ABSTRACT

Title of thesis: COMPARTMENTAL AND SIMULATION MODELS FOR EVALUATING MEDKIT PREPOSITIONING STRATEGIES FOR ANTHRAX ATTACK RESPONSE

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Since the 2001 anthrax attacks, public health officials have become concerned with planning for a potential large scale attack. Researchers have worked to model attack scenarios in order to evaluate various response policies. One response policy that has been proposed is to preemptively distribute antibiotics to the public in the form of MedKits before an attack occurs. Despite numerous models and studies, there has not been a model to study the effect of distributing MedKits on the expected number of deaths in an attack. We develop a discrete-time compartmental difference equation model to analyze the policy. The results show that distributing any number of MedKits reduces the number of deaths expected in all scenarios tested. We analyze under what circumstances the MedKits have the largest life-saving impact. We also develop a stochastic transition model to demonstrate the accuracy of the MedKits model results.

COMPARTMENTAL AND SIMULATION MODELS FOR EVALUATING MEDKIT PREPOSITIONING STRATEGIES FOR ANTHRAX ATTACK RESPONSE

by

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List of Abbreviations

CDC	Centers for Disease Control and Prevention
ICU	Intensive Care Unit
POD	Points of Dispensing
VMI	Vendor Managed Inventory

Chapter 1

Introduction

1.1 Bioterror Attacks

In recent years, the United States has become increasingly conscious of the threat of terror attacks. In particular, significant attention has been given to bioterrorism. In September 2001, five people were killed and seventeen others were infected after letters containing anthrax spores were mailed through the U.S. Postal Service [9]. While deadly, this attack was relatively localized, mostly affecting those receiving the letters and the postal workers transporting them. An anthrax attack could be realized on a much larger scale by the release of aerosolized spores in a large city. In such a case, thousands of people could easily be exposed to this deadly disease. Planning for a rapid response to such an attack is of great importance to various government officials and the general public.

1.2 Anthrax: Symptoms and Treatment

The bacteria *Bacillus anthracis* causes the disease commonly known as anthrax. There are three ways in which anthrax can be transmitted. The most common is transmission through broken skin. Most often this occurs when a person butchers an animal infected with anthrax. Anthrax contracted in this way is easily

treated and rarely fatal. The second form of transmission is ingestion, when a person eats infected meat. This form is relatively uncommon. The most dangerous form of transmission is inhalation anthrax. A person needs to inhale merely 8,000-10,000 tiny (1-5μm in diameter) anthrax spores to become infected [5, 17]. It has been reported that even just one kilogram of weapon-grade anthrax could be released into the air and infect as many as 1.5 million people [2]. Without intervention, the mortality rate would be extremely high.

There are three stages in anthrax disease progression. The first, incubation, begins at infection. During incubation, the infected individual experiences no symptoms and will not know if he has been infected. The average incubation time is approximately 11 days [5]. From the incubation stage, an infected individual progresses to the prodromal stage. The prodromal stage is characterized by non-headache neurological symptoms such as fever, fatigue, and muscle aches similar to the flu. An infected person next progresses to the fulminant stage, in which the individual is very ill and experiencing respiratory distress. Generally, death occurs within days of the emergence of symptoms.

Anthrax is most responsive to antibiotic treatments in its earliest stages. As such, prophylaxis is an extremely important aspect of attack response. Prophylaxis consists of an oral regimen of either ciproflaxin or doxycycline. A 60 day regimen of prophylaxis medication is recommended to prevent illness. Those that begin prophylaxis during the incubation stage and adhere to the entire 60 days of medication will not become ill. However, those who begin taking medication but then stop may progress to the prodromal and fulminant stages and possibly die.

Treatment for those who have already become ill consists of three antibiotics (rifampin, clindamycin, and either ciproflaxin or doxycycline). These drugs are administered intravenously and require the patient to be in an intensive care unit with access to ventilators, respiratory technicians, and the IV medications. Because patients are hospitalized during treatment, their adherence rate is 100%. However, not all patients recover even with treatment.

1.3 Priorities for Attack Response

The number one factor affecting the number of deaths resulting from an anthrax attack seems to be the speed of response. People who begin prophylaxis while in the incubation stage have a significantly reduced risk of death. Even after becoming ill, those who receive treatment or prophylaxis earlier have a better chance of survival.

Consequently, the priority of any response plan is to react as quickly as possible. There is research being conducted on ways to reduce the time between an attack and when it is first detected and how to best inform the public of an attack. The challenge with detection is that anthrax spores are colorless and odorless, so in general, an attack is detected only when the first person becomes ill, which may be days after the attack occurs. Many steps have also been implemented to minimize the time between detection and when prophylaxis medication can be made available to the public. This aspect of time reduction is the main focus of this thesis.

1.4 Plans for Response

Currently, local governments primarily use Points of Dispensing (PODs) as a means to distribute prophylaxis medication to the public. In the case of an attack, upon detection (usually at least 1 or 2 days after the attack), a local government can designate PODs in places such as school gymnasiums or community centers. These places would allow for the public to come and receive a regimen of prophylaxis medication. The dispensing capacity of PODs depends on the availability of workers as well as medication. It is assumed that no matter what, the dispensing center will need some time to build up to full dispensing capacity.

As soon as an attack is detected, local stockpiles of medication become immediately available. The federal government maintains a national stockpile from which it can send push packs of medication and ventilators to a local government within 12 hours of detection. There are also regional inventories called Vendor Managed Inventory (VMI) which can send supplies within 36 hours of detecting an attack [18].

In the early stages of distribution, the dispensing capacity is limited by the sizes of the local stockpile and the federal push pack. Once the VMI arrives, the supply is considered unlimited, and distribution is limited only by the rate that the PODs can handle. The recommended prophylaxis regimen is 60 days. Often, in order to provide prophylaxis to more people early, the PODs will distribute an abbreviated regimen of just 14 days until the VMI becomes available. Those people who received the shortened regimen must come back at a later time to receive the

remainder of their medication. This can be done when the demand is much less urgent [18].

There are other courses of action currently being considered with the goal of reducing the time before members of the public can begin prophylaxis. The U.S. Postal Service is investigating the possibility of delivering antibiotics directly to homes. Another option being considered is community-based stockpiles of supplies distributed to healthcare institutions before an event occurs. Similarly, pharmaceuticals could be distributed to first responders to be kept on-hand in case of an attack. Any combination of these and other measures could be implemented to better equip communities to handle attacks [8].

1.5 MedKits

Another measure under consideration is the pre-attack placement of pharmaceuticals directly into households. This strategy is the focus of the work in this thesis. The plan is to distribute prescription medication in the form of a kit called a MedKit to some or all households prior to an attack. Recipients would be instructed that the MedKit is for emergency use only and should not be opened except under direction of government authorities.

The Centers for Disease Control and Prevention (CDC) conducted a trial in 2006 with the Missouri Department of Health and Senior Services to study such a distribution. The study distributed a prototype MedKit to over 4,000 households and randomly assigned each a time interval between two and eight months for a

follow-up interview, during which they would return the kit. The results of the study were very positive with 97% of participants returning their MedKits (99% of those returned were intact). Of the 3% of households that did not return their MedKits, 96% had lost theirs while the other 4% (5 households) refused to return them. The study also looked at the participants' attitudes towards the MedKits, with a majority stating that they would like to have a MedKit to keep in their home after participating in the study. Most would be willing to pay for the MedKit [8].

The main advantage to the MedKit strategy is that individuals with MedKits could begin prophylaxis as soon as they become aware that an attack has occurred. They would not have to wait for a POD to begin distributing medication and then wait in line at the POD to receive the medication. As previously stated, time is a priority in beginning prophylaxis, so MedKit distribution should have a positive impact on the survival rate of an anthrax attack.

The goal of this thesis is to evaluate the effect of pre-event distribution of MedKits on the number of deaths that result from a large scale attack. We use compartmental and simulation models to investigate different scenarios and obtain estimates of the numbers of deaths in those scenarios.

1.6 Outline of Thesis

In Chap. 2, we present other models that have been implemented. We will look at some research studies of anthrax as well as response policies. We will review several compartmental and simulation models that have been designed for anthrax

attack response. We will also look at a specific compartmental model that was designed to evaluate various aspects of anthrax attack response and which is the basis for the model used in this thesis.

In Chap. 3, we present the MedKits model, a compartmental model that extends one presented in Chap. 2. We discuss the differences between the two models and give the details of the implementation.

In Chap. 4, a simulation model is presented to evaluate the accuracy of the MedKits model. We look at the changes needed in order to stochastically simulate an attack scenario.

In Chap. 5, we detail our findings. We give the results of the MedKits model showing the effect of the MedKit distribution on the expected number of deaths. We then present the results of the simulation and give our interpretation of the findings. We also briefly discuss runtime results.

Chapter 6 provides the conclusions to the thesis and ideas for future work.

Chapter 2

Literature Review

In this chapter we look at some of the work that has been done in anthrax research. We also give an overview of applicable types of models and look at the model we use as the basis of our MedKits model.

2.1 Anthrax Work

Since the 2001 anthrax attacks, public health officials and other researchers have been seeking the best plans for response to a future attack in order to save the maximum number of lives possible. Lindner provides a listing of practices for consideration by individual districts [12]. Among the alternatives discussed are traditional PODs, business PODs (in which businesses distribute medications to their employees), postal delivery, and first responder stockpiles. The guide discusses each method and some of the logistics involved. The guide also offers some advice on choosing the best set of policies for a specific community.

Real data is essential to developing a good model. Without data, there is no way to know what parameters are realistic in a model. Fortunately, there have not been many incidences of anthrax outbreaks from which to draw data. As a result, the majority of data used for all anthrax models comes from a handful of sources.

Brookmeyer and Blades compiled a comprehensive analysis of data in 2001 [5].

They based their analysis on data collected during an outbreak in 1979 in Sverdlovsk, Russia. In this case the source was not a terror attack but instead an accidental release of anthrax spores. Studying the data in this case has provided many of the commonly accepted characteristics of anthrax. For example, the mean length of the incubation period is 10.95 days, a number used in many anthrax models.

Holty et al. considered an array of reported anthrax cases between 1900 and 2005 in order to evaluate the effect of age, gender, and treatment factors in patient mortality. This provides a good source of data for models that include different treatment plans [10].

Researchers have also conducted studies relating to individual emergency plans. We are interested in data relating to MedKit distribution. The CDC's Division of Strategic National Stockpile studied the results and public opinions of such a plan in 2006-2007 in the St. Louis, Missouri, area. The goals of the study were to evaluate the ability of households to maintain their MedKit as directed and collect public opinions of the MedKits. The study included 4,076 households which were given a home MedKit and assigned a recall time of two, four, or eight months. After the assigned time period, the household was asked to return its MedKit and give a follow-up interview.

The results of the study were very positive for MedKits [8]. 97% of respondents returned their MedKits and 99% of these were intact and missing no pills. Only a small number of households could not return their MedKits or reported having taken the pills. 94% of participants said they would like to have MedKits in their homes.

Rinchiuso-Hasslemann and others conducted a series of discussion groups in New York in 2008 to gather information about public feelings of mass prophylaxis [14]. This study revealed the importance of disseminating information through a reliable source. People are more willing to comply with guidance if it comes from a source they trust. It also discovered the trend for people to wait to take their prophylaxis until they see how others respond to it. Because beginning prophylaxis quickly is urgent, this study suggests that more work should be done to encourage higher adherence to prophylaxis.

All of these studies, as well as others, provide the data and direction for the many anthrax attack models that have been and continue to be developed.

