of viruses, bacteria, or other germs (agents) used to cause illness or death in people, animals, or plants’. CDC also classifies the agents depending on how easily they can spread and the severity of illness or death they cause.

Table 1.2. A brief history of intentional use of agents.

14th century	Tatars catapult plague victim's bodies over the walls of Kaffa (the modern Crimean port of Feodosia, Ukraine) (Morens *et al*.,2004)
14 th -18 th century	Plague wipe out 1/3 of affected population
17th century	Smallpox contaminated blankets were distributed during the war between French and Indian
First world war	Intendently dispersion of cholera to Italy and plague to Italy by Germany.
Second WW	Experiments on prisoners using plague, cholera, plague resulted in 10000 deaths
The Rajneeshee Cult, in Oregon USA	*Salmonella typhimurium* caused an outbreak of salmonellosis where 751 people fell ill at salad bar and supermarkets, in 1984
Prior to 1950s	Several thousands of cases tularemia was recorded.
1932-1945	260,000 people died in 11 Chinese Cities by contaminated water supplies and food items
2001 USA	Intentional dissemination of anthrax spores through the US Postal System led to the deaths of 5 people, infection of 22 others.

Sourced from Kahrdori and bioterrorism and disaster medicine.

Agents listed in Table 1.3 may affect individuals by causing various diseases. Among the listed agents or diseases, some might not be infectious (e.g. Ricin toxin), while some are highly infectious and able to create epidemics (e.g. Ebola). According to this classification, we focus on agents that cause epidemics. In other words, we examine diseases that can be dispersed among population through various paths of infection.

Table 1.3: Categorization of agents by CDC.

	Category A	Category B	Category C
AGENTS / DISEASES	Anthrax	Brucellosis	Nipah virus
	Viral hemorrhagic diseases *	Epsilon toxin of *Clostridium perfingens*	Hanta virus
	Plague	Food safety threats	
	Smallpox	Glanders	
	Tularemia	Meliodosis	
	Botulism	Psittacosis	
		Q fever	
		Ricin toxin	
		Staphylococcal enterotoxin B	
		Typhus fever	
		Viral encephalitis alphaviruses**	
		Water safety threats	

*Ebola, Lassa, Machupo

**e.g. Venezuelan equine encephalitis, eastern equine encephalitis, western equine encephalitis

Due to the developments in science and medicine, populations in developed countries are not suffering from naturally-occurring infectious diseases such as measles, smallpox, and plague. However, these childhood diseases caused large amounts of deaths just before they eradicated or taken under control by appropriate treatment techniques, such as vaccination campaigns. Rather than fatal childhood diseases, world is currently suffering from sexually transmitted diseases (STDs) including HIV and hepatitis. According to WHO, "approximately 1.6 million people were living with HIV in 2001 in the WHO European Region. Estimations suggest that this number increased to 2.4 million people in 2008 and is still rising[2]". The most devastating

[2] WHO, http://www.euro.who.int/en/what-we-do/health-topics/diseases-and-conditions/hivaids

pandemic caused by a type of influenza virus, originated in Europe in 1918. Murray *et al*.. (2006) report that deaths reached to be 20 - 100 million people. In their study, authors implement data and rates of past pandemic (Spanish Flu) to the population of 2004, and obtain a result that shows the casualties of this disease in population of 2004. Recently, humanity overcomes from another strain of influenza virus swine flu (H1N1). Improved herd immunity that comes from past epidemics/pandemics, medical developments and better planning play important role in reducing the number of deaths significantly.

In case of a large scale epidemic, besides the human casualties, economy is one of the most affected fields. SARS outbreak that emerged in China (2003) represents a good example. SARS was dispersed to other continents and resulted in 3389 cases and 165 deaths (a death rate of 4.9 percent) reported in 27 countries (Wenzel *et al*., 2003), including Singapore, Canada, Ireland and US. The estimated cost of SARS was estimated to be 40 million dollars.

1.4. Epidemics and Disaster Management

An effective management of a disaster might save millions of people and also play an important role in recovering the disruptions in social life and economy. In this context, an effective action plan against an epidemic disaster is vital to lessen the negative impacts. Multidisciplinary approach and an organized, collaborative action between the related governmental and non-governmental organizations will be required during the design of an epidemic disaster surveillance plan. Furthermore, in choosing the right control policy, public health experts and governmental or nongovernmental funding

organizations will work in collaboration. Joint and synchronized efforts of various disciplines would strengthen the overall management of an epidemic.

Table 1.4. Disaster management phases for an epidemic and related operations.

Mitigation	• Risk analysis to measure the potential for extreme hazards • Planning a surveillance plan that address the managerial issues, human resource and supply capacity • Investing in vaccine production technology • Conduct research to predict dispersion speed and final size of a potential epidemic
Preparation	• Education of the health care providers, emergency medical staff essential for the successful surveillance activities and medical response. Prioritization of preventive medical service delivery. • Policy development • Coordination of public health officials • Production and storage of vaccines • Control the in and outflows of country. • Taking cautious action in borders and airports.
Response	• Putting surveillance plan into action. • Creating awareness among population by using mass media services • Provide effective health care delivery for both infected individuals and remained susceptible
Recovery	• Provide feedback on control policies and performance of the surveillance plans. • Collect relevant data and perform statistical analysis to update disease characteristics model parameters. • Analyzing the effectiveness of previous stages' management and strengthen the weaker areas.

In Table 1.4, we provide a list of operations that might be beneficial if implemented in case of an epidemic disaster. Managing an epidemic involves an interdisciplinary collaboration including, legal entities, researchers on social, medical sciences, OR/MS experts, and economists. Analyses, planning and optimization are critical for success of management concept, therefore, heavily used for disaster management.

Mathematical modeling is a powerful tool for determining the best or the most appropriate policy, assessing the effectiveness of chosen policy and understanding the patterns of disease transmission (Hethcote, 2009; Del Valle, 2005). Therefore, it has important contributions to disease intervention programs by providing insights to decision makers. During the planning stage of surveillance plans, many countries rely on mathematical disease dispersion modeling (Hethcote, 1989). Doyle *et al.* (2006), report in their study that their findings were considered by French Ministry of Health while they were planning the antiviral strategy against Influenza. They were able to answer 'how much to order' question which corresponds to an important lot sizing problem in the field of logistics and operation research. Therefore, the study of Doyle *et al.* (2006) provides a good example of how mathematical models serve to the field of epidemiology, public health and logistics.

1.5. Epidemiological Modeling

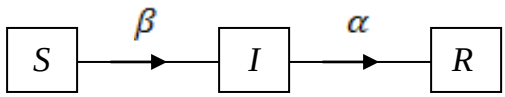
Recent science developments in applied mathematics and biological sciences provide insights for predicting possible hazards that a population will be

facing in case of an epidemic. In this thesis, we focus on infectious disease epidemiology. Our main interest is to analyze the dispersion and impact of an infectious disease in populations with different sizes.

1.5.1. Epidemiologic Modeling Concept

Epidemiologic modeling can be defined as the representation of disease dispersion through mathematical equations among a population. Since subpopulations are represented as compartments, these models are also called compartmental models. Basic stages are denoted as '*S*', '*I*,' ,'*R*' corresponding to susceptible, infected, recovered subpopulations, respectively. Susceptibles are healthy individuals that have no immunity against the agent. An individual is called infected if he/she confers with the responsible agent. When an infected individual survives he/she moves to the recovered class. Arrows represents the flow of individuals between classes and Greek letters show the rates of flow. This basic model is illustrated in Figure 2a. A model in which disease is terminated without immunity is called SIS (susceptible, infected and susceptible) as shown in Figure 2b.

(a)



(b)

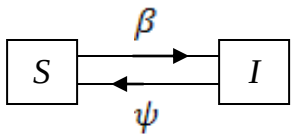


Figure 1.3: Basic compartmental models: (a) SIR and (b) SI.

Equation (1.1) shows the corresponding equations, where N denotes to total population.

$$\dot{S} = -{}^{\beta SI}/_{N}$$

$$\dot{I} = {}^{\beta SI}/_{N} - \delta I \qquad (1.1)$$

$$\dot{R} = \delta I$$

$\dot{S}$ denotes the rate of change in a susceptible population, similarly $\dot{I}$ and $\dot{R}$ represent the changes in infected and recovered proportion, respectively. In order to determine the final size of the population, rate of transitions between classes will be represented by differential equations (Brauer, 1984). The rate of β is the product of number of contacts per unit time and the transmission probability per contact. β can be taken as constant. This kind of population is called 'homogeneous mixing' population, in which everyone has the same chance to get infected (Valle *et al.*, 2005). Whereas, more realistic version of homogenous mixing is the situation in which β is non-constant and proportional to the population size. Heterogeneity can take many forms in terms of susceptibility, infectivity, contact rate and spatial network (Volz, 2008). Susceptible proportion may be divided into more than one category according to the health status, age, gender or any special condition. Some part of the infected subpopulation might be more active than remaining proportion or might be geographically separated. Moreover, two subpopulations might differ in response to an epidemic. These can be given as some instances that are describing the

heterogeneity in the model. In real life settings, non-uniform rates and status might be more logical due to the variety in contact rates during an epidemic, which leads to use partial differential equations that are more difficult to solve (Volz, 2008).

In Equation (1.1), the parameter β is an important determinant for determining final size of the epidemic and calculating the threshold quantity, which is also called basic reproductive number R_0. The parameter α represents the recovery rate; the rate of transition from I class to R class. Recovery rate is equal to mean duration time. In other words, individual recovers at a rate of α, thus, stays in I stage with an exponentially distributed mean duration of 1/α. (Brauer, 1984). Since the birth and death processes are not considered in the basic SIR model, R represent the individuals that have stayed in 'I' class for 1/α days and then recovered with full immunity or die. Each parameter corresponds to exponentially distributed waiting times in the compartments (Hethcote, 1989). These rates are expected to vary from disease to disease.

The basic steps of epidemiological modeling are similar to modeling concept used in operations research and management science. The modeling steps followed in this study is summarized in Figure 1.4.

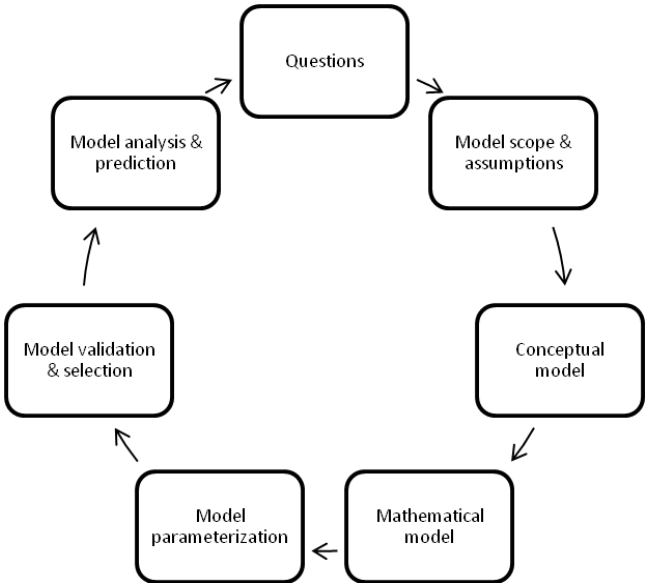


Figure 1.4 Wonham and Lewis's (2008) model building steps.

As the first stage of modeling, we should define the problem(s). After the definition of problem, appropriate research question(s) should be asked, such as what is the dispersion speed of a disease? Second, an appropriate framework for model should be drawn. The main considerations at the second step are how population, landscape, time, environment should be represented in this framework. Since not all real life variables and probabilities can be included in the model, we should make some assumptions, which should be clearly defined. For instance, if we assume that contact number is constant, then we should also make an assumption on population characteristics (homogenous or heterogenous mixing). Then we begin to visualize the model by using Kermack McKendric's basic compartmental model, as shown in Figure 1.3. More compartments can be added as needed. For instance, adding quarantine and isolation compartments would make the model more complex but also more realistic. After designing the conceptual model visually, mathematical representation of the model should be

constructed. In compartmental modeling, arcs represent flows and nodes represent stages. There will be rates assigned on flows representing the transitions from one compartment to another.

As an expected outcome of the model, we should also have a look at the threshold concept. Threshold is the number that determines the progression of an epidemic among a given population. Chowell and Brauer (2009) describe the basic reproductive number, R_0 as follows. "There is a difference in epidemic behavior when the average number of secondary infections caused by an average infective during his/her period of infectiousness called basic reproductive number". After building the mathematical model, parameters should be integrated, in order to run the model. These parameters can be obtained by estimation or can be derived from observed data.

An important concept in epidemiological modeling is the 'basic reproductive number', R_0, which represents the average number of secondary cases generated by a single infective introduced to a wholly susceptible population (Hethcote, 1982). In other words; if R_0 equals to '2', a person could transmit the disease to two other individuals, on average. R_0 is calculated as the product of 'β' the contact number, the fraction of infected people and the success rate of transmission between a susceptible individual and infected one. R_0 serves several purposes. First, R_0 stands for a threshold value which determines whether disease will die out or continue. In this context, if the calculated value of R_0 is greater than 1, the disease will continue, if the value is calculated to be equal or less than equal than 1, it can be said that disease will die out soon (Del Valle, 2005). Second, R_0 is used to evaluate the effectiveness of control policies by re-

calculating after the implementation. Varying values of R_0 determines the dependence of R_0 to exogenous factors such as differences in social contact patterns of a population, contact numbers, disease nature and transmission pattern, environmental factors, demographic structure of population (Hsu *et al*, 2004). Even in the same population, but at different time periods R_0 can be calculated with different values. Modeling is an experimental tool for testing theories and assessing quantitative conjectures.

The other benefits and purposes of epidemiologic modeling are defined by Hethcote (1982) and stated below:

1. Modeling provides concepts such as a threshold, reproduction number.
2. Models with appropriate complexity can be constructed to answer unique questions.
3. Modeling can be used to estimate key parameters by fitting data.
4. Models provide structures for organizing, coalescing and cross-checking diverse pieces of information.
5. Models can be used in comparing diseases of different types or at different times or in different populations.
6. Models can be used to theoretically evaluate, compare or optimize various detection, prevention, therapy and control programs.

Whether it is mathematical or analytical, all real life details cannot be considered in a model. Thus, assumptions are required in order to generate substantive solution. Assumptions of the model also mean restriction. Hethcote (1982) defines three limitations of epidemiological modeling;

- An epidemiological model is not reality; it is an extreme simplification of reality.
- Deterministic models do not reflect the role of chance in disease spread and do not provide confidence intervals on results.
- Stochastic models incorporate chance, but are usually harder to analyze than the corresponding deterministic model.

In the next Section, we describe how the results of epidemiologic modeling can be combined with logistics for better management of the epidemic disaster.

1.6. Logistics and Epidemiological Modeling

Surveillance plans are projections for possible disasters and prepared by city governments. Control policy decisions, capacity and resource planning and health care service delivery issues are included in a surveillance plan. Therefore, for the purpose of preparing for epidemics, epidemiologic modeling constitutes very important part of surveillance plans. Policy planning begins with determining the appropriate policy according to the characteristics of disease and population. As illustrated in Figure 2.6 in Chapter 2, taking large scale measures such as vaccination and quarantine requires strict authority and well coordination besides a special fund. Thus needs to be initiated by government with the involvement shareholders**.** The less complex individual level policy implementation includes activities that aim to increase the awareness of personal hygiene or avoiding close contacts, on disease dispersion.

Consider a situation in which vaccination is chosen as the control policy. There might be no or insufficient supply to satisfy the requirements. One of the considerations during planning stage is, analyses that need to be conducted to support make or buy decisions. Especially for vaccine procurement, vaccine packaging and storage conditions impose an important restriction on the decision. Another issue in planning vaccination policy is the prioritization. A prioritization should be done if disease impacts are higher on some part of the population, due to demographical characteristics. For instance, if disease constitutes a bigger threat for the school-aged children, they should get the treatment first. Administering these vaccines require additional care givers and related employees. Number of extra care givers should be sufficient to deliver all people in the targeted area in a given time period. Thus approximate numbers of employees need to be determined prior to an epidemic. Quarantine and isolation policies might require extra facilities and prioritization decision for whom to quarantine or isolated. Thus, facility location and capacity planning decisions should also be made.

Note that, all of the decisions regarding an epidemic disaster need to be planned, managed and implemented with the aim of "…providing adequate supply and human resources at the right time, to the destination, to the right people, in proper form; during the disaster and to maintain relatively fair living conditions after the disaster and being the part of continues improvement for strengthen possible weaker areas for possible future challenges." More precisely, this point is exactly where the epidemiological modeling meets **humanitarian** logistics.

CHAPTER 2

LITERATURE REVIEW

In this Chapter, we provide a summary of epidemiological modeling of diseases which could be used as potential candidates for bioterrorism. In particular, we focus our attention on influenza and category A diseases namely; smallpox, anthrax, SARS, viral hemorrhagic diseases (Ebola, Lassa Fever, Machupo) and plague. From these diseases, although Influenza is the most frequently observed pandemic or epidemic source, Smallpox, Anthrax, SARS, Plague are diseases which attract researchers' attention because of their potential use in bioterrorism. Since the main focus of this study is smallpox epidemic, we also make a brief introduction to the epidemiology of smallpox and review the related literature.

2.1 Population Specific Epidemiological Modeling

In this section, we conduct a literature review for epidemic modeling of most contemporary transmittable diseases by examining 70 research articles published between 1971- 2009.

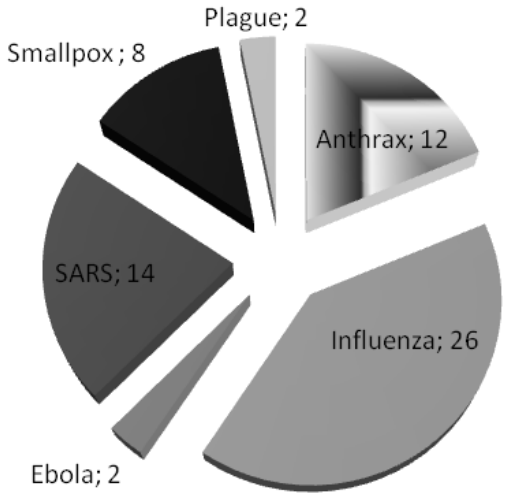


Figure 2.1. Distribution of diseases in literature review.

We use ISI Web of Knowledge database, with keywords ‘epidemic’, ‘epidemiological models’, ‘influenza’, ‘anthrax’, ‘smallpox’, ‘Ebola’, ‘Lassa Fever’, ‘Machupo’ and ‘SARS’. Figure 2.1 shows the distribution of selected diseases. Although the search engine found numerous studies, we only select studies those containing a statistical, mathematical, and analytic or empirical models. We also would like to address the variability of the epidemiological model outcomes with respect to country specific data. For instance, a research article which includes a model for smallpox dispersion among Portland population is a valid candidate for our review. In addition to these, we include a few research works which propose fundamental results in the field. For further

reading we refer readers to; Bratava *et al.,* (2006), Hupert *et al.,* (2002), Longini *et al.,* (2007).

Table 2.1 describes the characteristics of 70 selected studies in eight different categories. In the next sections, each category/column is described separately. First three columns give information about authors, publication date, and disease type. Fourth column includes specific population which the model is based on. Fifth, sixth and seventh columns indicate the overall methodology of the models. Eighth column indicates the control policy, if used in the model.

2.1.1. Publication Years of the Study by Disease

Modeling the influenza virus occurrences draws the most attention, due to its frequent strikes and rapid dispersion. Despite the limitations, such as considering only country specific research, we could observe that preparedness actions against influenza pandemic/epidemic have clear priority in many countries' surveillance agenda.

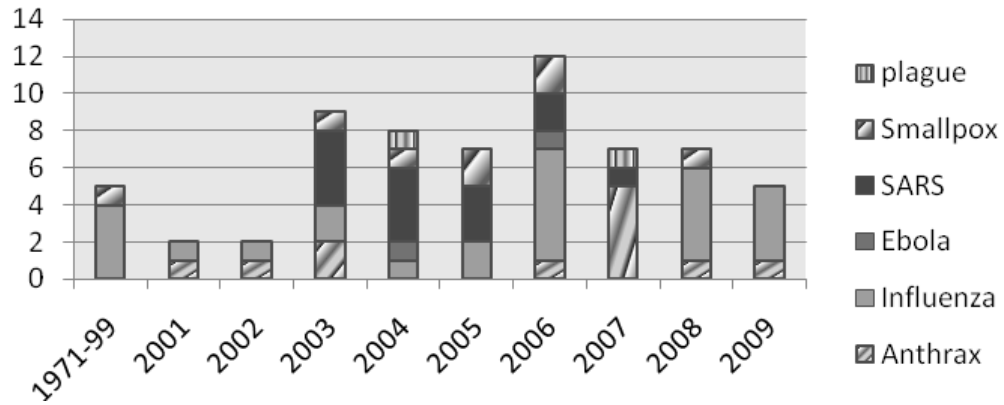


Figure 2.2. Distribution of research articles by date and disease.

Based on Figure 2.2, a dramatic increase is observed for SARS modeling in 2003. SARS is a new disease relative to others. Until the 2003 outbreak in China, virus CoV did not exist in literature. As a consequence of the outbreak in 2003, the virus was identified and many studies were conducted in many areas after this time. A recent bioterrorist attack in the US was attempted with an agent causing anthrax disease. We observe an increase in anthrax studies in 2007. Only two studies contain models based on Ebola. As reported by Chowell *et al.*, 2004 Ebola literature still suffers from lack of information. Limited data, and unidentified virus dynamics may be the factors causing the lack of interest in Ebola.

2.1.2. Epidemiologic Modeling Based On A Specific Population

The fourth column[3] of Table 2.1 indicates the population that the model builds upon or is tested on, and was conducted to explore the published models developed for a specific population or tested with real population data.

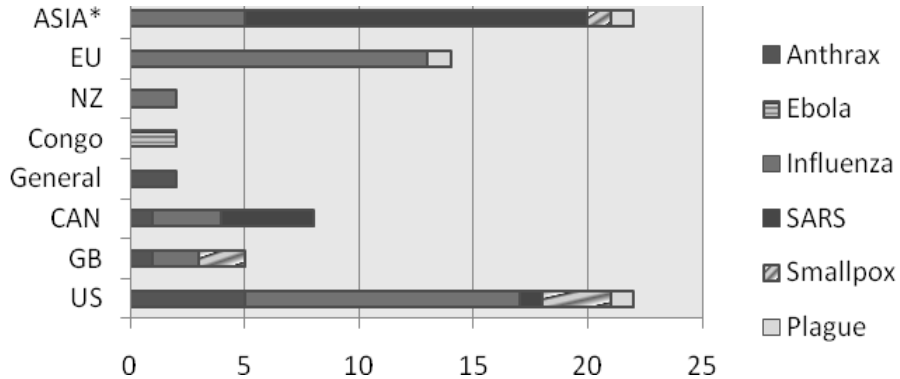


Figure 2.3. Distribution of research articles by population and disease

[3] 'ASIA*' in Figure 3 represents the populations of China, Japan, Singapore, N. Vietnam and South Asia in general. For more detail please check Table 2.1.

Figure 2.3 shows the distribution of studies including an epidemiological model for specific population.

Among 70 studies, 15 research articles include epidemiologic models of SARS. It is also observed that most of the studies examine disease dispersion in several cities of China. This may be due to the zero patient; the initial case was reported in Guangdong, China. Han *et al.* reviewed the research works that were published in China on SARS modeling and highlighted the national strengths and weaknesses in this area. U.S and European countries are currently showing increased interest in influenza modeling.

2.1.3. Methodology and Techniques of Epidemiologic Models

In Table 2.1, columns 5 to 7 indicate mathematical characteristics of studies such as methodology, technique and whether research includes compartmental model or its derivatives (SIR; Susceptible – Infected – Recovered, SEIR; Susceptible – Exposed – Infected – Recovered, and MSIRS; Maternal – Susceptible – Infected – Recovered – Susceptible).

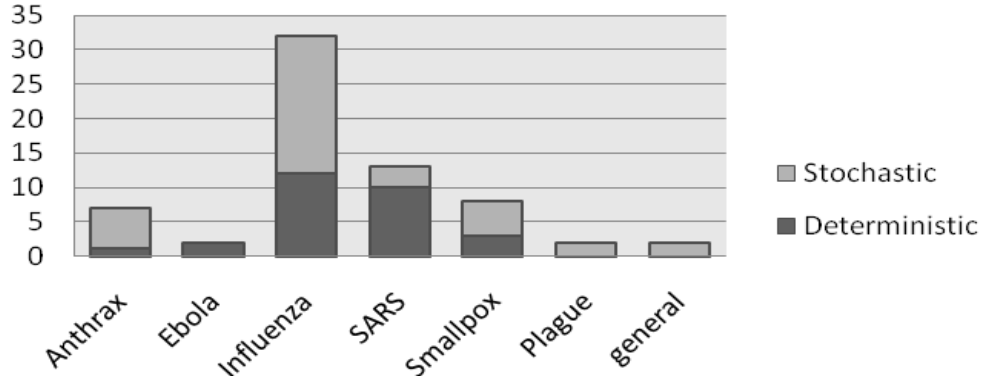


Figure 2.4 Distribution of methodologies employed in the models.

For a given initial condition, if there is no probability distribution involved in a model, then it is called a deterministic model. In contrast, stochastic models involve certain level of randomness. In stochastic models, while some level of probability is attained, the output will be much closer to the real world results. Figure 2.4 shows the distribution of methodologies. In this context, 28 research articles involve a deterministic model while 38 involve stochastic model. In general, stochastic approach is reported to be more appropriate for scenario analysis during mitigation and preparedness stages.

The column number 7 indicates the technique or tools to construct the model. Differential equations and simulation are the most common analytical tools used in epidemiological modeling. Nishiura and Tang (2004) examine the prediction of the smallpox epidemic outcome and make an evaluation of control policy through differential equations. Roberts *et al.* (2007) calculate R_0s of influenza both in the absence and after the implementation of control policy. Ruan *et al.* (2006) examine the impact of travelling on SARS dispersion via multi region compartmental model. Sattenspiel *et al.* (2003) examine the effectiveness of quarantine by calculating R_0. Volz (2008) models the progression of smallpox with heterogeneous contact rates. Chowell *et al.* (2009, 2006, 2007) calculate R_0s for pandemic influenza in various cities, Chowell *et al* (2004) evaluate the control policies that are implemented against Ebola in Congo and Uganda, and Chowell *et al*. (2005) examine the impact of the ability of diagnosing SARS on dispersion and the positive contribution of isolation policy.

Table 2.2. Distribution of simulation studies.

Simulation Type	Reference
Agent Based Simulation	12, 28, 30, 41
Individual Based Simulation	25
Monte Carlo Simulation Model	1, 16, 70
Discrete Event Simulation Model	1, 33, 45, 68
Network Based Simulation	18, 24

Simulation is an analytical tool that enables researchers/planners to visualize the impact of an epidemic among the population beyond equations. Of the 70 research works, 12 of them simulate disease dispersion. Table 2.2 shows the summary of simulation-based research articles.

All models developed with differential equations are supported with compartmental models. While these equations represent the changes from one class to another, using compartmental models allows this flow to be visualized and provides better understanding. As it can be seen from the Table 2.1, most of the compartmental models, especially those in which the impacts of control policies on disease dispersion are examined, include additional compartments such as isolation and quarantine.

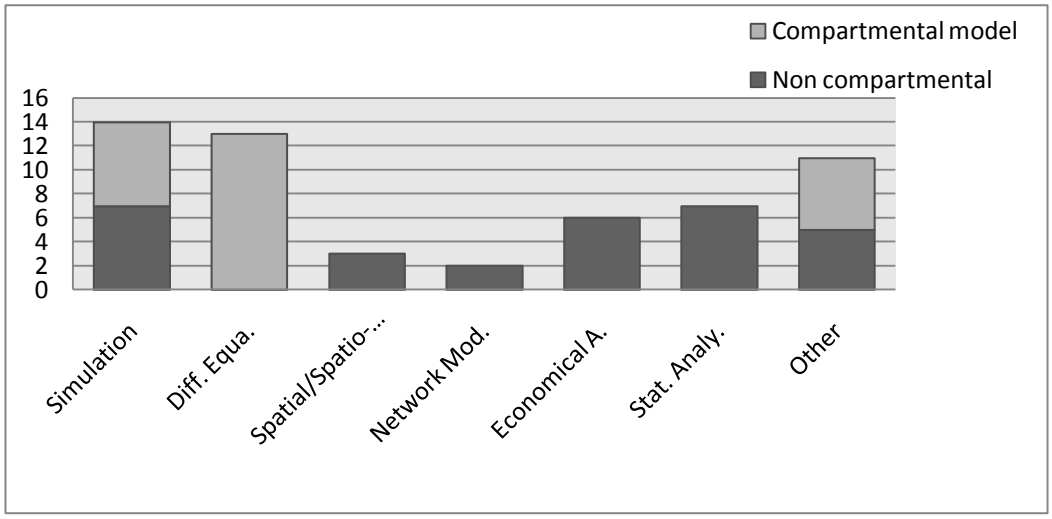


Figure 2.5. Distribution of techniques employed in the models.

Spatial and spatio-temporal models are used to examine the time and location dependent dispersion. Statistical analyses are conducted in most studies to predict the possible impacts of the epidemic using historical data. 'Other' techniques include the following: two level mixing structure (Ball, 2006), discrete time branching (Becker 1977, Nishiura 2007), second order Gaussian filter (Duncan, 2005), meta-population compartmental model (Riley, 2003), a network model (Webb *et al*., 2002), atmospheric dispersion model (Wein, 2003), discrete epidemic model, (Zhou *et al.*, 2004).

2.1.4. Control Measures and Logistical Consideration

As stated before, epidemiologic modeling provides insights for planning and mitigating against a possible disaster. An effective epidemic management requires combination of managerial decisions which are shown in Figure 2.6.

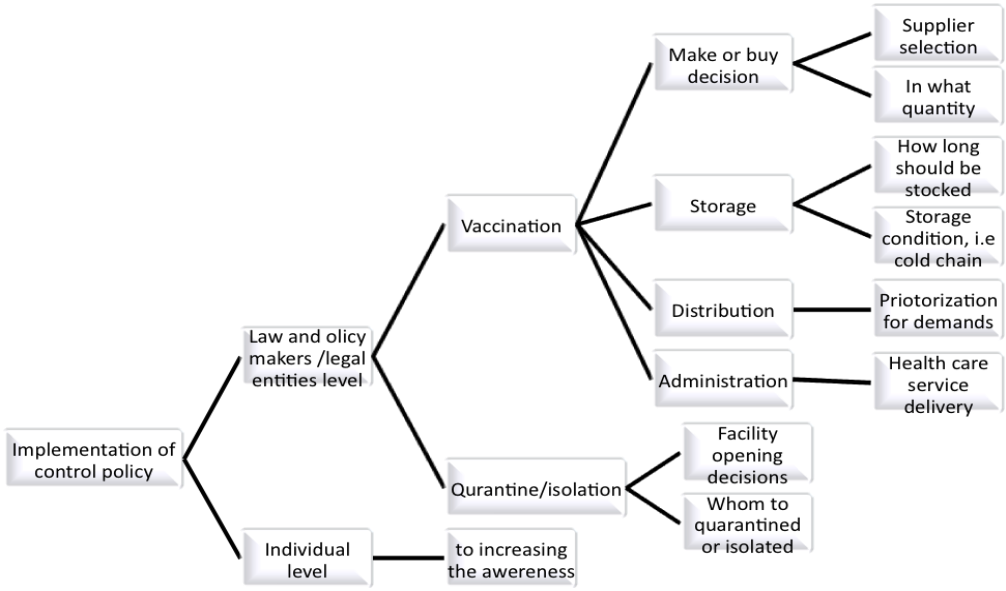


Figure 2.6. Logistics decisions should be made during epidemic management.

The chemical nature of vaccines and some drugs make their storage inconvenient. In addition, the handling, location and relocation of large quantities of medical supplies are associated with high costs. Success of encountering a disaster might be depending on the level of initial emergency service delivered. At the beginning of an epidemic, medical supplies and/or health care facilities might not be sufficient to serve all infected individuals in the population. Thus, in receiving the first response against a disaster -in this case against an epidemic-, it is crucial to optimize the number of facilities that deliver health care service. Medical resources might be limited at the very beginning of an epidemic. The decisions for distributing these resources will be crucial in overcoming an epidemic. In this context, Koyuncu and Erol (2010) propose a multi objective decision model in order to optimize resource allocations against Influenza pandemic for Turkey. Kaplan *et al.* (2009) analyze a smallpox attack**.** They construct a compartmental model in order to calculate

size of victims. They examine different control policies and specific vaccination policies. They also consider the health care delivery problem by including queuing theory into their research.

Budget is an important constraint in planning and should not be ignored in this process of overcoming the epidemic. Zaric and Brandeu (2001) suggest that the allocation of fixed budget for targeted intervention should be planned**.** John *et al.* (2001) focus on an anthrax related bioterrorist attack. They make a comparison cost of control activities and treatment and cost of preparedness activities against a possible attack. Authors conclude the study by suggesting preparedness activities will reduce both mortality and also cost much less. In another study, cost and benefit analysis is performed by Schoenbaum (1967) in order to show the economic impact of influenza from individual point of view. Meltzer *et al.* (1999) examine economic impact of vaccine-based interventions for Influenza in USA. They also consider vaccine administration for different age groups and include several objectives for vaccination policy. In a fashion similar to the study of John *et al.* (2001), Fitzner *et al.* (2001) claim that the benefits gained from vaccination program in Hong Kong, are much higher than the costs during the epidemic. Gupta *et al.* (2005) examine costs and benefits of implementing quarantine policy against SARS in Toronto. They conclude their research by highlighting the fact that quarantine would be the best policy in terms of cost effectiveness.

