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Mathematical Models for Infectious Disease Transmission with Stochastic Simulation of Measles Outbreaks

An Honors Thesis submitted in partial fulfillment of the requirements for Honors in
Mathematics.

By

Valerie Welty

Under the mentorship of Patricia Humphrey, Ph. D.

Abstract

As they are the leading cause of death among children and adolescents worldwide, it is of extreme importance to control the spread of infectious diseases. Information gained from mathematical modeling of these events often proves quite useful in establishing policy decisions to accomplish this goal. Human behavior, however, is quite difficult to recreate when using equations with pre-determined results, such as deterministic differential equations often used with epidemic models. Because of this, the focus of the research was to create a simulation of an outbreak, specifically of measles, by using an imaginary population experiencing simulated stochastic events on a discrete time scale. This allows us to model a more complex population, which includes various levels of immunization as well as different stages of infection. Another major factor that the program accounts for is the phenomenon of self-quarantine during a disease outbreak. An important supplement to mathematical analysis, the results from the program may provide new insight on dynamics of epidemics such as herd immunity and effective disease transmission.

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1 Introduction

Infectious disease has played a huge role in the shaping of history, even before the common era. Infections such as smallpox, leprosy, tuberculosis, meningococcal infection and diphtheria appear to have occurred in ancient Greek and Egyptian civilizations [1]. Scars attributed to smallpox have been found on Egyptian mummies dating back as far as 1570-1085 BCE, and may have killed Ramses V, the pharaoh of the 20th dynasty [1]. In pre-modern Europe, the development of civilization was impacted by the massive epidemics of Bubonic plague, which killed nearly 24 million Europeans. This and other plagues killed 90% of Europeans by 1110 CE, and also may have led to the collapse of the Han Empire in China [1]. Some of the political and sociological consequences of infectious disease can be seen in the era of colonization, where self-proclaimed discoverers brought infection to indigenous people, or vice versa. If the colonizers had developed some kind of immunity to an infection, introducing it into the susceptible native populations resulted in the death of large numbers of the native people. In many cases, colonizers were fighting to control the land and the people they “discovered,” and these deaths allowed for greater success in such a mission.

Sometimes, the opposite occurred; explorers would contract foreign infections from the native people and bring them back to their homeland. The infection would spread rapidly as they returned, if immunity was not existent in their home population. This is what may have begun the practice of quarantine, one of the first methods of infectious disease control. Early methods involved the requirement of ships to remain offshore for 40 days upon returning from a journey, before they were allowed to dock and unload [25]. This practice was first seen in the 14th century, and was generally only required of ships who were suspected of carrying major infections, such as the plague and influenza. Methods of quarantine would develop in different ways, such as the requirement of captains to prove the health of their sailors and the origin of any materials they brought back with them [2]. Such practices are still used in modern

times, to a certain extent. Currently, several infections in the United States remain listed as quarantine infections, where forced containment of infected individuals is permitted to stop the spread of the infection. This practice has continued to be effective in some cases, such as the prevention of an outbreak of Ebola in the US in 2014. Only a handful of infections resulted from an infected individual who had returned to the US after contracting Ebola while working in Liberia.

However, the greatest progress in not only disease prevention but towards disease eradication came as a result of vaccination. The first instance of intentional vaccination appears in an experiment performed by Edward Jenner in 1796 [4]. He noticed that milkmaids infected with cowpox did not become infected in smallpox outbreaks, and tested his hypothesis of immunity by innoculating a young boy with pus from a cowpox lesion. Jenner then directly exposed the boy to the smallpox virus, and he did not become infected. This and later experiments by Jenner formed the basis for the development of vaccines for a number of major infections. Since then, global vaccination policies have experienced radical success in infectious disease reduction. The introduction of the Polio vaccine in the 1950's has resulted in near eradication of the disease on a global scale. No cases of polio – caused by the wild virus – have occurred in the United States since 1993 [25]. The fully developed vaccine for Smallpox may be the largest success story of vaccination to date, as it has been declared eradicated globally; the only threat which seems to remain is its possible use in biological warfare. Yet another example of the success of vaccination is seen in the United States with measles, which was declared eliminated in 2000; however imported cases do cause yearly outbreaks.