2.2 Modeling

Mathematical modeling is integral to studying how systems actually work. With a good model, changes can be made and tested. This is particularly helpful in cases where it is not desirable to actually study the system in question, which is the case with anthrax attacks. Public health officials are very concerned with finding response policies that would save as many lives as possible if an attack occurred, and this requires studying how the policies affect the scenario. However, testing the success of response policies by releasing anthrax spores in a city and observing what happens is not the best option. Instead, creating mathematical models of attack scenarios allows us to observe the effects of response plans safely. Mathematical models can take on many forms depending on the system they are modeling.

One major decision that needs to be made for any model is whether it should be agent based or differential equation based. Rahmandad and Sterman discuss the pros and cons of both types of models [13]. An agent based model simulates each actor in a model. For example, an anthrax model that simulated the disease stage of each person in the population would be agent based. In contrast, compartmental models treat the entire contents of a compartment as the same. In the anthrax example, this would be consistent with considering all those in the incubation stage together.

Agent based models allow for more accuracy because many subtleties can be reflected in the model. These models allow for heterogeneity among those of the same type in a model. The downside of agent based models is that they are very computationally intensive and can often grow to be intractable even for simple systems.

Models that consider entire groups together are naturally faster computationally. These models involve compartments with transitions between them defined by functions of the numbers in each compartment. While providing for better computation, these models do have limitations. Most notable is the homogeneous treatment of members of a compartment.

Continuous advances in computer speed and capabilities make agent based models more practical than ever before. However, they still incur time costs that can be quite high. Because of the high numbers of people who can be affected by an anthrax attack, an agent based model would still be very large. As a result, we will focus on non-agent based models.

2.2.1 Compartmental Modeling

Compartmental models are one of the most commonly used to model scenarios in ecology, biomedicine, business and many other fields. Most compartmental models are intuitive representations of systems. The system to be modeled is partitioned into homogeneous compartments. For example, a simple model of the spread of an epidemic may consist of three compartments for those infected, those recovered (and no longer susceptible), and those still susceptible to the infection.

The other needed component of the compartmental model is a definition of the flow between compartments. Some common flows are constant, donor control, and recipient control. In donor control, the flow from compartment i to j is generally defined to be some function of the number in compartment i. The flow between compartments i and j for recipient control is generally some function of the number in compartment j. The flow equations can take many forms to realistically represent the system in question. Compartmental models are ideal for theoretical analysis and computer simulation. Walter and Contreras [15] provide a good introduction to compartmental models and the theory behind them. A more detailed look at compartmental model applications to medicine, including an in depth description of many of the common forms of flow equations can be found in Jacquez [11].

In 2003, Wein et al. developed a model of an airborne anthrax attack in order to compare response plans [16]. The model they developed included several components. A Gaussian plume model was used to simulate the dispersion of the spores. This helps to determine how many people will be infected in different locations rel-

ative to the point of attack. The model also considers age as a factor of infection. The disease stages are modeled as compartments with log-normal distributions for transitions, and a 2-stage queueing system is used to model the waiting times for the prophylaxis and treatment compartments.

To determine who will seek prophylaxis among those with no symptoms, the model incorporates information about how many people in a certain area have developed symptoms. If the fraction of people at that location who have developed symptoms (the anthrax burden) exceeds a set threshold, all people from that location are placed in the queue for prophylaxis.

This model looks at prioritizing the antibiotics queue and the treatment queue. For example, one policy considered is to give prophylaxis priority to those who are already symptomatic, then to people over the age of 55 who are asymptomatic. The simulations show that this prioritizing helps to decrease the number of deaths. The model also considered different threshold values for the prophylaxis queue. $p = 0$ corresponds to the ideal situation in which every one receives prophylaxis regardless of their exposure. If $p = 1$ (no one receives prophylaxis until they exhibit symptoms) 44% of those infected will die. Even just increasing p from 0 to 0.07 doubles the death toll. The conclusions from this model underscore the importance of rapid response and aggressive prophylaxis. They demonstrate that the way to obtain the best outcome is to provide prophylaxis to all people in the affected area as soon as possible, regardless of whether they have been infected.

Baccam and Boechler present another compartmental model of anthrax attacks [1]. The goal of this model is to simulate and evaluate various response plans

centering on an anthrax vaccination. The model consists of 11 compartments. There are compartments for those people who are uninfected and those who are in the incubation stage. There are two compartments for each of the early prodromal stage, an intermediate stage, and the fulminant stage for those in treatment and for those not in treatment. There are three end compartments for those who are prophylaxed (moved from either uninfected or incubation) and never get sick, those who recover after exhibiting symptoms and receiving treatment, and those who die. The model assumes that everyone who reaches the fulminant stage will die.

This model considers people who have inhaled different amounts of spores and thus have varying probabilities of becoming infected. There is also a graduated adherence rate which says 10% of people who receive prophylactic antibiotics do not take them, 15% take them for 15 days, 25% take them for each of 30 days, 45 days, and the full 60 day course. The model assumes a person's likelihood of becoming ill decreases the longer he continues to take his antibiotics, even if he does not complete the entire course.

Baccam and Boechler compare four policies. All assume that the entire population receives the prophylaxis prescribed in the policy. The first is post-exposure prophylaxis, the most commonly used policy now. The second policy combines post-exposure prophylaxis with a two dose vaccine. The third adds a pre-exposure dose of the vaccine to the post-exposure prophylaxis plan. The final policy combines all three with a pre-exposure vaccine, post-exposure prophylaxis, and two more doses of the vaccine. The policies involving the pre-exposure vaccine assume 50% of the population was vaccinated before the attack.

The model considers alternate parameter values to test its sensitivity. Scenarios are designed to test the effectiveness of the policies and how they are influenced by timing. The results for the first policy again show that if prophylaxis is distributed earlier, even by a couple of days, a large percentage of deaths can be prevented. The post-attack vaccines are most effective in saving the lives of those people who choose not to take their prophylaxis antibiotics. The pre-attack vaccines also help to save lives, particularly in scenarios where the prophylaxis distribution is slower. Therefore, pre-attack vaccines act as a way to buy more time for detection and response after an attack. The results of this model are generally consistent with the findings of other models that time is one of the most important factors in saving lives. The vaccines offer a measure to limit the detrimental effects of a delay.

Another compartmental model developed by Brandeau et al. uses a compartmental system to evaluate communication during a bioterror response [3]. The model includes compartments for the disease stages. There are also compartments for prophylaxis and treatment, as well as queues for both. The way asymptomatic people become aware of an attack is through public health and emergency response officials as well as the media. The model seeks to demonstrate the effects of communication policies. The authors have targeted aspects of the response scenario that directly relate to the number of deaths expected and developed communication plans to address these issues. The model is used to evaluate communication policies that affect the rate people become aware of the attack and the rate they seek prophylaxis and treatment. The authors also consider ways to decrease the fraction of people not exposed who seek prophylaxis as this has an adverse affect on those who have

been affected when the supply of prophylaxis is limited. They model the results of attempts to better direct people to specific PODs in order to reduce overcrowding at some PODs. They also look at the results of increasing prophylaxis adherence and the dispensing rate.

The model considers a variety of values for each of the relevant parameters to evaluate the effect each policy has on the mortality rate. As expected, the mortality rate declines with shorter detection time, faster rates of people seeking prophylaxis, limited numbers of unexposed seeking prophylaxis, equal distribution of those seeking prophylaxis among the PODs, better adherence rates, and increased distribution capacity. The paper provides practical communications strategies to accomplish these and the model provides evidence that they will in fact improve the outcome of the response policy in an attack.

Another compartmental model is presented by Bravata and Zaric [4, 18]. We will discuss the details of this model in Section 2.3.

2.2.2 Stochastic Modeling

Stochastic modeling allows systems to be modeled using random variables to give a distribution of likely results for a scenario. This can be useful alone as a way of evaluating the effects of uncertain parameters, or it can be used in conjunction with another model as a means of comparison to assess the accuracy of results.

Buckeridge uses stochastic modeling to evaluate detection of an attack [6]. Because detecting an attack earlier can save many lives, researchers are developing

syndromic surveillance systems to detect attacks as soon as possible. One such system is the BioSense system which gathers data on outpatient visits, laboratory orders, and prescriptions so that if there is a small increase in anthrax (or potentially other disease) indicators, an attack can be detected earlier than if officials wait to see seriously ill people being admitted to hospitals. Because these indicators occur randomly, the model must find a way to simulate them as random variables.

The model uses a Latin hypercube sampling approach to generate parameter values for the model. For each parameter (like the probability of an outpatient visit in the prodromal state or the time until blood culture growth), there are three equal probability bins. There is a small bin centered around the mean, and two larger bins on either side. Each of the healthcare parameters is distributed as either a Bernoulli or exponential random variable. The duration of the disease stages are also randomized with lognormal distributions.

The results of the simulation model were compared with clinical case studies of detection of actual outbreaks. The model study showed there is a careful balance between the specificity of syndromic surveillance and the sensitivity of the surveillance system. If the indicator levels that trigger a warning are too specific, there will be a high incidence of false alarms, which is undesirable. However, as this specificity is decreased, the surveillance system does not successfully detect all of the simulated attacks earlier than the clinical detection. The stochastic model allows data on the number of times the surveillance model detects an attack before the clinical detection. A deterministic model would only be able to provide an expected time of detection for the surveillance system.

2.3 A Compartmental Model of Anthrax Response

The model that we will use as a basis for our models is presented in Bravata et al. [4] and expanded upon in Zaric et al. [18]. The model is similar to the model described in Brandeau et al. [3]. This model is a compartmental model used to evaluate how different parameters affect the overall mortality rate in an attack scenario.

The model is run with a population of 5,000,000 people. The number of exposed individuals as well as the fraction of those not exposed who believe they were are given as input parameters. Also, the prophylaxis adherence rate and the arrival time of the push pack are input parameters. The model consists of 21 compartments representing the stages of the disease as well as the stages of treatment. There are compartments for those people who were unexposed and considered uninvolved in the scenario as well as compartments for those people who were not exposed but believe they were. The compartments are categorized by two statuses. Each compartment is representative of a disease stage (incubation, prodromal, fulminant, recovered, dead, not exposed) and an awareness/treatment stage (unaware, aware and seeking prophylaxis, in prophylaxis, seeking treatment, and in treatment). The flows between compartments are dictated by probabilities taken from Holty et al. [10] and Brookmeyer and Blades [5].

The simulation is run over a 2400 hour time horizon and in each iteration of time t, the model calculates the number that will transition between each pair of compartments (i, j) as $\phi_{ij}(t)$. At the end of each iteration, the number in each

compartment i is updated using this difference equation

$$X_i(t+1) = X_i(t) + \sum_{j=1}^{21} \phi_{ji}(t) - \sum_{j=1}^{21} \phi_{ij}(t) - \delta_i X_i(t), \tag{2.1}$$

where δ_i is the death rate from compartment i.

The model is run over a variety of scenarios. The results confirm expected outcomes. If the attack detection is later or prophylaxis supplies are delayed in becoming available, the number of deaths increases. Increasing the numbers held in the local stockpile decreases the number of deaths, as does increasing the dispensing capacity. The model also considers distributing only an abbreviated regimen of prophylaxis while the supplies are initially quite limited. If only 14-day regimens are distributed (with the assumption that these people will later return to pick up the remainder of their pills), prophylaxis can be distributed to a much larger number of people and the number of deaths will decrease. The results also demonstrated that the adherence rate to prophylaxis is a major contributor to saving lives. Increasing the adherence rate from 65% to 90% decreases the number of deaths by about 13.7% in the scenario tested. The model also revealed that the number of unexposed people seeking prophylaxis directly affected the expected number of deaths. If more people who do not need it seek prophylaxis, it prevents those who do need it from acquiring it as quickly.

The creators of this model also look at some cost analysis in their report. They present the cost of the various antibiotics used for prophylaxis and treatment. They also quantify the number of life years lost in an attack based on the average life years lost by a patient who dies (43.4 years). With these they can calculate the cost

per life year of the response scenario.