In the majority of research studies, control policies are compared and evaluated. In some of the studies, vaccination is chosen as the best policy, while in others quarantine and social distancing are claimed to be the best policy. As

expected, policies vary between disease types and the severity of the situation. The reason why different control policies are considered and approved for the same disease is the dependence of disease dispersion on many exogenous factors, such as agents' nature, demographic and social characteristics of population(s), ecologic environment of landscapes.

In addition to the evaluation of individual policies, some of the studies (Riley *et al.* 2003, Ferguson *et al.* 2005) recommended that a combination of policy vaccination and isolation policies would be sufficient to stop an epidemic. Nishiura and Tang (2004) emphasize the priority of smallpox vaccination among one subpopulation. More specifically, they recommend a priority should be assigned according to individuals' immune status. On the other hand, a SARS related study advocates quarantine as the best way to terminate an epidemic (Drake, 2006). Many models suggest that social distancing, solely or combined with another policy, have an important role on further dispersion. Social distancing includes individual based isolation, changing communication patterns such as preventing greetings which include kissing, avoiding close contacts, wearing protective masks, gloves. Del Valle *et al.* (2005) study on how behavioral changes effect the progression of a smallpox epidemic. They find out that even a small amount of change in contact rate damps the dispersion. It can be suggested that whether vaccination or quarantine policy is chosen, policies that are supported by individual level actions might terminate epidemic in shortest time periods.

2.2. Smallpox Models

Among all other category A type diseases, smallpox is different in terms of being the first disease that eradicated all over the world (Henderson *et al.*, 1999, Lane and Summer, 2005). Therefore, reporting only one case is enough to start an alert for a smallpox epidemic. Smallpox is also unique in terms of initial dispersion pattern. Unlike other pox species, smallpox has no natural reservoir (Parrino and Graham, 2006). Therefore the only way to introduce smallpox into population is intentional bioterrorist actions. Wein declares his thoughts on smallpox as a bio threat as; "*Ed Kaplan and I were aware that smallpox (Kaplan et al. 2002) and anthrax were considered the most dangerous bioterror threats both from reading (1999, Henderson) and from conversations*"[4]. In the next Section, we examine smallpox disease and review modeling research studies for smallpox.

2.2.1. Epidemiological Modeling for Smallpox

Smallpox, have originated over 3000 years ago, and it is one of the most devastating disease to humanity. The World Health Organization officially certified the eradication of smallpox on December 9, 1979.[5] Until that time disease was endemic for many countries in various continents. Endemic refers here as the persistence of the disease among population (Fenner *et al.*,1988). In the study of Fenner *et al.*, (1988) countries that are smallpox-endemic countries are listed from 1920 to 1978. It is estimated that smallpox is responsible for 500

[4] Homeland Security: From Mathematical Models to Policy Implementation Operation Research 57(4) pp. 801—811: 2009.

[5] http://www.cdc.gov/Features/SmallpoxEradication/

million people in the 19th and 20th centuries (Kennedy *et al.*, 2009). Besides, many survivors became permanently disabled.

The worldwide vaccination in the context of smallpox eradication program relies on ring vaccination. After the eradication, the compulsory vaccination was abandoned – with the result that about half of the world's population is not vaccinated (Wolff *et al.*, 2007). Vaccinated individuals also lost their immunity two decades after vaccinated (Hull *et al.*, 2003). Therefore, populations might be assumed to be fully susceptible for smallpox.

Although, re-introduction of this disease to population(s) is not considered likely these days, the suitable nature for bioterrorism and lethal power of this agent force academic and political world to think 'what if' question. As stated before, smallpox can re-emerge due to the leakage from one of the smallpox storage laboratories or due to an intentional release. Almost every smallpox researches in the literature reviewed in this Thesis, consider bioterrorism scenarios. Models and related literature review will be examined in detail in later sections.

Major control measures that lead to the eradication of smallpox disease are reported to be active surveillance, outbreak investigation, outbreak control, rapid communication of disease intelligence (Foege *et al.*, 1971), and isolation (Hull *et al.*, 2003). As observed from the literature, modeling disease progression and related analytical models that provide insights on optimal demand and supply balance have been an important reference point for a surveillance action plan that

will be designed by governments, non-governmental organizations such as WHO and other decision makers.

In order to make more accurate plans against an epidemic, it is required to determine the size of individuals that need to be treated, cared, isolated, vaccinated and hospitalized. Epidemiological modeling enables researchers to determine these outputs. As inputs, one might consider the structure of populations e.g. the demographic structure or immunity status for a specific disease, other might consider the host parasite interaction. Independently what kind of epidemic modeling study is conducted, disease dynamics represented as an important part of the study. For successful modeling of smallpox epidemics we need to examine the disease characteristics.

2.2.1.1. Variola Virus

Taxonomically, Variola virus belongs to the family Poxviridae, subfamily Chordopoxvirinae, and genus orthopoxvirus, which includes vaccinia (smallpox vaccine), monkeypox virus, and several other animal poxviruses[6]. Smallpox is a severe disease which might result in death, permanent disability and most optimistically permanent scars mostly on face. Disease develops in various forms of variola as a result of host and agent factors and/or interactions that determine the disease type (Koplan *et al.*, 1979). Hemorrhagic type which has almost 100% fatality rate, a special form of virus, flat type which is mostly occured in unvaccinated children with almost 100% fatality rate (Hull *et al.*, 2003). Variola major which is known as classical smallpox (see Figure 2.7) has

fatality rate of 30% (Fenner *et al.*, 1988).Variola minor, a milder form which has flu like symptoms has 1% fatality rate only (Fenner *et al*., 1988) and modified type which develops in vaccinated individuals, has fatality rate lower than 10% (Koplan *et al.*, 1979).

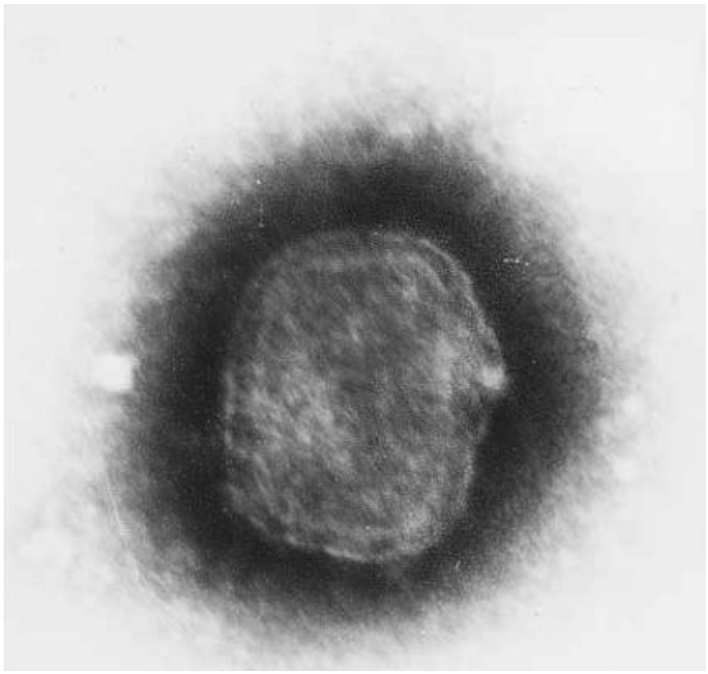


Figure 2.7. Electron micrographs of Variola Major (*Source: Diagnosis and management of smallpox, 2002*).

2.2.1.2. Disease Transmission and Epidemiology

Smallpox considered in this study is a severe disease that is caused by virus, *Variola Major*. Smallpox can be transmitted through close contacts with an infected person, via inhalation of contaminated air or having contact with a contaminated object (Fenner *et al*, 1988). Airborne nature of smallpox allows disease to spread quickly. During the 20th century, it is estimated that smallpox was responsible for 300–500 million deaths (Wollf *et al.*, 2007).

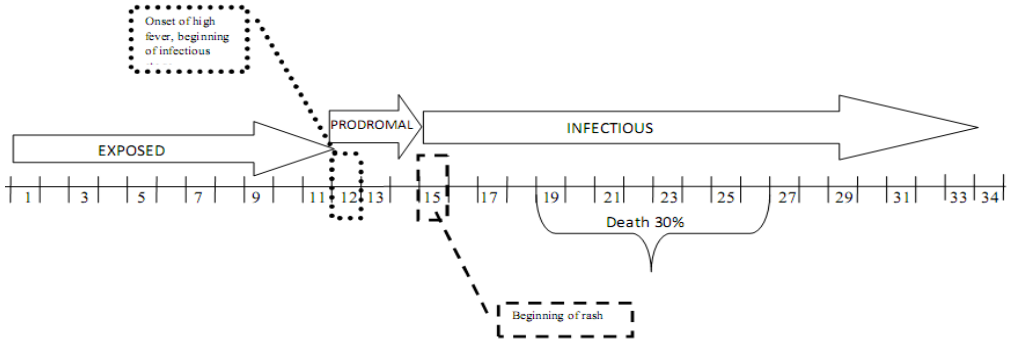


Figure 2.8. Smallpox progression timeline.

Although, smallpox is a highly infectious disease, transmission requires prolonged face-to-face contact (Lane and Summer, 2009). Contrary to influenza which has couple of days of incubation period; smallpox has longer incubation period (Hull *et al.*, 2003). Longer incubation period is a characteristic for smallpox and varies between 7 to 19 days (Fenner *et al.*, 1988). Average estimation of this period is 15 days (Fenner *et al.*, 1988). Note that the incubation period is the elapsed time that begins with being exposed to an agent and ends when adequate replication of virus, spreading the body and induce immune system (Fenner *et al.*, 1988).

An individual stays asymptomatic till the beginning of high fever, which corresponds to the end of latent period. It should be highlighted that until the last three days of the incubation period, individual is uninfectious and asymptomatic. During these three days, the infectiousness begins but disease symptoms do not show up. This stage is called prodromal stage. In prodromal stage, an individual

is able to infect susceptibles at a 'reduced infectivity' rate (Fenner *et al.*, 1988). We also consider this reduced impact on disease dispersion.

2.2.1.3. Treatment and Control Measurements against Smallpox

There is no specific treatment defined for smallpox (Breman *et al.*, 2002). Vaccination provides an option as prophylaxis and control policy measurement. Other control policies that were used throughout the history are, isolation, quarantine, social distancing. The effectiveness of control policies differs according to the disease and population characteristics. Among all the policies, vaccination is different from others because vaccination can be implemented prior to exposure as well as after the exposure.

2.2.1.3.1 Vaccine and Vaccination Strategies

Roberts *et al.*, (2007) consider scenarios including different medical treatments for smallpox targeted antiviral treatment and antiviral propyhlaxis (TATP). Smallpox vaccine that is produced from dead or weakened vaccinia virus which belongs to orthopoxvirus family (Hull *et al.*, 2003, Fulginiti *et al.*, 2003), provides a reduction in the magnitude of course of the disease.

Vaccination is generally safe and effective for prevention of smallpox however, it may also cause adverse reactions which might be life threatening. Further details[7] on associated adverse reaction can be found in Fulginiti *et al.*, (2003). As reported in Kerrod *et al.*, (2005), in Edinburg 1942, the number of deaths related with the adverse reaction of vaccines exceeded the number of

[7] Centers for Disease Control and Prevention. Smallpox vaccination and adverse reactions: guidance for clinicians. MMWR Morb. Mortal. Weekly Report 2003; 52(RR-4):1–28.

disease induced deaths. For this reason, Edinburg Ministry of Health proposed to terminate the vaccination (Millard, 1945).

Administration of vaccines to susceptible population can be considered in the context of prophylaxis. Vaccination within the first three days of exposure reduces the severity of disease. On the other hand, if a vaccine is administered within 4th-5th days of exposure, it still might reduce the fatality rate from 30% to 11% (Fulginiti *et al.*, 2003). For smallpox, there are several vaccination strategies available to be implemented:

- Mass vaccination
- Ring vaccination
- Targeted vaccination.

Ferguson *et al.*, (2003), compare benefits and drawbacks of several vaccination policies. In the ring vaccination or containment vaccination policy, suspected contacts are traced and given an appropriate dose of vaccine when found (Halloran *et al*., 2002; Hull *et al*., 2003). It is an effective policy which results in the minimum usage of vaccine and lowers the vaccine induced complications including deaths. On the other hand, the suspected contactsneeds to be determined, found and vaccinated within limited days. In the targeted vaccination, first the prioritization criteria are determined. For instance, individuals who are older than a specific age, a neighborhood or territory which is affected by smallpox are selected. On the contrary to ring vaccination, targeted vaccination does not require any contact tracing activity.

2.2.1.3.2 Quarantine

Both quarantine and isolation are both result in separation of infected individuals from rest of the population. Cetron *et al.*,(2005) define the difference between quarantine and isolation as compulsory, restricted structure of quarantine policy which may also be required a special separated facility.

2.2.1.3.3 Isolation

Hospitalization might be defined as a different type of isolation. Some required conditions should be met in order to mention on a physical separation such as infected rooms that are under negative pressure. (Kerrod *et al.*, 2005, Wallin *et al.*, 2007, Cetron *et al.*, 2005).

2.3. Basic Models in Literature

In this section, we provide a review of key epidemiological modeling studies for smallpox disease. Studies are selected according to the distribution of models. First, exponentially distributed models are examined, and then smallpox models with more realistic distribution are provided.

2.3.1. Models with Exponential Distribution

After the eradication, in research studies models are built on the assumption of a potential attack. Compartmental structure is widely used. Solely or combined, the effectiveness of control policies is evaluated.

Gani and Leach (2003) argue that some key aspects such as herd immunity in modeling are disregarded. In their study, they calculate R_0 as 3, 5 and 6, and propose an epidemic model including quarantine vaccine additional classes based on the data corresponding to Kosovo outbreak in 1972. Chen *et al.*, (2004)

align two different models. They call this process as docking. Their aim is to see if the results that are obtained from agent based simulation and compartmental models are fit each other with the same data.

Duncan (2005) estimates the parameters of smallpox outbreak in London between 1708 and 1748. Kretzschmar *et al*., (2004) use stochastic discrete time-branching process in order to show the disease dispersion. They conclude their study by emphasizing that ring vaccination measurement is effective only if the number of index cases is small. Partially, similar to the study of Chen *et al*. (2004), Carley *et al*., (2003) also use BioWar simulation tool to examine the disease dispersion by considering additional details. They create a social network and engage them with daily actions considering time variable. Halloran *et al*., (2002), construct a stochastic simulation model of disease dispersion in a heterogeneously mixing population, in order to compare the effectiveness of mass and target vaccination. They found out targeted vaccination is more effective per dose, in the existence of some level of herd immunity among population. Similarly, Kaplan *et al*., (2002) compare target vaccination and mass vaccination and conclude that deaths would be lower if the mass vaccination policy is implemented. Bozette *et al*., (2003) construct a stochastic compartmental model and compare the effectiveness of mass vaccination, ring vaccination and prophylactic vaccination in a homogeneously mixing population under six scenarios.

Meltzer *et al*. (1999) report that while quarantine is an effective way to stop an epidemic, due to the implementation requirements of quarantine, it becomes a hard challenge. Authors also report that historical data shows mass

vaccination only may not be enough to stop the epidemic. They suggest that in order stop the epidemic, combination of quarantine and mass vaccination policy should be used. Research study by Feguson *et al*. (2003), reviews those studies and provides valuable insights as a review of epidemiologic model construction tools and implementation of control measurements. Halloran *et al*. (2006), construct a stochastic simulation model to evaluate combination of vaccination and isolation as a control policy. Aldis and Roberts (2005), examine the disease dispersion through a system of integral equations and compare various control policies. They find out that prior mass vaccination is not an efficient way to implement due to the risk of adverse reactions. Del Valle *et al*., (2005), construct a compartmental model considering individuals having both normal and low level activity. Besides well known control policies, objective is to show the effect of lowering contact numbers on to dispersion of disease, during the epidemic. They conclude that changing contact patterns results in reduction in the dispersion speed of the disease. House *et al.*, (2010) construct a model that combines differential equations, meta population approach and individual based structure. They aim to determine the optimal spatial scale for intervention and analyze the sensitivity of results with regards to the assumptions that made on the contact pattern.

More realistic results can be obtained through a general distribution. We give a brief review on smallpox models which distributed un-exponentially in the following section.

2.3.2. Models with General Distribution

Besides exponentially distributed differential equation models reviewed above, some of the studies consider time lags between horizontal incidences (Hethcote, 1994). In other words, as in smallpox disease progress, after entering body, virus should duplicate itself in order to reach to a sufficient number to cause the disease. Therefore, between acquiring the virus and becoming infected there is a time lag called incubation period (Callaghan and Murray, 2002). This time delay can be defined mathematically through differential equations and its derivatives (Allen, 2006). If this time lag is fixed such that, $t = n\Delta t, n = 1,2,3,..,\Delta t$, (Allen *et al.*, 2000) then a first order linear differential equation with a discrete delay as represented in Equation (2.1) can be appropriate to model the epidemic (Allen, 2006).

$$\frac{dx}{dt} = ax(t) + bx(t-\tau) + f(t) \qquad (2.1)$$

If reaction is occurred with a non-fixed time steps, [0, τ], this kind of delay is called continuous delay (Allen, 2004). Mathematically, the change of rate in this continuous interval is represented with integro-differential equations given below.

$$\frac{dx}{dt} = ax(t) + b\int_0^{\tau} x(t-s)\,ds + f(t) \qquad (2.2)$$

Although delay differential equations are more complicated to solve, the result would be more realistic. Jiao at al. (2008) study an epidemic model with vaccination measurement and two delays corresponding to latent period and infectious period. Feng *et al.*, (2007) compare the results of an epidemic model

with different distributions. Also suggest that gamma distribution reflects more realistic results but is more complicated to solve. Similarly, Lloyd (2001) studies an exponentially distributed SIR model then converts it to more realistic Infectious Period Distribution (IPD) and discusses the results.

Table 2.1. Summary of literature review

Author(s)	Date	Infectious Disease	Population	Method		Epidemiological Model	Technique	Control Policy	Ref
				Det.	Sto.				
Amouroux *et al.*	2008	Influenza	North-Vietnam		X	None	Agent based model	None	28
Araz *et al.*	2009	Influenza	Arizona State University	X		SEIR	Simulation	School closures and reopenings	22
Atti *et al.*	2008	Influenza	Italy		X	SEIR	Individual based SIR	Vaccination, AVP, SD and air travel distriction	25
Ball	2006	Smallpox	Brazil		X	SIR	Other: two level mixing structure	Vaccination	67
Barett *et al.*	2005	Smallpox	Portland		X	None	Simulaiton	None	18
Becker	1977	General	Sao Paulo		X	None	Other: discrete time branching	Vaccination	46
Bravata *et al.*	2006	Anthrax	USA			SEIR	Cost and benefit analysis	Prophylaxis and treatment	32
Brookmeyer *et al.*	2003	Anthrax	USA cities		X	None	Statistical analysis	None	17
Carpenter *et al.*	2009	Influenza	Canada		X	None	Agent based model	None	30

Carter *et al.*	1986	Influenza	USA cities		X	None	Decision models	Vaccination	9
Chowell *et al.*	2009	Influenza	Canada, USA	X		SEIR	Differential equations	None	14
Chowell *et al.*	2006	Influenza	Geneva Swit	X		SEIHR	Non linear differential equations	Isolation	7
Chowell *et al.*	2006	Influenza	Geneva Swit	X		SEIR	Epidemiologic modelling	None	44
Chowell *et al.*	2004	Ebola	Congo and Uganda	X		SEIR	Differential equations	None	50
Chowell *et al.*	2005	SARS	Hong Kong, Ontario and Singapore	X		SEIJR	Differential equations	Isolation	51
Chowell *et al.*	2007	Influenza	San Francisco	X	X	SEIR/SIR	Differential equations	Hospitalzation	58
Chowell *et al.*	2008	Influenza	USA,EU	X		SEIR	Epidemiologic modelling	None	60
Chowell *et al.*	2004	SARS	Canada, Far Eastern	X		None		None	54
Christakosa	2007	Plague	W.Europe, India		X	None	Spatio- temporal modelling	None	49
Donnelly *et al.*	2003	SARS	Hong Kong			None	Statistical analysis	None	66

Doyle *et al.*	2006	Influenza	France		X	None	Simulation	Vacc, AVT, AVP	1
Drake *et al.*	2003	SARS	Singapore		X	SEIR	Simulation	Communicaiton of epidemic	70
Duncan		Smallpox	London	X		SEIR	Other: second order Gaussian filter	None	39
Eichner *et al.*	2003	Smallpox	Nigeria	X		None	Statistical analysis	None	38
Eyup *et al.*	2009	Influenza	General			None	Multi objective decision model	None	29
Ferguson *et al.*	2005	Influenza	South Asia		X	None	Simulation	TAP and SD	15
Fitzner *et al.*	2001	Influenza	Hong Kong		X	None	Economical analysis	Vaccination	2
Flahault *et al.*	1994	Influenza	EU	X		SEIR	Simulation	None	61
Germann *et al.*	2006	Influenza	USA cities		X	None	Agent based model	TAP, mass vacc., school closuring, isolation	12
Grais *et al.*	2004	Influenza	USA cities	X		SEIR	Simulation	None	21
Griffin *et al.*	2004	Influenza	UK		X	None	Spatio-temporal	None	3
Guptaa *et al.*	2005	SARS	Toronto	X		None	Economical analysis	Quarantine	56
Hak *et al.*	2006	Influenza	NL		X	None	Decision models	None	42
Hsieh *et al.*	2007	SARS	Taiwan	X		SIR		Quarantine	37

Hsu *et al.*	2004	SARS	Taiwan		X	SEIR	Differential equations	Quarantine/isolation	71
Hupert *et al.*	2002	Anthrax, Plague..	USA		X	None	Simulation	None	33
John *et al.*	2001	Anthrax	Canada			None	Economical analysis	Prophylaxis	31
Koyuncu & Erol	2010	Influenza	Turkey			None	Decision models	AVP & other preventive treatments	63
Lee *et al.*	2009	Anthrax	General		X	None		None	26
Lee *et al.*	2008	Influenza	USA		X	None	Simulation	None	41
Legrand *et al*	2009	Anthrax	GB		X	None	Markov Chain Monte Carlo	None	10
Li *et al.*	2004	SARS	Hong Kong, Singapore	X		None	Statistical analysis	None	48
Lokone & Finkenstadt	2006	Ebola	Congo	X		SEIR	Markov Chain Monte Carlo	None	64
Longini *et al.*	2005	Influenza	South East Asia		X	None	Case analyzing	Several control strategies	65
Meltzer *et al.*	1999	Influenza	US cities		X	None	Simulation	Vaccination	16
Miller *et al*	2004	Plague	Texas		X	None	Simulation	None	11
Miller *et al*	2006	Smallpox	San Antonio		X	None	Simulation	Combination of	68

							control policies	
Nishiura	2007	Influenza	Germany; Prussia		X	None	Other: discrete time branching	None	19
Nishiura & Tang	2004	Smallpox	Japan	X		SEIJR	Differential equations	Vaccination	5
Nishiura *et al.*	2004	SARS	Japan	X		SEIR	Simulation	Isolation, Quarantine, preventive treatments	57
Pyle & Rees	1971	Various	Chicago		X	None	Statistical analysis	None	34
Riley *et al.*	2006	Smallpox	GB		X	None	Spatial, individual based model	Vaccination, Isolation	4
Riley *et al.*	2003	SARS	Hong Kong		X	comp*	Other: meta pop.	None	53
Rizzo *et al.*	0	Influenza	Italy	X	X	SEIR	Simulation	AVP, SD, Vacc.	27
Roberts *et al.*	2007	Influenza	Auckland	X		SIR	Differential equations	SD, TAVP, AVP, home quarantine	20
Ruan *et al.*	2006	SARS	USA	X		SEIR	Differential equations	None	40
Sattenspiel *et al.*	2003	Influenza	Canada	X		SIR	Differential equations	Quarantine	47

Schoenbaum	1987	Influenza	USA	X		None	Cost and benefit analysis	Prophylaxis	36
van Genugten *et al.*	2003	Influenza	NL		X	None	Scenario analysis	Vaccination AVT	6
Volz	2008	Smallpox	Portland		X	SEIR	Differential equations	Quarantine	13
Wanga *et al.*	2007	SARS	Beijing	X		comp*	Simulation	None	52
Webb & Blaser	2002	Anthrax	USA		X	None	Other: network modeling	None	24
Wein *et al.*	2003	Anthrax	USA	X		None	Other: atmospheric dispersion model	None	62
Yang *et al.*	2007	Influenza	Eastern*		X	None	Statistical analysis	None	23
Zaric *et al*	2008	Anthrax	general		X	SEIR	Simulation	None	35
Zhang *et al.*	2005	SARS	China	X		comp*	Simulation	Quarantine	59
Zhou *et al.*	2004	SARS	China	X		EIQJR	Other	Quarantine	69

CHAPTER 3

PROPOSED MODELS FOR SMALLPOX

In this chapter, we consider four alternative models; disease dispersion under no control, dispersion under quarantine and hospitalization policies, dispersion under vaccination strategy and a scenario that includes combination of quarantine, hospitalization and vaccination policies.

First, Model 1 is examined in the absence of any control policy. Second, Model 2 is examined in order to observe the effects of quarantine and hospitalization on disease dispersion. Third, a model with vaccination is examined. Final model incorporates quarantine and hospitalization measures with vaccination.

3.1. Model 1: No Control Or Preventive Measures

In the first model, dispersion of smallpox disease is examined with a compartmental model. A conceptual compartmental model is developed, corresponding system of ordinary differential equations are given and related parameters are described.

Table 3.1 List of compartments for Model 1

Notation	Definition
S	Number of susceptible individuals
E	Number of exposed individuals
P	Number of individuals in prodromal class
I	Number of infected individuals
R	Number of recovered individuals
D	Number of individuals who dies from smallpox
N	Total population size

Table 3.1 displays the list of compartments used in Model 1. S represents the number of susceptible individuals who are not exposed to the agent. E represents number of individuals who become exposed. Note that individuals are asymptomatic and uninfectious during the exposed period. As illustrated in Figure 2.8, the duration of this period is 12 days on average (Fenner *et al.*, 1988). Therefore, the rate of moving from exposed class to the next class is 1/12. In other words, individuals stay in this compartment for 12 days without suffering any symptoms of disease. After 12 days, individuals move from exposed class to the Prodromal class 'P', which corresponds to asymptomatic but infectious disease stage. Prodromal stage can be distinguished with the unusual high fever and lasts three days on average (Fenner *et al.*, 1988). Patient in this compartment can infect susceptible individuals with a

reduced infectivity rate. According to the timeline of smallpox, after three days of prodromal stage, an individual moves to the infected class in which he/she spends 19 days on average (Fenner *et al.*, 1988). An individual who enters into the infected class 'I' either die or recover.

3.1.1 Conceptual Model and Parameter Estimation

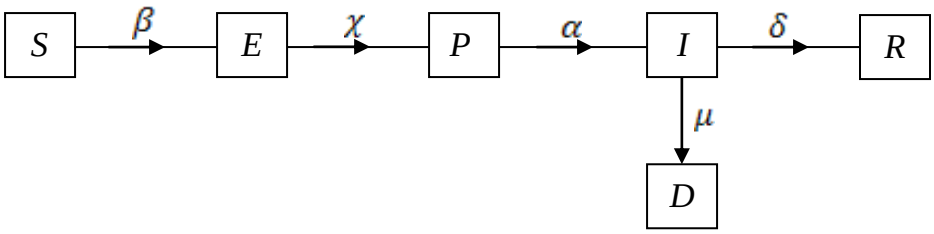


Figure 3.1. Conceptualization of the Model 1: without any control measurements.

Flows of individuals between compartments are shown in Figure 3.1. Greek letters represent the rates of movements between compartments and correspond to exponentially distributed waiting times in compartments (Hethcote, 2009). Waiting times are referred as the duration of the disease stages and illustrated the timeline presented in Figure 2.8.

Table 3.2 Parameters for basic model

Parameter	Definition	Value
χ	Transmission rate from exposed to prodromal compartment	1/12
α	Transmission rate from prodromal to infected compartment	1/3
δ	Recovery rate	1/16
μ	Death rate	0.0268
ε	Reduced infectivity rate	.3

Table 3.2 shows the transfer rates between the compartments. Susceptible individual becomes exposed as a result of a successful contact with an infectious individual. Individuals are assumed to move along the compartments with exponentially distributed rates. Exposed individual move to prodromal stage with a rate of χ, which corresponds to exponentially distributed waiting time of $1/\chi$ in exposed class. According to Figure 3.1, exposed individuals move from P class to infected class 'I' with a rate of α, similarly, the mean duration of stay in P class corresponds to $1/\alpha$. An infected individual recovers with a rate of δ and dies with a rate of μ. Since the mean time in infectious class is $1/(\mu+\delta)$, the fraction of $\mu/(\mu+\delta)$ of infected individuals die as result of smallpox disease. Since smallpox case fatality rate is clearly defined as 30% (Fenner *et al.*, 1988), setting $\mu/(\mu+\delta)=0.30$ gives the the rate of individuals who move to the death class. This corresponds to 0.0268 (Del Valle, 2005).

3.1.2. Mathematical Representation

According to the Figure 3.1, the transfers from one compartment to another can be represented by set of ordinary differential equations. Mathematical representation of the conceptual model provided in Figure 3.1 is given below.

$$\dot{S} = -\beta S(I + \varepsilon P)/(S + I + P) \quad (1)$$

$$\dot{E} = \beta S(I + \varepsilon P)/(S + I + P) - \chi E \quad (2)$$

$$\dot{P} = \chi E - \alpha P \quad (3)$$

$$I = \alpha P - \mu I \quad (4)$$

$$\dot{D} = \mu I \quad (5)$$

'$\dot{X}$' denotes to the first derivative with respect to time *t* or change in the value of *X*(*t*). Therefore, the first equation defines the decrease in the number of susceptible individuals due to the successful contacts with infectious individuals. Second equation shows the change in number of individuals in the exposed class. Susceptibles who acquired the disease agent transfer to exposed class and after spending some time leave exposed class at a rate of χ. In the third equation, it can be observed that P class includes individuals who transfer from E class and leave P class with the rate of α. Similarly, I class consists of individuals who move from P class to infectious class and leave I class due to disease induced death or recovery. Finally 'R' represents the recovery class, and can be calculated as; *R= N-S-I-E-P*.

3.2. Model 2: Dispersion under Quarantine and Hospitalization

In the previous model, the rates, related transfers from one class to another and mathematical representation are analyzed. In this section, a model with quarantine and hospitalization policy is examined. Two additional compartments are added to the basic model therefore two additional rates are introduced. First, conceptual model and related parameters are provided, next mathematical representation and interpretation of mathematical model is given.

The objective of Model 2 is to determine the numbers of individuals who needs to be hospitalized. In order determine and or evaluate the optimal policy decisions, isolation and hospitalization measures are considered. In this model, individuals that are suffering from smallpox should be kept in specially equipped rooms (Kerrod *et al*., 2005, Wallin *et al*., 2007, Cetron *et al.*, 2005). In case of single incidence, some of the hospitals rooms might be redesigned. In the absence of smallpox, this redesign might not be likely. Through modeling, the number of people that are hospitalized can be forecasted; and in theory, this would help hospital authority to make more accurate planning.

3.2.1 Conceptual Model and Parameter Estimation

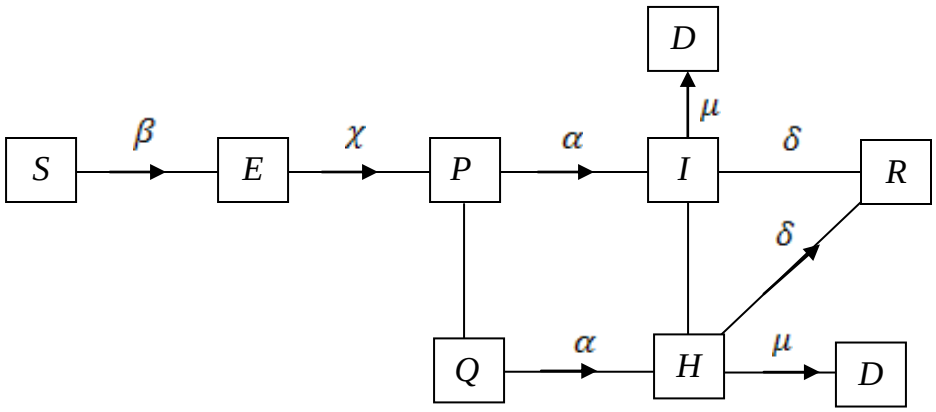


Figure 3.2: Conceptualization of Model 2: with control measurements quarantine and hospitalization.

The aim of Model 2 is to evaluate the effectiveness of isolation and hospitalization control measures. One of the differences from Model 1 is that Model 2 includes additional two compartments. Therefore, individuals are monitored under control with given parameters.

Notation with additional compartments is provided in Table 3.3. Since the smallpox has asymptomatic long latent period of 12 days, an individual might not be aware of the exposure.

Table 3.3: List of compartments used in Model 2.