Despite this, infectious disease continues to remain a large problem, especially given the challenges of world travel, anti-vaccination movements, and quickly developing new strains of infection. It remains globally the number one killer of infants and children, as 50% of under 5 deaths are due to infectious disease. In 2010, the

number of global deaths due to infectious disease was 15 million, which is only a small decrease from 1990 where 16 million deaths were observed [3]. Two-thirds of these deaths in 2010 were caused by only 20 out of about 1400 known pathogens, including infections such as Tuberculosis and HIV, which are the leading causes of infectious disease deaths. Infections with known vaccinations still occur in large numbers as well, especially in countries where vaccines are difficult to obtain. In developed countries, vaccination levels for the MMR vaccine, the vaccination for measles, mumps and rubella, and for other vaccines remain relatively high. Yet, the recent issue with anti-vaccination movements may threaten the low levels of infections especially in the US. One cause of anti-vaccination movements in the United States is the increasingly prevalent fear of the existence of adverse reactions to vaccines, particularly the MMR vaccine. A study published in 1998 by English scientist Andrew Wakefield supported the hypothesis of a link between the MMR vaccine and autism. Following this, multiple epidemiological studies performed over a decade found no such link, and Wakefield's study was retracted 12 years after its publication. In fact, one journalist investigated the claim that many of the aspects of the study were fraudulent, and noted that Wakefield was involved in a lawsuit against the manufacturers of the MMR vaccine at the time of the study [5]. Despite the retraction of the study, the sensationalized headline of the link between MMR and autism has had lasting effects on parents' decisions to vaccinate their children. The vaccine-autism link was supported and spread by celebrities such as television star Jenny McCarthy, whose own son was diagnosed with autism. She has since written several books on child vaccinations and autism. Should this possible anti-vaccination movement become more pronounced, infectious disease incidence could return to levels higher than those recorded in the past few decades.

The anti-vaccination movement may have been the cause of several outbreaks of measles larger than those recorded in the past decade, with the most notable

occurring in 2014 when 383 infections occurred within an Amish community in Ohio [25]. Another recent outbreak began in December 2014, where an infected traveler to Disneyland in California caused an estimated 147 secondary cases in the United States, and an additional 158 cases in an unvaccinated religious community in Quebec [6].

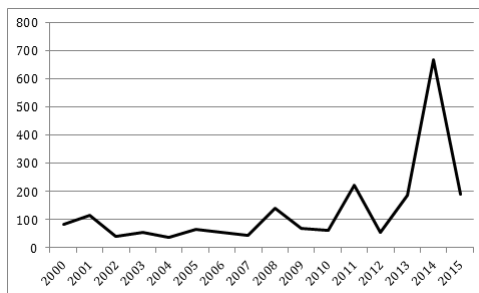


Figure 1: Yearly cases of Measles in the US since elimination in 2000, based on data from the World Health Organization [7]

Public health policies, especially in regards to vaccination, aim to prevent resurgences and maintain elimination of infectious diseases. These are shaped by the results of studies done over a variety of fields, including areas in mathematics and statistics. The use of mathematical modeling of outbreaks using difference and differential equations is now widely used to study how a disease will disperse in certain situations. However, before discussing the modeling process further, we introduce important biological and mathematical concepts relevant to the study of disease outbreaks.