The model does have limitations and some confusing details that we will clarify and improve. The model does not contain a compartment for death but instead eliminates people from the model when they die. While this is a reflection of reality in that people do leave the population upon death, it is not a truly closed system. There is also some confusion about how multiple transitions from the same compartment in the same iteration are handled to ensure people are moved as they should be. The rate of adherence to prophylaxis is incorporated unclearly in a way that those that have been entirely adherent seem to still be susceptible to illness.

In the next chapter, we develop a compartmental model which expands upon this model to improve the issues above and provide for our study of the effect of MedKit distribution.

2.4 Discussion

There are models of the progression of anthrax that are based on data analysis. These models have focused on the spread of anthrax spores after an attack and the distributions of times spent in the disease stages.

Other models have incorporated dispersion and disease progression models to evaluate various attack response plans. There are compartmental models as well as stochastic simulation models that have examined how communication policies, timing, and prophylaxis, treatment, and vaccines affect the number of deaths in an attack scenario. Many of these models share similar conclusions. All conclude that

time is one of the most influential factors. This has guided researchers to focus on policies which reduce response time either by decreasing the time until detection or decreasing the time to organize and respond once an attack has been detected.

Additional research has been conducted on the feasibility of distributing MedKits prior to an attack to help decrease the time before prophylaxis can begin. Studies have collected data on public opinion as well as the likelihood that people would still be able to use their MedKits in the event of an attack.

No one has yet developed a model to study the effects of the MedKits on the number of deaths in an attack. This idea is the inspiration for the work in this thesis. We will extend the model presented by Zaric [18] and use MedKit data gathered by the CDC [8] to develop a model to evaluate attack scenarios with MedKit policies.

Chapter 3

The MedKits Compartmental Model

3.1 Extending the Model

In order to evaluate the effect of MedKit distribution on the number of expected deaths in an attack scenario, we began with the model described in the previous chapter presented by Zaric et al. [18]. The original model consists of 21 compartments representing the stages of disease progression and treatment. Transitions between compartments are governed by equations dependent on the probability that a person progresses from compartment A to compartment B in a given hour. We keep the compartmental structure of that model and calculate many of the transition equations in the same way. Like the original model, our new MedKits model is a discrete-time model that simulates a 2400-hour time horizon.

There are some limitations to the original model which we have addressed for the MedKits model. The original model does not represent a closed system. After people become ill, they either recover or die. The model contains a compartment for those people who recover, but people who die are simply removed from the model. This reflects what happens in reality when people die and are removed from the population. However, a better compartmental model should have the same number of agents at the end of simulation as it had at the beginning.

Also, the model contains a compartment for those people in the incubation

stage who are receiving prophylaxis. Each hour the probability of progressing in illness is calculated considering the probability of becoming prodromal times $1 - \alpha$, (the probability of not adhering to prophylaxis). This gives the impression that a person could not adhere in one hour and then become adherent again in the next. In actuality, it should be a one time decision whether a person will adhere completely or not.

The model is also not completely precise about how to handle people who can progress both in disease stage and treatment stage in the same hour. We address each of these issues in the MedKits model.

The MedKits model includes a compartment for death, as well as separate compartments for those in prophylaxis who are adherent and those who are not. We prioritize transitions and create a two-stage iteration so that those transitions relating to disease progression, death, and recovery are handled first. To extend the model to include people who have MedKits in their homes, we add new compartments to the model and change transitions where necessary to reflect how people move between the new set of compartments. In the following sections we will discuss the details of the MedKits Model.

3.2 The Compartments

Our MedKits model contains 28 compartments in all. From this point, we will refer to the compartments by the disease and treatment stages they represent or by their numbers as appropriate.

Initially, everyone is unaware that an attack has occurred. Each individual is either exposed or not exposed. Individuals who have been exposed to the anthrax spores are in the incubation stage and have the potential to progress to the prodromal and fulminant stages as well as death. As these people become aware of the attack and their potential exposure, they will seek prophylaxis, and as they become ill, they will seek treatment. Because there are dispensing capacities for both prophylaxis and for treatment, these people may have to wait in a queue prior to receiving the medication.

Those not exposed are broken into two subgroups: those who know they were not exposed and those who think they may have been exposed. People who know they are not exposed will never seek prophylaxis or treatment and cannot become ill, so these people remain in the same not exposed compartment for the duration of the simulation. The people who believe they may have been exposed, but actually were not, cannot become ill but will seek prophylaxis as they become aware of the attack. They will enter the same queue as those people who have been exposed to wait for prophylaxis. However, because they cannot become ill, this is modeled by separate compartments without flow to the next disease stage.

When a person becomes ill, his probability of becoming more ill or dying depends partially on how early prophylaxis was started. As a result those in prophylaxis during the prodromal stage are broken into two compartments depending on if the prophylaxis began in the incubation stage or the prodromal stage. Likewise, those in the fulminant stage are broken into multiple compartment based on when they began prophylaxis and if or when they began treatment.

In our compartmental model, at every iteration, each individual is in exactly one compartment. So for example, if a scenario begins with 100 people, after each iteration of the model, the people will move between compartments, but the sum of the numbers in each compartment will always be 100. This way, we ensure that no one is lost, and we only need to count the number in compartment 22 (the compartment for death) at the end of the simulation to know how many people died.

Just like the rest of the population, people with MedKits all begin unaware of the attack and are either exposed or not exposed. Those who know they have not been exposed are no different than those without MedKits who know they are not at risk. Therefore, we place these people in the same compartment we already have for unexposed individuals. Those who were not exposed but think they may have been will begin taking their MedKit as soon as they become aware of an attack, but they can never become ill and will not join the queue for prophylaxis. Instead they move into another new compartment for taking their MedKits, and they remain here for the rest of the simulation.

We have a compartment corresponding to each disease stage for those people who have MedKits and are unaware of the attack. These people are not yet taking their MedKits because they do not yet know they should. Once they become aware that an attack has occurred and that they are at risk, they begin taking their MedKits and enter the existing compartments for those receiving prophylaxis. The main difference between these people and those who began unaware and did not have MedKits is that these people skip over the compartment for the prophylaxis

queue. Altogether, there are five new compartments for the people who receive MedKits prior to an attack.

We add one more compartment to our model to make more precise the transition to prophylaxis in the incubation stage. People who begin prophylaxis have some probability α of adhering to it, in which case they cannot become ill. However if they do not adhere to prophylaxis for the full 60-day regimen, they have a chance of progressing to the prodromal disease stage. We make the decision of whether each person will adhere as soon as that person begins prophylaxis. We create two separate compartments for people in prophylaxis. Compartment 7 is only for people who do not adhere fully, and compartment 28 is for those who will adhere fully. The number beginning prophylaxis times α gives the number moving into compartment 28. These people can not become ill, so they remain in this compartment for the remainder of the simulation. The rest of the people beginning prophylaxis are placed in compartment 7, and it is assumed that they will not adhere to their prophylaxis and therefore, can become ill.

Tables 3.1 and 3.2 list all of the compartments and what disease stage and treatment stage they represent.

3.3 Model Assumptions

The MedKits model follows the timeline described below which is based on the scenarios described in [18]. The details of the timeline, as well as the capacities described could be adjusted to reflect different scenarios. For example, we assume

Table 3.1: List of compartments.

Number	Exposure, Treatment Status	Progression of Disease	Treatment Began	MedKit
1	Exposed, unaware	Incubation	n.a.	No
2	Exposed, unaware	Prodromal	n.a.	No
3	Exposed, unaware	Fulminant	n.a.	No
4	Aware of exposure	Incubation	n.a.	No
5	Aware of exposure	Prodromal	n.a.	No
6	Aware of exposure	Fulminant	n.a.	No
7	In Prophylaxis, not adherent	Incubation	Prophylaxis begun in incubation	Both
8	In Prophylaxis	Prodromal	Prophylaxis begun in incubation	Both
9	In Prophylaxis	Prodromal	Prophylaxis begun in prodromal	Both
10	In Prophylaxis	Fulminant	Prophylaxis begun in incubation	Both
11	In Prophylaxis	Fulminant	Prophylaxis begun in prodromal	Both
12	In Prophylaxis	Fulminant	Prophylaxis begun in fulminant	Both
13	In Treatment	Prodromal	Treatment begun in prodromal	Both
14	In Treatment	Fulminant	Prophylaxis or Treatment begun in prodromal	Both
15	In Treatment	Fulminant	Prophylaxis - incubation, treatment - fulminant	Both
16	In Treatment	Fulminant	Prophylaxis - none or begun in fulminant	Both
17	Exposed	Recovered	n.a.	Both
18	Not Exposed	n.a.	n.a.	Both

Table 3.2: Continuation of Table 3.1

Number	Exposure, Treatment Status	Progression of Disease	Treatment Began	MedKit
19	Potential exposure, not seeking prophylaxis	n.a.	n.a.	No
20	Potential exposure, seeking prophylaxis	n.a.	n.a.	No
21	Potential exposure, in prophylaxis	n.a.	n.a.	No
22	Exposed	Dead	n.a.	Both
23	Potential exposure, not seeking prophylaxis	n.a.	n.a.	Yes
24	Potential exposure, in prophylaxis	n.a.	n.a.	Yes
25	Exposed, unaware	Incubation	n.a.	Yes
26	Exposed, unaware	Prodromal	n.a.	Yes
27	Exposed, unaware	Fulminant	n.a.	Yes
28	Adhering to prophylaxis	Prophylaxed	Prophylaxis begun in incubation	Both

the attack is detected after 48 hours. However, if new research provides a way to detect an attack earlier, the timeline could be changed to model the new scenario.

3.3.1 Timeline

We consider a time period of 100 days for this model, so we simulate the model over $t = 1, ..., 2400$. We assume $t = 0$ is the time of the attack. The attack is detected at $t = 48$ hours. It takes five hours to prepare the local stockpile for distribution, so medication and intravenous antibiotics (IVs) from this source become available at $t = 53$ hours. The push pack from the national stockpile arrives 12 or 24 hours

after detection and requires another four hours to prepare for distribution. So more IVs, ventilators, and antibiotics become available at $t = 64$ or $t = 76$ hours. VMI becomes available 36 hours after detection at $t = 84$ hours. At this point we no longer have capacity restrictions based on availability of antibiotics and IVs. The VMI is assumed to be sufficient to meet all needs. We assume it takes 48 hours for the PODs to reach full dispensing capacity, which occurs at time $t = 96$ hours.

3.3.2 Resource Capacities

We assume that each dispensing center operates for 14 hours per day and, at full capacity, can dispense 1,000 doses per hour during that time. We assume there are a total of 10 PODs, for a total of 10,000 doses per hour over 14 hours per day. To simplify the model slightly, we recalculate the doses per hour spread out over 24 hours per day. This means at full capacity, the entire collection of PODs can dispense 5,833 doses per hour. We assume that the dispensing capacity begins at 0 at time $t = 48$ hours (time of detection which we will call T_D) and increases linearly over the next 48 hours to reach full capacity, $D_{\max}$, at $t = 96$ hours. So the dispensing capacity at time t is as follows:

$$D(t) = 0, t < T_D \tag{3.1}$$

$$D(t) = [(t - T_D)/48] * D_{\max}, T_D < t < 48 + T_D \tag{3.2}$$

$$D(t) = D_{\max}, t > 48 + T_D \tag{3.3}$$

This is, of course, the rate at which PODs could dispense antibiotics assuming they had sufficient inventory. The rate is also restricted by the level of inventory in

the local stockpile and the push pack.