Notation	Definition
S	Number of susceptible individuals
E	Number of exposed individuals
P	Number of individuals in prodromal class or compartment.
I	Number of infected individuals
R	Number of recovered individuals
D	Number of individuals who died from smallpox
Q	Number of quarantined individuals
H	Number of individuals that required hospitalization

After 12 days, when individual moves to the prodromal stage, unusual high fever might trigger an individual to go to hospital. An individual is still asymptomatic in this stage, therefore, he/she can be held under observation till the indication of the source of unusual fever. If the onset of the fever is sourced from smallpox, this individual under the observation is taken under hospitalization.

We assume that as result of high fever individual would seek medical attention and go to hospital (Longini, 2007) and is taken under medical observation with a rate of γ, as provided in the Table 3.4. According to the conceptual model, individual spends some time in 'Q' class and then removed from 'Q' class to 'H' hospitalized class with the rate of α. It is also possible that an individual might ignore the high fever occurred in prodromal stage and might stay at home without seeking any medical attention. This individual would then become infectious with

the onset of heavier symptoms of smallpox and eventually have to go to hospital. Therefore, according to the model, an individual can transfer to 'H' class from 'I' class with a rate of σ. Besides, corresponding to the waiting time between 'P' and 'I' classes, a transfer is also allowed from 'Q' class to 'H' class with the same rate of α.

Table 3.4: Parameters used in Model 2.

Notation	Definition	Value
χ	Transmission rate from exposed to prodromal compartment	1/12
α	Transmission rate from prodromal to infected compartment	1/3
δ	Recovery rate	1/16
μ	Disease induced death rate	0.0268
ε	Reduced infectivity rate	0.3
γ	Rate of taken under control in prodromal stage	0.3
σ	Rate of taken under control in infectious stage	0.08
μ_2	Disease induced death rate of treated individuals	0.008

We consider quarantine and hospitalization instead of quarantine and isolation. The fundamental reason behind this is to assess the requirements for both quarantine and hospitalization facilities. So as to plan these requirements by proposing appropriate control measures to public health officials. In case of an emergency, some of the existing facilities can be used as an emergency facility for additional capacity. Foreseeing the disease dispersion and necessary requirements

with this model would provide flexibility in terms of supplies and workforce. Therefore, the aim is to consider the medical service supply and make emergency plans considering the existing supplies.

Longini (2007) suggests that 47.5% of infected individuals go to hospital at the end of the first day of fever, whereas, remaining go to hospital at the end of the third day. Since the fraction of 47.5% corresponds to the fraction of individuals that are taken under quarantine from prodromal class, and mathematically it can be shown as: $\phi/(\alpha+\gamma)$. We set this equation to 47, 5% and find γ =0.3. Similarly, the rate of hospitalization in the infectious stage of disease is $\sigma/(\sigma+\mu+\delta)$, and setting this to the remaining part leads to σ =0.08. We set these γ and σ values as baseline parameters. Note that these values can be valid only under the assumption of the mean infectious disease stage duration is exponentially distributed.

3.2.2 Mathematical Representation

According to the Figure 3.2, system of ordinary differential equations for the Model 2 is developed and presented below.

$$\dot{S} = -\beta S(I + \varepsilon P)/(S + I + P) \quad (6)$$

$$\dot{E} = \beta S(I + \varepsilon P)/(S + I + P) - \chi E \quad (7)$$

$$\dot{P} = \chi E - (\alpha + \gamma)P \quad (8)$$

$$\dot{I} = \alpha P - (\mu + \delta + \sigma)I \quad (9)$$

$$\dot{D} = \mu(I + H) \quad (10)$$

$$\dot{Q} = \gamma P - \alpha Q \quad (11)$$

$$\dot{H} = \sigma I + \alpha Q - (\mu_2 + \delta)H \quad (12)$$

$$R = N - S+E+P+I+Q+H \quad (13)$$

The first two equations are common for both Model 1 and Model 2. 'P' class equals to difference of individuals that move from exposed class and transfer to 'I' class. The number of individuals in 'I' class is equal to the difference of incoming individuals and outgoing individuals. Similarly, the number of individuals in 'Q' and 'H' classes are equal to the differences of incoming and outgoing individuals.

The solution of this model and related figures are provided in Chapter 5. Different results are obtained for different parameter values and full table of results is provided in the Appendix.

3.3. Model 3: Model with Vaccination

Among all control policies, vaccination is different because vaccination might be used as both control policy and/or preventive measure. On the contrary, opening an isolation facility prior to the occurrence of an epidemic is not likely, so isolation is a control policy that can be realized only after the epidemic starts. In this section, we consider vaccination policy in addition to quarantine and isolation/hospitalization in Model 2. One of the objectives in considering different policies is to compare the effectiveness of interventions within given parameters.

Especially for the vaccination policy, we would like to estimate the vaccine requirements for better timing of the orders to stop the dispersion of epidemic as early as possible.

3.3.1 Conceptual Model and Parameter Estimation

In case of smallpox, vaccination is declared as the most effective way to control and prevent the epidemic (Hull *et al*., 2003). As stated previously, vaccination can reduce the fatality rate from 30% to 11%, if administered within the first 10 days of exposure. It may also decrease the severity of the disease, if individual is vaccinated within the first four days of exposure. Once an individual is vaccinated, he/she acquires immunity for long years.

Table 3.5. Full list of parameters used in Model 3.

Parameter	Definition	Value
β	Transmission coefficient	
χ	Transmission rate from exposed to prodromal compartment	1/12
α	Transmission rate from prodromal to infected compartment	1/3
δ	Recovery rate	1/16
μ	Death rate	0.0268
ε	Reduced infectivity rate	0.3
γ	Rate of taken under control in prodromal stage	0.3
σ	Rate of taken under control in infected stage	0.0268
μ_2	Disease induced death rate of vaccinated individuals	0.008

Φ	Fraction of vaccinated individuals at susceptible class	0.2
Ψ	Fraction of vaccinated individuals at exposed class	0.08
μ_3	Vaccine induced deaths among vaccinated exposed	10^{-6}
V_{es}	Vaccine effectiveness for susceptible indviduals	0.95
V_{ee}	Vaccine effectiveness for exposed individuals	0.80

According to the conceptual model provided in Figure 3.3, vaccinated susceptible individual can either be immunized or remains susceptible due to the vaccine ineffectiveness. Assuming limited availability of the vaccines, we assume that one individual can receive only one dose of vaccine. Therefore, we also count individuals who are not effectively vaccinated.

3.3.2 Mathematical Representation

Based on the conceptual model in Figure 3.3., we establish the following system of differential equations. Note that due to the nonlinearity of Equations (14) to (23), we obtain a nonlinear system of differential equations, which cannot be solved exactly.

$$\dot{S} = -(1-\phi)\beta S(I+\varepsilon P)/(S+I+P) - \phi S \quad (14)$$

$$\dot{E} = (1-\phi)\beta S(I+\varepsilon P)/(S+I+P) - (1-\psi)\chi E - E\chi \quad (15)$$

$$\dot{P} = (1-\psi)\chi E - \alpha P \quad (16)$$

$$\dot{I} = \alpha P - (\mu+\delta)I \quad (17)$$

$$\dot{V}_s = \phi S - (1 - V_{es})\beta V_S(I + \varepsilon P)/S + I + P - V_s\mu_3 \quad (18)$$

$$\dot{V}_E = (1 - V_{es})\beta V_S(I + \varepsilon P)/S + I + P - \chi V_E - V_E\,\mu_3 \quad (19)$$

$$\dot{P}_V = \chi V_E - \alpha P_V \quad (20)$$

$$\dot{I}_V = \alpha P_V - (\mu_2 + \delta)I_V \quad (21)$$

$$\dot{R} = \delta I + V_S V_{es} + I_v\delta \quad (22)$$

$$\dot{D} = I\mu \quad + I_V\mu_2 + (V_{S+}V_E)\mu_3 \quad (23)$$

According to both conceptual and mathematical models, the change in susceptible class can be defined as the outflow of exposed individuals who are previously in 'S' class. Individuals might transfer to the vaccinated class 'V' with a rate of ϕ. Similar to S class, individuals in exposed class either move to vaccinated class with a rate of ψ or move to prodromal class with a rate of χ. Individuals in the prodromal class move to 'I' class with a rate of α. Since the vaccination cannot prevent or stop the symptoms of smallpox, individuals that are vaccinated in the exposed class continue to move to prodromal class with the same rate as unvaccinated individuals do. The only difference is that vaccinated individuals might have milder course of smallpox; therefore vaccination might not shorten the mean duration of the compartment. After the prodromal phase, both vaccinated and unvaccinated individuals move to recovery class with a rate of δ, or they die at rate of μ/ (μ+ δ). Note that, although the death rates can be calculated with the same

logic, disease induced death rates among vaccinated and unvaccinated individuals are different from each other.

Calculation of the death rates of unvaccinated individuals for Model 3 is given below.

$\mu / (\mu + \delta) = 30\%$

$\mu = 0.0268$.

While vaccination might reduce the fatality rate from 30% to %11, death rate of vaccinated individuals is equals to;

$\mu_2 / (\mu_2 + \delta) = 11\%$, therefore $\mu_2 = 0.008$.

Rate of vaccine induced death is 10^{-6}, which is derived from the literature (Fenner *et al.*, 1988). Vaccinated susceptible individuals move to the recovered class due to the high effectiveness of vaccines. They might die due to the adverse effects of vaccine at a rate of 10^{-6}. Parameter values and numerical solution of these models are provided in Chapter 5.

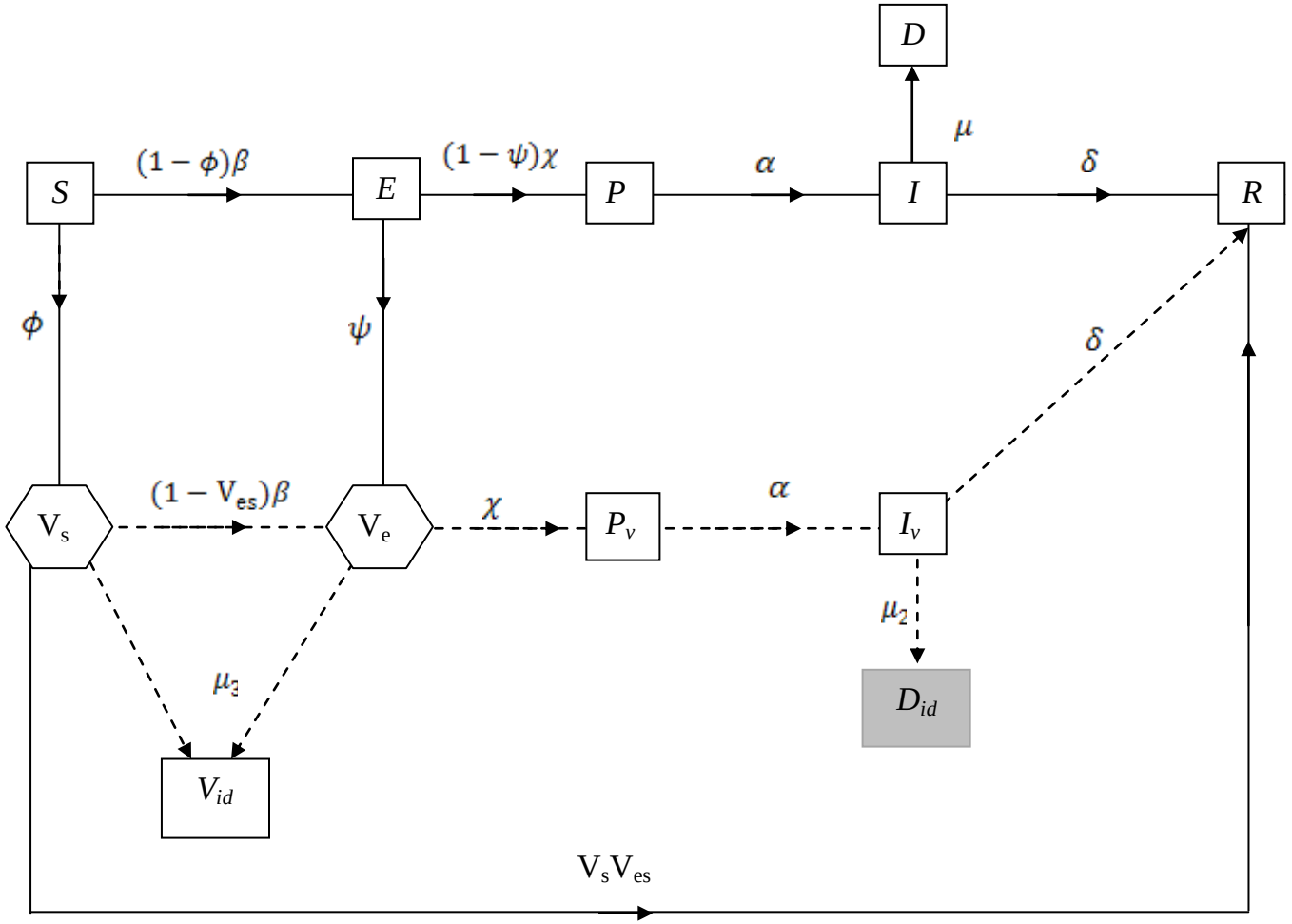


Figure 3.3. Conceptualization of the Model 3.

3.4. Model 4: Combination of Policy Measures

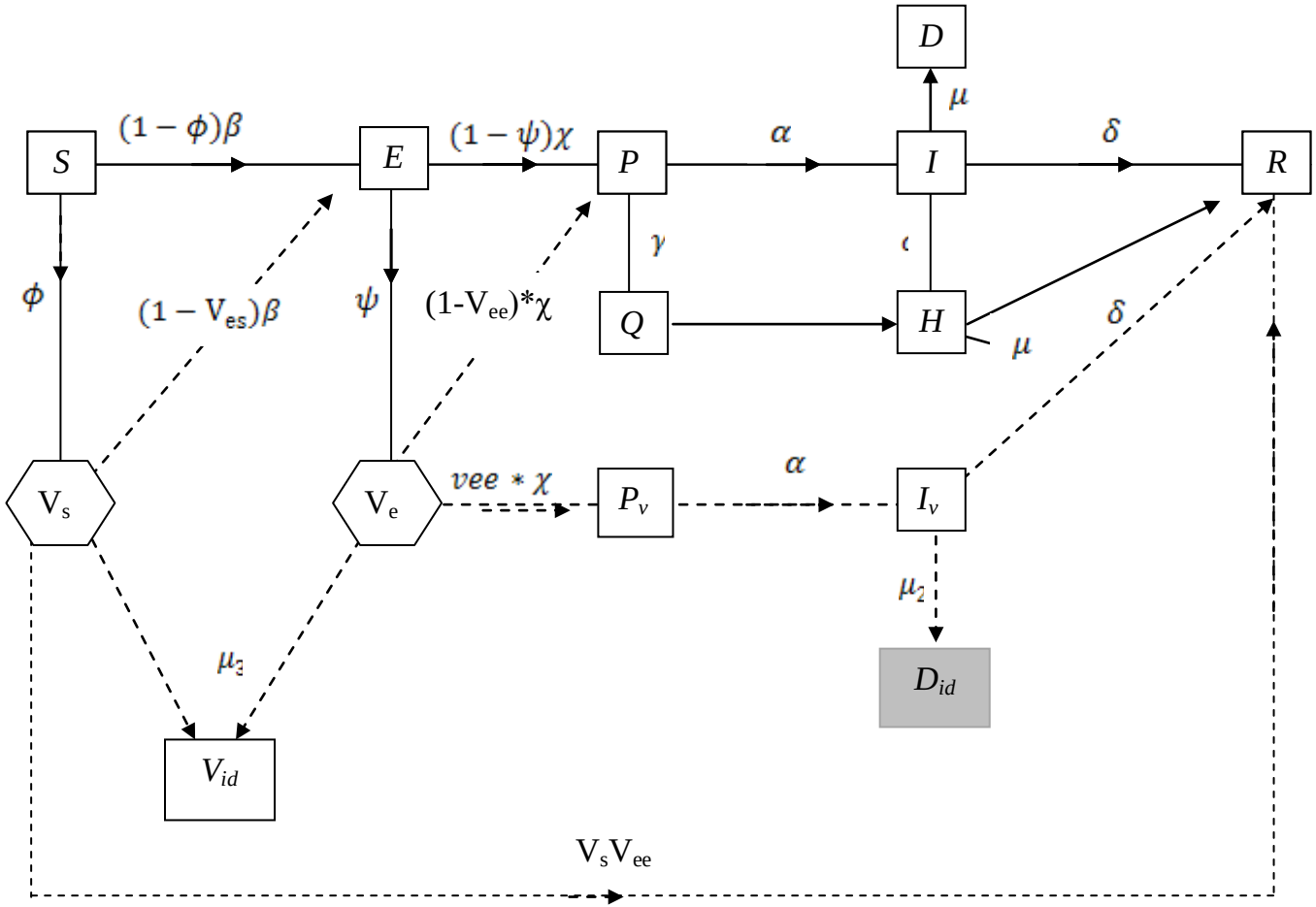


Figure 3.4. Conceptualization of Model 4.

3.4.1 Conceptual Model and Parameter Estimation

In Chapter 2, while analyzing the Table 2.1, we briefly examined different effects of control policies in case of an epidemic by reviewing studies from literature. Immunity status and contact patterns among the population and the resources that are required for the implementation of the policy and the availability might be the important factors that shape the policy decision making process. For a specific disease, quarantine may be the best policy and might result in termination of the epidemic in the shortest time. Official quarantine might need restricted rules and additional capacity, even might require a facility. Opening a facility is another problem beyond the operations research concerns; it might also include high costs. Another aspect of quarantine is the disturbance that will be created among the population, or more specifically among the residents. Although vaccination might seem as an attractive option, implementation of a vaccination strategy requires an effective health care service due to the limited time of vaccine availability. Therefore, timely vaccinated individuals will have lower probability of death in addition to reduced infectivity.

According to the last model provided in Figure 3.4, a susceptible individual can have a preventive vaccine shot. If this individual develops immunity as a result of vaccination, he/she moves to the recovered compartment. If vaccine efficiency is realized as zero, then he/she will move along the classic stages of the disease. Alternatively, susceptible individuals may become exposed as a result of contact with an infectious. An exposed individual if detected and vaccinated in days

between the first day and 10th days of exposure than move along the alternative 'dotted lined' path which resulted in reduced death rate. Detection through contact tracing of individuals is not considered.

3.4.2. Mathematical Representation

As can be seen from Figure 3.4, Model 4 is the most complicated model involving 14 different compartments and additional disease dynamics. Assuming exponentially distributed parameters, we establish the following system of nonlinear differential equations. Numerical solutions to this system for different scenarios and different parameter values are provided in Chapter 5.

$$\dot{S} = \frac{-(1-\phi)\beta S(I+\varepsilon P)}{S+I} - \phi S \tag{24}$$

$$\dot{E} = \frac{(1-\phi)\beta S(I+\varepsilon P)}{S+I} + (1-v_{ES})\beta\frac{(I+\varepsilon P)}{S+I} - \psi E - (1-\psi)E\chi \tag{25}$$

$$\dot{P} = (1-\psi)E\chi - (\gamma+\alpha)P + V_E(1-v_{EE})\chi \tag{26}$$

$$\dot{I} = \alpha P - (\mu+\sigma+\delta)I \tag{27}$$

$$\dot{R} = \delta(I+I_V+H) + S_V v_{ES} \tag{28}$$

$$\dot{Q} = \gamma P - \alpha Q \tag{29}$$

$$\dot{H} = \alpha Q + \sigma I - H(\mu+\delta) \tag{30}$$

$$\dot{D} = \mu(I+H) + \mu_2 I_V \tag{31}$$

$$\dot{S_V} = \phi S - S_V v_{ES} - \mu_3 S_V - (1-v_{ES})\beta\frac{(I+\varepsilon P)}{S+I} \tag{32}$$

$$\dot{E_V} = \psi E - E_V v_{EE}(\mu_3+\chi) - E_V(1-V_{EE})\chi - \mu_3 E_V \tag{33}$$

$$\dot{P_V} = (1-v_{EE})\chi E_V - \alpha P_V \tag{34}$$

$$\dot{I_V} = \alpha P_V - (\mu_2 + \delta) I_V \quad (35)$$

$$\dot{D_V} = \mu_3 (S_V + E_V) \quad (36)$$

$$\dot{R} = \dot{S} + \dot{E} + \dot{P} + \dot{I} + \dot{Q} + \dot{H} + \dot{S_V} + \dot{E_V} + \dot{P_V} + \dot{I_V}$$

Model 4 incorporates all intervention strategies. Compartment dynamics has the same logic as Models 1, 2 and 3. Individuals flow into a compartment with a rate which corresponds to the mean duration of the period. After spending mean duration time in the related compartment, individuals either leave the system due to death or continue to flow till they become recovered.

We run each model with the initial values provided in Table 3.5. We wish to focus on the importance of vaccination in case of a smallpox epidemic.

Smallpox vaccine is not produced in Turkey. Therefore, in case of a vaccination strategy, vaccines should be purchased from an official producer. In this case, important concern is when to order, how frequently and how much to order. The 'buy' decisions bring along many other technical concerns. As a special product,vaccine requires special conditions for the temperature of storage area, packaging and disposal after usage. This unique characteristic of this product might result in high costs associated with holding the vaccines in inventory.

In theory, every individual requires treatment therefore, every individual should be vaccinated. However in practice, individuals that suffer from a specific disease might be affected differently. Some are having milder course of disease while some are suffering from the most severe form of the same disease. Similarly, the attitudes

of individuals towards vaccination might be differed. Some might get voluntarily vaccinated while some might refuse to be vaccinated. We are not including the behavioral effects or attitudes of individuals towards vaccination in our models. We rely on the parameters which are well defined in the literature. Using these parameters in Model 3 we obtain approximate number of individuals that will be vaccinated. We integrate this output with an inventory planning model to determine optimal cost and timing of vaccine procurement. In the next chapter we present an inventory model and present a solution methodology based on dynamic programming.

CHAPTER 4

CONTROL POLICY DETERMINATION AND OPTIMAL INVENTORY MODEL

Alternative control policies and related decisions in case of an epidemic are introduced in the previous Chapters. In this Chapter, we focus on vaccination strategy accompanied with quarantine and hospitalization as the control policy for a possible smallpox attack. Although vaccination does not provide full treatment, it provides decreased infectivity and milder course of smallpox. Some important decisions and related questions regarding the vaccination policy planning can be listed as;

- Whether to import/outsource the vaccines or to produce them in homeland. This decision also involves supplier selection, and order placement issues.
- Lot sizes of vaccine orders and related inventory decisions, both in normal and emergency situations.
- Strategic and operational decisions regarding the storage and distribution of the vaccines. How and where vaccines should be stored?
- An effective waste management for the vaccine related wastes should be planned.
- All prioritization considerations, including which part of the population should get vaccinated first, elderly or children?

- Administration of the health care services, including how many people will get vaccinated by each care giver?

All of these considerations are in the interest of Operations Research and Management Science (OR/MS) field. There are numerous research articles pointing resource allocation (Zaric *et al.*, 2004, 2006), and various optimization models (Longini *et al.*, 1990) considering different types of policies.

In this thesis, we focus on finding optimal vaccine ordering policy. In case of an emergency due to the zero stocks of smallpox vaccines in Turkey, vaccines should be acquired from non-governmental health organizations, for instance WHO. Therefore determining the approximate need for vaccine will become a crucial challenge due to the limited time of administration.

4.1. Inventory Model for Smallpox Vaccines

We developed a model in order to determine appropriate lot sizes. We use single commodity inventory model under deterministic time varying demand rate. For determining the optimal inventory policy two similar models are considered. One is formulated by Wagner and Whithin (1957). Objective here is to determine the optimal quantity in order to minimized the sum of reorder cost and holding cost,

Table 4.1. Notations for Wagner-Whitin Algorithm.

Notation	Definition
D	Demand at time period t
K	Fixed reorder cost
H	Holding cost
T_H	Finite and discrete time horizon
q_t	Amount of order at the beggining of time period t
I_t	Inventory level at the end of the time period t
y_t	A binary variable; 1, if an order is placed in time period t, 0, otherwise

$$\text{Minimize} \quad \sum_{t=1,\_T_H} (ky_t + \boldsymbol{h}I_t) \tag{4.1}$$

$$\text{Subject to;} \quad I_t = I_{t-1} + q_t - d_t, \qquad t = 1,\ldots\ldots, T_H \tag{4.2}$$

$$q_t \leq y_t \sum_{r=t,\ldots,n} d_r, \tag{4.3}$$

$$I_0 = 0, \tag{4.4}$$

$$I_t \geq \mathbf{0}, \qquad t = 1,\ldots\ldots, T_H$$

$$q_t \geq \mathbf{0}, \qquad t = 1,\ldots\ldots, T_H$$

$$y_t \in \{0,1\}, \qquad t = 1,\ldots\ldots, T_H$$

In the above model, Equation (4.1) is the objective function, which minimizes the reorder cost for each time period $t = 1, \ldots, T_H$. Equation (4.2) represents the inventory balance constraints. Equation (4.3) stated that for each time

period $t=1,\ldots, T_H$ q_t is zero if y_t is 0. Equation (4.3) defines the initial inventory. In this model, stockouts are not allowed and lead time is assumed to be zero.

In terms of solution algorithm, we employ dynamic programming technique which is a common technique for making a sequence of interrelated decisions (Hillier and Liebermann, 1990). The uniqueness of this technique comes from the non-standard mathematical formulation (Hillier and Liebermann, 1990). The effect of the policy decision at each stage is to transform the current state to a state associated with the beginning of the next stage. Therefore the equations for each problem may differ in order to find solutions to the problem.

Our purpose is to find the optimal order size and order timing given the vaccine requirements for each period. By that way, the redundant orders will be eliminated. It should be noted that since this model is conceptual and will be elaborated, lead time assumed to be zero. Therefore the period that an order is placed will affect the next order quantity. Therefore solving the problem through dynamic programming is appropriate because of the dependency between periods. The solution procedure is designed to find an optimal policy for the overall problem. Since the overall cost of ordering and waste management of vaccines are limited with budgets, we aim to find an optimal policy for vaccine orders in order to minimize the costs related to vaccines and maximize of effectiveness of the vaccination campaign.

After determining the demand for vaccines according to the results of epidemic models presented in Chapter 3, we use the following notation to construct the dynamic programming model.

Table 4.2 Notation for Alternative Dynamic Programming Solution.

Notation	Definition
C_{ij}	Cost associated with arc (i,j) in network presentation of lot scheduling problem used for Wagner-Whitin Algorithm
f_j	Minimum cost period i to the end of the horizon
H	Holding cost per unit per time period
S	Setup cost to initiate an order.
N	Number of periods

$$c_{ij} = S + \sum_{k=i+1}^{j-1} h\,(k-i)d_k, \quad j>i$$

s.t., i=1,..,n

j=1,..,n+1

In our case, we need to determine when to order and how much to order in order to minimize the purchasing cost and meet the needs for vaccines. The index *i* stands for the period which the order is taken place. The index *j* represents the next order period. c_{ij} represents setup and holding cost of ordering in period *i* to meet the requirements through *j*-1 periods. In that sense; c_{18} is the cost of ordering in period 1 to satisfy the demands in periods 1 through 7.

'S' represents the setup cost for placing an order. In this case, set up cost is the amount of money that is tie to the order. This also includes the regulatory costs such as transportation costs, insurance costs and customs costs. Since the capital is

tied to unsold inventory, it takes a time to breakeven point in order to generate profit from that inventory. In this context, the accuracy of demand is important in order not to tie additional hundred thousand dollars. Beside the demand, the lead times should be accurately integrated into the purchasing decision especially for a product such as vaccine. In this model, we assume that lead time is zero and setup cost is constant regardless of demand quantity but differs for different population size. Solution of this problem provided in Chapter 5.

CHAPTER 5

NUMERICAL RESULTS AND ANALYSIS

In this Chapter, we provide numerical results and analysis for the proposed epidemiological and inventory models. In the first part of the Chapter, four different epidemiological models are solved under three different scenarios. In each scenario, different problem setting and different population size are considered for a potential bioterrorist attack with smallpox. Through these scenarios, we aim to compare size of the affected population. In the first scenario, bioterrorist attack is assumed to be taking place through a ventilation of a class on a university campus with initial susceptible population size of 5000 people, which includes students, staff, and visitors. In the second scenario, bioterrorist attack is assumed to take place at several locations in a city. In this study, we consider the third largest city of Turkey, Izmir with population size 3,500,000. According to the last scenario, a larger bioterrorist attack is assumed to affect the whole country, namely Turkey, with population size of 75,000,000.

In the second part of the Chapter, the proposed inventory model is solved through dynamic programming and optimal vaccine order size with minimum total cost is obtained. Note that three different bioterrorist attack scenarios are assumed to be taking place within the borders of Turkey. For this reason we have to point out

the absence of smallpox vaccine production and storage facilities in Turkey. Therefore, we focus on developing an optimal vaccine procurement strategy by determining the order size and the order timing through deterministic single commodity inventory model (Laporte, 2004).

The results of both epidemiological modeling and inventory models are presented in the next sections. Based on the literature, we run all models for three different R_0 values ranging from 3 to 7 (Meltzer *et al*. 2001, Kaplan *et al*. 2002, Halloran *et al*. 2002, Bozette *et al*. 2003, Gani and Leach, 2003). Inventory model is run under the value of R_0=3 for all scenarios and total costs are compared.

5.1. Overview of Numerical Results Analysis

Before proceeding to results, we first present general assumptions and parameters that are common for all models. Since smallpox vaccination program was terminated in late 70s, we assume that the whole population is fully susceptible to the agent. Population is assumed to be homogenously mixing; therefore every individual has the same chance to get infected. Since we compare the outcome of the epidemic under the different R_0 values, we computed β as follows;

$$(= R0 / ((\varepsilon / (\alpha + (1/\delta + \mu))) \quad (5.1)$$

All exposed individuals are assumed to be infected. Isolation in Model 2 is defined as the separation of individuals who go to the hospital due to the high fever symptom in the prodromal stage. These individuals might be taken under control in

terms of observing the course of disease. If the fever is followed by rash symptom within 3 to 4 days, then individual is diagnosed as a smallpox patient and isolated from the rest of the population. All exposed individuals are assumed to become infected. They move to quarantine class with the same rate as moving from prodromal to infectious class. Table 5.1 displays the list of parameters used in the models.

Table 5.1. List of parameters used in the models.

Notation	Definition	Value
χ	Transmission rate from exposed to prodromal compartment	1/12
α	Transmission rate from prodromal to infected compartment	1/3
δ	Recovery rate	1/16
μ	Death rate	0.0268
E	Reduced infectivity rate	0.3
Γ	Rate of taken under control in prodromal stage	0.3
Σ	Rate of taken under control in prodromal stage	0.08
Φ	Fraction of vaccinated individuals at susceptible class	0.2
Ψ	Fraction of vaccinated individuals at exposed class	0.8
μ_3	Vaccine induced deaths among vaccinated exposed	10^{-6}
V_{es}	Vaccine effectiveness for susceptible	0.95
V_{ee}	Vaccine effectiveness for exposed	0.80

5.2. Numerical Results and Discussions for Model I

Model 1 is the simplest model without any control measures. We run the solution algorithm coded in Matlab 7.0. for all scenarios and for varying parameters. In each scenario, we consider fully susceptible populations with the size of 5000, 3,500,000, 75,000,000 individuals, respectively. Due to the small size of the population, we assume that only 0.01 of the population of campus is exposed to disease outside the campus.

5.2.1. Scenario 1

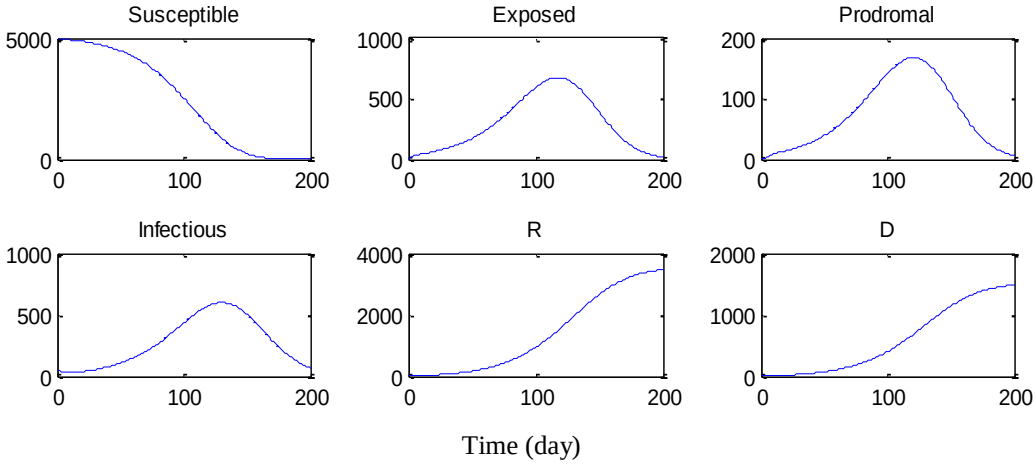


Figure 5.1. Solutions to system of differential equations for Model 1 and Scenario 1.

The system of nonlinear differential equations (1)-(5) given in Chapter 3 has been numerically solved in seconds by using the Matlab function 'ode45' on a personal computer with 1 GB RAM and 2.4 Ghz processor. The results obtained for each compartment are plotted and presented in Figure 5.1. From the figure, we can observe that smallpox epidemic lasts approximately 200 days.