2 Factors that Affect Outbreaks

Outbreaks of airborne infectious diseases, such as measles, are characterized by a variety of factors, some of which are related to human behavior. One of these factors, vaccination, has an obvious effect on the severity of an outbreak, or lack thereof. As mentioned above, strong vaccination policies have led to the virtual elimination

of diseases such as smallpox, polio, and measles in the United States. Additional benefits of vaccination can be seen in the concept of “herd immunity,” which occurs when a large enough percent of the population is vaccinated. A common parameter used in modeling infections, the basic reproduction number R_0 , describes aspects such as contact rates, duration of infection and infectiousness of the causative agent. Contact rates, as well as the pattern of these contacts, often have a strong impact on the transmission and spread of infectious disease. Contact patterns are some of the more complicated aspects of predicting outbreaks, due to the fact that human behavior is quite complex and not consistent among all people. These factors will be discussed individually in further detail.

2.1 Basic Reproduction Number

The basic reproduction number R_0 is defined as the average number of secondary infections directly caused by one infected individual in a completely susceptible population [8, 9]. Contact rates, of course, have a large effect on this parameter, as contacts must generally be made for infection to be possible. Another determinant of R_0 is the duration of infectiousness; individuals with longer infectious periods will contact and thus possibly infect more individuals over the entire span of the infection. If infectiousness precedes symptoms, it is likely to increase R_0 given that contact rates may remain at high levels prior to symptoms. Lastly, the basic reproduction number may be affected by how long a disease survives in a given environment. While this mostly applies to infectious agents in which fomite (through objects) transmission plays an important role, it also may have effects for airborne diseases. One such example is with measles, where infected particles may remain in the air for up to 2 hours after an infected person has left a room [10]. A combination of the above factors may be the reason that measles has a high basic reproduction number, in comparison to other airborne infections. It is estimated to be 12 – 18, which is more than double

Disease	R_0	transmission
Measles	12-18	airborne
Pertussis	12-17	airborne
Malaria	5-100	mosquito
Rubella	6-7	airborne
Diphtheria	6-7	saliva
Smallpox	5-7	airborne
Polio	5-7	fecal-oral route
Mumps	4-7	airborne
SARS	2-5	airborne
HIV/AIDS	2-5	sexual contact
Influenza	2-3	airborne
Ebola	1.5-2.5	bodily fluids

Table 1: Basic reproduction numbers for common infectious diseases [9, 11, 12]

that of most other airborne infections, seen in table 1.

R_0 cannot be directly measured from data for infections which have an effective vaccine or for which immunity is conferred after infection. This is because R_0 measures the average secondary infections in a *completely susceptible* population, so it may only be calculated for infections in which this is the case. It is for this reason that another parameter exists, the effective basic reproduction number, which we denote here as R_e . It is defined as the basic reproduction number observed when a part of the population is immune [8]. There are equations giving the relationship between R_0 and R_e which make it possible to estimate one, given a value of the other. For infections with existing vaccines, R_e is the reproduction number we estimate from outbreak data. It can be used as a measure of the strength of the infectious agent in the outbreak for some infections. For example, since the elimination of measles, its value for R_e has been estimated to be 0.52 for 2001 to 2011 in the United States [14]. A recent study on the 2014/2015 outbreak in Disneyland in found a value of 0.69 (95% CI: 0.48, 1.04) for R_e of measles, which was not significantly different than the previous decade's estimation [14]. In theory, estimations of R_e for the pre-vaccination era should be close to the values of R_0 given above, as per the definition of the basic

reproduction number. Although several methods with varying complexity exist for the estimation of R_e from data, a rough estimate can be found instead by

$$R_e = R_0 (1 - v * v_e). \quad (2.1)$$

where v is vaccine coverage and v_e is vaccine effectiveness [8]. Here, $v*v_e$ describes the proportion of individuals that have successfully received immunity, and thus $1 - v*v_e$ is the proportion of unprotected individuals in the population. If we assume for the Disneyland outbreak that $v_e = 0.98$, the estimated vaccine effectiveness of two doses of the MMR vaccine, we would obtain the above estimated value of $R_e = 0.69$ with the following combinations of R_0 and v values:

R_0	v
12	0.9617
15	0.9735
18	0.9813
5.85	0.9
6.38	0.91
7.01	0.92

Table 2: Estimated parameters for an outbreak that result in $R_e = 0.69$ using equation 2.1