Until the VMI becomes available, the PODs dispense only an abbreviated prophylaxis regimen of 14 days, rather than the full 60-day supply. This allows the limited supply to be spread to more people when they really need it. It is assumed that those who receive only the 14-day regimen will return later, when demand is not so urgent, to receive the remainder of their regimen. We assume that the local stockpile contains 50,000 doses or 3,571 abbreviated regimens. When the push pack arrives, it contains an additional 2,718,000 doses or 194,143 abbreviated regimens. The VMI is assumed to contain enough doses for everyone to receive the full 60-day regimen.

Treatment capacity is also controlled by the availability of the supplies needed for treatment. Treatment requires IV antibiotics, ventilators, respiratory technicians, and ICU beds. The IV antibiotics are described in terms of days. Each person in treatment requires one day of IV medication for each day of treatment. There must be at least one day of IV medication available to begin treating one person. We assume the local stockpile contains 500 days of IV antibiotics, the push pack provides an additional 21,492 days, and the VMI contains enough IV antibiotics for all who need them. There are 100 ventilators available at the time of attack and 100 more arrive in the push pack. There are 200 respiratory technicians and each can monitor 10 patients. There are 2,000 ICU beds available. At the beginning, treatment capacity is slowed by the limited availability of IV antibiotics. Once the VMI becomes available, there are enough IVs for everyone, and the number of ventilators becomes the slowing factor.

3.4 Calculating the Number in Each Compartment

Initially, people can be in only compartments 1, 18, 19, 23, or 25. $X_i(t)$ is the number of people in compartment i at time t. We say that P is the total population size, N is the number of people exposed to the anthrax spores, M is the number of people who received MedKits prior to the attack, p_M is the probability that they still have their MedKits and can use them (assumed to be 95% [8]), and β is the probability that a person not exposed believes he or she was exposed. The initial numbers in each compartment are as follows

$$X_1(0) = (P - p_M M)N/P, \tag{3.4}$$

$$X_{18}(0) = (1 - \beta)(P - N), \tag{3.5}$$

$$X_{19}(0) = \beta(P - p_M M)(1 - N/P), \tag{3.6}$$

$$X_{23}(0) = \beta p_M M(1 - N/P), \tag{3.7}$$

$$X_{25}(0) = p_M MN/P, \tag{3.8}$$

$$X_i(0) = 0, \text{ for i=2,..., 17, 20..., 22, 24, and 26,..., 28.} \tag{3.9}$$

The model is completely dependent on a set of equations defining the transitions between compartments. These equations describe the expected number of people who will move between a pair of compartments at time t based on the probability of moving from one state to the other. In the original model, for each pair of compartments, $\phi_{ij}(t)$ gives the number of people who move from compartment i to compartment j at hour t. The number of people in compartment i at time $t + 1$

is calculated using the following difference equation

$$X_i(t+1) = X_i(t) + \sum_{j=1}^{28} \phi_{ji}(t) - \sum_{j=1}^{28} \phi_{ij}(t). \tag{3.10}$$

This equation leads to some confusion as a person could progress in both disease and treatment status in the same hour. For example, a person in the incubation stage waiting in the queue for prophylaxis could simultaneously move into prophylaxis and become prodromal. We account for this type of situation by calculating the transitions in two steps. First, we calculate all transitions relating to disease progression. We update the number of people in each compartment. Then we calculate the transitions relating to awareness and treatment status and update the number in each compartment again. In this model, $\phi_{ij}(t)$ is the number of people who move from compartment i to compartment j at time t due to illness, recovery or death, and $\psi_{ij}(t)$ is the number of people who move due to awareness, prophylaxis, or treatment. We use these two separate difference equations to calculate the number of people, $X_i(t+1)$ in compartment i at time $t+1$,

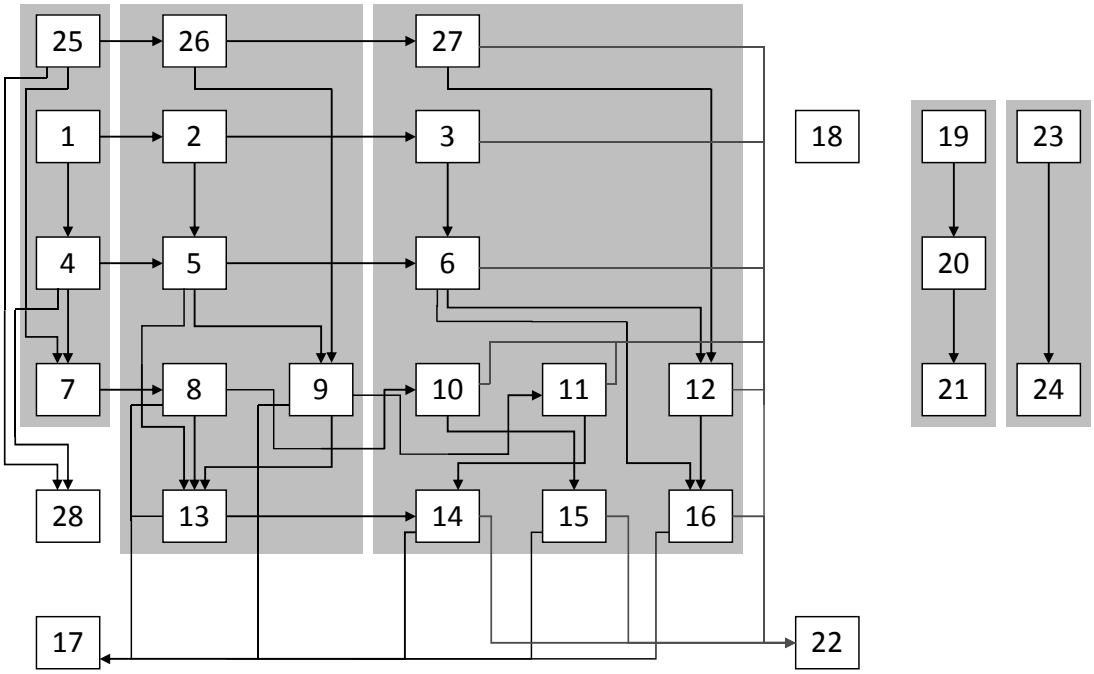
$$Y_i(t) = X_i(t) + \sum_{j=1}^{28} \phi_{ji}(t) - \sum_{j=1}^{28} \phi_{ij}(t), \tag{3.11}$$

$$X_i(t+1) = Y_i(t) + \sum_{j=1}^{28} \psi_{ji}(t) - \sum_{j=1}^{28} \psi_{ij}(t). \tag{3.12}$$

3.5 The Transitions

Because the transitions between compartments represent actual possibilities, not every pair of compartments can have people move between them. For example, someone in the incubation stage will not die from anthrax without progressing

Figure 3.1: This figure shows the possible flows between all compartments in the model. The listing of the compartments is given in tables 3.1 and 3.2.



through the prodromal and fulminant stages first. Also, reverse transitions are prohibited, e.g. aware to unaware. For these pairs of compartments, the probability of transition is zero. The following sections will define all of the nonzero transition equations. Fig. 3.1 shows all of the possible flows between compartments in the model.

As stated previously, there are two types of transitions. The first is transitions relating to disease progression, recovery, or death. The second type is transitions relating to awareness, prophylaxis, or treatment status. We give priority to the first type of transitions in our model (these are the transitions we denote by $\phi_{ij}(t)$). At

each iteration, we calculate all of the first transitions and move people to their new compartments, then we calculate the second set of transitions ($\psi_{ij}(t)$) and move people again.

3.5.1 Progression from Incubation to Prodromal

The distribution for the incubation time is commonly calculated in the following way [18, 16]. The probability of becoming prodromal is $p(t) = (F(t+1) - F(t))/(1 - F(t))$, where $F(t)$ is the cumulative distribution function of incubation time distributed lognormally with mean 10.95 days, and 2.1392 and 0.713 are the mean and standard deviation respectively of the variable's natural logarithm [5]. So the transition equations for moving from incubation to prodromal are of the form

$$\phi_{i,i+1}(t) = p(t)X_i(t), \text{ for i = 1, 4, 7, and 25.} \tag{3.13}$$

3.5.2 Progression from Prodromal to Fulminant

The rate of becoming fulminant is dependent on the length of time a person has been prodromal. Without prophylaxis or treatment, in the first three days after symptoms develop, the rate of progression from prodromal to fulminant is $\gamma = 0.0026$. After the first three days of symptoms, the rate of progression from prodromal to fulminant rises to $\eta = 0.0181$ [10]. We keep a counter and calculate $\theta_2(t)$, $\theta_5(t)$, and $\theta_{26}(t)$ to be the fraction of those in compartments 2, 5, and 26 respectively who have become prodromal in the last 72 hours. These fractions are

calculated as

$$\theta_j(t) = \min\{1, \sum_{v=1}^{72} \phi_{j-1,j}(t-v)/X_j(t)\}. \tag{3.14}$$

So at time t, the fraction of people in the prodromal stage without prophylaxis or treatment who will become fulminant is calculated as $\theta_i\gamma + (1-\theta_i)\eta$ and the transition equations are

$$\phi_{i,i+1}(t) = (\theta_i\gamma + (1-\theta_i)\eta)X_i(t), \text{ for i = 2, 5, and 26.} \tag{3.15}$$

For those receiving prophylaxis or treatment, the expected time to become fulminant is 122.4 hours, so the probability of becoming fulminant each hour is calculated to be 1/122.4 [18, 10]. These transition equations are

$$\phi_{i,j}(t) = (1/122.4)X_i(t), \text{ for (i,j) pairs (8,10), (9,11), and (13,14).} \tag{3.16}$$

3.5.3 Progression to Recovery and Death

Patients in the prodromal or fulminant stages can recover from anthrax if they are receiving treatment. For each compartment there is a probability of recovery, and the number moved from that compartment to compartment 17 (recovered) each hour is the number in the compartment multiplied by the probability of recovery. We use the recovery rates presented in [18]. So we have the following transition equations

$$\phi_{j,17} = X_j(t)/21.7, \text{ for j = 8, 9, and 13,} \tag{3.17}$$

$$\phi_{j,17} = X_j(t)/720, \text{ for j = 14, 15, and 16.} \tag{3.18}$$

Only patients in the fulminant stage can die from the disease. The death rate from all other compartments is zero. Each compartment representing a fulminant stage has a probability of death [18], and the number moved each hour from that compartment to death is calculated in the same way that the number recovered is calculated. The transition equations are

$$\phi_{i,22}(t) = (1/26.4)X_i(t), \text{ for i = 3, 6, 10, 11, and 27,} \tag{3.19}$$

$$\phi_{i,22}(t) = (1/38.4)X_i(t), \text{ for i = 12 and 16,} \tag{3.20}$$

$$\phi_{i,22}(t) = (1/24)X_i(t), \text{ for i = 14 and 15.} \tag{3.21}$$

Table 3.3 gives the probabilities of all possible transitions because of illness, recovery, or death.

3.5.4 Awareness of Exposure

We assume a constant rate at which people become aware of their exposure or potential exposure. We use the awareness rates used by Zaric et al. [18]. For those people not showing symptoms and those in the prodromal stage, the probability of becoming aware is 1/3 each day or 1/72 each hour. For those people already in the fulminant stage, the probability of becoming aware is 1/2 each day or 1/48 each hour. These probabilities give the following transitions equations for moving from unaware (compartments 1, 2, 19, and 3) to aware (compartments 4, 5, 20, and 6 respectively);

$$\psi_{1,4} = (1/72)Y_1(t), \tag{3.22}$$

$$\psi_{2,5} = (1/72)Y_2(t), \tag{3.23}$$

Table 3.3: Fraction of each compartment that becomes ill, dies, or recovers each hour.