Table 5.2. Numerical results for Model 1, Scenario 1

Model 1, Scenario 1							
S_0=5000, I_0=50							
R_0	E	*E	P	*P	I	*I	D
3	4979	675	4973	168	3470	601	1486
5	5000	1134	5000	280	3535	941	1515
7	5000	1435	5000	352	3536	1126	1516

**Represent the maximum number of individuals in a day in the corresponding disease stage*

Table 5.2 shows the results that are obtained by running the Model 1 for 200 days of scenario 1 in the absence of interventions. The first column of the Table 5.2 displays varying R_0 values and columns indicated by E, P, I and D display the cumulative number of individuals in Exposed, Prodromal, Infectious and Death classes within 200 days. Columns represented by *E, *P, and *I indicate the maximum number of individuals or peak numbers observed in a single day until the disease disappears.

As expected, with the increasing R_0 values, we observe increase in both peak and cumulative number of cases in each compartment. Note that approximately %30 of exposed individuals die with given parameters and under the assumptions.

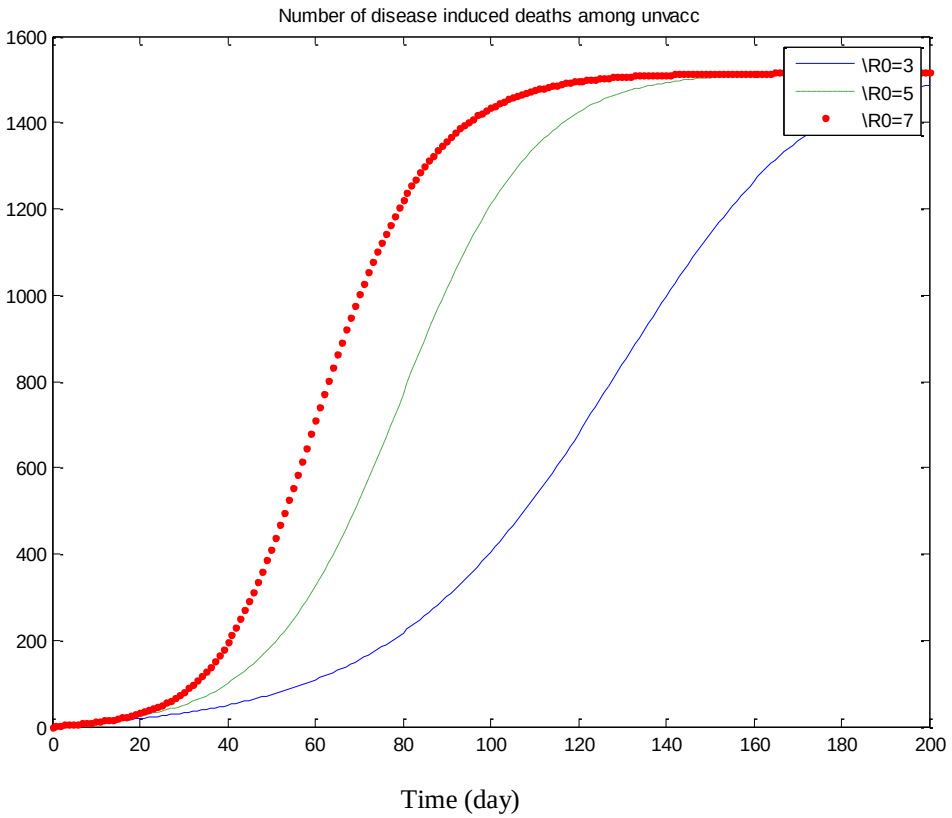


Figure 5.2. Number of disease induced deaths during disease progression.

The values of R_0 are chosen among the suggested smallpox basic reproductive ratio values. As seen from the Figure 5.2, the number of disease induced deaths are increasing day by day as the value of R_0 is increased for Model 1, Scenario 1.

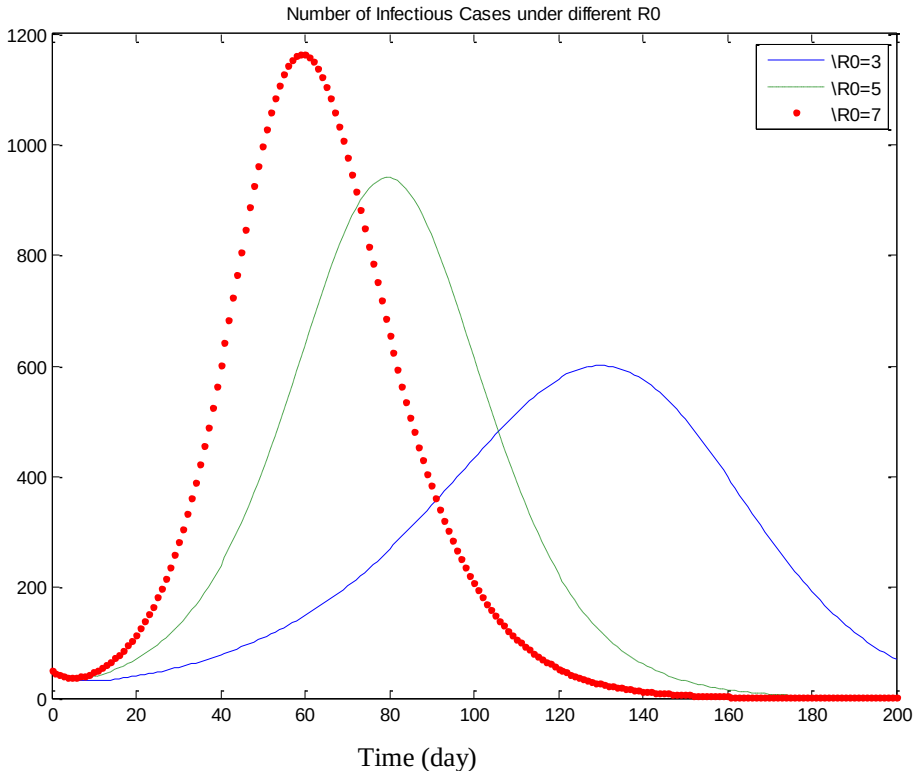


Figure 5.3. Number of infectious cases during disease progression for different R_0 values.

Similarly, in the absence of any control policy, the numbers of infected individuals are proportionally increasing as the value of R_0 is increased. The peak number of infectious cases denoted by *I in Table 5.2 can directly be observed from Figure 5.3.

5.2.2. Scenario 2

Similar results are obtained for Scenario 2, in which the population size is 3.5 million.

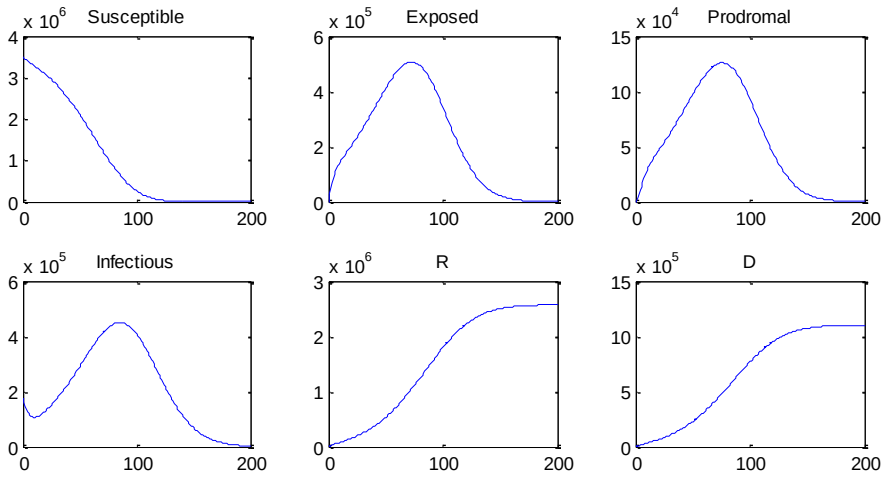


Figure 5.4. Solutions to system of differential equations for Model 1 and Scenario 2.

Table 5.3. Numerical results for Model 1, Scenario 2.

Model 1, Scenario 2							
S_0=3,500,000 I_0=175,000							
R_0	E	*E	P	*P	I	*I	D
3	3,499,396	505,686	3,499,468	125,966	2,575,475	449,835	1,101,949
5	3,499,651	834,422	3,499,990	206,165	2,577,576	692,139	1,102,884
7	3,499,519	1,050,631	3,499,995	257,754	2,577,618	824,390	1,102,902

** Represent the maximum number of individuals in a day in the corresponding disease stage*

Table 5.3 shows the results for Model 1 obtained by running scenario 2 in the absence of interventions. In this scenario, initial size of the susceptible population is 3.5 million and 175 thousand people are assumed to be infectious at time zero.

Similar to Table 5.2, the first column of the Table 5.3 displays varying R_0 values and columns indicated by E, P, I and D displays the cumulative number of individuals in Exposed, Prodromal, Infectious and Death classes. For different force of infections, the potential risk for whole city can be clearly observed from the table. Note that if there is no intervention or control policy, over one million people will die as a result of a potential terrorist attack. Under the given assumptions, it is very likely to have 824,390 people infected and seeking medical attention in a single day.

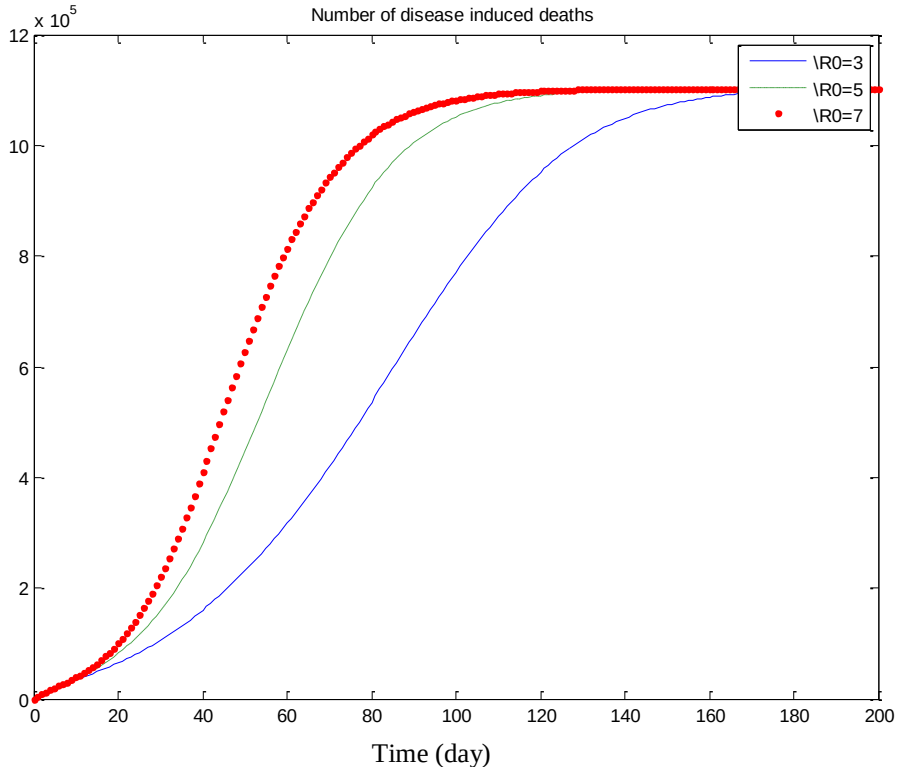


Figure 5.5. Number of disease induced deaths during disease progression for Model 1, Scenario 2.

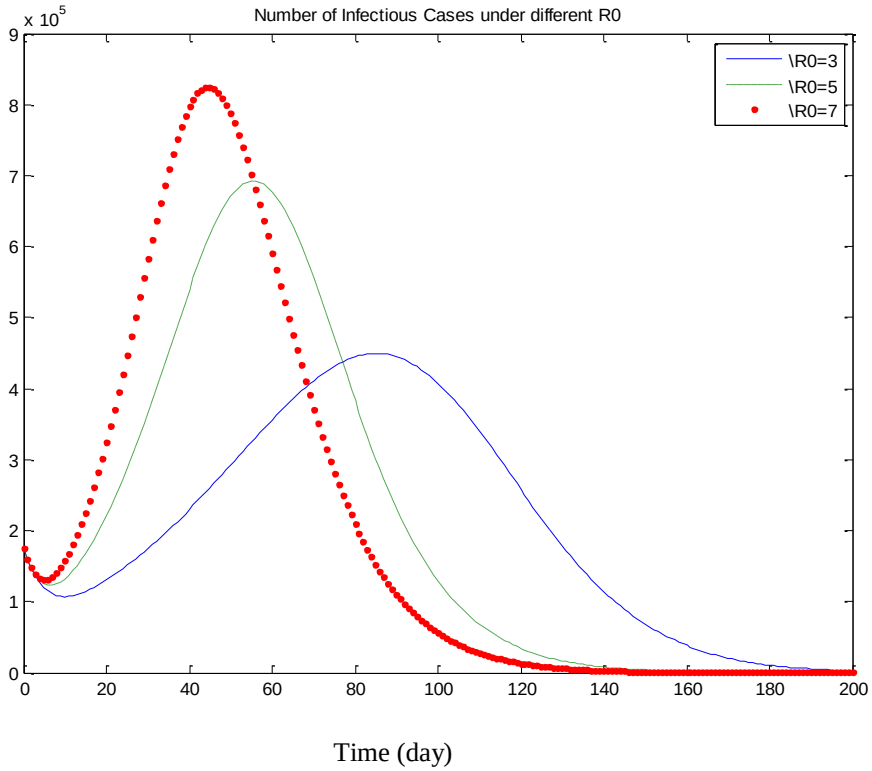


Figure 5.6. Number of infectious cases during disease progression for different R_0 values for Model 1, Scenario 2.

According to Figures 5.5 and 5.6 it can be observed that in absence of control policies, incidences are increased as the population size is increased. The curves might seem similar however it should not be forgotten that in case of emergency supply levels might be same regardless to the population sizes. Therefore, resources should be well allocated at the local level for a population size of 5000. The allocation of the resources can be planned at the strategical level for a population of a city or nationally for a population of a country.

5.2.3. Scenario 3

The numerical results for scenario 3, which is based on a nation-wide bioterrorist attack in Turkey, are given in Table 5.4. In this scenario, initial size of the susceptible population is 75 million and 3.75 million people are assumed to be infectious at time zero. Without any intervention or control policy, significant proportion of whole population might be lost due to disease-induced death.

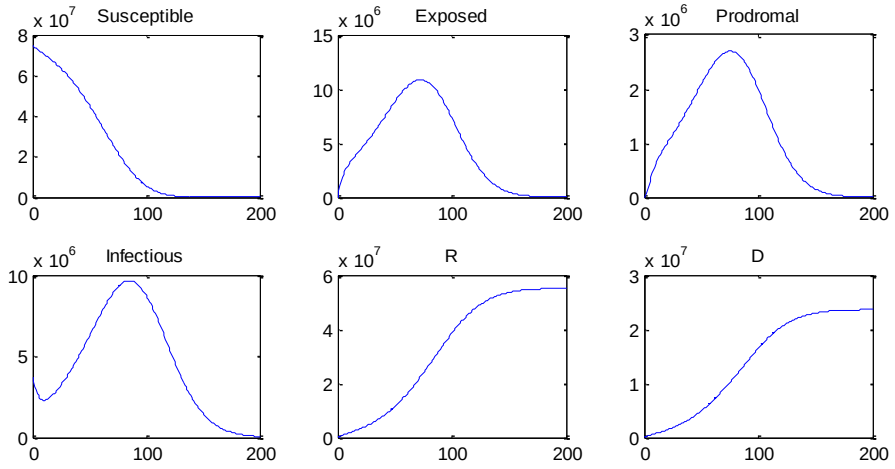


Figure 5.7. Solutions to system of differential equations for Model 1 and Scenario 3.

Table 5.4. Numerical results for Model 1, Scenario 3

Model 1, Scenario 3							
S_0=75,000,000, I_0=3,750,000							
R_0	E	*E	P	*P	I	*I	D
3	74,987,055	10,836,066	74,988,606	2,698,633	55,188,760	963,8287	23,613,189
5	74,992,518	17,880,458	74,999,748	4,417,836	55,233,788	14,831,140	23,633,225
7	74,989,704	22,513,592	74,999,916	5,523,846	55,234,667	17,665,426	23,633,620

**Represent the peak number of individuals in corresponding disease stage*

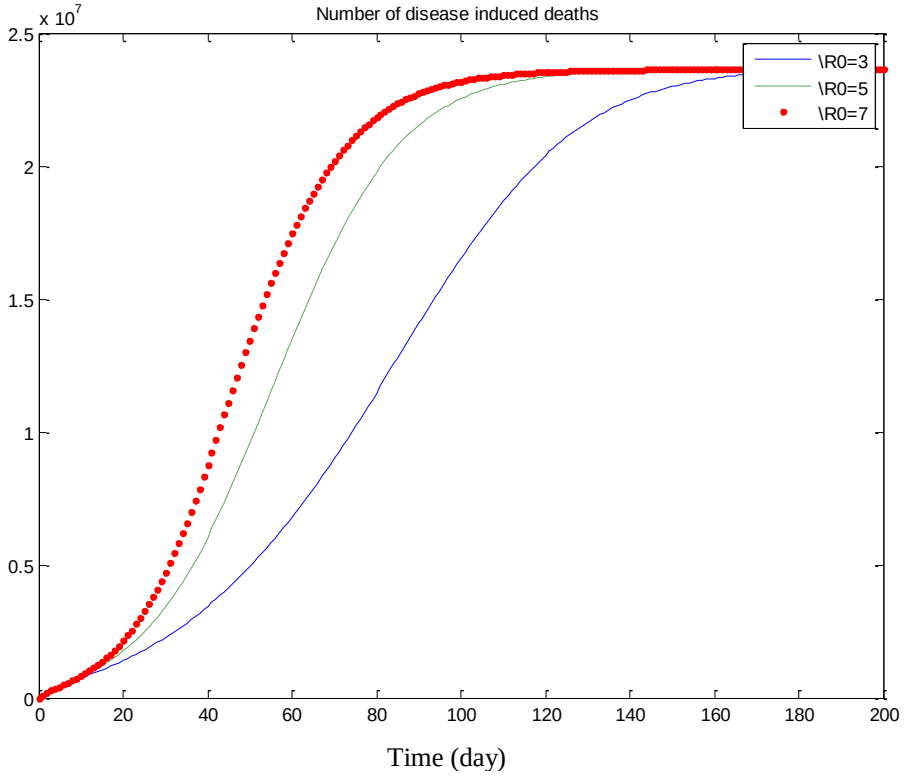


Figure 5.8. Number of disease induced deaths during disease progression for Model 1, Scenario 3.

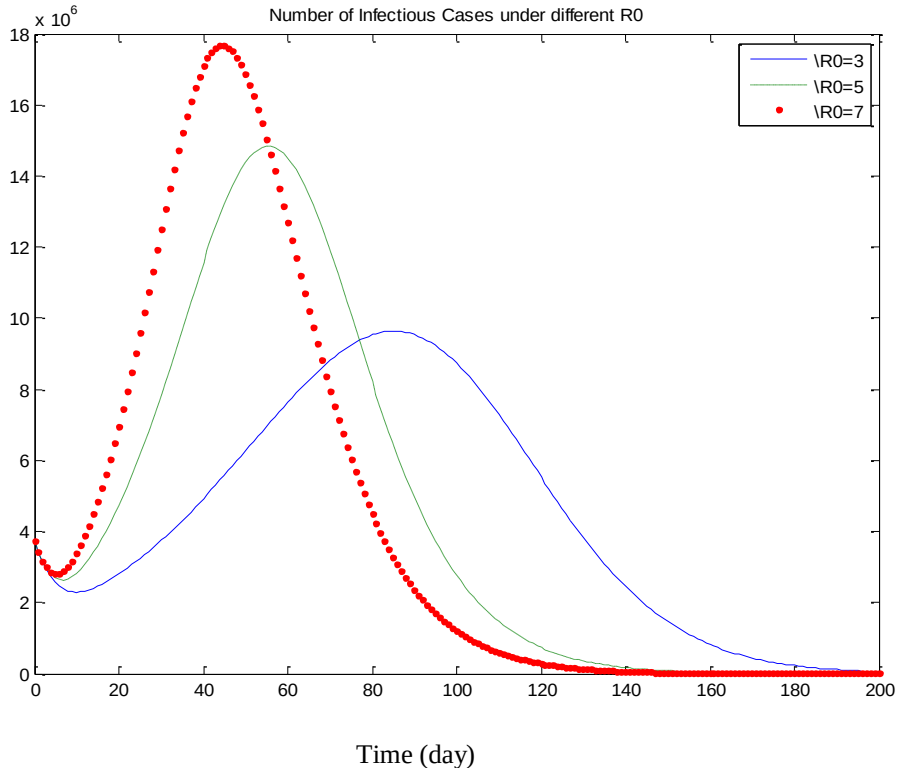


Figure 5.9. Number of infectious cases during disease progression for different R_0 values for Model 1, Scenario 3.

After analyzing the first model for three different scenarios, the strong need for control and preventive measures become obvious. In order to analyze and compare the effect of quarantine and isolation/hospitalization control policies we present the analysis of Model 2 in the next Section.

5.3. Numerical Results and Discussions For Model 2

In Model 2, quarantine and hospitalization control measures are considered in addition to the disease dynamics Model 1. Exposed individuals move to quarantine class with a rate of Φ and infected individuals who have previously not attended exposed class, move to hospitalization class with a rate of σ. We run the solution algorithm for all scenarios and varying parameters. In each scenario, we consider fully susceptible populations with the size of 5000, 3,500,000, 75,000,000 individuals respectively.

In Chapter 3, it is stated that among 47,5% of individuals who experience high fever go to the hospital and are taken under observation. Individuals are taken under observation corresponds to quarantine by a fraction of 47,5%. This means the fraction of $\gamma/(\alpha+ \gamma)$ individuals are taken under quarantine. Setting this fraction to 47,5% gives; γ as 0.6. If 75% of these individuals attend to hospital due to the onset of high fever, the rate is increased to 1.0. Similarly, in case of the fraction of 92% of individuals are quarantined, γ becomes 1,0. The rates which calculated with corresponding fractions of quarantined and hospitalized individuals are shown in the Table 5.5.

Table 5.5. Vaccination rates of susceptibles and exposed individuals corresponding to the fractions of being under control in Model 2.

γ		σ	
Fractions (%)	Rates	Fractions (%)	Rates
47,5	0.3	20	0.02
64	0.6	47,5	0.08
75	1	60	0.13
0	0	92	1

Similarly, the hospitalization rates are calculated as follows; individuals who do not go to hospital due to the onset of high fever are assumed to seek medical help at the end of the prodromal period, which corresponds to infectious period. Therefore, $\sigma /(\delta+ \sigma)$ fraction of individuals are hospitalized. Rates are obtained through setting these fractions to the values vary between 20-92%.

5.3.1. Scenario 1

Due to the small size of the first population, we assume that only 0.01 of the population of campus is exposed to disease outside the campus. The system of nonlinear differential equations (6)-(13) given in Chapter 3 has been numerically solved in seconds by using the Matlab function 'ode45'. The results obtained for each compartment are plotted and presented in Figure 5.10. From the figure, we can observe that smallpox epidemic lasts approximately 200 days.

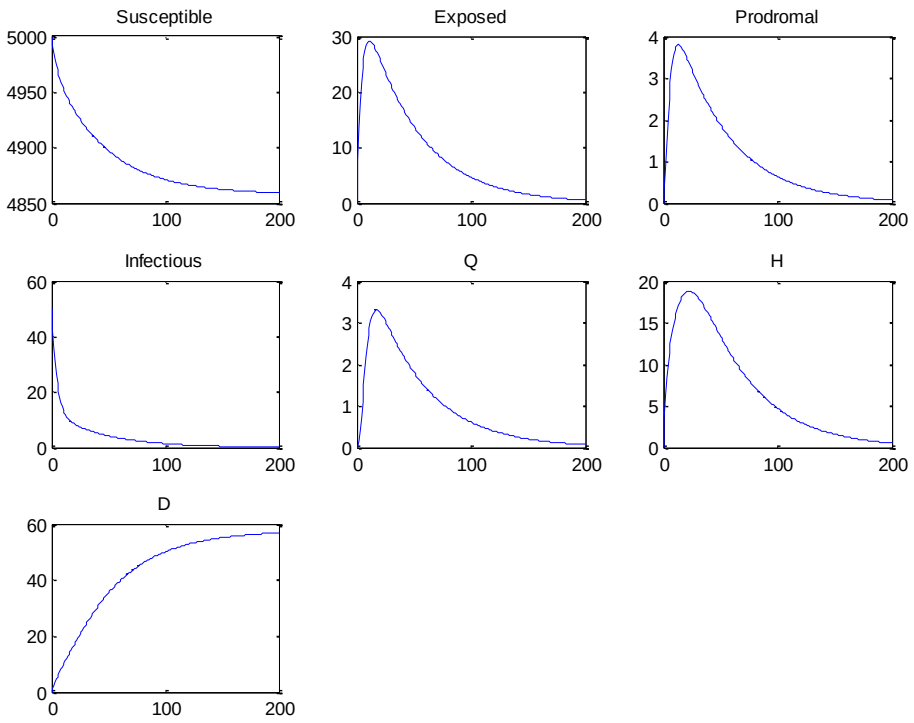


Figure 5.10. Solutions to system of differential equations for Model 2 and Scenario 1.

Figure 5.10 shows the results that are obtained by running the Model 2 for 200 days of scenario 2 under the quarantine and hospitalization control measures. The first column of the Table 5.6 displays varying R_0 values and columns indicated by E, P, I and D displays the cumulative number of individuals in Exposed, Prodromal, Infectious and Death classes within 200 days. Columns represented by *E, *P, and *I display the maximum number of individuals or peak numbers observed in a single day until the disease disappears.

Table 5.6. Total numbers of classes within 200 days and peak numbers for each class.

Model 2, Scenario 1									
S_0=5000, I_0=50									
R_0	Γ	σ	E	*E	P	*P	I	*I	D
3	0	0.08	1371	173	1329	42	481	79	368
	0.3	0.08	140	29	74	4	47	50	57
	0.6	0.08	91	28	33	3	32	50	42
	1	0.08	74	28	19	2	27	50	37
	0.3	0.02	549	42	287	6	189	50	170
	0.3	0.13	82	24	43	3	28	50	39
	0.3	1	10	7	5	1	5	50	18
5	0	0.08	4999	1044	4999	258	1865	490	1514
	0.3	0.08	1195	93	623	12	241	50	340
	0.6	0.08	294	50	105	4	59	50	102
	1	0.08	174	48	43	3	36	50	67
	0.3	0.02	4990	730	2626	96	1523	281	1496
	0.3	0.13	365	43	192	6	70	50	121
	0.3	1	19	11	10	1	5	50	21
7	0	0.08	5000	1497	5000	365	1866	670	1515
	0.3	0.08	4995	780	2629	102	990	197	1505
	0.6	0.08	1314	80	467	7	187	50	380
	1	0.08	396	71	99	4	56	50	133
	0.3	0.02	5000	1221	2632	160	1535	442	1515
	0.3	0.13	3055	377	1582	49	446	73	803
	0.3	1	31	16	16	2	6	50	24

According to the Table 5.6, the best result obtained when the individuals taken under control and observation with high rates. It is an optimistic option for this model. In reality, health care facilities might not be responding this suddenly increasing smallpox cases. Therefore, it is needed to be run more realistic rates for Model 2. For this model, we advocate that exposed individuals should be separated from the rest of the population, in order to reduce the number of the secondary cases. Therefore, we set σ parameter to the second highest value and set γ to 0.3 which corresponds to the value mentioned in Longini *et al.*, (2007)

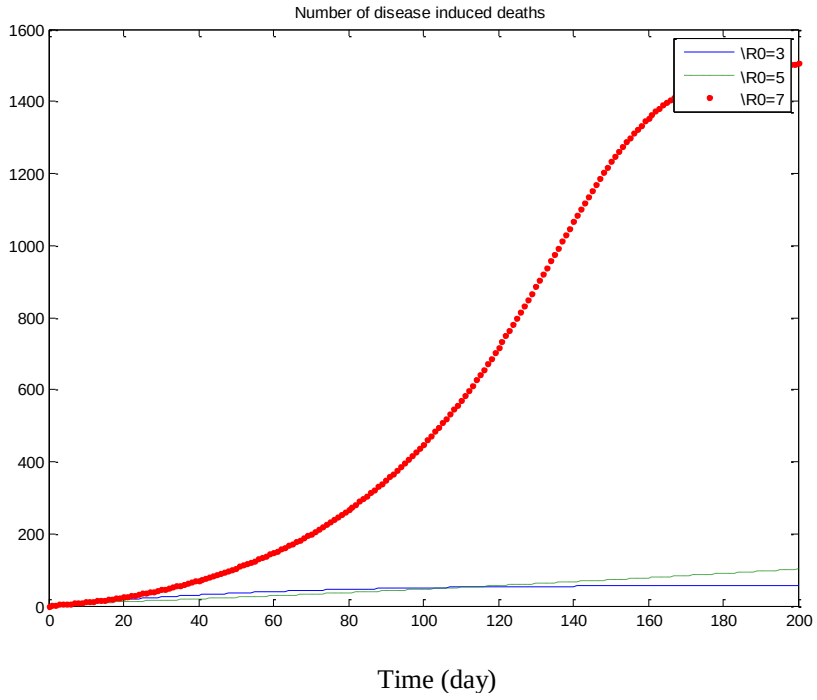


Figure 5.11. Number of disease induced deaths during disease progression for Model 2, Scenario 1.

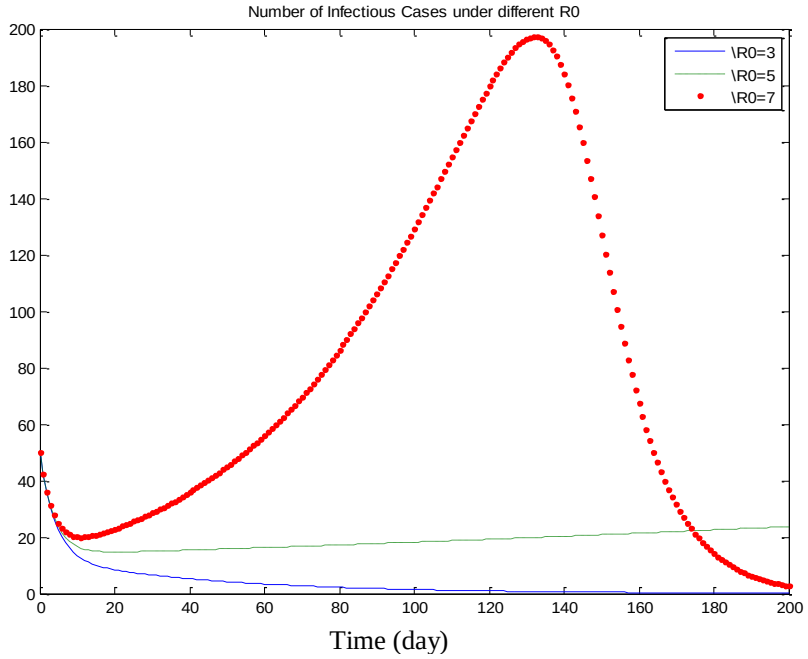


Figure 5.12. Number of infectious cases during disease progression for different R_0 values for Model 2, Scenario 1.

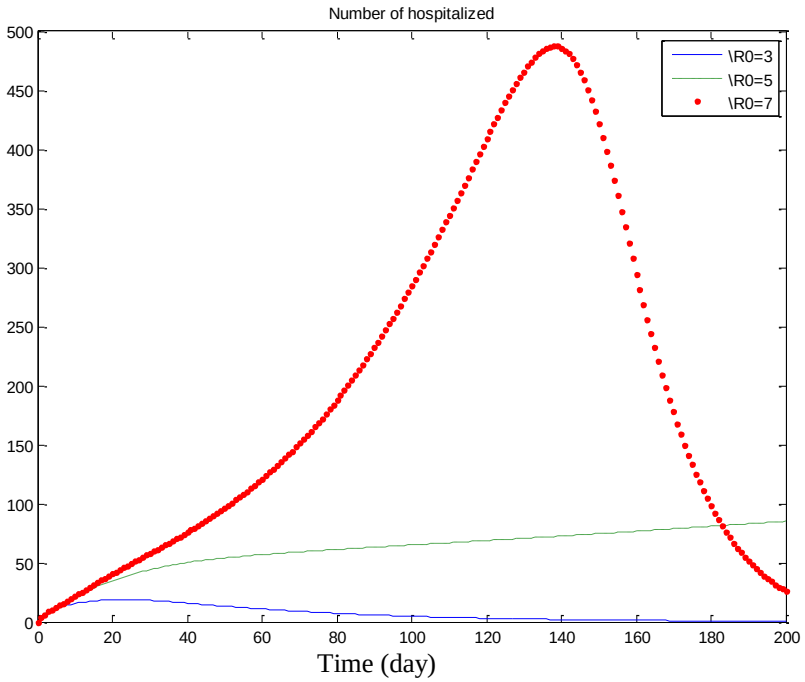


Figure 5.13 Number of hospitalized individuals under different values of R_0s for Model 2, Scenario 1.

When the R_0 reached its highest value which is 7, numbers of deaths, infectious cases and hospitalized individuals are dramatically increased.