Compartment	Becomes prodromal	Becomes fulminant	Dies	Recovers
1	p(t)			
2		$\theta_2\gamma + (1-\theta_2)\eta$		
3			1/26.4	
4	p(t)			
5		$\theta_5\gamma + (1-\theta_5)\eta$		
6			1/26.4	
7	p(t)			
8		1/122.4		1/21.7
9		1/122.4		1/21.7
10			1/26.4	
11			1/26.4	
12			1/38.4	
13		1/122.4		1/21.7
14			1/24	1/720
15			1/24	1/720
16			1/38.4	1/720
25	p(t)			
26		$\theta_{26}\gamma + (1-\theta_{26})\eta$		
27			1/26.4	

$$\psi_{3,6} = (1/48)Y_3(t), \tag{3.24}$$

$$\psi_{19,20} = (1/72)Y_{19}(t). \tag{3.25}$$

$$\tag{3.26}$$

We assume those with MedKits have the same awareness rates as those without. The probabilities of moving from compartments 25, 26, 23, and 27 to the awareness states are the same as above.

$$\psi_{23,24} = (1/72)Y_{23}(t), \tag{3.27}$$

$$\psi_{26,9} = (1/72)Y_{26}(t), \tag{3.28}$$

$$\psi_{27,12} = (1/48)Y_{27}(t). \tag{3.29}$$

The probability of moving from compartment 25 to a state of awareness and prophylaxis in a given hour is also 1/72; however, this compartment splits transitions between two prophylaxis compartments. This transition will be discussed in the following section.

3.5.5 Entering into Prophylaxis and Treatment

For those people with MedKits, entering into prophylaxis occurs at the time of awareness. So transitions from compartments 26 to 5, 27 to 6, and 23 to 24 occur at the rate of becoming aware for those compartments. From compartment 25, people also move into prophylaxis at the awareness rate of 1/72 per hour. However from this point we decide if each person will be adherent to the full course of prophylaxis (and move into compartment 28) or if they will not adhere (moving to compartment 7) and be at risk of progressing to the prodromal stage. We calculate the number who move from compartment 25 to 28 and 7 respectively as

$$\psi_{25,28}(t) = \alpha(1/72)Y_{28}(t), \tag{3.30}$$

$$\psi_{25,7}(t) = (1-\alpha)(1/72)Y_{28}(t). \tag{3.31}$$

for all $t \geq T_D$.

People without MedKits move into a queue for prophylaxis when they become aware of their exposure or potential exposure. From this queue, the number of people who can be given prophylaxis in an hour is limited by the capacity described in section 3.3.2. This capacity is spread across all compartments waiting

for prophylaxis to calculate the probability of moving from any one of them into prophylaxis. Likewise, treatment capacity must be spread across all compartments waiting for treatment to determine the probability of moving into treatment from any compartment.

Those in compartments 5 and 6 are considered to be in both the queue for treatment and the queue for prophylaxis because they have already developed symptoms but have not received any prophylaxis. Obviously they would take treatment over prophylaxis since they have already become ill. So we calculate those moving to treatment first. If they do not move into treatment, then they would continue to seek prophylaxis that hour.

We first calculate the number of people who will move into treatment at time t based on the availability of IV antibiotics ($IV(t)$), ventilators ($V(t)$), respiratory technicians ($T(t)$), beds ($B(t)$) and the number of people waiting for treatment (even if the capacity is higher, there will not be more people moved to treatment than are waiting for it). The number of people currently in treatment is $\sum_{i=13}^{16} Y_i(t)$, so the available number of materials is the number of materials not expected to be used by those people. People in compartments 5, 6, 8, 9, 10, 11, and 12 are all waiting for treatment. The number who will be treated, $CT(t)$ is calculated as

$$CT(t) = \min\{\max[\min(IV(t), V(t), 10T(t), B(t)) - \sum_{i=13}^{16} Y_i(t), 0], \sum_{i=5}^{6} Y_i(t) + \sum_{i=8}^{12} Y_i(t)\}. \tag{3.32}$$

So the probability of moving to treatment from any one compartment is

$$\pi(t) = CT(t)/[\sum_{i=5}^{6} Y_i(t) + \sum_{i=8}^{12} Y_i(t)]. \tag{3.33}$$

So we calculate the following transitions to treatment

$$\psi_{5,13}(t) = \pi(t)Y_5(t), \tag{3.34}$$

$$\psi_{6,16}(t) = \pi(t)Y_6(t), \tag{3.35}$$

$$\psi_{8,13}(t) = \pi(t)Y_8(t), \tag{3.36}$$

$$\psi_{9,13}(t) = \pi(t)Y_9(t), \tag{3.37}$$

$$\psi_{10,15}(t) = \pi(t)Y_{10}(t), \tag{3.38}$$

$$\psi_{11,14}(t) = \pi(t)Y_{11}(t), \tag{3.39}$$

$$\psi_{12,16}(t) = \pi(t)Y_{12}(t). \tag{3.40}$$

After the people who have been moved to treatment are removed from compartments 5 and 6, we calculate the transitions into prophylaxis. We let the available inventory of prophylactic antibiotics at time t be $I(t)$. The number of doses dispensed to each person at time t (i.e. 14 or 60 depending on availability) is denoted $d(t)$. The dispensing capacity per hour of the PODs (not considering availability of medication) is denoted by $D(t)$. The number of people waiting for prophylaxis at time t is $L_q(t) = Y_4(t)Y_{20}(t) + (1 - \pi(t))(Y_5(t) + Y_6(t))$. Each hour we calculate $CP(t)$, the number of people who will begin prophylaxis in that hour, by

$$CP(t) = \min\{I(t)/d(t), D(t), L_q(t)\}. \tag{3.41}$$

We use this number to calculate the probability of moving from each of compartments 4, 5, 6, and 20 into prophylaxis by

$$\rho(t) = CP(t)/L_q(t). \tag{3.42}$$

And with this we calculate the transitions into prophylaxis

$$\psi_{4,7}(t) = (1-\alpha)\rho(t)Y_4(t), \tag{3.43}$$

$$\psi_{4,28}(t) = (\alpha)\rho(t)Y_4(t), \tag{3.44}$$

$$\psi_{5,9}(t) = \rho(t)(1-\pi(t))Y_5(t), \tag{3.45}$$

$$\psi_{6,12}(t) = \rho(t)(1-\pi(t))Y_6(t), \tag{3.46}$$

$$\psi_{20,21}(t) = \rho(t)Y_{20}(t). \tag{3.47}$$

3.6 Updating the Inventory Levels

After each iteration, we must recalculate the available supplies. The number of beds and respiratory technicians is assumed constant throughout the simulation, so for all t, we have

$$B(t+1) = B(t), \tag{3.48}$$

$$T(t+1) = T(t). \tag{3.49}$$

We say t_L is the time lag before local inventories become available (assumed to be 5 hours in our model), t_P is the time before the push pack arrives (12 or 24 hours), t_{PR} is the time lag after arrival before the push pack is ready to use (4 hours), and t_V is the time until the VMI becomes available (36 hours). I_L and IV_L are the local supply of antibiotics and IVs respectively. I_P, IV_P, and V_P are the additional supply of antibiotics, IVs, and ventilators contained in the push pack. We update the supplies in the following manner: If $t = T_D + t_L$,

$$I(t+1) = I(t) - CP(t)d(t) + I_L, \tag{3.50}$$

$$IV(t+1) = IV(t) - \sum_{j=13}^{16} X_j(t) + IV_L, \tag{3.51}$$

$$V(t+1) = V(t). \tag{3.52}$$

If $t = T_D + t_P + t_{PR}$,

$$I(t+1) = I(t) - CP(t)d(t) + I_P, \tag{3.53}$$

$$IV(t+1) = IV(t) - \sum_{j=13}^{16} X_j(t) + IV_P, \tag{3.54}$$

$$V(t+1) = V(t) + V_P. \tag{3.55}$$

The VMI provides enough antibiotics and IVs for everyone in the population P, so for at $t = T_D + t_V$, we have

$$I(t+1) = I(t) - CP(t)d(t) + I_L, \tag{3.56}$$

$$I(t+1) = I(t) - CP(t)d(t) + 60P, \tag{3.57}$$

$$IV(t+1) = IV(t) - \sum_{j=13}^{16} X_j(t) + 3000P, \tag{3.58}$$

$$V(t+1) = V(t). \tag{3.59}$$

For all other times when no new inventory is added, we have

$$I(t+1) = I(t) - CP(t)d(t), \tag{3.60}$$

$$IV(t+1) = IV(t) - \sum_{j=13}^{16} X_j(t), \tag{3.61}$$

$$V(t+1) = V(t). \tag{3.62}$$

Chapter 4

A Simulation Model

The MedKits model gives a completely deterministic view of the attack scenario. It moves people between compartments strictly based on the probability that they should move. If one in ten people should move from compartment 1 to compartment 2 this hour, then one in ten of those people will move. However, this is not the way things work in reality. Perhaps this hour only one in twelve people will get sick, but in the next hour, one in eight will. There can be a substantial difference between an expected value and a random realization of a scenario. It is this uncertainty that we are concerned about in this chapter. It would be beneficial to know how accurate the results of the MedKits model are in an uncertain world. How do the results vary if the compartment transitions are random? Will we still see the same trends in the data? To answer these questions we develop a simulation model to test the accuracy of the MedKits model results.

4.1 Model Overview

Two styles of simulation could be used in this model. The first is an agent-based model, in which each individual's path through the compartments would be simulated. We consider person 1 who begins in compartment 1, and has certain probabilities of moving to compartment 2 or compartment 4. We stochastically

decide if and where he moves. We do this for each person in the model for each hour of simulation. This would theoretically provide a very realistic representation. However, due to the large populations we consider and the number of time periods used in the model, this type of simulation is impractical and perhaps infeasible.

Instead we consider a simulation model in which we treat the compartments as wholes. For each compartment, in each hour, we model as a random variable the number who will move from that compartment to another. The overall structure of the model is the same as the MedKit model. We use the same 28 compartments, and the set of possible transitions is the same. We run the model over a 2400-hour time horizon. In each hour, the model samples the appropriate random variables, calculates the number moved for each transition, and moves people using equations 3.11 and 3.12. The prophylaxis antibiotics and treatment supplies are all available in the same quantities at the same times, and they are updated each hour in the same way as in the MedKits model.

4.2 Changes to the Model

Each person in a compartment has the same probability of making a transition. The transition of that individual can be represented with a Bernoulli random variable. A positive result means the individual moves, and a negative result means he does not. Thus, the transitions of the entire compartment can be modeled as a binomial random variable with parameters n and p, where n is the number of people in the compartment and p is the probability of the transition. All of the transitions

relating to disease progression, recovery, death, and awareness are controlled by probabilities and can be modeled with binomial random variables.

The transitions to prophylaxis and treatment depend upon the availability of antibiotics and supplies. These transitions are not made randomly in the same way as the others. We assume that people cannot enter prophylaxis or treatment if the supplies are not available to them. But if there are people waiting, and the supplies become available, people will certainly transition into prophylaxis or treatment up to capacity.

A binomial random variable requires an integer for the parameter n, as it represents a number of trials. One of the biggest changes to the model is ensuring that all compartments contain an integer number of people at all times so that we are able to calculate binomial random variables for the appropriate transitions. This begins with reformulating the initial conditions to produce only integer compartment values at the start of our simulation.

4.2.1 Initial Conditions

As described in Section 3.4, P is the population size, N is the number of people exposed to the anthrax, M is the number of MedKits distributed, p_M is the 95% of those with MedKits that are able to find and use them, and β is the fraction of unexposed people who believe they have been exposed. We initially place people only in compartments 1, 18, 19, 23, and 25. We would like to place integer numbers of people in these compartments while still nearly approximating the ratios

determined by the input parameters. Instead of using the equations given in Section 3.4, we calculate the numbers in the compartments in the following manner.

Because they represent people, we assume the input parameters P and N are integers. We know the total number not exposed is $P - N$. We must break this group into those who know they were not exposed and those who believe they were. We first calculate a rounded number that know they were not exposed by

$$X_{18}(0) = round[(P - N)(1 - \beta)]. \tag{4.1}$$

So we now assume $P - N - X_{18}(0)$ is the total number who have not been exposed but think they have been. These people are broken into two compartments based on whether they have a MedKit. We calculate the number with MedKits who think they have been exposed but actually have not as

$$X_{23}(0) = round[\frac{Mp_M}{P}(P - N - X_{18}(0))]. \tag{4.2}$$

Since both of the above groups have been rounded to the nearest whole number, we calculate the number who believe they have been exposed and do not have a MedKit as the difference

$$X_{19}(0) = P - N - X_{18}(0) - X_{23}(0). \tag{4.3}$$

Similarly, we know that N is the number of people exposed, and they are broken into two groups either with or without MedKits. Those with MedKits are calculated by

$$X_{25}(0) = round[\frac{Mp_M}{P}N]. \tag{4.4}$$

Then we simply calculate the number without MedKits to be

$$X_1(0) = N - X_{25}(0). \tag{4.5}$$

Calculating the initial conditions in this way guarantees that as long as P and N are input as integers, each compartment begins with an integer number of people.

4.2.2 Stochastic Transitions

As stated above, all transitions relating to disease progression, death, and recovery can be modeled with binomial random variables. In the MedKits model, the expected number for each transition is defined to be the number of people in the compartment multiplied by the probability of the transition. In general, we change each of these to a binomial random variable with parameters n equal to $X_i(t)$ and p equal to the transition probability. However, there are a few issues that need to be considered.

There are some transitions in the model which move people from the same compartment into two other compartments. For example, from compartment 13 (people in the prodromal stage receiving treatment) a person could transition to either compartment 17 (recovery) or compartment 14 (fulminant). Each of these transitions should be modeled with a binomial random variable. Each of these random variables will be a number between 0 and $X_i(t)$. This leads to the possibility that the sum of the two transitions could be greater than $X_i(t)$. This means there are fewer people in compartment 13 than we are attempting to move.

To address this issue, we use a two-stage calculation method. For each com-

partment with more than one transition from it, we first calculate the number of people who will leave the compartment for all transitions. We then calculate the number of those transitions that will be of each type. Consider the following example. We denote a binomial random variable with parameters n and p as described by $B(n, p)$. The number of people in compartment 13 at time t is $X_{13}(t)$. People in compartment 13 move to compartment 14 with probability 1/122.4 and to compartment 17 with probability 1/21.7. We calculate the number of people that will move out of compartment 13 ($M_{13}(t)$) due to either transition at time t as

$$M_{13}(t) = B(X_{13}(t), 1/122.4 + 1/21.7). \tag{4.6}$$

We generate a second binomial random variable to determine how many of these transitions will be to compartment 14 by

$$\phi_{13,14}(t) = B(M_{13}, \frac{1/122.4}{1/122.4 + 1/21.7}). \tag{4.7}$$

We then calculate the number of transitions to compartment 17 as the difference between $M_{13}(t)$ and $\phi_{13.14}(t)$. This process preserves the distributions of transitions while preventing the rare case in which the sum exceeds the number of people available to transition. A similar result could be obtained by calculating a multinomial random variable with a probability vector containing the probabilities of all the possible transitions as well as the probability of remaining in the initial compartment.

For the transitions from prodromal to fulminant that depend on length of time in the prodromal stage, it is not possible to correctly represent two populations with two different rates of transition as a single binomial random variable. So instead, we separate each calculation into two random variables. Consider compartment 2. We

estimate the number of people in the compartment that have entered within the last 72 hours, $N_2(t)$, by taking the minimum of the number in the compartment and the number counted in the last 72 hours ($count_2(t)$). We calculate the number of these people who will move as $B(N_2(t), \gamma)$. The number of people in the compartment who have been there for more than 72 hours is $X_2(t) - N_2(t)$. The number of these who will transition is $B(X_2(t) - N_2(t), \eta)$. The total number of transitions $\phi_{2,3}(t)$ is the sum of these two random variables.

The following is a list of all of the transitions related to disease progression, recovery and death in the simulation model. For i = 1, 4, 7, and 25,

$$\phi_{i,i+1}(t) = B(X_i(t), p(t)). \tag{4.8}$$

For i = 2, 5, and 26,

$$N_i(t) = \min\{X_i(t), count_i(t)\}, \tag{4.9}$$

$$\phi_{i,i+1}(t) = B(N_i(t), \gamma) + B(X_i(t) - N_i(t), \eta). \tag{4.10}$$

For (i, j) pairs $(8, 10)$, $(9, 11)$, and $(13, 14)$,

$$M_i(t) = B(X_i(t), 1/122.4 + 1/21.7), \tag{4.11}$$

$$\phi_{i,j}(t) = B(M_i(t), (1/122.4)/(1/122.4 + 1/21.7)), \tag{4.12}$$

$$\phi_{i,17}(t) = M_i(t) - \phi_{i,j}(t). \tag{4.13}$$

For i = 14 and 15,

$$M_i(t) = B(X_i(t), 1/720 + 1/24), \tag{4.14}$$

$$\phi_{i,17}(t) = B(M_i(t), (1/720)/(1/720 + 1/24)), \tag{4.15}$$

$$\phi_{i,22}(t) = M_i(t) - \phi_{i,17}(t). \tag{4.16}$$

For i = 16,

$$M_{16}(t) = B(X_{16}(t), 1/720 + 1/38.4), \tag{4.17}$$

$$\phi_{16,17}(t) = B(M_{16}(t), (1/720)/(1/720 + 1/38.4)), \tag{4.18}$$

$$\phi_{16,22}(t) = M_{16}(t) - \phi_{16,17}(t). \tag{4.19}$$

For i = 3, 6, 10, 11, and 27,

$$\phi_{i,22}(t) = B(X_i(t), 1/26.4). \tag{4.20}$$

And for i = 12,

$$\phi_{12,22}(t) = B(X_{12}, 1/38.4). \tag{4.21}$$

For each iteration of the simulation, the model generates values from all of the transition equations $\phi_{ij}(t)$ and then generates the intermediate values $Y_i(t)$ as in the MedKits model using equation 3.11.

4.2.3 Prophylaxis and Treatment Transitions

The transitions based on awareness can be calculated with the same binomial random variable technique. We calculate transitions for the compartment pairs $(2, 5)$, $(3, 6)$, $(26, 9)$, $(27, 12)$, $(1, 4)$, $(19, 20)$, and $(23, 24)$ using $B(n, p)$ where n is the number in the compartment and p is the probability of becoming aware.

For the transition from compartment 25 to awareness (when we make the decision of adherence to prophylaxis), we use a two-stage calculation similar to the one described above. We calculate the number that will move from compartment 25 based on the probability of awareness, 1/72, as $M_{25}(t) = B(Y_{25}(t), 1/72)$. Then we

calculate a second random variable with probability α that they adhere and move to compartment 28, $\psi_{25,28}(t) = B(M_{25}(t), \alpha)$. The number moved to compartment 7 is the difference between $M_{25}(t)$ and $\psi_{25,28}(t)$.

As stated at the beginning of this chapter, the transitions to prophylaxis and treatment are not random but controlled by the availability of medication and supplies. It would be inappropriate to model these transitions with binomial random variables. However, because people transition from these compartments into other compartments where transitions are determined by binomial random variables, it is important that we ensure that these transitions are all integers. This also makes sense in the real scenario since there is not a situation where half a person could move into treatment.

The way we handle this issue is as follows. First we calculate those moving to treatment. The treatment capacity, $CT(t)$, and the probability of being treated from any individual compartment, $\pi(t)$, are the same as in the MedKits model. We find an initial number to move from each compartment i by taking the floor of $Y_i(t)\pi(t)$. Because there are seven compartments from which people can move into treatment (5, 6, 8, 9, 10, 11, and 12) and we took a floor function for each, we could have enough capacity to move up to six more people into treatment (depending on how large the remainder was for each floor function). To divide up this remaining capacity we iterate until the number moved is the largest integer less than $CT(t)$. Each time we use a multinomial random variable to choose one of the seven compartments to draw another person from (first checking that that compartment has another person available). This ensures that we do not move more

people from a compartment than are in that compartment. It also maintains integer numbers of people in all compartments while still distributing treatment across the compartments approximately according to $\pi(t)$.

We follow the same procedure for calculating the number who will move into prophylaxis. There are four compartments (4, 5, 6, and 20) containing people waiting for prophylaxis. We first subtract the number that moved into treatment from compartments 5 and 6. We calculate the capacity, $CP(t)$, and probability of moving into prophylaxis, $\rho(t)$, as in the MedKits model. We then calculate the initial transitions using the floor function of $Y_i(t)\rho(t)$, and then distribute any additional prophylaxis randomly among the four compartments. As for compartment 25, once we calculate the number moving from compartment 4 into prophylaxis we use a binomial random variable to determine the number moving to compartments 28 and 7.

At each iteration of the model, we generate values for the transitions using the equations $\psi_{ij}(t)$ and then calculate $X_i(t+1)$ using equation 3.12 from the MedKits model.

Chapter 5

Results

We conduct a number of computational experiments with the following goals in mind. First, we aim to show that the MedKits model is a useful tool for predicting the impact of distributing MedKits before an attack. Second, we would like to evaluate the accuracy of the MedKits model results by comparing them with the results of the simulation model. The results in this chapter reflect specific scenarios on which the model was tested. We attempt to model relevant changes to all important parameters. The model can, however, be used to model other scenarios as needed.

5.1 MedKits Model

This section discusses results and observations related to the deterministic MedKits model. All numbers are the expected numbers of deaths for specific scenarios.

5.1.1 Scenarios

We run the MedKits model using the set of scenarios described by Zaric et al. [18]. Any of these assumptions can easily be changed to model different scenarios. We assume a population size of 5,000,000 people. We consider three sizes of attacks

in which 50,000, 500,000, and 1,250,000 people are exposed. We consider three possible values for β (the fraction of people who believe they are exposed but are not). These β values are 0.01, 0.1, and 0.5. Different sources cite both 90% and 65% prophylaxis adherence rates, so we consider both. We also consider push pack arrival either 12 hours or 24 hours after time of detection (Zaric et al. [18] uses both, though the CDC [7] states the push pack can be delivered anywhere in under 12 hours). We consider the number of MedKits distributed prior to an attack in 11 increments of 500,000 between 0 and 5,000,000. Zero MedKits corresponds closely to the model of Zaric et al. [18], while 5,000,000 MedKits corresponds to the entire population receiving MedKits prior to attack (though we still assume only 95% have access to their MedKits, and the rest will need to go to a POD to receive prophylaxis [8]). We test every combination of these parameters for a total of 396 scenarios.

5.1.2 Results

Tables 5.1, 5.2, and 5.3 give charts with the full results of these simulations. In every scenario, increasing the number of MedKits distributed decreases the expected number of deaths.

Table 5.1: Data results from MedKits model, $N = 50000$. This table shows the expected number of deaths for each scenario described by N, β, α, and Tpush, the time until the push pack arrives. For each scenario we tested MedKit distribution levels in intervals of 500,000 from 0 to 5,000,000.