5.3.2. Scenario 2

Table 5.7 shows the results for Model 2 obtained by running scenario 2 under quarantine and isolation measures. In this scenario, initial size of the susceptible population is 3.5 million and 175 thousand people are assumed to be infectious at time zero. Similar to Table 5.6, the first column of the Table 5.7 displays varying R_0 values and columns indicated by E, P, I, and D display the cumulative number of individuals in Exposed, Prodromal, Infectious and Death classes. For different force of infections, the potential risk for whole city can be clearly observed from the table. Recall that if there is no intervention or control policy, over one million people will die as a result of a potential terrorist attack. Under the given base line parameters, 193,895 people will die and 175,000 people will be infected and seeking medical attention in a single day.

Table 5.7. Total numbers of classes within 200 days and peak numbers for each class.

Model 2, Scenario 2									
S_0=3500000, I_0=175000									
R_0	Γ	σ	E	*E	P	*P	I	*I	D*
3	0	0.08	3181901	254119	3137090	63470	1192241	175000	932575
	0.3	0.08	473786	99309	249341	12951	162075	175000	193895
	0.6	0.08	311054	96152	111159	8538	111255	175000	145867

	1	0.08	254447	94160	63661	5867	93729	175000	128934
	0.3	0.02	1739088	141747	910474	18628	609285	175000	547161
	0.3	0.13	277974	81696	146395	10581	97252	175000	135892
	0.3	1	33241	22540	17599	2656	17493	175000	62556
5	0	0.08	3499642	780201	3499977	2E+05	1362297	366146	1E+06
	0.3	0.08	3262505	212996	1707500	28037	685788	175000	972366
	0.6	0.08	987203	171024	352445	15225	199780	175000	345400
	1	0.08	590349	163472	147662	10199	124715	175000	229532
	0.3	0.02	3499623	605713	1842082	79557	1158941	233364	1E+06
	0.3	0.13	1206201	146587	633242	19180	234489	175000	404177
	0.3	1	64153	37855	33938	4485	18431	175000	71873
7	0	0.08	3499519	1103044	3499993	3E+05	1362310	493509	1E+06
	0.3	0.08	3499502	651959	1842090	85664	750263	175000	1E+06
	0.6	0.08	3472036	267530	1239222	23901	524395	175000	1E+06
	1	0.08	1324658	240573	331143	15014	192032	175000	446187
	0.3	0.02	3499518	959808	1842099	1E+05	1158986	347612	1E+06
	0.3	0.13	3499049	393877	1841817	51810	580407	175000	1E+06
	0.3	1	106617	53401	56356	6370	19717	175000	84653

Corresponding to Table 5.7, the general results are provided in Figure 5.14 for the Model 2, Scenario 2.

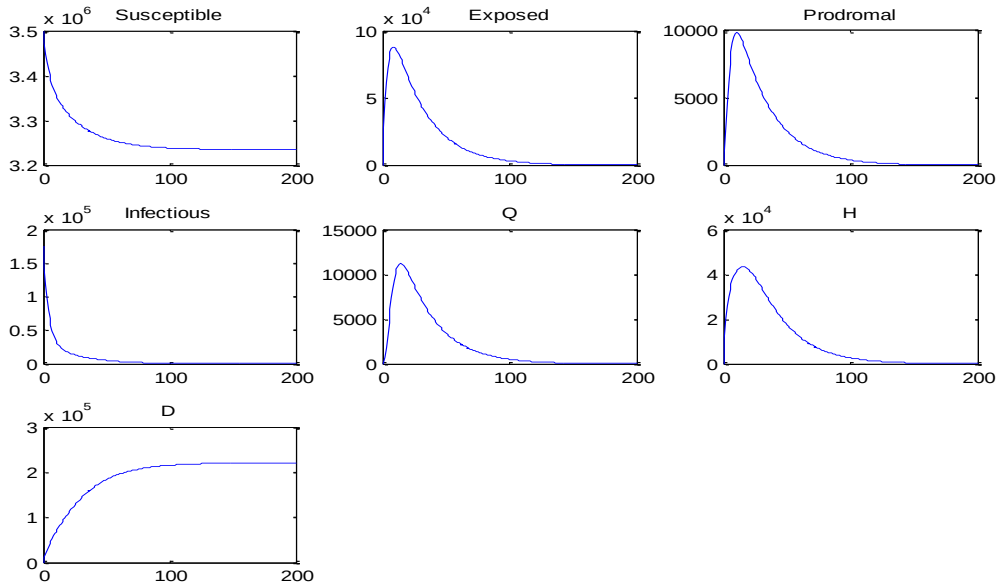


Figure 5.14 Solutions to system of differential equations for Model 2 and Scenario 2.

Figure 5.15 shows the number of infectious individuals under different R_0 values. Comparing with the previous Scenario, due to the bigger population size, even when under the condition of higher value or R_0, new cases are not occurred. This means despite the susceptible state of the population, size is the important factor in the frequency of the new case occurrence.

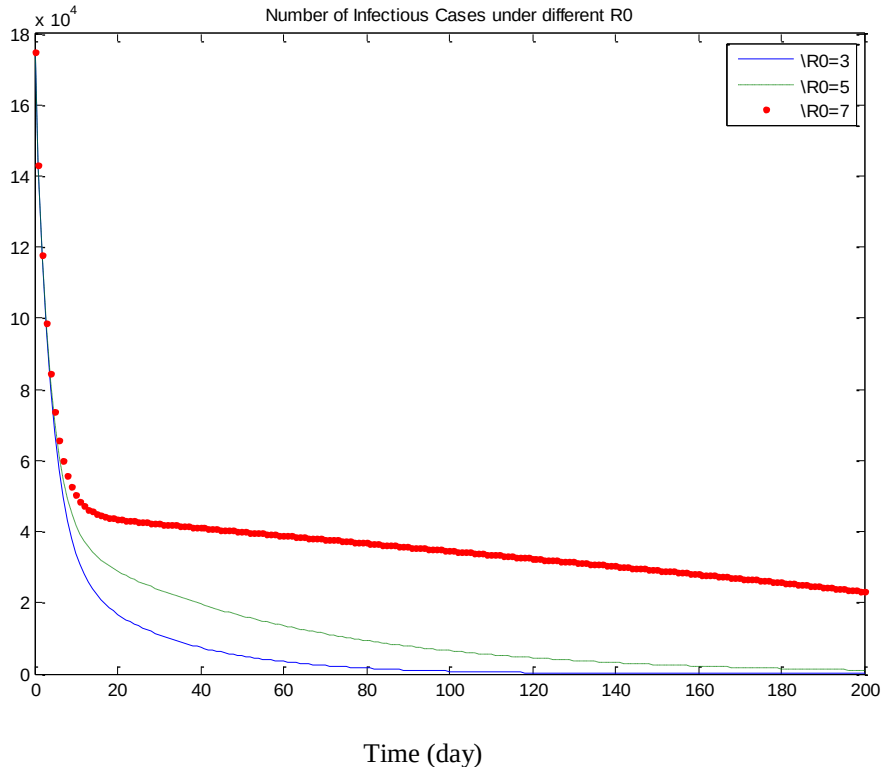


Figure 5.15: Number of infectious individuals under different values of R_0s for Model 2, Scenario 2.

Figure 5.16 shows the disease-induced deaths and when the R_0 value reaches to the higher value, numbers of deaths increased dramatically due to the higher potential of being infected. Number of hospitalization is shown in the Figure 5.17. there might be a question asked that while the number of infectious cases are not increasing, why an increase in hospitalization occurred. The initial numbers of infected individuals are 175,000 and assumption can allow the infectious individuals to be hospitalized without any time limit, therefore initially, the population at this stage tends to grow proportional to the value of R_0, and begins to decrease due the lack of new cases. Figure 5.16 shows the numbers of deaths and as seen from the

Table 5.7 the numbers of deaths are increasing in both conditions and proportionally to the value of R_0.

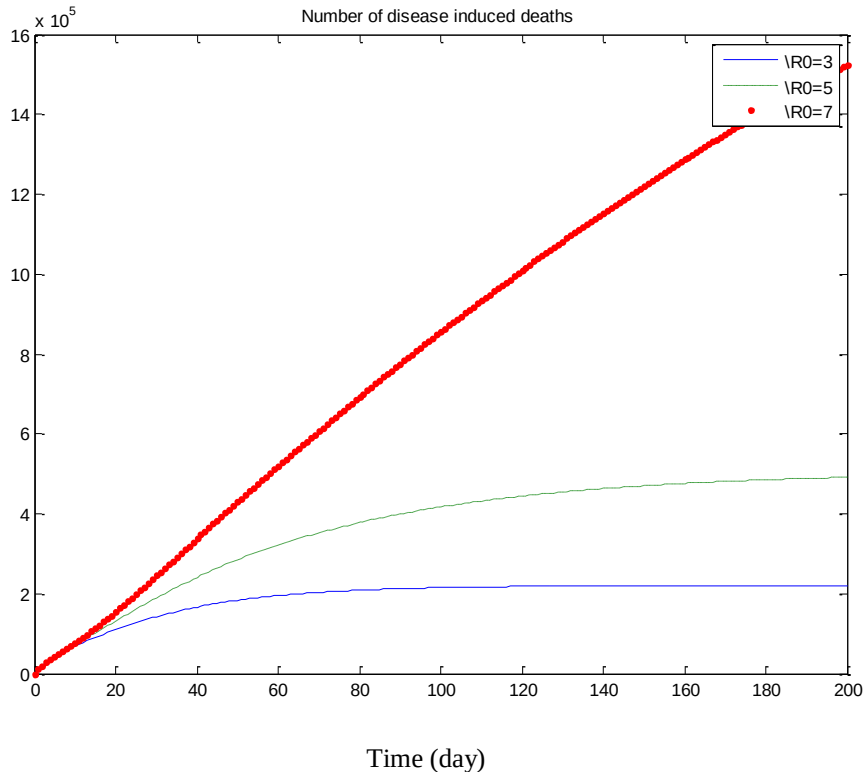


Figure 5.16 Number of disease induced deaths during disease progression for Model 2, Scenario 2.

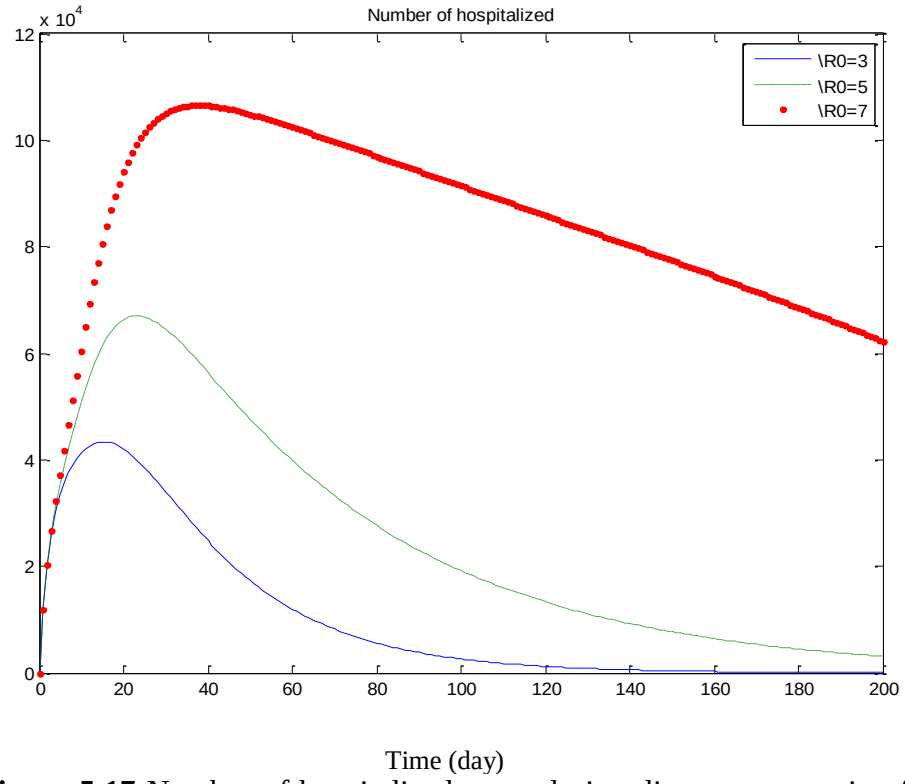


Figure 5.17 Number of hospitalized cases during disease progression for Model 2, Scenario 2.

5.3.3. Scenario 3

The numerical results for scenario 3, which is based on a nation-wide bioterrorist attack in Turkey, are given in Table 5.8. In this scenario, initial size of the susceptible population is 75 million and 3.75 million people are assumed to be infectious at time zero. It is observed that, in the existence of control policy total size of epidemic decreased to 25 million of individual with the given baseline parameters.

Table 5.8. Total numbers of classes within 200 days and peak numbers for each class for Model 2, Scenario 3.

Model 2, Scenario 3									
S_0=75000000, I_0=3750000									
R_0	γ	σ	E	*E	P	*P	I	*I	D*
3	0	0.08	68183584	5445643	67223354	1360081	25548029	3750000	19983750
	0.3	0.08	10152557	2128053	5343015	277515	3473026	3750000	4154883
	0.6	0.08	6665443	2060417	2381986	182949	2384044	3750000	3125718
	1	0.08	5452444	2017729	1364165	125747	2008473	3750000	2762865
	0.3	0.02	37266163	3037427	19510165	399162	13056111	3750000	11724887
	0.3	0.13	5956589	1750624	3137039	226727	2083978	3750000	2911979
	0.3	1	712315	482992	377131	56917	374852	3750000	1340487
5	0	0.08	74992339	16718148	74999522	4131352	29192073	7844485	23632576
	0.3	0.08	69910816	4564195	36589283	600801	14695455	3750000	20836405
	0.6	0.08	21154353	3664802	7552387	326262	4280995	3750000	7401422
	1	0.08	12650342	3502978	3164197	218539	2672466	3750000	4918543
	0.3	0.02	74991917	12979552	39473183	1704979	24834448	5000732	23631223
	0.3	0.13	25847153	3141171	13569482	410990	5024774	3750000	8660931
	0.3	1	1374717	811173	727248	96106	394943	3750000	1540135
7	0	0.08	74989690	23636270	74999893	5766014	29192351	10574444	23633579
	0.3	0.08	74989321	13970475	39473382	1835266	16077071	3750000	23632291
	0.6	0.08	74400764	5732864	26554773	512377	11237032	3750000	22899639
	1	0.08	28385537	5155143	7095929	321733	4114965	3750000	9561141
	0.3	0.02	74989672	20567223	39473607	2692345	24835411	7448683	23633521
	0.3	0.13	74979631	8440154	39467486	1110420	12437302	3750000	23606201
	0.3	1	2284648	1144321	1207636	136496	422507	3750000	1814002

Corresponding to Table 5.8, general results of the Model 2 for the Scenario 3 are provided below.

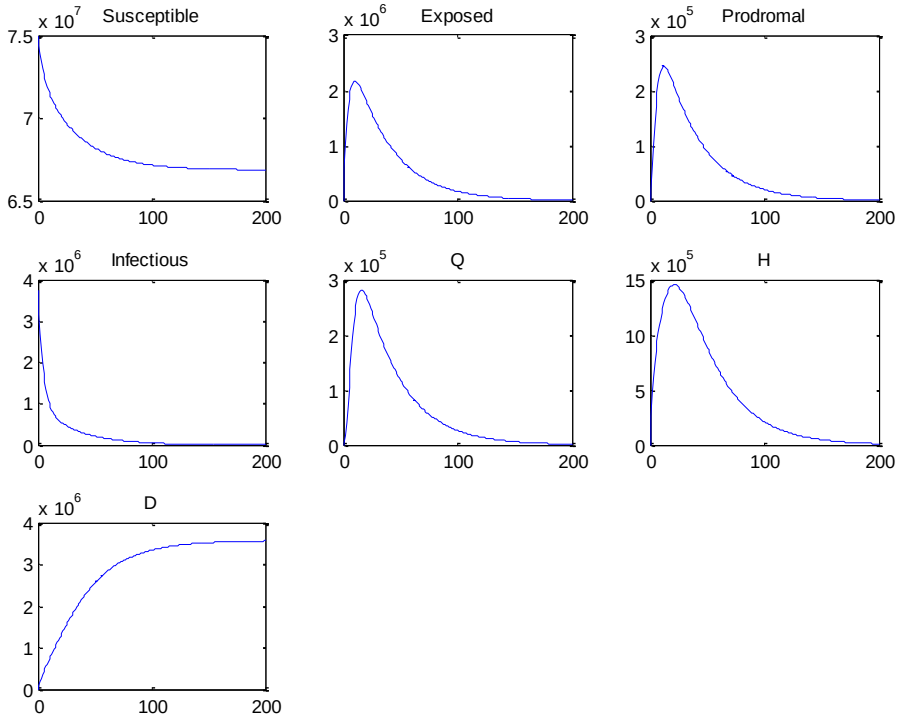


Figure 5.18 Solutions to system of differential equations for Model 2 and Scenario 3.

According to the Figure 5.19, there is an unexpected increase in the curve. Since the incubation period is long, the generation of new cases might take time. This unexpected increase reflects the individuals who are going thorough infectious period at the end of the incubation period. This increase can only be observed under the condition of the highest value of R_0. There are 3,750,000 individuals are initially sick and the higher occurrence of secondary cases per infective is resulted in a dramatic increase after the long incubation period. It should be noted that the

numbers of infected individuals are not increasing further due to the very large population size, as expected.

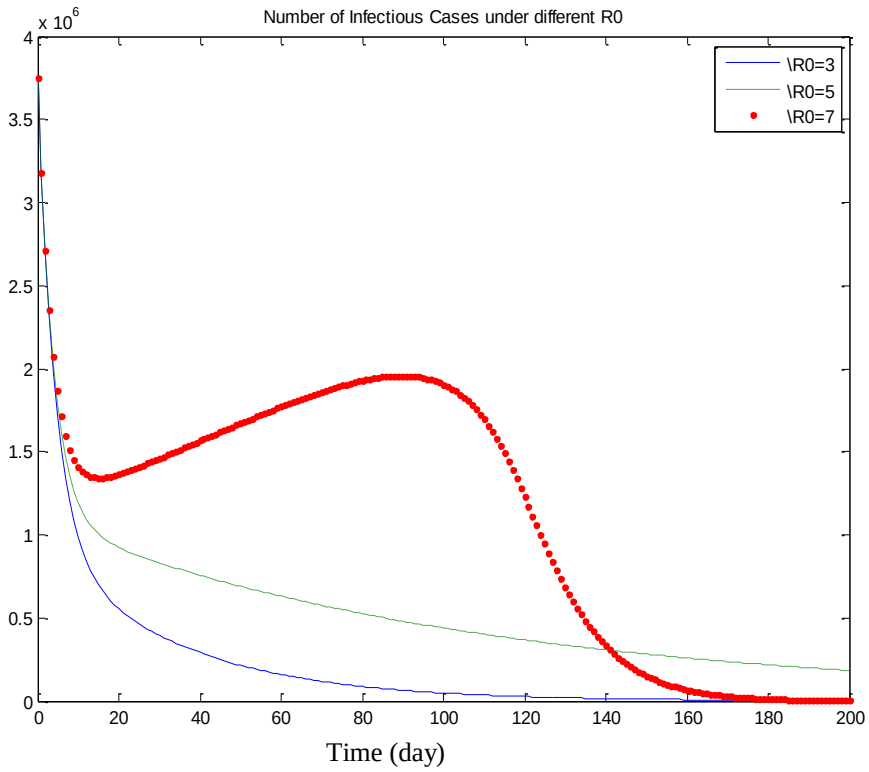


Figure 5.19 Number of infectious individuals under different values of R_0s for Model 2, Scenario 3.

According to the Figure 5.20 the numbers of deaths are increasing corresponding to the R_0 values and the volume of initial infected population. As observed from the Table 5.8, deaths count for the 30% of infected people, due to the variation in the parameters, number of deaths can result less than 30%.

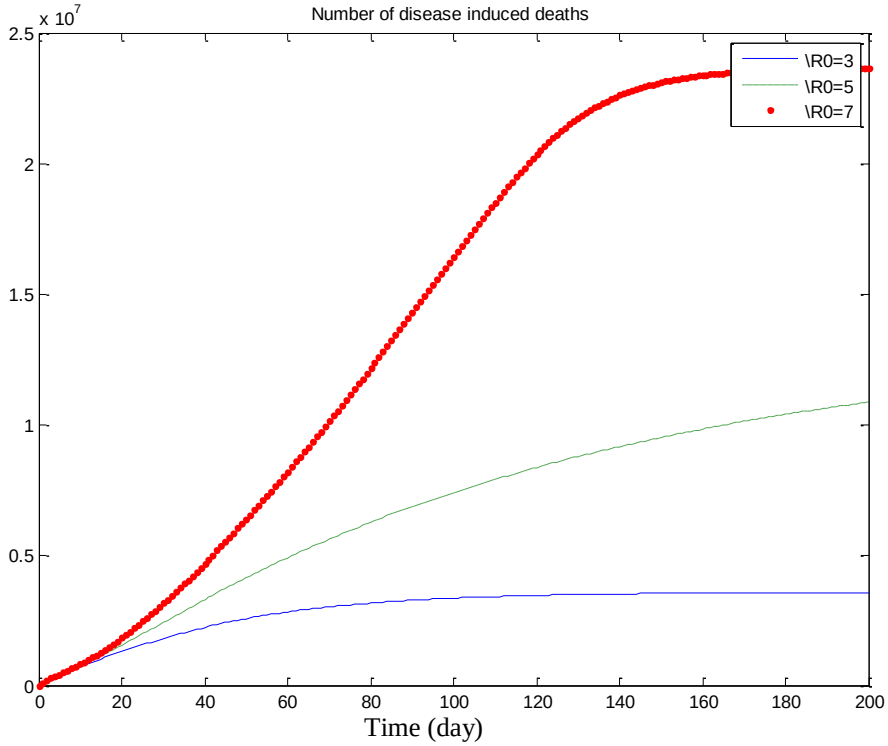


Figure 5.20 Number of deaths under different values of R_0 for Model 2, Scenario 3.

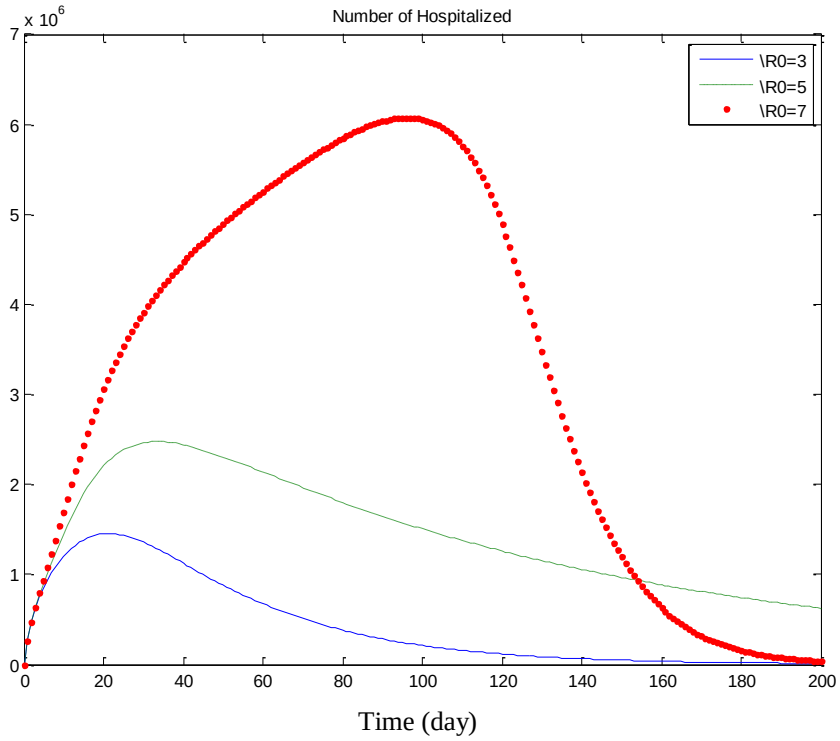


Figure 5.21 Number of hospitalized cases during disease progression for Model 2, Scenario 3.

In case of the implementation of quarantine and isolation policy, there will be an additional capacity requirements raised. As seen from the tables and figures that are presented, the volume of requirements are increasing as the R_0 and the size of population increased. Implementation might not be problem when the population size is small. However, the response action plans cannot be done neither according to the value of R_0 and neither according to the initial population numbers. Since these plans should have the ability to cover similar crisis, response plan is expected to be robust. If not, the plan either insufficient in covering the disaster or resulted in excess supply. In this context, this implementation might be reconsidered and

individual level isolation can be courage by the campaigns and the educative actions for stopping smallpox epidemic.

In the next section, the results of vaccination policy, which is believed to be the most effective way in decreasing the speed of epidemic, are examined.

5.4. Numerical Results and Discussions for Model 3

In Model 3, we evaluate the situation in which vaccination is chosen as a control measure. Similar to the previous models, we run the solution algorithm coded in Matlab 7.0. for all scenarios and varying parameters. In each scenario, we consider fully susceptible populations with the size of 5000, 3,500,000, 75,000,000 individuals respectively. Due to the small size of the population, we assume that only 0.01 of the population of campus is exposed to disease outside the campus.

The system of nonlinear differential equations (13)-(26) given in Chapter 3 has been numerically solved in seconds by using the Matlab function 'ode45' on a personal computer with 1 GB RAM and 2.4 Ghz processor.

5.4.1. Scenario 1

The first scenario includes 5000 susceptible and 50 infected individuals. We assume that, individuals can be vaccinated before the exposure as preventive treatment or might be vaccinated after exposure. Vaccine effectiveness is considered therefore, not all vaccinated individuals are directly immunized. Rates of vaccination which are ϕ and ψ computes with considering the fractions of

individuals that might be vaccinated. Baseline and alternative parameters and corresponding fractions are given in the Table 5.9.

Table 5.9 Vaccination rates of susceptible and exposed individuals

Φ		Ψ	
Fractions (%)	Rates	Fractions (%)	Rates
-	0	90%	0.8
20%	0.2	-	0
40%	0.4	50%	0.4
100%	1	100%	1

Table 5.10 shows the results that are obtained by running the Model 3 for 200 days of scenario 1 in the existence of vaccination measure. The compartment 'vaccinated exposed' or E_V gives us the total number of individual that might require vaccines. Since the attitudes towards smallpox vaccination is not considered in this model, we assume that all individual in this class is vaccinated. The first column of the Table 5.10 displays varying R_0 values and columns indicated by E, P, I, E_v, D displays the cumulative number of individuals in Exposed, Prodromal, Infectious, Vaccinated exposed, Death classes up to 200 days. Columns represented by *E, *P, Ev* and *I display the maximum number of individuals or peak numbers observed in a single day until the disease disappears.

Table 5.10 Total numbers of classes within 200 days and peak numbers for each class for Model 3, Scenario 1

Model 3, Scenario 1											
S_0=5000, I_0=50											
R_0	ϕ	ψ	E	*E	P	*P	I	*I	E_v	*E_v	D*
3	0	.8	23	8	58	2	77	50	270	44	264
	.2	.8	8	7	22	2	52	50	102	34	5040
	.4	.8	4	5	11	1	45	50	53	24	5037
	1	.8	0	0	1	0	37	50	6	4	5035
	.2	0	97	37	98	9	105	50	2	1	5006
	.2	.4	16	11	29	3	57	50	97	32	5037
	.2	1	7	5	21	2	51	50	103	35	5040
5	0	.8	102	14	247	4	201	50	1147	82	949
	.2	.8	14	11	38	3	63	50	175	59	5043
	.4	.8	7	8	19	2	50	50	87	40	5039
	1	.8	0	0	2	0	38	50	10	6	5036
	.2	0	171	70	172	17	157	53	3	1	4984
	.2	.4	28	18	50	4	72	50	169	58	5038
	.2	1	11	9	35	3	61	50	176	60	5044
7	0	.8	474	47	1073	29	713	107	5036	543	3730
	.2	.8	20	15	54	5	74	50	248	87	5046
	.4	.8	9	11	26	3	55	50	120	56	5040
	1	.8	0	0	3	0	39	50	14	9	5036
	.2	0	246	106	247	26	209	77	5	2	4961
	.2	.4	40	25	72	7	87	50	242	86	5040
	.2	1	194	12	148	4	1091	45	29	2979	86

As observed from the table the number of deaths are the lowest under the high vaccination rates. Since these vaccination rates correspond to the most optimistic scenario, we should evaluate the results under varying and more realistic values in order to obtain more valid results. Therefore, we set the vaccination baseline rates to 0.2 for the susceptible population and 0.08 to exposed population. The general results obtained for each compartments of the first population are plotted and presented in Figure 5.22. From the figure, we can observe that smallpox epidemic lasts approximately 200 days.

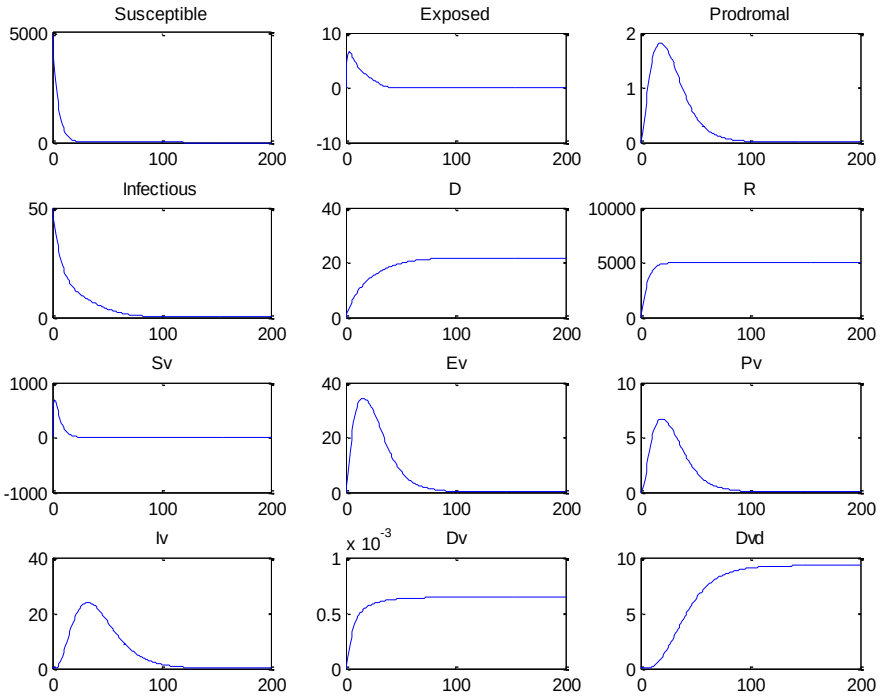


Figure 5.22: Solutions to system of differential equations for Model 3 and Scenario 1.

Figure 5. 23 show the number of infectious cases under varying values of R_0 for the Model 3 and Scenario 1. According to the model under the effects of given

baseline parameter, infectious number is decreased. In the lowest value of R_0 infectious cases are rapidly decreased relative to the higher numbers of R_0. Therefore, with the given initial conditions and rates, it can be suggested that vaccination solely effective for the population size 5000. In the existence of higher values of R_0, although there are no new cases produced, solely vaccination strategy might not be respond effectively as expected.

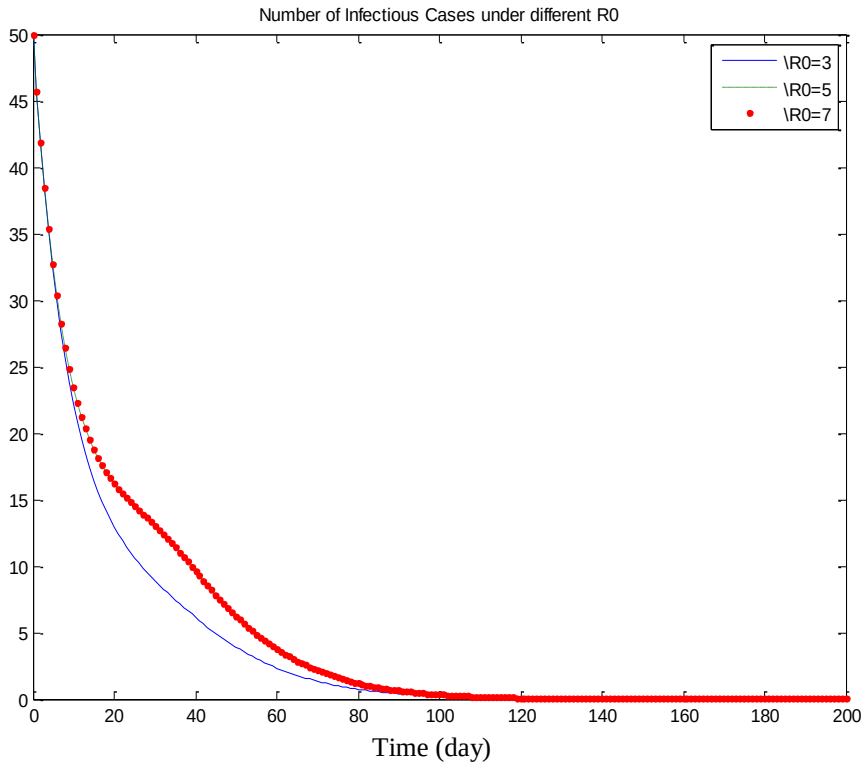


Figure 5.23 Number of infectious individuals under different values of R_0s for Model 3, Scenario 1.

Although vaccination is perceived as the only therefore most effective measure in order to stop or slower the epidemic, many concerns are brought up due

to the adverse effects of vaccines with the implementation. The vaccine induced deaths are counted as 1 in a million (Fenner at al. 1988) and corresponding number of deaths under varying R_0 values are represented in Figure 5.23. According to the figure 16 of 5000 people might be die in 200 days period. Since the effectiveness of treatments is not considered in the model, more realistic result might be less than 16 people. Comparing the vaccination deaths with the scenario in the absence of measure might provide neutralized prejudgments on vaccination.