				Medkits Distributed										
N	β	α	Tpush	0	500000	1000000	1500000	2000000	2500000	3000000	3500000	4000000	4500000	5000000
50000	0.01	0.65	12	5686	5668	5651	5635	5620	5607	5594	5581	5570	5562	5555
50000	0.01	0.9	12	4247	4227	4208	4191	4174	4159	4144	4131	4118	4109	4102
50000	0.01	0.65	24	5816	5782	5750	5719	5690	5662	5636	5611	5587	5564	5555
50000	0.01	0.9	24	4395	4357	4320	4285	4252	4221	4191	4163	4137	4112	4102
50000	0.1	0.65	12	6179	6028	5908	5813	5740	5684	5641	5609	5585	5568	5555
50000	0.1	0.9	12	4822	4648	4509	4400	4315	4250	4200	4163	4136	4116	4102
50000	0.1	0.65	24	6396	6214	6064	5943	5846	5768	5706	5657	5617	5585	5559
50000	0.1	0.9	24	5068	4858	4686	4546	4434	4345	4274	4217	4171	4135	4107
50000	0.5	0.65	12	20404	17263	14353	11739	9502	7734	6543	6010	5718	5596	5558
50000	0.5	0.9	12	19659	16395	13367	10642	8304	6451	5199	4617	4288	4149	4105
50000	0.5	0.65	24	20905	17733	14785	12121	9821	7977	6693	6099	5771	5620	5564
50000	0.5	0.9	24	20182	16886	13819	11043	8642	6709	5358	4717	4348	4176	4113

Table 5.2: Data results from MedKits model, $N = 500000$. This table shows the expected number of deaths for each scenario described by N, β, α, and Tpush, the time until the push pack arrives. For each scenario we tested MedKit distribution levels in intervals of 500,000 from 0 to 5,000,000.

				Medkits Distributed										
N	β	α	Tpush	0	500000	1000000	1500000	2000000	2500000	3000000	3500000	4000000	4500000	5000000
500000	0.01	0.65	12	63174	61528	60193	59120	58266	57591	57059	56649	56343	56122	55964
500000	0.01	0.9	12	49533	47665	46147	44927	43958	43193	42592	42129	41787	41541	41368
500000	0.01	0.65	24	65358	63414	61800	60472	59386	58501	57781	57191	56709	56319	56006
500000	0.01	0.9	24	51996	49793	47960	46452	45219	44216	43401	42736	42196	41760	41414
500000	0.1	0.65	12	76251	71074	66879	63565	61051	59228	57960	57105	56539	56183	55977
500000	0.1	0.9	12	64094	58361	53684	49967	47129	45062	43621	42650	42011	41610	41382
500000	0.1	0.65	24	79074	73534	68984	65322	62470	60334	58789	57701	56941	56406	56034
500000	0.1	0.9	24	67227	61103	56040	51939	48729	46310	44557	43321	42461	41860	41446
500000	0.5	0.65	12	229042	195316	163617	134524	108788	87369	71427	62385	58357	56585	56011
500000	0.5	0.9	12	222153	187225	154364	124162	97387	75022	58258	48563	44075	42069	41420
500000	0.5	0.65	24	233684	199732	167743	138275	112057	90017	73288	63335	58943	56863	56088
500000	0.5	0.9	24	226983	191824	158667	128084	100816	77817	60247	49619	44733	42382	41506

Table 5.3: Data results from MedKits model, $N = 1250000$. This table shows the expected number of deaths for each scenario described by N, β, α, and Tpush, the time until the push pack arrives. For each scenario we tested MedKit distribution levels in intervals of 500,000 from 0 to 5,000,000.

				Medkits Distributed										
N	β	α	Tpush	0	500000	1000000	1500000	2000000	2500000	3000000	3500000	4000000	4500000	5000000
1250000	0.01	0.65	12	243624	213235	189537	173737	162312	153842	147982	144243	142010	140733	140083
1250000	0.01	0.9	12	216219	183985	158606	141316	128620	119132	112517	108275	105743	104303	103578
1250000	0.01	0.65	24	253854	221752	196081	178592	166319	157012	150346	145889	143073	141327	140245
1250000	0.01	0.9	24	227143	193154	165752	146714	133099	122692	115182	110132	106937	104967	103758
1250000	0.1	0.65	12	316532	270358	230672	198544	175337	161549	152082	146040	142639	140898	140099
1250000	0.1	0.9	12	291942	243554	201803	167786	142910	127711	117135	110321	106461	104491	103596
1250000	0.1	0.65	24	328062	280588	239381	205470	180140	165061	154736	147876	143778	141511	140272
1250000	0.1	0.9	24	304099	254384	211076	175234	148181	131626	120113	112390	107744	105178	103788
1250000	0.5	0.65	12	611627	526042	444727	368867	300062	240478	193028	161455	147731	141927	140169
1250000	0.5	0.9	12	595527	506917	422662	343974	272483	210406	160726	127290	112207	105665	103675
1250000	0.5	0.65	24	621907	535902	454053	377507	307809	247048	198038	164414	149281	142661	140368
1250000	0.5	0.9	24	606221	517182	432382	352995	280593	217315	166039	130503	113942	106493	103898

5.1.3 Analysis

The parameter α has a generally linear effect on the number of deaths. With a lower adherence rate, more people are expected to die, but the difference is relatively constant across the MedKit distribution. This is reasonable since adherence is not at all dependent on where a person gets his prophylaxis.

The time lag until the push pack arrives affects the data as expected. More people will die with a 24-hour delay than with a 12-hour delay. Higher MedKit distribution does help to close this gap. For example, we consider the scenario in which 1,250,000 people are exposed, $\alpha = 0.9$, and $\beta = 0.5$. With no MedKits, the expected number of deaths for $t = 12$ is 595,527 compared with 606,221 for $t = 24$, a difference of 10,694 lives. With MedKits distributed to the entire population, the number of deaths for $t = 12$ is 103,675 compared with 103,898 for $t = 24$. The MedKits reduce the difference in deaths to just 223 lives. The reason for this result is that with MedKits, most people do not have to wait for the push pack to arrive to begin prophylaxis. They can begin as soon as they become aware of their exposure. The small remaining difference in deaths can be attributed to the 5% of people who are unable to use their MedKits and are therefore affected by the delay in the push pack arrival.

Fig. 5.1 gives a graph showing trends in the data. In this graph, we consider six of the scenarios. All were for $\alpha = 0.65$ and $t = 24$ hours until the push pack arrives. We consider the cases where $N = 50,000$ and $N = 1,250,000$ for each of the three possible values of β. The graph shows the percentage of those who were

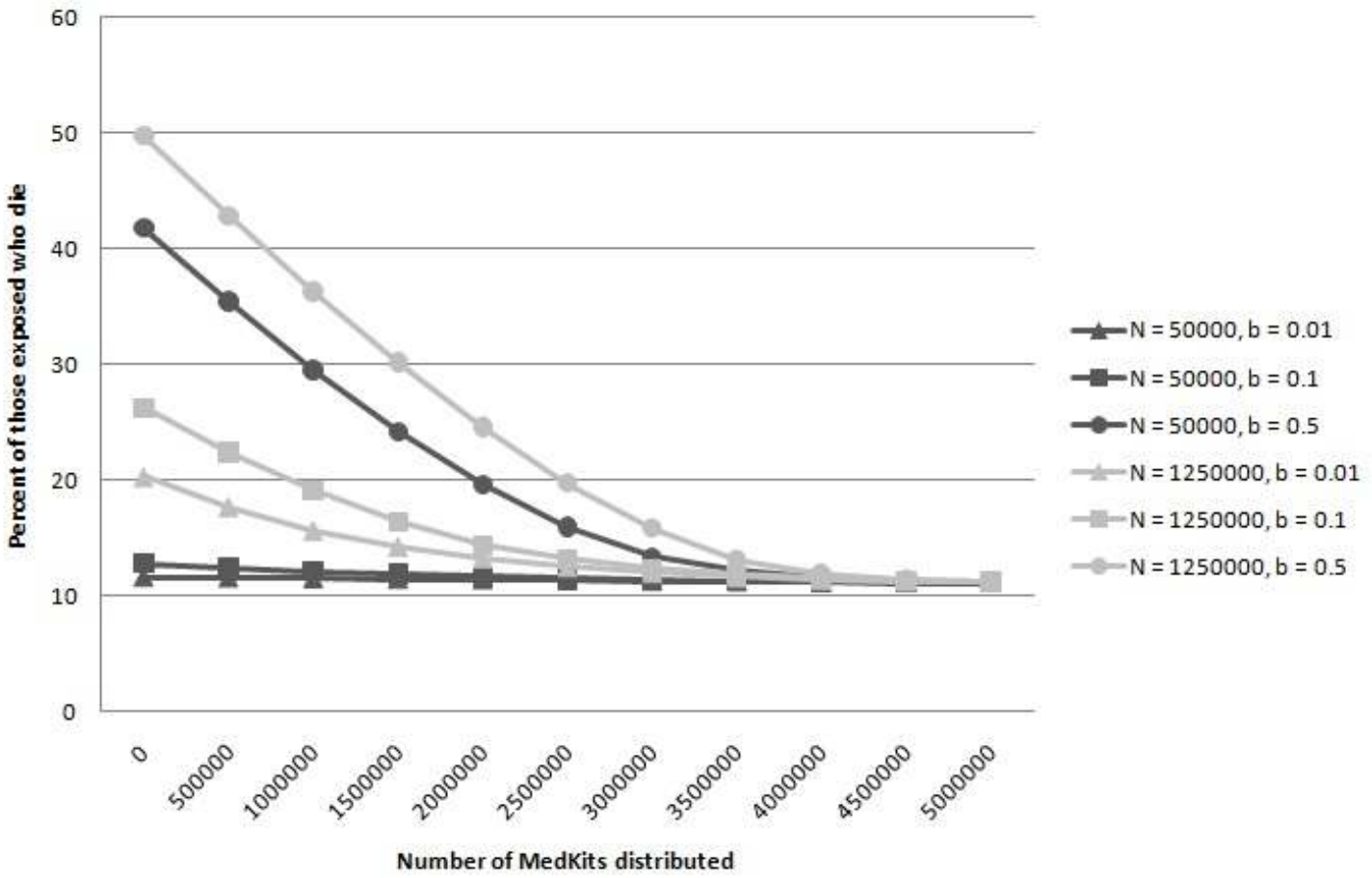


Figure 5.1: This chart shows the expected percentage of those infected that die in six chosen scenarios. In all of these scenarios, $\alpha = 0.65$ and $t = 24$ hours.

infected that are expected to die. In every scenario, as the number of MedKits increased, the deaths decreased.

The data makes it obvious that the number of people exposed is directly related to the number of people expected to die. However, it also reveals that with larger exposures, a larger fraction of those exposed will die if no MedKits are distributed. For example, we compare the cases where $N = 50,000$ and $N = 1,250,000$ with all other parameters equal ($\alpha = 0.9$, $\beta = 0.5$, and $t = 12$). With no MedKits, the percent of those exposed who die is 39.3% for the smaller exposure compared with 47.6% for the larger exposure. However, with the whole population receiving MedKits, the expected percentages are 8.210% and 8.294% respectively. Distributing the MedKits makes the percentage difference almost imperceptible.

The fraction of those not exposed who believe the have been, β, seems to be the parameter with the biggest effect on the results. When no MedKits are distributed, larger values of β force significantly higher death percentages. For example, as shown in Fig. 5.1, with $\alpha = 0.65$, $t = 24$, and $N = 1,250,000$, the percentage of those exposed who will die is 20.3% (253,854 people) with $\beta = 0.01$ compared to 49.8% (621,907 people) with $\beta = 0.5$ when no MedKits are distributed. This means that more than twice as many people are expected to die in the same scenario, just because a much larger number of people believe they were exposed. Distributing MedKits to the entire population reduces these percentages to 11.220% and 11.229% respectively (a difference of just 123 people). The MedKits have a drastic effect on the outcome in this case.

In both of the above situations, the reason for the trends has to do with the

queue for prophylaxis. Both larger exposures and larger groups who believe they have been exposed cause larger numbers of people to seek prophylaxis. In the case of larger β, many of these people that seek and receive prophylaxis do not actually need it and could be taking it away from people who do need it. Because the supply of prophylaxis is limited, especially early in the scenario, many people who need prophylaxis are forced to wait for it. Beginning prophylaxis as early as possible is key to survival, so when these people must wait, their risk of death increases greatly. The greatest benefit of the MedKits is that most of the people who have them can begin prophylaxis immediately upon becoming aware. They do not get in the queue, and the queue remains small for the remaining people who do have to seek this source of prophylaxis. As a result, distributing any number of MedKits reduces the deaths, but distributing them to the entire population virtually eliminates the differences in death percentages caused by exposure size or β size with all other parameters equal.

The MedKits reduce the number of deaths in every scenario. They have the largest effect on scenarios in which the number of people exposed or potentially exposed is high. They also act as a defense against unexpected delays in prophylaxis dispensing.

5.2 Simulation Model

The goal of the stochastic Simulation Model is to generate data which can be compared to the MedKits model data to evaluate its accuracy. Because of the

increased runtime from generating so many random variables, it is impractical to test all 396 scenarios presented for the deterministic model. Instead we choose a selection of scenarios that are representative of the whole collection. We run the Simulation Model for the following nine scenarios. For all, we let $\alpha = 0.65$, $\beta = 0.1$ and $t = 12$. We test each of the three values of N with $M = 0$, 2,500,000, and 5,000,000. For each scenario, we run 100 replications. We determine the average number of deaths for the 100 replications of the scenario and compare this with the deterministic result. Table 5.4 shows the results of this analysis.

The data in Table 5.4 shows that even when all transitions not based on capacity are allowed to vary, there is very little change in the results. Seven of the nine scenarios tested have the deterministic result fall within the 95% confidence interval of the average result from the simulation model. Even for those in which the deterministic result was not within this confidence interval, the percent difference between the deterministic and average number of deaths is extremely small (the largest percent difference being only about 1/3 of a percent). These results provide confidence that the MedKits model can accurately predict the expected number of deaths in an attack scenario.

The deterministic MedKits model is the more valuable model for decision-making purposes. However, the simulation model adds credibility to the results of the MedKits model. It shows that across a variety of scenarios, the MedKits model consistently and accurately predicts the expected number of deaths.

Table 5.4: Simulation model results. For all scenarios, $\alpha = 0.65$, $\beta = 0.1$, and $t = 12$ hours. Column 6 gives a 95% confidence interval around the average. Column 7, Difference, is Average - Deterministic. Column 8 states whether the deterministic result falls within the 95% confidence interval of the average. Column 9, is the percent deviation between the deterministic and the average, calculated as 100*Difference/Average.

Scenario		Number of Deaths						
N	M	Deterministic	Average	Std. Dev.	95% Conf. Int.	Difference	In C.I.	% Deviation
50,000	0	6,179	6,185.56	71.87	±15.07	6.56	Yes	0.016
50,000	2,500,000	5,684	5,703.3	76.17	±14.93	19.3	No	0.338
50,000	5,000,000	5,555	5,561.78	72.52	±14.21	6.78	Yes	0.122
500,000	0	76,251	76,223.98	236.70	±46.39	-27.02	Yes	-0.035
500,000	2,500,000	59,228	59,265.85	261.24	±51.20	37.85	Yes	0.064
500,000	5,000,000	55,977	56,011.12	217.71	±42.67	34.12	Yes	0.061
1,250,000	0	316,532	316,346.28	373.33	±73.17	-185.72	No	-0.059
1,250,000	2,500,000	161,549	161,558.24	368.88	±72.30	9.24	Yes	0.006
1,250,000	5,000,000	140,099	140,044.86	318.48	±62.42	-54.14	Yes	-0.039

5.3 Run Time Results

Both models were run in Matlab, version 2009a on a 2.8GHz Intel Pentium 4 processor with 512MB RAM and Fedora Core 5 operating system. For the MedKits model, the time per run was relatively consistent over all scenarios with an average time of 1.238 seconds. The simulation model was much slower due to the generation of thousands of binomial random variables. The time per replication was directly related to the number of people exposed. For the scenarios with 50,000 people exposed, the average run time was approximately 14.7 seconds. For 500,000 exposed, the time increased to an average of 26.8 seconds. And for 1,250,000 exposed, the times averaged 49.4 seconds. The average times were slightly lower for the scenarios with more MedKits distributed. Table 5.5 contains a summary of all the runtime results.

Table 5.5: We show the runtime results for both models. The top portion shows the number of seconds for a single run in each scenario calculated as the average over the 100 runs of that scenario. The bottom portion shows the average number of seconds for a single run of the MedKits model.

Averages over 100 Simulation Model Runs			
	M values		
N values	0	2,500,000	5,000,000
50,000	15.118	14.594	14.319
500,000	27.835	26.343	26.124
1,250,000	54.489	47.743	46.073

Average over 396 MedKit Model scenarios
1.238

While the simulation model can take hours to run enough replications to obtain an average result, the deterministic model is very fast. Given a specific scenario, the expected number of deaths can be calculated in a matter of seconds, making this model very practical as a tool for predicting attack scenario outcomes.

Chapter 6

Conclusions

6.1 Summary

We have discussed two new compartmental models to simulate anthrax attacks. The first is based on the model developed by Zaric et al. [18]. It has significant changes that clarify aspects of the original model and extend it to consider the effect of distributing MedKits prior to attack on the expected number of deaths. The model contains 28 compartments representing various disease and treatment stages. Transitions between the compartments are calculated deterministically based on probabilities of progressing (for disease stages, recovery, death, and awareness) and capacity (for prophylaxis and treatment).

We ran the model on a variety of attack scenarios, and showed that in every case, distributing more MedKits prior to an attack reduces the expected number of people who die. We saw that the number of people exposed and the number of unexposed people who believe they were have the largest affect on the number of deaths. When these numbers are large, the number of deaths, as well as the percentage of those exposed who die are both larger. Distributing MedKits to the entire population minimizes the effects of these parameters. With all other parameters the same, a scenario with a small number exposed and a scenario with large number exposed have large differences in percent of exposed who die without

MedKits, but when MedKits are distributed to the whole population, the percent who die is almost identical between the scenarios. A similar result occurs in like scenarios where β is varied. The most valuable benefit of MedKits seems to be that they reduce the competition for prophylaxis. They remove people from the prophylaxis queue, making that medication available to others who need it.

These results show that MedKits are always effective in reducing the number of deaths in an anthrax attack, but the impact is amplified in situations where large numbers of people are exposed or believe they are. Further research may show that MedKits are particularly desirable in large cities, where both these parameters are likely to be high and the competition for prophylaxis will be greater.

The second model is used to verify that the MedKits model results are accurate. This model considers stochastic transition equations rather than the deterministic probability based transitions of the MedKits model. We model the transitions relating to disease progression, recovery, death, and awareness using binomial random variables. We reformulate the initial conditions as well as the prophylaxis and treatment transitions to ensure that every compartment always contains an integer number of people (a requirement for the binomial random variable).

We ran this model over a selection of the scenarios used for the MedKits model. We used 100 replications for each scenario and calculated the average number of deaths. Analysis showed that in every case the deterministic result yielded by the MedKits model was very close to the average from the simulation model. In seven of the nine scenarios tested, the deterministic result was within a 95% confidence interval around the average result, and in all of the cases the percent difference

between the two was less than 1/2 of a percent.

The MedKits model runs very quickly, allowing the results of a scenario to be calculated in just seconds. The simulation model is much slower, but we were able to use it to gather results verifying the MedKits results.

The MedKits model is limited by the accuracy of the input parameters. In particular, it is difficult to be certain how many people are infected in an attack because those that never leave the incubation stage appear the same as those who are not infected. At best, the parameters N and β are estimates based on the current available data. Also, we consider two prophylaxis adherence rates, 65% and 90%, but is difficult to predict what the actual adherence rate will be as it depends on the individuals in the population. Obviously the more precise the scenario and the flow variables are, the more accurate the result will be. The model is designed in such a way that new data about disease progression assumptions or other scenarios could easily be incorporated.

From these results, we conclude that the MedKits model is a good approximation of what happens in an anthrax attack and can be trusted as a source of estimated deaths. Local governments can be confident that, assuming input parameters are chosen carefully, the MedKits model will give reliable results quickly.

6.2 Contributions

The main contribution of this model is the integration of both disease progression and emergency logistics. The original model [18] does this, and the MedKits

model extends it to include another element of emergency preparedness. The model could be extended further to consider other aspects as well. Although both compartmental models and simulation models have been used to model anthrax attack response logistics, we believe this to be the first use of stochastic simulation to enhance a compartmental model in this setting.

The model provides a good balance of detail with simplicity. The compartmental design makes the model intuitive while still allowing the many intricacies of attack scenarios to be modeled. This allows the model to be accessible to public officials that may not have a rigorous mathematical modeling background, but still incorporates enough detail to make it useful. The model does make some assumptions that are more simplistic than the situation being modeled (e.g. making the number infected an input parameter rather than using a diffusion model to determine who would be affected by a specific point source attack). However it is designed in such a way that more complexity can be added if desired without redesigning the entire model.

The model gives national, state, and local public health officials a tool to evaluate plans for implementing MedKit distribution into emergency planning. While officials still need to carry out their own investigations and cost evaluations, this gives them a source of data about the effects of the MedKits in particular scenarios.

6.3 Future Work

There are several clear extensions to this work. One of the goals of the model is to aid local governments in making decisions about whether to distribute MedKits in their communities. The model shows the benefits of MedKit distribution, but another big aspect of the decision making process is the cost. This is something that varies by community based on its size and its plans to pay for the MedKits, so we leave the cost analysis to individual jurisdictions. Some things that would need to be included in the decision is how to handle expiration dates of the medication as well as the fear that people would take the pills without being told and develop resistance to them. Bicknell discusses these kinds of issues [2].

Another consideration in developing a response plan is the public's attitude. Studies have been carried out to evaluate such public perceptions. Rincuiuso-Hasslemann et al. [14] discuss a series of surveys conducted in New York to evaluate the public's opinions about various response measures. Thoughts are presented on how to increase the prophylaxis adherence rate. The CDC's study of MedKit distribution [8] included a survey of participants' opinions about MedKits. In that study, 94% of participants said they would like to have MedKits in their homes.

For the models in this report, we assumed most of the parameters to be constant. For example, we assumed a constant adherence rate throughout the model, but it could be easily adjusted to incorporate α changing over time. Also, the time of detection is fixed at $t = 48$ hours after attack. However, an attack is typically discovered only when a person becomes ill. To make the model more realistic, the time

of detection could be determined by considering transitions to the prodromal stage. The BioSense system has been developed to track outpatient visits, prescriptions and laboratory orders with an eye toward detecting attacks as early as possible [6]. Including this system in the model would lead to dynamic detection time simulation.

For the simulation model we varied the transitions. Another logical simulation would be to vary the arrival times of the push pack and VMI. For example, we consider two possibilities for arrival time of the push pack (12 and 24 hours), however [7] states that the push pack can be delivered within 12 hours. So there is some probability that it could arrive in under 12 hours depending on the distance it has to travel, traffic, and other unpredictable factors. Because time is a huge factor in preventing deaths, simulation of these time variations would be of great interest.

The MedKits model could be integrated with a dispersion model for the spread of spores [6, 16]. This dispersion model could include weather data as well as population density in different areas to determine the likely number of people infected. This would allow for health officials to determine the likely results of an attack in a specific location without having to do their own study of how many people would be affected to determine an input number of infected individuals.

While the MedKits model is specifically designed to model an anthrax attack, it could be adjusted to model different noncommunicable diseases. With more elaborate changes, the model could be made to reflect endemic diseases as well.

Obviously the possibilities for further advances are endless. As new emergency plans are developed they will need to be modeled and evaluated. The model we have developed provides a stand-alone tool for health officials to use in evaluating their

own emergency preparedness plans and hopefully provides enough flexibility to be integrated with other models as needed in the future.

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