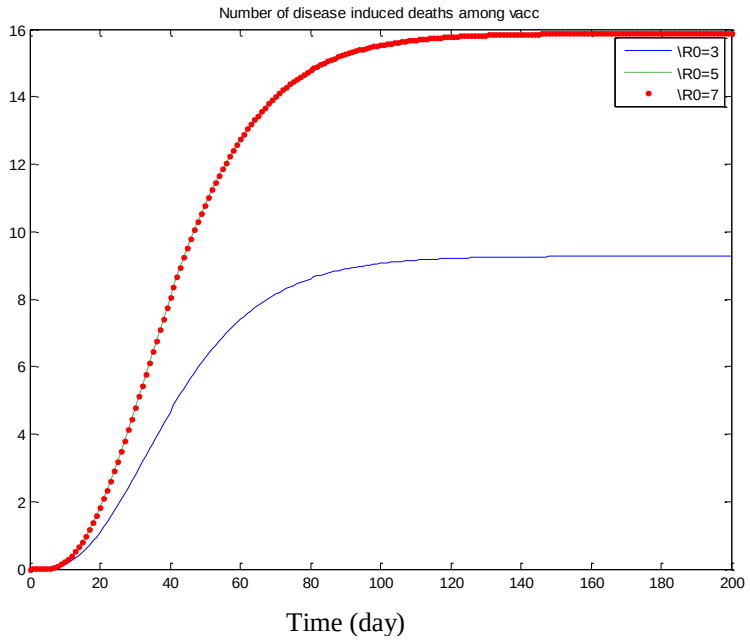


Figure 5.24 Number of disease induced deaths among vaccinated individuals under different values of R_0s for Model 3, Scenario 1.

There are many doubts on implementing vaccination policy, due to the adverse effects. These two Figures might be beneficial in order to breaking down the prejudgment for smallpox vaccination. Since these deterministic models are rely on

many assumption, in real life the numbers of deaths might be lower that these results. Also it can be easily observed from the Figure 5.24 the numbers of deaths among unvaccinated individuals are more than vaccinated individuals.

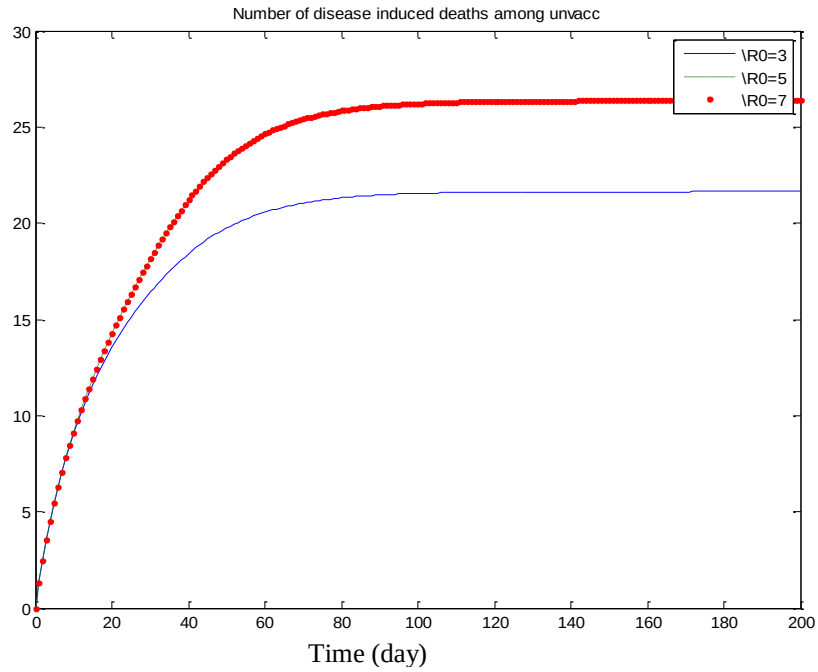


Figure 5.25 Number of disease induced deaths among unvaccinated individuals under different values of R_0s for Model 3, Scenario 1.

5.4.2. Scenario 2

In the second scenario we set the initial values of infected and susceptibles as 3,500,000 and 175,000 respectively. Table 5.11 shows the model results under the baseline and alternative vaccination rates. The corresponding numbers for infected, deaths among unvaccinated and deaths among vaccinated are shown in the Figures

5.26, 5.27 and 5.28 respectively and shows the general results of the model which run under the baseline parameters.

Table 5.11 Total numbers of classes within 200 days and peak numbers for each class for Model 3, Scenario 2

Model 3, Scenario 2											
S_0=3,500,000, I_0=175,000											
R_0	ϕ	ψ	E	*E	P	*P	I	*I	E_v	* Ev	*D
3	0	.8	76142	27658	196440	8001	264294	175000	907735	149890	893026
	.2	.8	22156	21643	58843	5565	169214	175000	271896	106287	3634509
	.4	.8	10563	15713	29002	3341	148328	175000	134324	66416	3628444
	1	.8	0	0	2286	294	129631	175000	11431	6983	3623042
	.2	0	220195	99758	221180	23910	282832	175000	4112	1666	3556550
	.2	.4	40803	34291	74568	7715	180219	175000	249940	96503	3627391
	.2	1	17997	18197	55286	5211	166724	175000	276425	108160	3636071
5	0	.8	306449	45958	753440	14740	633431	175000	3500088	272996	2945972
	.2	.8	35514	35905	94366	9268	194076	175000	436043	177270	3641772
	.4	.8	16964	26035	46616	5448	160656	175000	215912	108627	3632067
	1	.8	0	0	3795	488	130687	175000	18976	11600	3623413
	.2	0	351011	166708	352608	39738	374817	175000	6619	2803	3517380
	.2	.4	65438	56929	119624	12921	211754	175000	400991	161396	3630363
	.2	1	28826	30180	88604	8662	190042	175000	443012	180109	3644262
7	0	.8	356671	64149	928429	31039	777559	175000	4285139	574047	3807788
	.2	.8	47653	50034	126685	12873	216695	175000	585390	246954	3648380
	.4	.8	22940	36234	63085	7454	172183	175000	292200	149094	3635455
	1	.8	0	0	5292	681	131735	175000	26462	16186	3623781
	.2	0	468597	231831	470761	54918	457511	175000	8908	3913	3482171
	.2	.4	87727	79371	160419	18054	240306	175000	537779	224560	3633056
	.2	1	38671	42048	118937	12018	200331	160060	88213	594667	251040

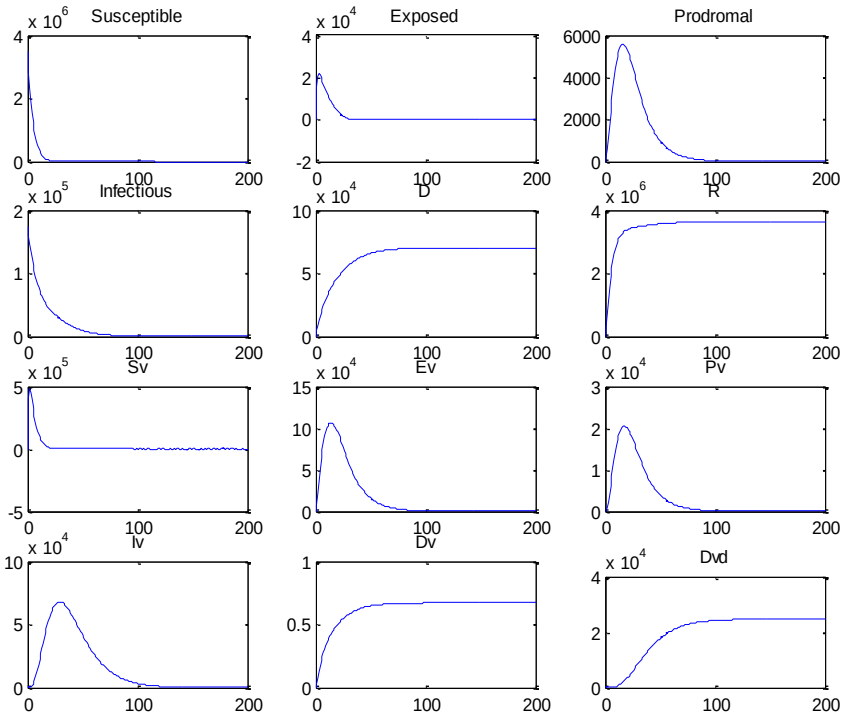


Figure 5.26 Solutions to system of differential equations for Model 3 and Scenario 2.

It can be seen from the Figure 5.26 that infected cases are increased as the value of R_0 increase. In Figure 5.27 and 5.28 the number of deaths among vaccinated and unvaccinated individuals under different values of R_0 are compared. In result of the comparisons, it can be seen that number of deaths among unvaccinated individuals are much higher than vaccinated individuals.

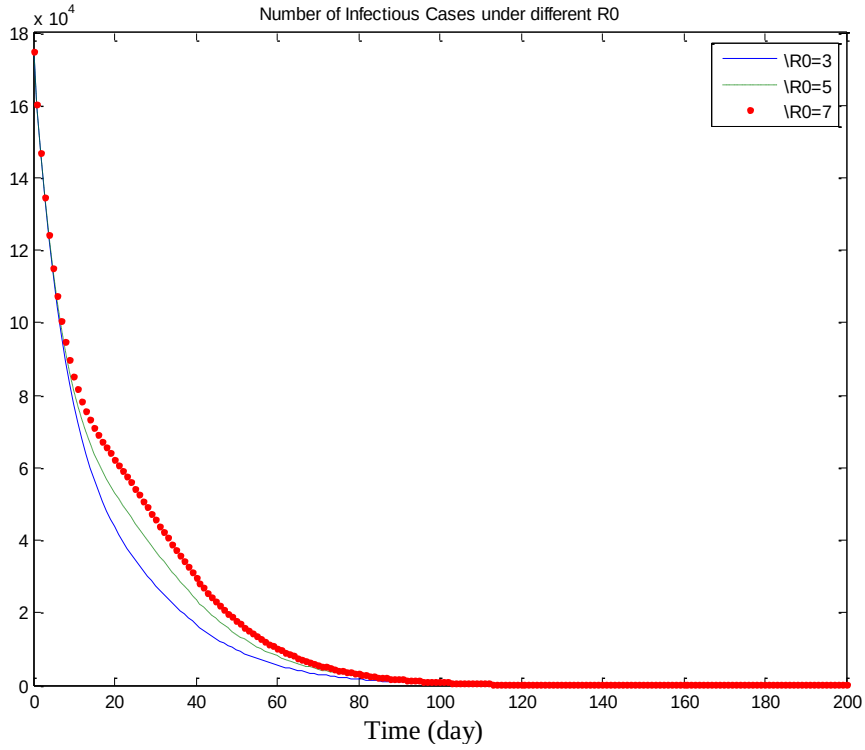


Figure 5.27 Number of infectious cases under different values of R_0s for Model 3, Scenario 2.

The effects of vaccination upon number of deaths are compared in the Figure 5.26 and 5.27. According to the Table 5.11, in one day during the epidemic, the maximum vaccine requirement can reach to 106,287 with given baseline parameters and when the R_0 values equals to 3.

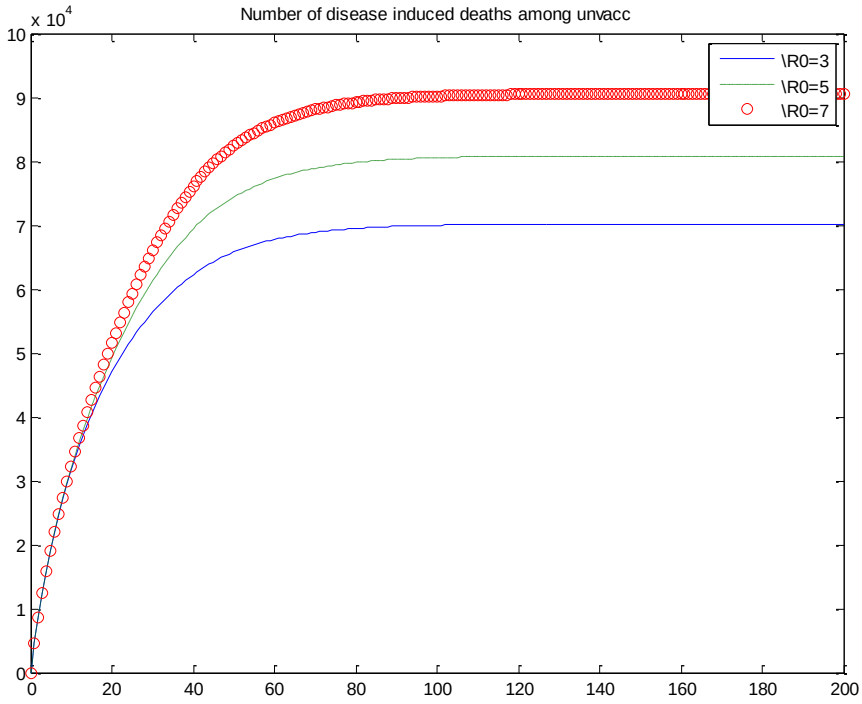


Figure 5.28 Number of disease induced deaths under different values of R_0s for Model 3, Scenario 2.

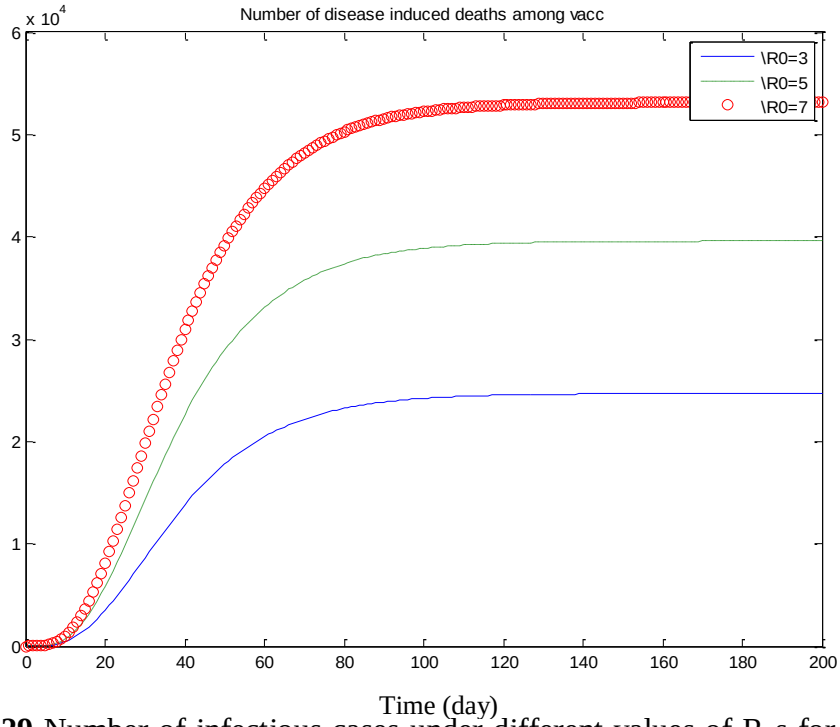


Figure 5.29 Number of infectious cases under different values of R_0s for Model 3, Scenario 2.

5.4.3. Scenario 3

In scenario three, Model 3 is run for the population size which is equal to 75,000,000 with 3,750,000 initial infected individuals. Table 5.12 displays varying R_0 values and columns indicated by E, P, I , E_v, D display the cumulative number of individuals in Exposed, Prodromal, Infectious, Vaccinated exposed, Death classes up to 200 days. General results, which are obtained from baseline parameters, are presented in Figure 5.29.

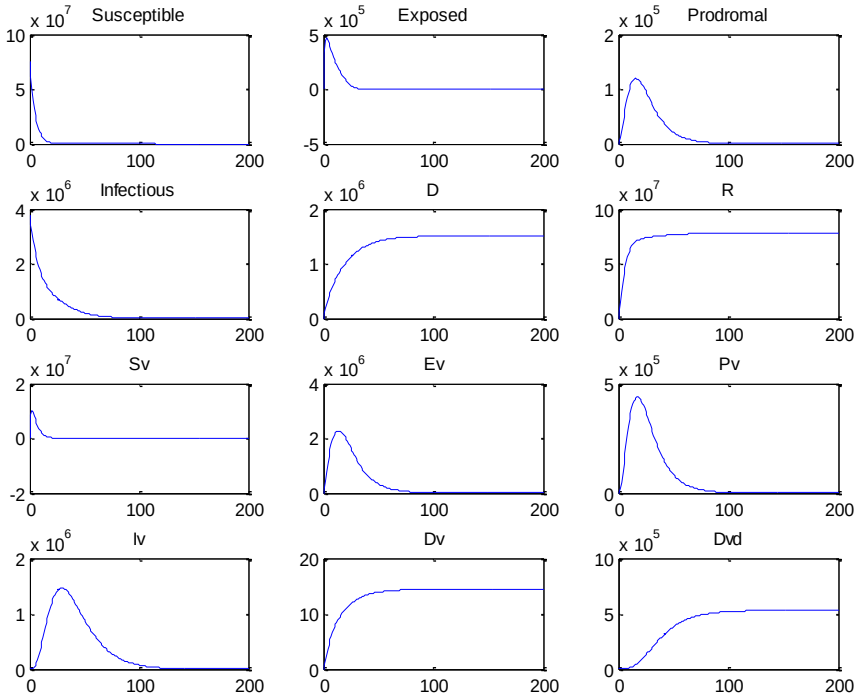


Figure 5.30 Solutions to system of differential equations for Model 3 and Scenario 3.

The results that are obtain from the run presented in Table 5.12. According to the Table 5.12 the maximum vaccine requirement can reach to 2,277,542 in one day during the epidemic.

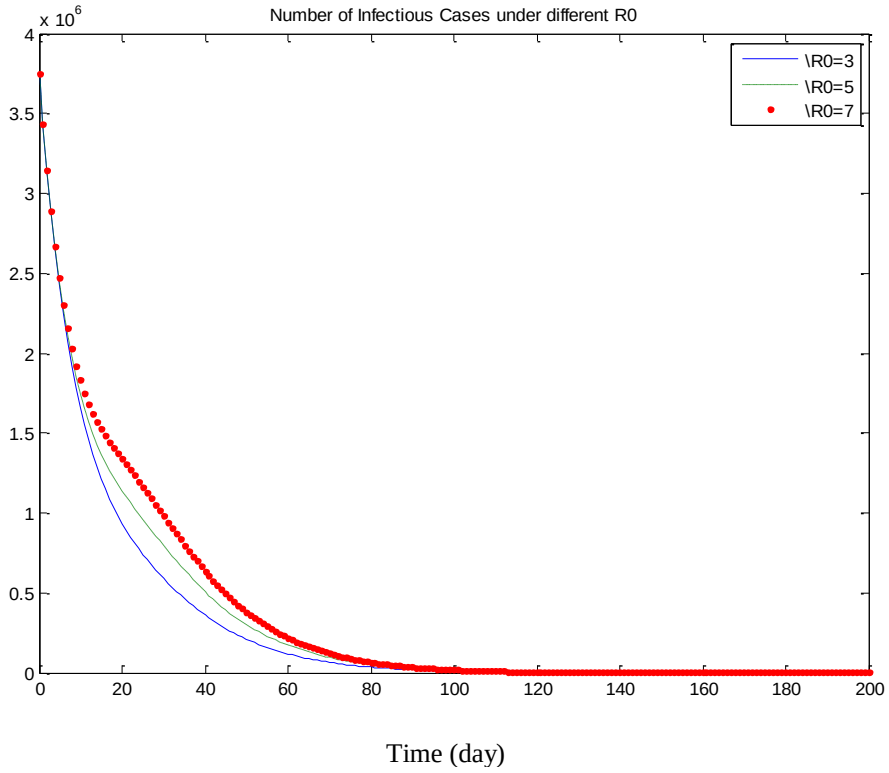


Figure 5.31 Number of infectious individuals under different values of R_0s for Model 3, Scenario 3.

As seen from the Figure 5.30, under the vaccination policy even under the highest R_0 value new cases are not occurred. Furthermore, under the baseline parameters for vaccination, infectious numbers are decreasing continuously. Values in each class can be seen in Table 5.12.

Table 5.12 Total numbers of classes within 200 days and peak numbers for each class for Model 3, Scenario 3.

Model 3, Scenario 3											
S_0=75,000,000, I_0=3,750,000											
R_0	ϕ	ψ	E	*E	P	*P	I	*I	E_v	* Ev	*D
3	0	.8	1631603	592638	4209432	171447	5663437	3750000	19451464	3212027	19136263
	.2	.8	474766	463742	1260923	119248	3626009	3750000	5826345	2277542	77882326
	.4	.8	226339	336722	621468	71603	3178467	3750000	2878371	1423221	77752371
	1	.8	0	0	48991	6300	2777799	3750000	244952	149636	77636618
	.2	0	4718456	2137660	4739581	512415	6060691	3750000	88106	35699	76211778
	.2	.4	874360	734821	1597877	165285	3861844	3750000	5355841	2067827	77729812
	.2	1	385633	389897	1184696	111655	3572654	3750000	5923406	2317621	77915807
5	0	.8	6566779	984861	16145151	315852	13573516	3750000	75001866	5850537	63127972
	.2	.8	761007	769412	2022127	198600	4158762	3750000	9343783	3798782	78037961
	.4	.8	363523	557922	998917	116732	3442638	3750000	4626677	2327664	77830006
	1	.8	0	0	81326	10460	2800430	3750000	406628	248566	77644569
	.2	0	7521673	3572329	7555881	851487	8031788	3750000	141832	60052	75372435
	.2	.4	1402242	1219903	2563368	276923	4537580	3750000	8592672	3458571	77793488
	.2	1	617694	646790	1898648	185621	4072334	3750000	9493108	3859616	78091334
7	0	.8	7642947	1374492	19894916	665118	16661983	3750000	91824412	12300408	81595446
	.2	.8	1021143	1072244	2714677	275852	4643467	3750000	12544065	5291621	78179577
	.4	.8	491575	776445	1351827	159729	3689634	3750000	6261417	3194900	77902606
	1	.8	0	0	113405	14589	2822881	3750000	567019	346836	77652457
	.2	0	10041375	4967712	10087720	1176818	9803802	3750000	190888	83848	74617951
	.2	.4	1879854	1700784	3437558	386892	5149418	3750000	11523832	4812214	77851195
	.2	1	828674	901165	2548612	257538	4527229	3750000	12742850	5379349	78251136

The effects of vaccination policy on deaths are shown in Figures 5.31 and 5.32, respectively. In Figure 5.31, it can be seen the number of death among vaccinated individual. It is easily observed that there is a significant difference between the number of deaths among unvaccinated individuals.

According to the initial assumptions, the success of treatment, the level of immunity and the strength of immunity are not included in these models. Therefore, deaths are counted directly as 30% of infected individuals.

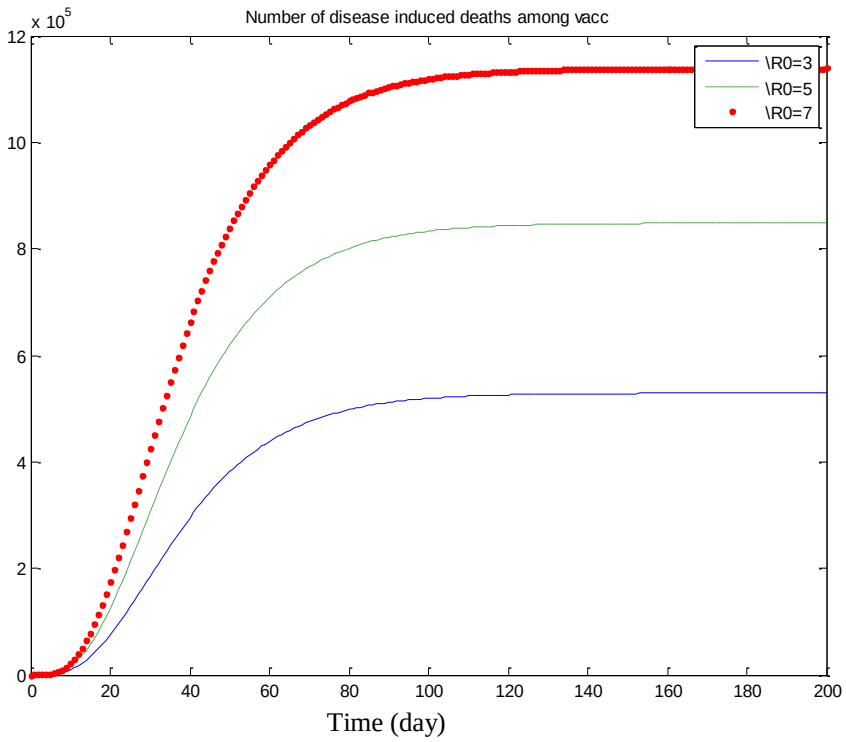


Figure 5.32 Number of disease induced deaths among vaccinated individuals under different values of R_0s for Model 3, Scenario 3.

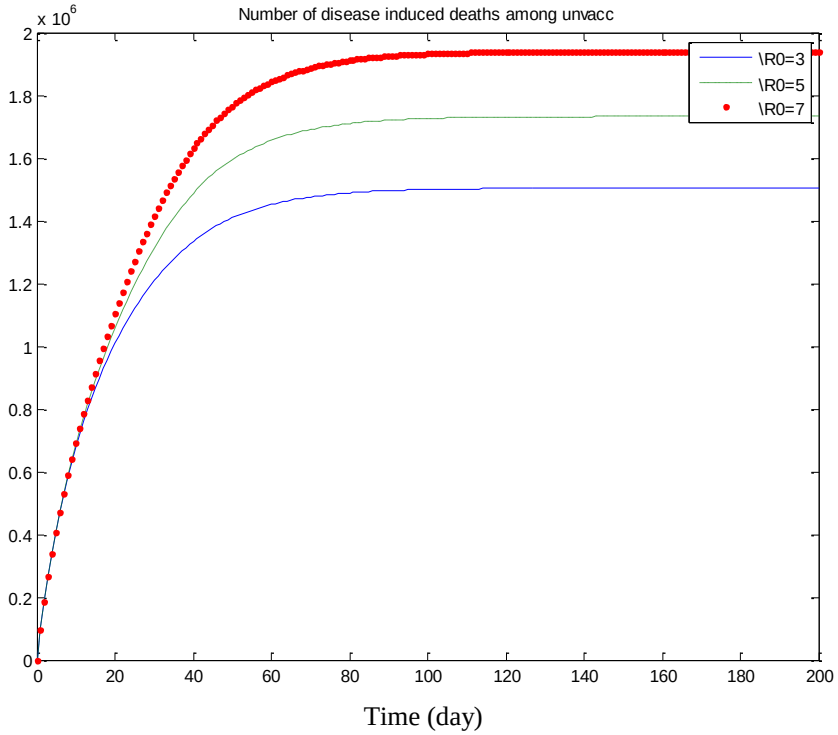


Figure 5.33 Number of disease induced deaths among unvaccinated individuals under different values of R_0s for Model 3, Scenario 3.

One of the main important considerations in vaccination is the allocation of health care givers. Table 5.13 shows the class size of the 'vaccinated exposed' for each scenario of Model 3, under the different R_0 values.

Table 5.13 Class sizes of E_v and $*E_v$ under different values of R_0 with given baseline parameters; ϕ=.2, ψ=.8

	R_0	E_v	* Ev
Scenario 1	3	102	34
	5	175	59
	7	248	87
Scenario 2	3	271896	106287
	5	436043	177270
	7	585390	246954
Scenario 3	3	271896	106287
	5	436043	177270
	7	585390	246954

All control policies has own advantages and disadvantages. Physical separation might be effective for lowering an epidemic however it might involve replanning the layout of an existed facility or planning the new one. Vaccination is said to be the most effective measure for smallpox but it might require additional workforce. Therefore, in case of an implementation the planning and allocation of workforce should be carefully managed. As seen from the Table 5.13, the need for health care givers or vaccinators might be significantly different in terms of quantity. In the first scenario, it might be easy to vaccinate at most 248 people during 200 days. However, vaccination of the population of a city or a country may require additional caregivers. Also involves high degree of organization and information flow. 585,390 individual can be vaccinated during the 200 days however, the workforce may not be available for vaccination these individuals in a limited time. Therefore, time limitation should be considered and time factor should be involved workforce allocation plans.

5.5. Numerical Results and Discussions for Model 4

In Model 4we evaluate the combined policy decision which involves vaccination, quarantine and hospitalization together. Similar to the previous models, we run the solution algorithm coded in Matlab 7.0. for all scenarios and varying parameters. In each scenario, we consider fully susceptible populations with the size of 5000, 3,500,000, 75,000,000 individuals respectively. The system of nonlinear differential equations (24)-(36) given in Chapter 3 has been numerically solved in seconds by using the Matlab function 'ode45' on a personal computer with 1 GB RAM and 2.4 Ghz processor.

5.5.1. Scenario 1

The results that are obtained from the model presented in Table 5.13. is easily observed that a combined implementation significantly reduced the numbers in each class. For the first scenario, despite the varying numbers of R_0, number of hospitalized cases almost equal. Class sizes under different parameters are provided in Table 5.14 and Figure 5.33 shows the general solutions.

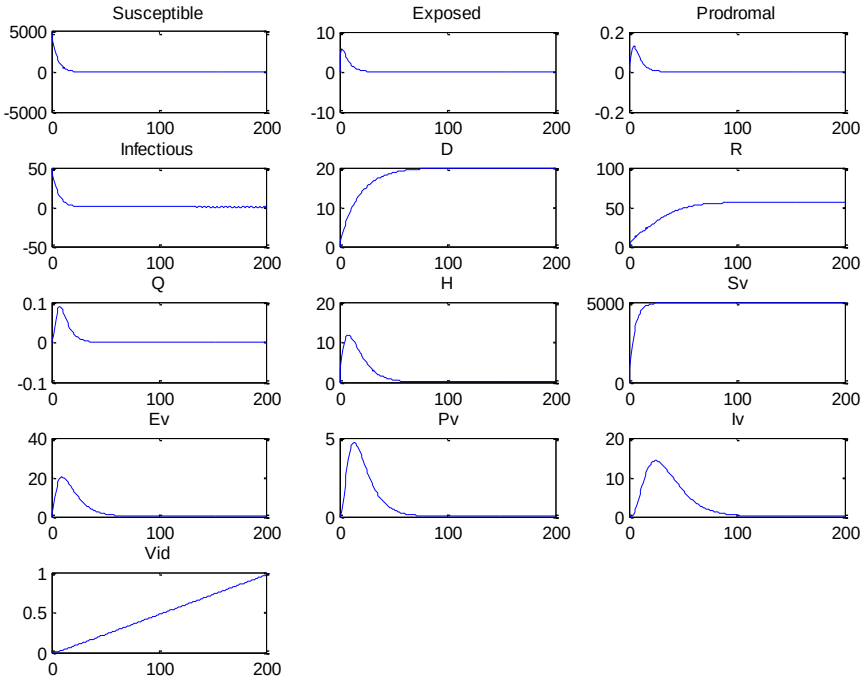


Figure 5.34 Solutions to system of differential equations for Model 4 and Scenario 1.

Table 5.14 Total numbers of classes within 200 days and peak numbers for each class for Model 4, Scenario 1.

Model 4, Scenario 1															
S_0=5,000 I_0=50															
R_0	ϕ	ψ	γ	Σ	E	*E	P	*P	I	*I	H	*H	*D	E_v	* Ev
	0.2	0.8	0.3	0.08	4	6	0	0	20	50	17	12	20	41	20
	0.4	0.8	0.6	0.13	2	4	0	0	16	50	21	16	18	23	13
	0.4	0.8	0.6	1	0	2	0	0	5	50	32	36	16	5	3
3	0	0.8	0	1	1	3	0	0	5	50	32	36	16	8	6
	0.2	0.8	0.3	0.08	7	9	1	0	20	50	17	12	23	68	34
	0.4	0.8	0.6	0.13	4	7	0	0	16	50	21	16	20	38	21
	0.4	0.8	0.6	1	1	3	0	0	5	50	32	36	16	8	6
5	0	0.8	0	1	1	6	0	0	5	50	32	36	17	13	10
	0.2	0.8	0.3	0.08	10	13	1	0	20	50	18	12	27	96	47
	0.4	0.8	0.6	0.13	5	9	0	0	16	50	21	16	21	53	29
	0.4	0.8	0.6	1	1	5	0	0	5	50	32	36	16	11	8
7	0	0.8	0	1	2	8	0	0	5	50	32	36	17	19	14

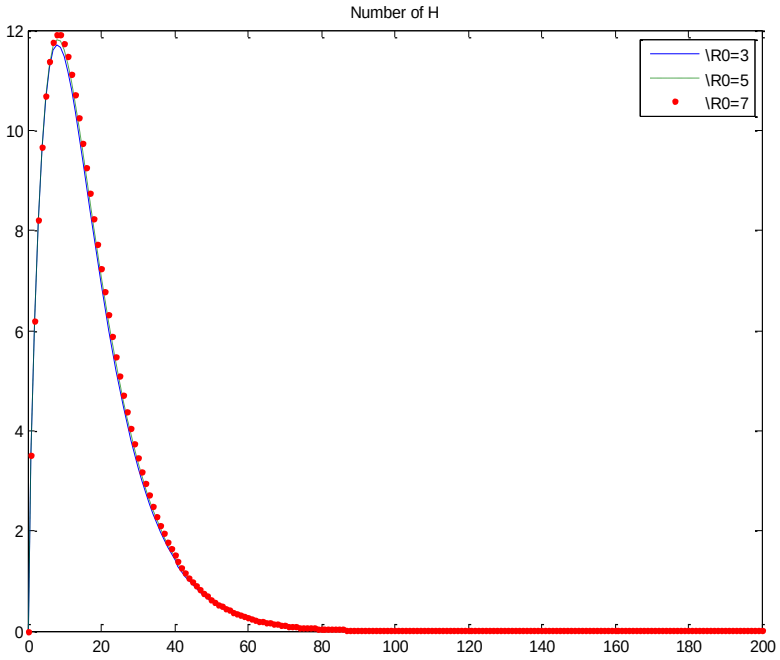


Figure 5.35: Number of hospitalized cases under different values of R_0 for Model 4 and Scenario 1.

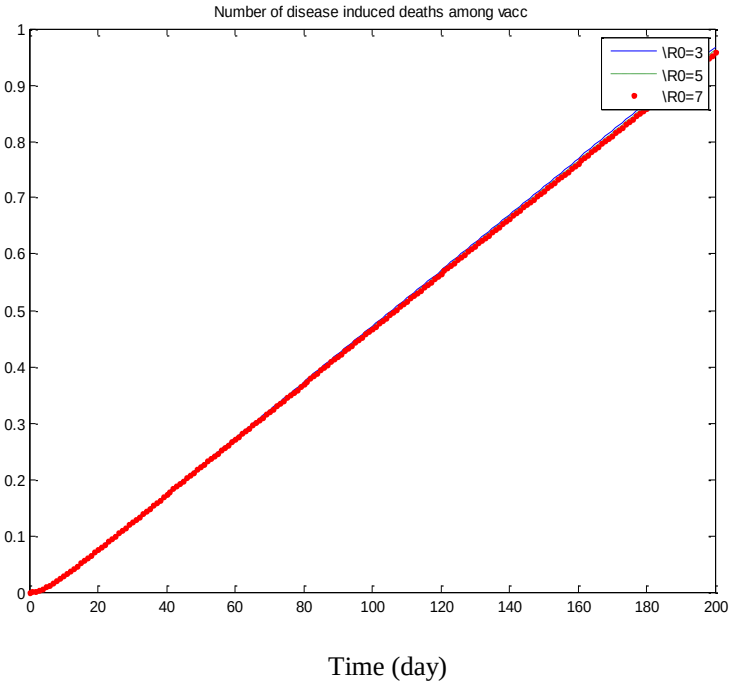


Figure 5.36: Number of disease induced deaths among vaccinated individuals under different values of R_0s for Model 4 and Scenario 1.

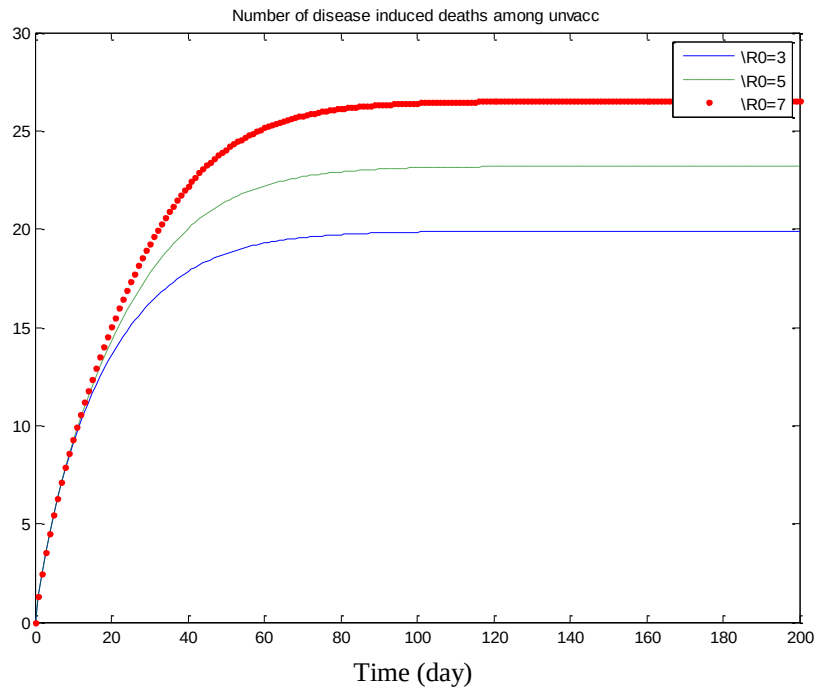


Figure 5.37: Number of disease induced deaths among vaccinated individuals under different values of R_0s for Model 4 and Scenario 1.

5.5.2. Scenario 2

In the second scenario, we are run the combined model for the population size 3,500,000 in order to observe the effect of combined interventions. Significant reductions in compartments are obtained. These reductions is presented in the Table 5.14 and supported by the Figures.

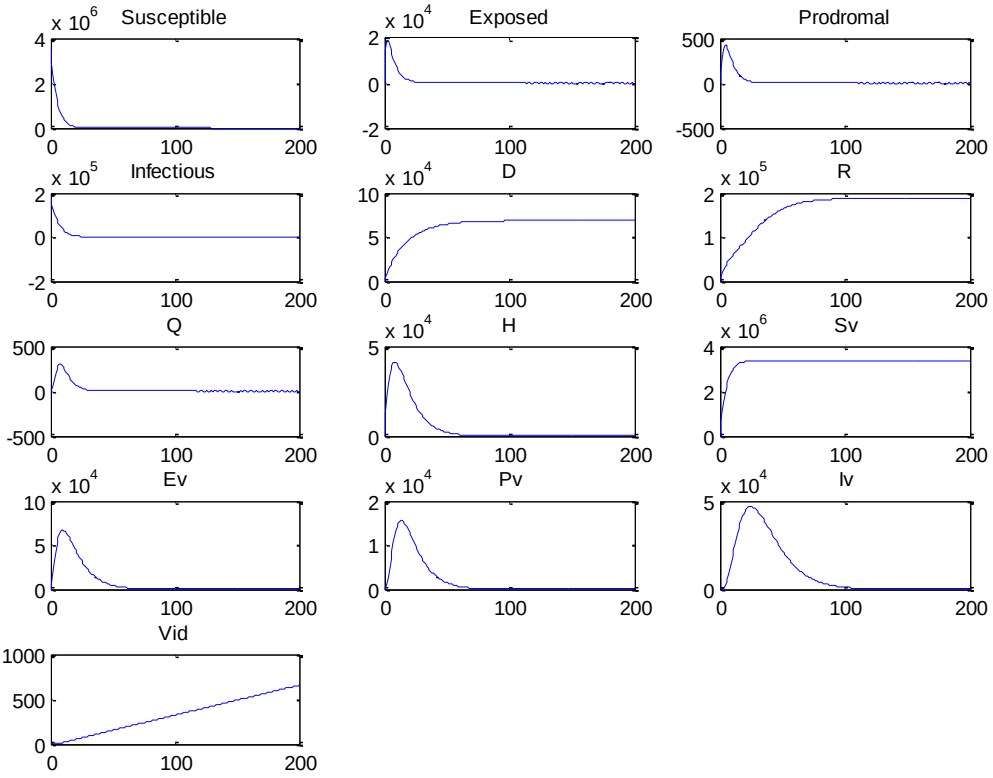


Figure 5.38: Solutions to system of differential equations for Model 4 and Scenario 2.

Table 5.15 Total numbers of classes within 200 days and peak numbers for each class for Model 4, Scenario 2

Model 4 , Scenario 2															
S_0=3,500,000, I_0=175,000															
R_0	ϕ	ψ	Γ	Σ	E	*E	P	*P	I	*I	H	H-	*D	E_v	* Ev
	0.2	0.8	0.3	0.08	0.2	0.8	0.3	0.08	13854	18758	1475	421	70772	175000	59221
	0.4	0.8	0.6	0.13	0.4	0.8	0.6	0.13	7273	13121	528	205	55694	175000	73372
	0.4	0.8	0.6	1	0.4	0.8	0.6	1	1573	6932	120	91	16490	175000	111777
3	0	0.8	0	1	0	0.8	0	1	2651	11610	569	270	16516	175000	111913
	0.2	0.8	0.3	0.08	0.2	0.8	0.3	0.08	22952	31154	2444	699	71130	175000	60151
	0.4	0.8	0.6	0.13	0.4	0.8	0.6	0.13	11929	21795	866	340	55790	175000	73939
	0.4	0.8	0.6	1	0.4	0.8	0.6	1	2620	11541	201	151	16495	175000	111930
5	0	0.8	0	1	0	0.8	0	1	4431	19324	951	450	16538	175000	112159
	0.2	0.8	0.3	0.08	0.2	0.8	0.3	0.08	31874	43463	3394	975	71481	175000	61065
	0.4	0.8	0.6	0.13	0.4	0.8	0.6	0.13	16436	30411	1194	474	55883	175000	74487
	0.4	0.8	0.6	1	0.4	0.8	0.6	1	3666	16140	281	211	16500	175000	112083
7	0	0.8	0	1	0	0.8	0	1	6223	27016	1335	629	16560	175000	112406

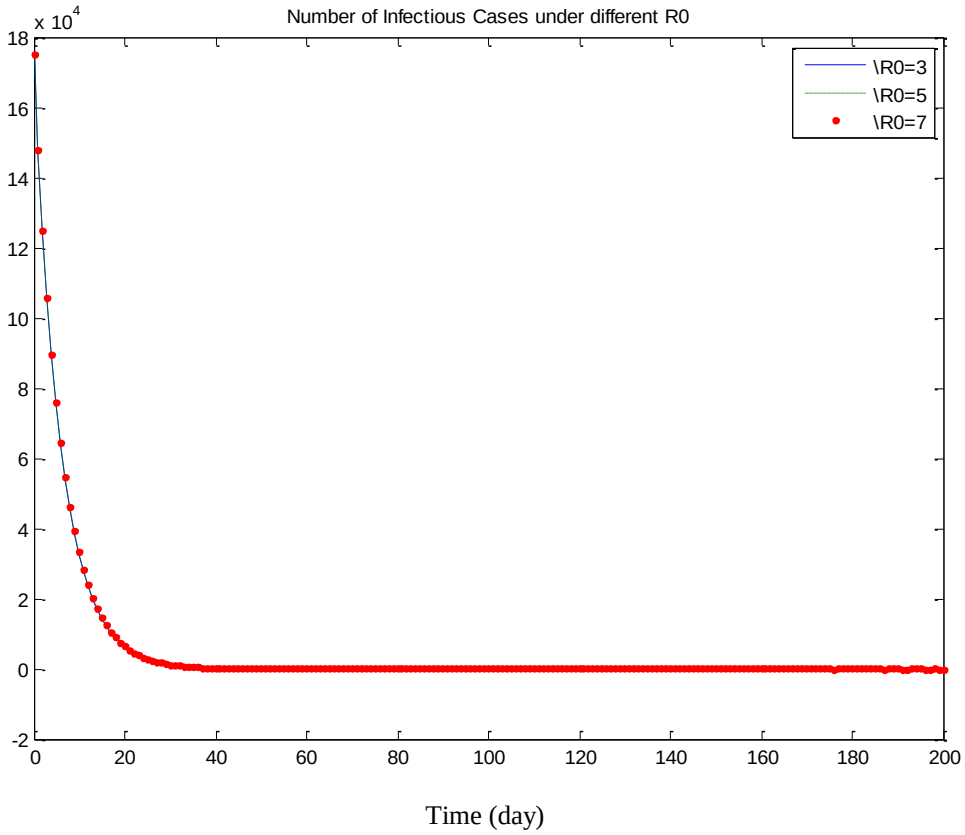


Figure 5.39: Number of infectious individuals under different values of R_0s for Model 4 and Scenario 2.

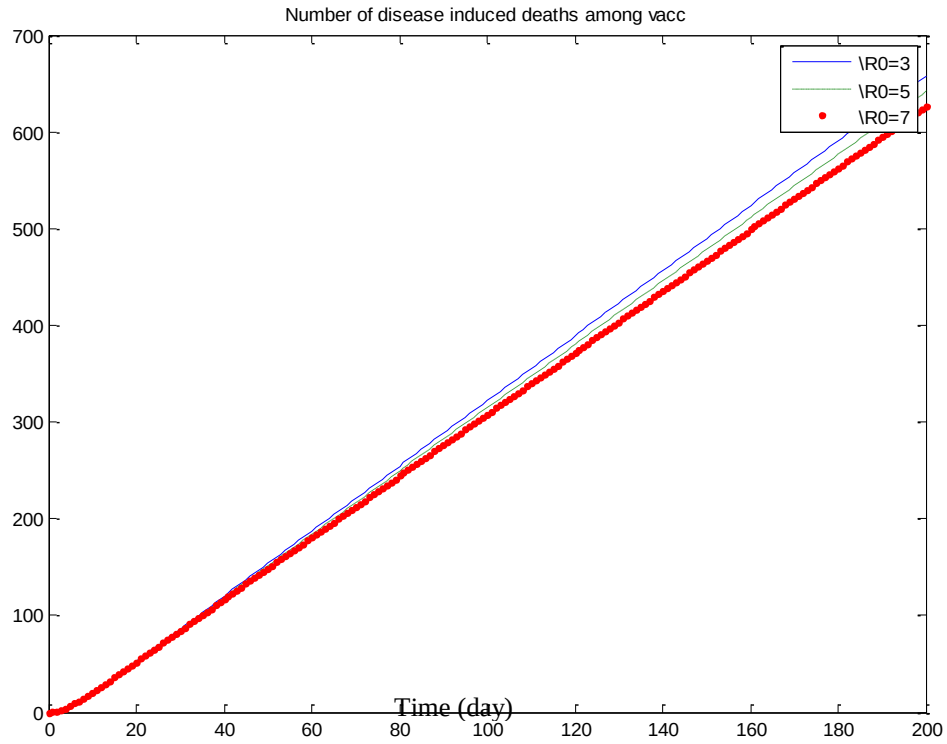


Figure 5.40: Number of disease induced deaths among vaccinated individuals under different values of R_0s for Model 4 and Scenario 2.

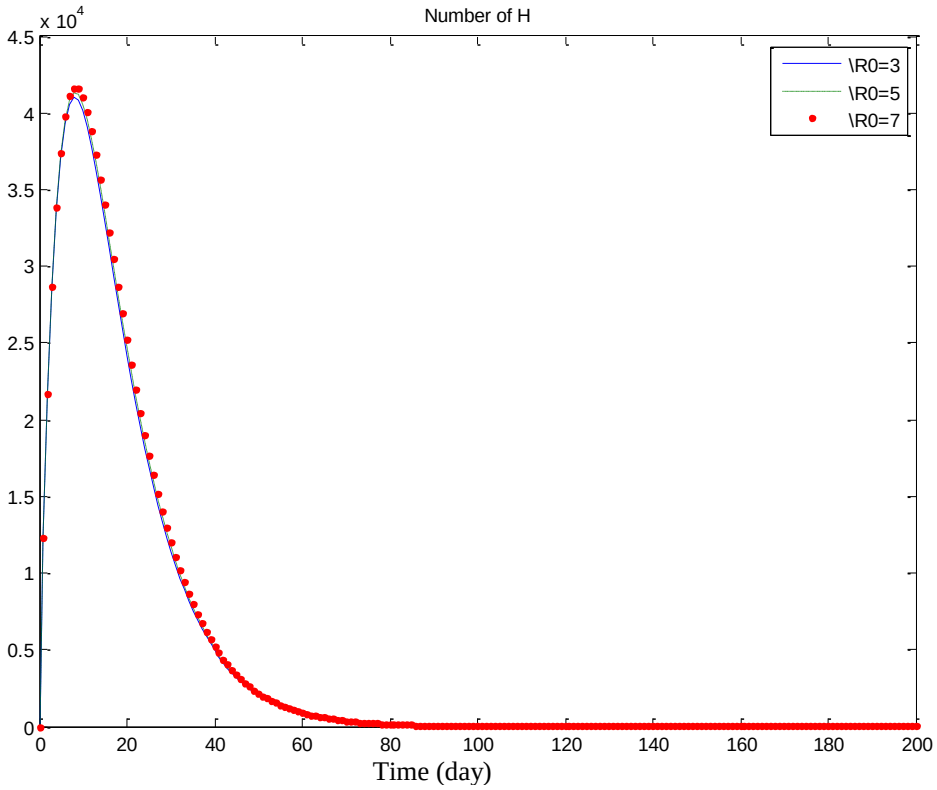


Figure 5.41: Number of hospitalized cases under different values of R_0 for Model 4 and Scenario 3

5.5.3. Scenario 3

The last scenario for the last model reflects similar results as obtained from the previous models. The results are shown in the Table 5.15 and also supported by the figures that are represented in following:

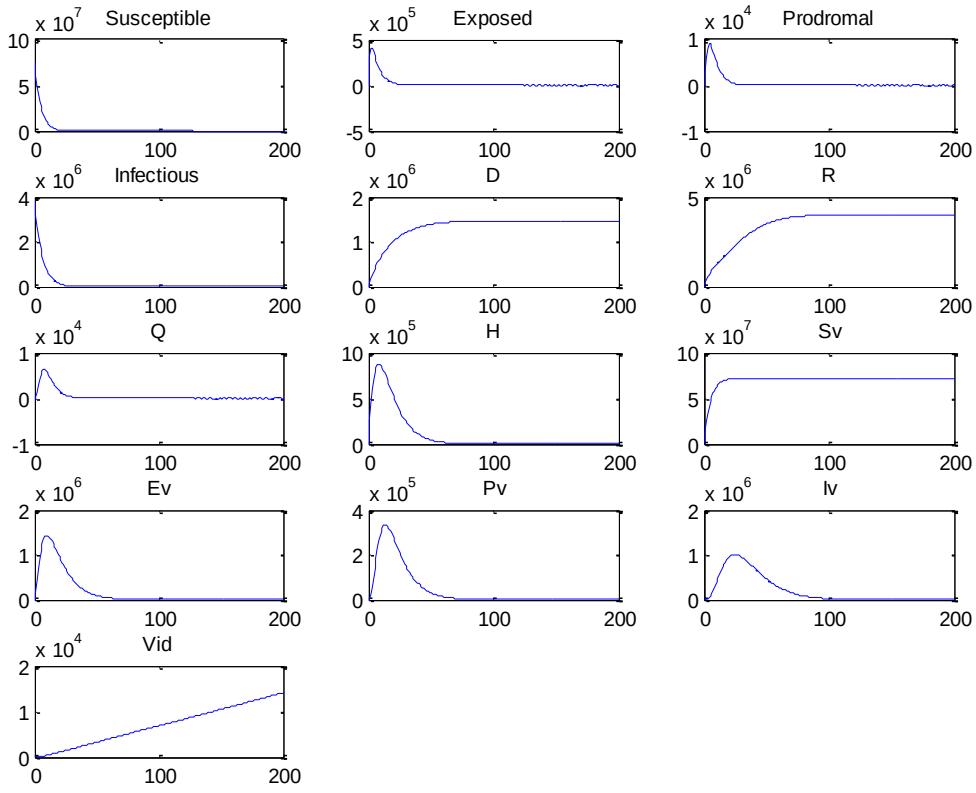


Figure 5.42: Solutions to system of differential equations for Model 4,Scenario 3.

Table 5.16 Total numbers of classes within 200 days and peak numbers for each class for Model 4, Scenario 3.

Model 4, Scenario 3															
S_0=75,000,000, I_0=3,750,000															
R_0	ϕ	ψ	γ	Σ	E	*E	P	*P	I	*I	H	H-	*D	E_v	* Ev
3	0.2	0.8	0.3	0.08	296869	401968	31608	9026	1516540	3750000	1269011	878393	1470612	2883119	1436089
3	0.4	0.8	0.6	0.13	155836	281154	11311	4397	1193434	3750000	1572255	1207431	1307519	1520922	875734
3	0.4	0.8	0.6	1	33700	148549	2580	1945	353363	3750000	2395219	2727258	1167055	347685	255507
3	0	0.8	0	1	56802	248798	12192	5788	353913	3750000	2398139	2727617	1195546	585606	428621
5	0.2	0.8	0.3	0.08	491823	667606	52369	14982	1524206	3750000	1288958	885458	1697343	4776835	2382796
5	0.4	0.8	0.6	0.08	294020	493741	21302	7979	1512737	3750000	1272538	884327	1468339	2864121	1645570
5	0.4	0.8	0.6	0.13	255620	467024	18559	7291	1195501	3750000	1584398	1212887	1424197	2495429	1448649
5	0	0.8	0	1	94963	414089	20379	9638	354383	3750000	2403403	2728763	1242631	978804	714100
7	0.2	0.8	0.3	0.08	683017	931372	72734	20886	1531726	3750000	1308526	892465	1919754	6634464	3320020
7	0.4	0.8	0.6	0.13	352192	651651	25576	10154	1197502	3750000	1596157	1218294	1537179	3439069	2012670
7	0.4	0.8	0.6	1	78550	345858	6013	4528	353561	3750000	2401771	2729175	1222471	810451	595040
7	0	0.8	0	1	133362	578920	28612	13483	354857	3750000	2408698	2729923	1289987	1374265	999849

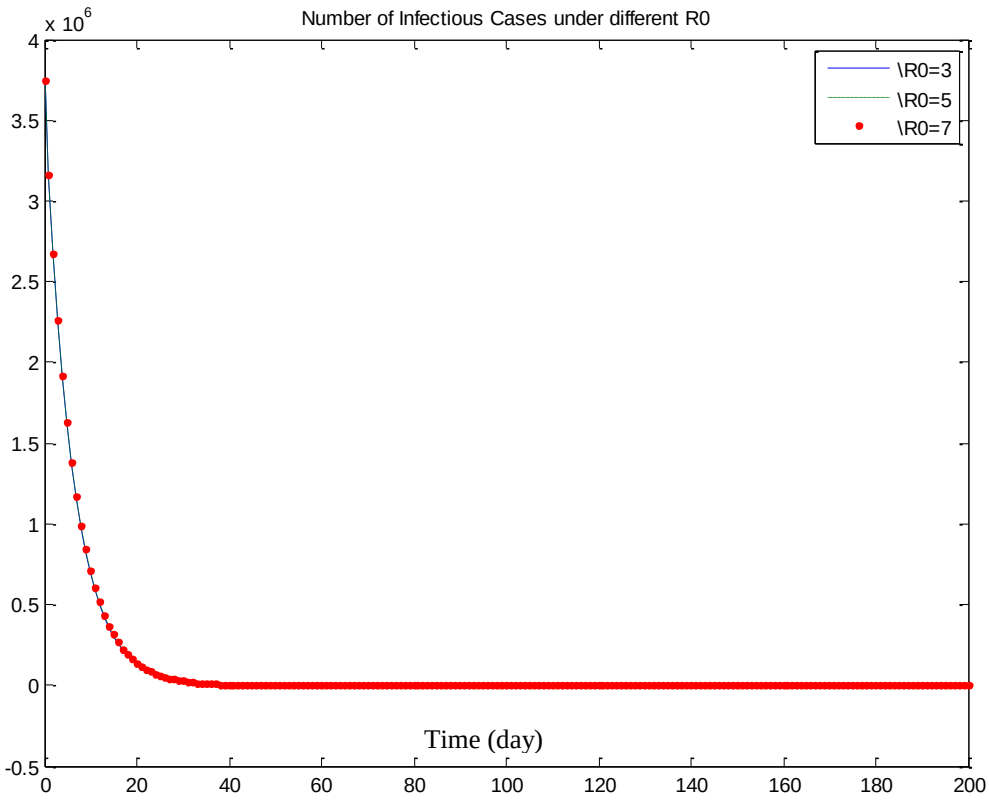


Figure 5.43: Number of infectious cases under different values of R_0s for Model 4, Scenario 3.

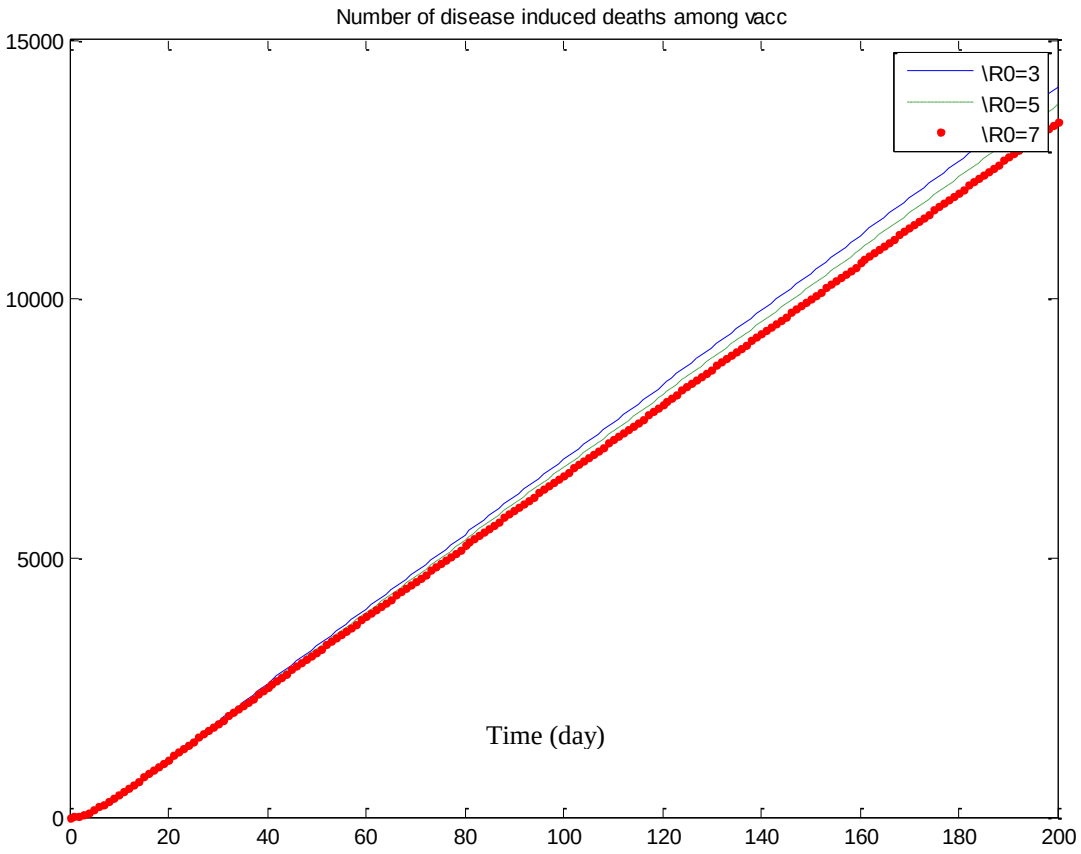


Figure 5.44: Number of disease induced deaths among vaccinated individuals under different values of R_0s for Model 4 and Scenario 3.

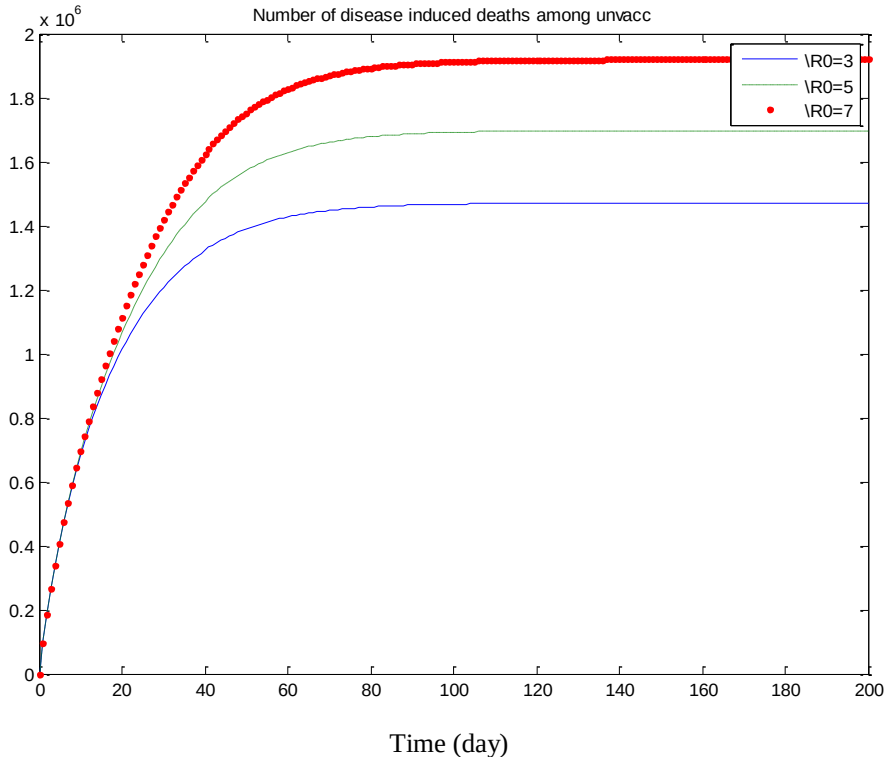


Figure 5.45: Number of disease induced deaths among unvaccinated individuals under different values of R_0s for Model 4 and Scenario 3.

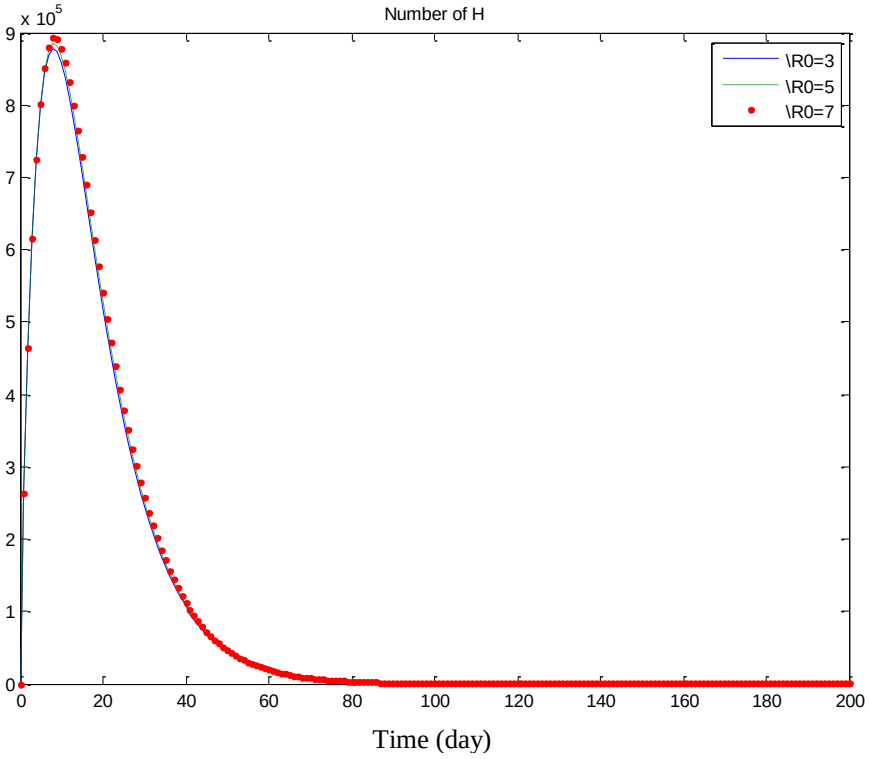


Figure 5.46: Number of hospitalized cases under different values of R_0 for Model 4 and Scenario 3.

5.6. Results and Analysis of Dynamic Programming for Inventory Model

At the beginning of the thesis we emphasize the integration of epidemiological output to the field of logistics. As an output we determine total number of to be vaccinated individual in a time period 35 days, with given parameters and for the population size of Izmir. The outcome we obtain from epidemiological modeling is integrated to a deterministic single commodity inventory model. Through this model, we are able to determine the optimal order policy.

Table 5.17. Days and corresponding demands for the population size of 3,500,000.

T	D	T	D	T	D	T	D	T	D
1	0	9	90310	17	104650	25	81000	33	51380
2	7020	10	95890	18	102960	26	77110	34	48220
3	21070	11	100090	19	100780	27	73210		
4	36480	12	103100	20	98190	28	69320		
5	50930	13	105050	21	95240	29	65500		
6	63620	14	106080	22	91980	30	61770		
7	74350	15	106290	23	88480	31	58170		
8	83200	16	105780	24	84800	32	54700		

T: time period, D: Forecasted demand

Table 5.18 Demands for vaccines for the population size of 5,000.

T	D	T	D	T	D	T	D	T	D
1	0	9	28	17	34	25	31	33	23
2	2	10	30	18	34	26	30	34	22
3	6	11	31	19	34	27	29		
4	11	12	32	20	34	28	28		
5	15	13	33	21	33	29	27		
6	19	14	34	22	33	30	26		
7	23	15	34	23	32	31	25		
8	25	16	34	24	31	32	24		

T: time period, D: Forecasted demand

The forecasted demand for populations size 5000 and 3,500,000 are provided in Table 5.17 and Table 5.18, respectively. Demands estimated as compartment size of vaccinated individuals in exposed class. Demand in period *i* represents the number of individuals in the 'vaccinated exposed' class corresponding in number of day equal to i^{th} time period. Demands for both of three population size are considered. The numbers in Table 5.17 corresponds to the vaccine requirement of a city with population size 3,500,000. Demands of the first 34 days are considered in order to study the first response for blocking or lowering the dispersion, therefore reducing the number of secondary cases. As suggested in literature, responding at first days of the attack is crucial for lowering the cumulative incidence number. Since smallpox vaccines are not hold as an inventory and in the absence of smallpox vaccine

production, vaccine should be procured as quickly as possible. Therefore, the aim should be to make vaccines available at the early stage of the epidemic. In the absence of production of vaccines, the main consideration here is when to buy and how much to order.

5.2.1 Solution for The Optimal Inventory Policy Problem Through Dynamic Programming

We set the setup cost to 10000$/TL, in order to meet the needs of the first population. Recalling from previous chapters, first population represents a university campus population with 5000 people. We set the rate of vaccinated exposed individuals to baseline parameters; ψ=0.8, and ϕ=0.2 and R_0 = 3. With given parameters it is calculated that, total of 271,896 individuals vaccinated, which is corresponds to 7% of the population.

Table 5.19. Optimal order policy for population size 5000.

Order period	Order amount
1	357
17	34
18	34
19	34
20	34
21	33
22	361
	Total cost: 42905

The first order takes place at the first day in order to cover the demands of 16 days. From the 17^{th} day to 22^{nd} day orders placed day by day, under the assumption of lead time is zero. The order of 22^{nd} day takes place in order to cover the remaining 12 day. In this path of order policy concludes with a cost that 42,905$/TL.

For the bigger population, which is 3,500,000 we set the setup cost to 500,000$/TL for the second population sample. Rates in this models are the baseline parameters which are ψ=0.8, and ϕ=0.2 and R_0 = 3. Since the aim is to determine the optimal order policy for different population, variations among models or the values of rates and R_0 are not considered. According to the model, these results are obtained through dynamic programming. The part of order periods and related quantities are shown in the Table 5.20. The minimum cost calculated as 14,608.069$/TL.

Although the setup cost is high, due to the assumptions, orders take places very frequently. The result might be very different when the lead times are considered. However this model can provide insights for the importance of planning vaccine purchasing in case of any need. Table 5.20 shows the vaccine requirement for each day.

Table 5.20 Optimal order policy for population size 5000.

Order period		Order amount
1		107317
5		84572
6		105623
7		123462
8		138209
9		150118
10		159511
11		166641
12		171798
13		175156
14		176940
15		177270
16		176303
17		174150
18		170915
19		328423
21		305609
23		278905
25		250661
27		222846
29		114814
30		108032
31		101499
32		95252
33		173006
	Total cost:	4,237,032

In case of a smallpox attack, vaccines might be supplied from USA or other stocking point. There might be a long lead time associated with high setup costs. Therefore, the give an initial response to a bioterrorist attack, decision makers might be aided from the outputs obtained from epidemiological modeling. At that time, the

output might not reflect the actual quantity of need. However, receiving vaccines that priory planned, might save many lives and reduce the rate of secondary attack therefore decrease the speed of smallpox disease progression among the population.

CHAPTER 6

CONCLUSION AND FUTURE RESEARCH DIRECTIONS

Turkey geographically bridges East and West which positions the country as a transit center for many diseases. We wish to emphasize the importance of the location of Turkey in the dispersion of a disease. An epidemic might be close at hand. Therefore, it is expected to conduct many epidemiologic researches in this field in order to examine disease dispersion. We would want to take our part in this mission. Furthermore, besides obtaining epidemiological outputs, our intent is to examine epidemiologic problem from the logistics point of view. In order to obtain relevant data for using in logistical analysis, we experienced that we should go through the mathematical and epidemiological side of this field. Thus, this thesis includes the initial stage of a long research.

In this thesis, before examining in the highly interdisciplinary field of epidemiological modeling, present literature for epidemiological modeling for several diseases is systematically reviewed. We study on smallpox disease which was eradicated. Re-emerge of this disease might occur as a result of a bioterrorist attack. Since a bioterrorist attack is considered, we find appropriate to review epidemiological modeling studies for possible agents that might be used as bio-weapon supply. The classification, which is provided by CDC, is taken as basis;

therefore, we examine diseases that are included in Category A. Summary of literature review is provided in Table 2.1. First columns inform about the general characteristics of the research studies e.g. the examined disease and date of the study. Secondly models characteristics are examined. The methodology that is employed in, the tool that is used to built model and the existence of a compartmental structure are analyzed. Since the outputs of epidemiologic modeling is related with public health concerns, we examine the control policies that are suggested or examined in each research study. Although there are many valuable research studies that are conducted on epidemiological modeling, there are very few studies which address the logistical concerns. Therefore, in order to point out these concerns, a decision tree is presented. Decision tree shows the intervention strategies and related decisions that might be made. In order to examine one of the logistics problem given in the decision tree, we built four different deterministic models for smallpox which includes 3 different control policies. Estimating the size of compartments provides insights for determining demands of each compartment. After the determination of appropriate control policy for smallpox, we consider one of the decisions related with that policy. We define demands and examine the purchasing of the supply quantities. Therefore a deterministic inventory model is suggested and solved through dynamic programming. In summary in this thesis we examine the epidemiological modeling in context of a disaster management stage. We suggest an intervention strategy in context of public health implementation and we determine an optimal order policy in the context of logistics.

While building the models, we define many alternative scenarios besides simple assumptions. In order not to miss the topic of this thesis, these ideas are decided to be conducted as research studies. They are explained in the following paragraph of this Chapter.

Employing deterministic approach results in many assumptions that assume many rates and variables as constant. Therefore the results might not reflect the possible real outcomes. In order to fix the effects of assumptions on model, first of all we wish to examine the epidemiological models with stochastic approach. By that way, it is able to add variability and probability into model and obtain more realistic 'demand' data for examine logistics concerns. The inventory model in which is examined in Chapter 4 and solved in Chapter 5 is also deterministic therefore needs to be cleared from the assumptions of stockout condition and zero lead time. In order to prove the effectiveness and efficiency of order policy, effects of stockout will be considered in two different point of views. First the loss of usage is considered. Since the inventory is unique and has a limited shelf life any delay in receiving the product might ended with loss of usage and associated costs. We emphasize the importance of timely response for any disaster is crucial for the managing the rest of the disaster management process with given references in literature. Therefore stockouts or ineffective usage of vaccines brings unsuccessful policy implementation and therefore the policy fails to reduce the speed of disease dispersion among population. In order to monitor the effects on the disease dispersion, we wish to allow stockouts. Similarly, lead time is assumed to be zero, a model which considers non zero lead

time will be built. Thirdly, inventory model is run under the assumption of constant holding cost regardless of the quantity of order. From the economical point of view, this assumption hardly reflects the actual amount of money that will be tied and should be included in the cost function. Finally, variability will be allowed and more elaborated model will be provided as a research study.

REFERENCES

1. Doyle, A., Bonmarin, I., Lévy-Bruhl, D., Le Strat, Y., Desenclos, JC. (2006). "Influenza pandemic preparedness in France: Modeling the impact of interventions." *Epidemiol Community Health,* 60, 399-404.

2. McGhee, SM., Hedley, A.J., Fitzner, KA., Shortridge, KF. (2001). "Cost-effectiveness study on influenza prevention in Hong Kong". *Health Policy,* 56, 215–234.

3. Griffin, T., Gania, R., Fleming, D., Hall I., Penna, C., Leach, S., (2004). "Modelling the, impact of pandemic influenza in the UK", *International Congress Series,* 1263, 243– 246.

4. Riley, S., Ferguson, NM. (2006). "Smallpox transmission and control: Spatial dynamics in Great Britain", *PNAS*, 103(33), 12637–12642.

5. Nishiura, H., Tang, M. (2004). "Modeling for a Smallpox- vaccination policy against possible bioterrorism in Japan: the impact of long lasting vaccinal immunity", *Journal of Epidemiology,* 14(2), 41-50

6. Van Genugten, M.L.L., Heijnen, M.L.A., Jager, J.C. (2003) "Pandemic Influenza and Healthcare Demand in the Netherlands: Scenario Analysis", *Emerging Infectious Diseases* 9(5), 531-538

7. Chowell, G., Ammon, C.E., Hengartner, N.W., Hyman, J.M. (2006). "Transmission dynamics of the great influenza pandemic of 1918 in Geneva, Switzerland: Assessing the effects of hypothetical interventions", *Journal of Theoretical Biology,* 241(2), 193-204

8. Markel, H., Lipman, H.B., Navarro, J.A., Sloan, A., Michalsen, J.R., Stern, A.M., Cetron, MS. (2007). "Nonpharmaceutical Interventions Implemented by US Cities During the 1918-1919 Influenza Pandemic", *Journal of American Medical Association,* 298(6), 644-654

9. Carter, W.B., Beach, L.R., Inui T.S., Kirscht J.P., Prodzinski, JC. (1986). "Developing and Testing a Decision Model for Predicting Influenza Vaccination Compliance". *Health Services Research,* 20(6), 897-932

10. Legrand, J., Egan, J.R., Hall, I.M., Cauchemez, S., Leach, S., Ferguson, N.M.

(2009), "Estimating the Location and Spatial Extent of a Covert Anthrax Release", *PLoS Computational Biology* 5(1), 1-10

11. Miller, G., Randolph, S., Gower, D., (2004). "Simulating the Response of a Rural Acute Health-care Delivery System to a Bioterrorist Attack". *International Journal of Disaster Medicine*, 2, 24-32

12. Germann, T.C., Kadau, K., Longini, I.M, Jr., Macken, C.A. (2006), "Mitigation strategies for pandemic influenza in the United States", *PNAS*, 103(15), 5935–5940

13. Volz, E. (2008), "Susceptible-infected-recovered epidemics in populations with heterogeneous contact rates". *Eur. Phys. J. B*, 63(3), 381-386

14. Chowell, G., Bauer, F. (2009), *Mathematical and Statistical Estimation Approaches in Epidemiology*, Heidelberg, CT: Springer

15. Ferguson, N.M., Cummings, D.A.T., Cauchemez, S., Fraser, C., Riley, S., Meeyai, A., Iamsirithaworn, S., Burke, D.S. (2005), "Strategies for containing an emerging influenza pandemic in Southeast Asia", *Nature*, 437(7056), 209-214

16. Meltzer, M.I., Cox, N.J., Fukuda, K. (1999). "The Economic Impact of Pandemic Influenza in the United States". *Emerging Infectious Diseases*, 5(5), 659-671

17. Brookmeyer, R., Blades, N. (2003), "Statistical models and bioterrorism: Application to the US Anthrax Outbreak", *Journal of the American Statistical Association*, 98(464), 781-788

18. Barrett, C.L., Eubank, S.G., Smith, J.P. (2005), "If Smallpox strikes to Portland…" *Scientific American*, 292(3), 54-61

19. Nishiura, H. (2007). "Time variations in the transmissibility of pandemic influenza in Prussia, Germany, from 1918-19". *Theoretical Biology and Medical Modelling*, 4(20), 1-9

20. Roberts, M.G., Baker, M., Jennings, L.C., Sertsou, G., Wilson, N. (2007), "A model for the spread and control of pandemic influenza in an isolated geographical region" , *J. R. Soc. Interface*, 4(13), 325-330

21. Grais, R.F., Ellis, J.H., Kress, A., Glass, G.E. (2004), "Modeling the Spread of Annual Influenza Epidemics in the US.: The Potential Role of Air Travel", *Health Care Management Science*, 7(2), 127-134.

22. Araz, Özgür M., Lant, Tim W., Jehn, M. (2009), "A Pandemic Influenza Simulation Model for Preparedness Planning", Proceedings of the 2009 Winter Simulation Conference.

23. Yang, Y., Halloran, M.E., Sugimoto, J.D., Longini, I.M., Jr. (2007), "Detecting Human-to-Human Transmission of Avian Influenza A (H5N1)", *Emerging Infectious Diseases,* 13(9), 1348-1353

24. Webb, G.F., Blaser, M.J. (2002), "Mailborne transmission of anthrax: Modeling and implications" *PNAS* , 99(10), 7027–7032

25. Atti, M.L.C., Merler, S., Rizzo, C., Ajelli, M., Massari, M., Manfredi, P., Furlanello, C., Tomba, G.S., Iannelli, M. (2008), "Mitigation Measures for Pandemic Influenza in Italy: An Individual Based Model Considering Different Scenarios", *PLoS ONE,* 3(3), 1-11.

26. Lee, EK., Chen, CH., Pietz, F., Benecke, B. (2009), "Modeling and Optimizing the Public-Health Infrastructure for Emergency Response", *Interfaces,* 39(5), 476–490

27. Rizzo, C., Lunelli, A., Pugliese, A., Bella, A., Manfred, P., Tomba, G.S., Ianelli, M., Ciofi, M.L. (2008), "Scenarios of diffusion and control of an influenza pandemic in Italy", *Epdemiology and Infection,* 136, 1650-1657.

28. Amouroux, E., Desvaux. S., Drogoul, A., Bui, T.D., Ho, T.V., Ha, Q.T., (2008), "Towards Virtual Epidemiology: An Agent-Based Approach to the Modeling of H5N1 Propagation and Persistence in North-Vietnam", *PRIMA*, LNAI 5357, 26–33.

29. Kiremitci, C.E., Yurt, B., Damla, I. (2009), "Matematiksel Epidemiyoloji: Pandemik A/H1N1 Gribi Vakası", *Istanbul University Journal of the School of Business Administration*, 38(2), 197-209.

30. Carpenter, C., Sattenspiel, L. (2009), "The Design and Use of an Agent-Based Model to Simulate the 1918 Influenza Epidemic at Norway House, Manitoba", *American Journal Of Human Biology*, 21(3), 290–300

31. John, R., Finlay, B., Blair, C. (2001), "Bioterrorism in Canada: An Economic Assessment of Prevention and Postattack Response", *Can J Infect Dis* , 12(5), 275-284

32. Bravata, D.M., Zaric, G.S., Holty, J.C., Brandeau, M.L., Wilhelm, E.R., Mcdonald, K.M., Owens, D.K. (2006), "Reducing Mortality from Anthrax

Bioterrorism: Strategies for Stockpiling and Dispensing Medical and Pharmaceutical Supplies", *Biosecurity and Bioterrorism: Biodefense Strategy, Practice, and Science,* 4(3), 244-262

33. Hupert, N., Mushlin, A.I., Callahan, M.A. (2002), "Modeling the Public Health Response to Bioterrorism: Using Discrete Event Simulation to Design Antibiotic Distribution Centers", *Medical Decision Making*, 22(suppl. 1), 17-25.

34. Pyle, G.F., Rees, P. (1971), "Modeling Patterns of Death and Disease in Chicago", *Economic Geography*, 47(4), 475-488.

35. Zaric, G.S., Bravata, D.M., Holty, J.C., McDonald, K.M., Douglas, M.M., Owens, D.K., Brandeau, M.L. (2008) "Modeling the Logistics of Response to Anthrax Bioterrorism" *Medical Decision Making*, 28(3), 332-350

36. Schoenbaum, S.C. (1967) "Economic Impact of Influenza: The Individual's Perspective", *The American Journal of Medicine ,* 82 (suppl. 6A), 26-30

37. Hsieha, Y.H., King, C.C., Chen, C.W.S.C., Hod, M.S., Hsue, S.B., Wu, Y.C. (2007), "Impact of quarantine on the 2003 SARS outbreak: A retrospective modeling study Taiwan" *Journal of Theoretical Biology*, 244(4), 729–736

38. Eichner, M., Dietz, K. (2003), "Transmission Potential of Smallpox: Estimates Based on Detailed Data from an Outbreak", *American Journal of Epidemiology*, 158(2), 110-117

39. Duncan, S. R. (2005) "Estimating the Disease Parameters for Smallpox in London Over The Period 1708 to 1748", *Proc. 16th IFAC World Congress on Automatic Control*, Prague, Czech Republic, Th-E02-TP/7

40. Ruan, S., Wang, W., Levin, S.A. (2006), "The effect of global travel on the spread of SARS" *Mathematical Biosciences and Engineering*, 3(1), 205-218

41. Lee, B.Y., Bedford, V.L., Roberts, M.S., Carley, K. (2008), "Virtual epidemic in a virtual city: simulating the spread of influenza in a US metropolitan area" *Translational Research*, 151(6), 275–287.

42. Hak, E., Meijboom, M.J., Buskens, E. (2006), "Modelling the health-economic impact of the next influenza pandemic in The Netherlands" *Vaccine*, 24(44-46), 6756–6760.

43. Schuffham, P.A., West, P.A. (2002), "Economic evaluation of strategies for the control and management of influenza in Europe" *Vaccine*, 20(19-20), 2562-2578.

44. Chowell, G., Ammon, C.E., Hengartner, N.W., Hyman, J.M. (2006), "Estimation of the reproductive number of the Spanish flu epidemic in Geneva, Switzerland", *Vaccine*, 24(44-46), 6747–6750

45. Malone, J.D., Brigantic, R., Muller, G.A., Gadgil, A., Delp. W., McMahon, B.H., Lee, R., Kulesz, J., Mihelic, M. (2009), "U.S. airport entry screening in response to pandemic influenza: Modeling and analysis", *Travel Medicine and Infectious Disease*, 7(4), 181-191

46. Becker, N., (1977), "Estimation for discrete time branching processes with application to epidemics", *Biometrics*, 33(3), 515-522

47. Sattenspiel, L., Annheriring, D. (2003), "Simulating the Effect of Quarantine on the Spread of the 1918–19 Flu in Central Canada", *Bulletin of Mathematical Biology*, 65(1), 1–26

48. Li, Y., Yu, I.T.S., Xu, P., Lee, J.H.W., Wong, T.W., Ooi, P.L., Sleigh, A.C. (2004), "Predicting super spreading events during the 2003 severe acute respiratory syndrome epidemics in Hong Kong and Singapore", *American Journal of Epidemiology*, 160(8), 719-728

49. Christakosa, G., Oleab, R.A., Yua, H.L. (2007), "Recent results on the spatiotemporal modelling and comparative analysis of Black Death and bubonic plague epidemics", *Public Health*, 121(9), 700–720

50. Chowell, G., Hengartner, N.W., Castillo-Chaves, C., Fenimore, P.W., Hyman, J.M. (2004), "The basic reproductive number of Ebola and the effects of public health measures: the cases of Congo and Uganda" *Journal of Theoretical Biology*, 229(1), 119–126

51. Chowell, G., Fenimore, P.W., Castillo-Garsow, M.A., Castillo-Chaves (2005), "SARS outbreaks in Ontario, Hong Kong and Singapore: the role of diagnosis and isolation as a control mechanism", *Journal of Theoretical Biology*, 224(1), 1-8

52. Wanga, W., Ruan, S. (2004), "Simulating the SARS outbreak in Beijing with limited data", *Journal of Theoretical Biology*, 227(3), 369–379

53. Riley, S., Fraser, C., Donnelly, C.A., Ghani, A.C., Abu-Raddad, L.T., Hedley, A.J., Leung, G.M., Ho, L.M., Lam, T.H., Thach, T.Q., Chau, P., Chan, K.P., Lo, S.V., Leung, P.Y., Tsang, T., Ho, W., Lee, K.H., Lau, E.M.C., Ferguson, N.M., Anderson, R. (2003), "Transmission Dynamics of the Etiological Agent of

SARS in Hong Kong: Impact of Public Health Interventions", *Sciencexpress*, 300(5627), 1961-1966

54. Chowell, G., Castillo-Chaves, C., Fenimore, P.W., Kribs-Zaleta, C.M., Arriola, L., Hyman, J.M. (2004), "Model Parameters and Outbreak Control for SARS", *Emerging Infectious Diseases*, 10(7), 1258-1263

55. Gupta, A.G., Moyer, C.A., Sterna, D.T. (2005), "The economic impact of quarantine: SARS in Toronto as a case study", *Journal of Infection*, 50(5), 386–393

56. Nishiura, H., Patanarapelert, K., Sriprom, M., Sarakorn, W., Sriyab, S., Tang, I.M. (2004), "Modelling potential responses to severe acute respiratory syndrome in Japan: the role of initial attack size, precaution, and quarantine", *J Epidemiol Community Health*, 58, 186–191

57. Chowell G, Nishiura H, Bettencourt L.M., (2007), "Comparative estimation of the reproduction number for pandemic influenza from daily case notification data", *J R Soc Interface*, 4(12), 155-166

58. Zhang, J., Zhien, J., Lou, J., Ma, Z., Wu, J. (2005), "A compartmental model for the analysis of SARS transmission patterns and outbreak control measures in China", *Applied Mathematics and Computation*, 162(2) 909–924

59. Chowell, G., Miler, M.A., Viboud, C. (2009), "Seasonal influenza in the United States, France, and Australia: transmission and prospects for control", *Epidemiol Infect.*, 6(6) 852–864

60. Flauhault, A., Deguen, S., Valleron, A.J., (1994), "A Mathematical Model for the European Spread of Influenza", *European Journal of Epidemiology*, 10(4), 471-474

61. Wein, M., Craft D.L., Kaplan, E.H. (2003), "Emergency response to an anthrax attack", *PNAS*, 100(7), 4346-4351

62. Koyuncu, M., Erol, R. (2010), "Optimal Resource Allocation Model to Mitigate the Impact of Pandemic Influenza: A Case Study for Turkey", *J Med Syst*, 34(1), 61–70

63. Lekone, P.E., Finkenstadt, B.F., (2006), "Statistical Inference in a Stochastic Epidemic SEIR Model with Control Intervention: Ebola as a Case Study", *Biometrics*, 62(4), 1170 – 1177

64. Longini, I.M., Jr, Nizam A, Xu S, Ungchusak, K., Hanshaoworakul, W., Cummings, D.A.T, Halloran, M.E. (2005), "Containing pandemic influenza at the source", *Science.;* 309 (5737), 1083-1087

65. Donnelly, C.A., Ghani, A.C., Leung, G.M., Hedley, A.J., Fraser, C., Riley, S., Abu-Raddad, L.J., Ho, L.M., Thach, T.Q., Chau, P., Chan, K.P., Lam, T.H., Tse, L.Y., Tsang, T., Liu, S.H., Kong, J.H.B, Lau, E.M.C., Ferguson, N.M., Anderson, R.M. (2003), "Epidemiological determinants of spread of causal agent of severe acute respiratory syndrome in Hong Kong", *Lancet*; 361(9371), 1761–1766

66. Ball, F., (2006), "Optimal vaccination schemes for epidemics among a population of households, with application to variola minor in Brazil", *Statistical Methods in Medical Research.* 15(5), 481–497

67. Miller, G., Randolph, S., Patterson, J.E. (2006), "Responding to Bioterrorist Smallpox in San Antonio*", Interfaces*, 36(6), 580–590

68. Zhou, Y., Ma, Z., Brauer, F. (2004), "A discrete epidemic model for SARS transmission and control in China", *Mathematical and Computer Modelling*, 40(13), 1491-1506

69. Drake, J.M., Chew, K.S., Ma, S. (2006), "Societal Learning in Epidemics: Intervention effectiveness during the 2003 SARS Outbreak in Singapore", *PLoS ONE*, 1(1), 1-8

70. Hsu, S., Hsieh, Y.H. (2006), "Modeling intervention measures and Severity-dependent public response during severe Acute respiratory syndrome outbreak", *SIAM J. APPL. MATH,* 66(2), 627–647

71. Kaplan, E.H., Craft, D.L., Wein, L.M. (2003), "Analyzing bioterror response logistics: the case of smallpox", *Mathematical Biosciences,* 185(1), 33-72

72. Hethcote, H.W. (1989), Three basic epidemiological models, *in Applied Mathematical Ecology*, S. Levin *et al.*(Eds.) Springer, Berlin/Heidelberg

73. Del Valle, S., Hethcote, H., Hyman, J.M., Castillo-Chavez, C. (2005), "Effects of behavioral changes in a smallpox attack model", *Mathematical Biosciences* 195(2), 228–251

74. Chen, L.C., Kaminsky, B., Tummino, T., Carley, K.M., Casman, E., Fridsma, D., Yahja, A. (2004), Lecture Notes in Computer Science, Springer Berlin/Heidelberg

75. Rutherford, W.H., Boer, J. (1983), "The definition and classification of disasters", *Injury: the British Journal of Accident Surgery,* 15(1), 10-12

76. Muschkatel, A.H., Weschler, L.F. (1985), "Emergency Management and the Intergovernmental System", *Public Administration Review (Special Issue)*,45, 49-56

77. Altay, N., Green III, W.G. (2006), "OR/MS Research in Disaster Operations Management", *European Journal of Operational Research,* 175(1), 475–493

78. Kovacs, G., Spens, K.M. (2007), "Humanitarian Logistics in Disaster Relief Operations", *International Journal of Physical Distribution & Logistics Management,* 37(2), 99-114

79. Khardori, N., (2006), "Bioterrorism and Bioterrorism Preparedness: Historical Perspective and Overview", *Infectious Disease Clinics of North America*, 20, 179–211

80. Wenzel, R.P., Edmond, M.B. (2003), "Managing SARS amidst Uncertainty", *New England Journal of Medicine,* 348(20), 1947-1948

81. Rothman, K.J., (2002). Epidemiology: an introduction. Publisher: Oxford University Press.

82. Fenner, F., Henderson, D.A., Arita, L, Jezek, Z., Ladnyi, L.D. (1988), Smallpox and Its Eradication. Publisher: World Health Organization, Geneva.

83. Hethcote, H.W., (2009), "The Basic Epidemiology Models: Models, Expressions for R_0, Parameter Estimation, and Applications", Mathematical Understanding of Infectious Disease Dynamics, World Scientific Publishing Co. Pre. LTD

84. Brauer, F., (2008). Lecture Notes in Mathematics. Publisher: Springer Berlin/Heidelberg.

85. Wonham, M.J., Lewis, M.A. (2008). A Comparative Analysis of Models for West Nile Virus Epidemiology. CT: Springer-Verlag Berlin Heidelberg.

86. Carley K, Fridsma D, Casman E, Altman N, Chang J, Kaminski J, Nave D, Yahja A, (2003), BioWar: Scalable Multi-Agent Social and Epidemiological Simulation of Bioterrorism Events. *NAACSOS conference proceedings,* Pittsburgh, PA.

87. Allen, L.J.S, Burgin, A.M. (2000), "Comparison of deterministic and stochastic SIS and SIR models in discrete time", *Mathematical Biosciences,* 163(1), 1-33.

88. Fulginti, A, Papler, A., Lane, M.J. (2003), "Smallpox Smallpox Vaccination: A Review, Part I. Background, Vaccination Technique, Normal Vaccination and Revaccination, and Expected Normal Reactions", *Clinical Infectious Diseases,* 37(2), 241-250

89. Fulginti, A, Papler, A., Lane, M.J. (2003), "Smallpox Vaccination: A Review, Part II. Adverse Events", *Clinical Infectious Diseases,* 37(2), 251-271.

90. Liu,P., Chen, L, Cui, X. (1999), "A Discrete Analogue of an Integrodifferential Equation", *Computers and Mathematics with Applications* 37(1999), 41-55

91. Gani, R., Leech, S., (2001), "Transmission potential of smallpox in contemporary populations", *NATURE,* 414(6865), 748-751

92. Jiao, J, Chen., L., Cai, S. (2008), "An Seirs Epidemic Model with Two Delays and Pulse Vaccination", *Jrl Syst Sci & Complexity,* 21(2), 217-225

93. O'Callaghan, M., Murray, A.G. (2002), "A tractable deterministic model with realistic latent period for an epidemic in a linear habitat", *J. Math. Biol.* 44(3), 227–251.

94. Aldis, G.K., Roberts, M.G. (2005), "An integral equation model for the control of a smallpox outbreak", *Mathematical Biosciences* 195(1) 1–22.

95. Mortimer, P.P. (2003), "Can Postexposure Vaccination against Smallpox Succeed?", *Clinical Infectious Diseases,* 36(5), 622-629.

96. Halloran, M.E., Longini M.I., Jr., Nizam, A., Yang, Y. (2002), "Containing Bioterrorist Smallpox", *Science,* 298, 1428-1432

97. Breman, J.G., Henderson, D.A.,(2002), "Diagnosis and Management of Smallpox", *The New England Journal of Medicine,* 346(17), 1300-1308

98. Nishiura, H. (2009), "Determination of the appropriate quarantine period following smallpox exposure: An objective approach using the incubation period distribution", *Int. J. Hyg. Environ. Health* 212(1), 97–104.

99. Kaplan, E.H., Craft, D.L., Wein, L.M. (2002), "Emergency response to a smallpox attack: The case for mass vaccination", *PNAS,* 99(16), 10935-10940.

100. House, T., Hall, I., Danon, L., Keeling, M.J. (2010), "Contingency planning for a deliberate release of smallpox in Great Britain–the role of geographical scale and contact structure", BMC Infectious Diseases, 10, 25

101. Longini I.M., Jr., Halloran, M.E., Nizam A., Yang, Y., Xu, S., Burke, D.S., Cummings, D.A.T, Epstein, J.M. (2007), "Containing a large bioterrorist smallpox attac: a computer simulation approach", *International Journal of Infectious Diseases,* 11(2), 98-108

102. Murray, C.J.L., Lopez, A.D., Chin, B., Feehan, D., Hill, K.H. (2006), "Estimation of potential global pandemic influenza mortality on the basis of vital registry data from the 1918–20 pandemic: a quantitative analysis", *Lancet*, 368(9554), 2211–2218.

103. Hethcote, H.W. (1976), "Qualitative Analyses of Communicable Disease Models", *Mathematical Biosciences,* 28, 335-356

104. Cetron, M., Landwirth, J., (2005), "Public Health and Ethical Considerations in Planning for Quarantine", *Yale Journal of Biology and Medicine*, 78(5), 325-330

105. Kretzschmar, M., van den Hof, S., Walliga, J., van Wijngaarden, J. (2004), "Ring Vaccination and Smallpox Control", *Emerging Infectious Diseases,* 10(5), 832-841

106. Koplan P.J., Foster, S.O., (1979), "Smallpox: Clinical Types, Causes of Death, and Treatment", *The Journal of Infectious Diseases*, 140(3), 440-441

107. Elderd, B.D., Duklc, V.M., Dwyer, G. (2006), "Uncertainty in predictions of disease spread and public health responses to bioterrorism and emerging diseases" *PNAS*, 103(42), 15693–15697

108. Chen, L.C., Kaminsky, B., Tummino, T., Carley,K.M., Casman, E., Fridsma, D., Yahja, A. (2004), *Lecture Notes in Computer Science,* 3037/2004, Springer Berlin / Heidelberg

109. Lloyd, A.L., (2001) Realistic Distributions of Infectious Periods in Epidemic Models: Changing Patterns of Persistence and Dynamics, *Theoretical Population Biology,* 60(1), 59-71

110. Lane, J.M., Summer, L. (2005), "Smallpox as a weapon for bioterrorism", *Bioterrorism and Infectious Agents,* (Eds.) Fong and Alibek, Springer, Berlin

111. Parrino J., Graham, B.S. (2006), "Smallpox vaccines: past, present and future", *Annals of Allergy, Asthma and Immunology*, 118(6), 1320-1326

112. Wallin, A., Luksiene, Z., Zagminas, K., Surkiene, G. (2007), "Public health and bioterrorism: renewed threat of anthrax and smallpox", *Medicina (Kaunas)*, 43(4), 278-284

113.Kennedy, R.B., Ovsyannikova, I., Poland, G.A. (2009), "Smallpox vaccines for biodefence", *Vaccine*, 27, 73-79

114.Kerrod, E., Geddes, A.M., Regan, M., Leach, S. (2005), "Surveillance and control measures during smallpox outbreaks", *Emerging Infectious Diseases*, 11(2), 291-297

115.Ghiani, G., Laporte, G., Musmanno, R. (2004), Introduction to Logistics Systems Planning and Control, England: John Wiley and Sons

116.Hillier, F.S., Lieberman, G.J. (2001), Introduction to Operations Research 7th Edition, McGraw Hill

117.van Wassenhove, L.N. (2006), "Humanitarian aid logistics: supply chain management in high gear", *Journal of the Operational Research Society*, 57, 475-489

118.Wollf, M.W., Venzke, C., Zimmermann, A., Hansen, S.P., Djurup, R., Faber, R., Reichl, U. (2007), "Affinity choromatography of cell culture derived vaccinia virus", AIChe 2007 Annual Meeting, Salt Lake City, UT

119.Mangili, A., Gendreau, M., (2005), "Transmission of infectious diseases during commercial air travel" *The Lancet*, 365(9463), 989-996

120.Blanty, J.M. (2005), M.S. Green et al. (eds.), Risk Assessment and Risk Communication Strategies in Bioterrorism Preparedness, 77–92, Springer

121.Morens, D.M., Folkers, G.K., Fauci, A.S. (2004), "The challenge of emerging and re-emerging infectious diseases", *Nature*, 430(6996), 242-249

122.Farmer R and Miller D,(2004), Lecture notes on epidemiology and public health medicine. 1991, Oxford: Blackwell Scientific Publications.

123.Bhopal R.S. (2002), Concepts of epidemiology: an integrated introduction to the ideas, theories, principles, and methods of epidemiology. New York : Oxford University Press

124.Porta M, (2008), A dictionary of epidemiology, 5th Edition, New York: Oxford University Press,

APPENDIX

ABBREVIATIONS

Reference	Abbreviation(s)	Full definition
[1], [6], [20]	AVT	Antiviral Treatment
[1], [25], [27], [63]	AVP	Antiviral Prophylaxis
[20]	TAVP	Targeted Antiviral Prophylaxis
[15], [20], [27]	SD	Social Distancing
[1], [27]	Vacc.	Vaccination
[15]	TAP	Targeted Antiviral Prophylaxis
[52], [53], [59]	Comp.	Compartmental Models
[60]	EU	France and Austria
[54]	Canada, Far Eastern	Toronto, Hong Kong, Singapore
[23]	Eastern	Sumatra, Indonesia and Eastern Turkey