There are two possible explanations, then, for an estimated R_e value of 0.69 in the Disneyland outbreak. One is that the values of 12-18 hold for R_0 , but that the vaccination level of the Disneyland population at the time of the outbreak was somewhere in the range of [0.9617, 0.9813]. This would be quite higher than the reported value for the state of California, 0.91. The alternate explanation is that the vaccination level of the Disneyland population was close to 0.91, and the actual R_0 values for current strains of measles is much lower than described, possibly in the range of 5 to 7. While these estimations are not precise, it might be of significance for future studies to investigate whether the current value of R_0 is less than that which

was found in older studies.

R_e provides us with critical information about the possibility of an outbreak; if $R_e < 1$, the infection will not spread successfully in the population because on average, an infected person will infect less than one other person. However, if $R_e \geq 1$, an outbreak of the disease is much more likely. This can be seen in mathematical models determined by R_e values [21]. Although estimates of R_e for measles are currently below this threshold of 1, a decrease in the vaccination level of the population may cause the value of R_e to increase significantly beyond 1. This is one of the ways in which we can see the indirect impact of vaccination on disease transmission and outbreak possibility.

2.2 Vaccination

As seen above, vaccination has had a significant impact on the reduction of infectious disease incidence. Global vaccination policies have proven successful in increasing vaccination coverage for many existing vaccines. Since the mid 1990's, US vaccination coverage of the MMR vaccine has remained around 91 percent. Other major vaccinations have also seen coverage rates greater than 90 percent since 2010 for children, as seen in table 3. However, the highest vaccination coverage for MMR was seen in the period of 1982 to 1987 where rates were between 97 and 98 percent. While the current coverage of 91 percent gives no indication that measles eradication is immediately threatened at this level, outbreaks do appear to be increasing in size since the late 2000's (see introduction, figure 1). It is possible that if coverage were to drop, even by 1 or 2 percent, elimination could suffer. This is a possibility due to the loss of what is called herd immunity, which protects those who are unable to get vaccinated. Vaccine exemptions occur for a variety of reasons including personal, religious, philosophical, and medical. For those who have disorders or infections which compromise their immune systems, vaccines which contain the live virus may not be administered

because infection would likely result. Therefore, vaccine coverage must be maximized in all other individuals of the population for those with medical exemptions to receive the indirect benefits. This is possible with the phenomenon of herd immunity.

Vaccine	2010	2011	2012	2013	2014
DTaP (≥ 3 doses)	95	95.5	94.3	94.1	94.7
Poliovirus (≥ 3 doses)	93.3	93.9	92.8	92.7	93.3
MMR (≥ 1 dose)	91.5	91.6	90.8	91.9	91.5
Hib (primary series)	92.2	94.2	93.3	93.7	93.3
HepB (≥ 3 doses)	91.8	91.1	89.7	90.8	91.6
Varicella (≥ 1 dose)	90.4	90.8	90.2	91.2	91

Table 3: Estimated vaccination coverage among children aged 19–35 months for common vaccinations recommended for that age, National Immunization Survey, United States [15]

2.2.1 Herd Immunity

Herd Immunity is achieved when a high enough proportion of the population is vaccinated; the unvaccinated individuals will receive indirect benefits from those who are vaccinated. That is, an unvaccinated individual will have a smaller probability of becoming infected when a certain portion of the population is vaccinated. This is due to the fact that an infectious individual is not likely to encounter a susceptible individual to whom they can transmit, and so the infection would be more likely to die out instead of spreading through the population where it may then reach an unvaccinated individual. It was discovered in the 1970's that the incidence of a disease would decrease when the proportion who are immune exceeds $1 - 1/R_0$ [17]. This discovery, however, is limited by several factors, such as assumptions that the population is mixing homogeneously and that immunity was assigned randomly through the population. These assumptions, while popular in introductory disease modeling, are not often reasonable to make if we want to obtain the most accurate model possible. Contacts are not random, as individuals tend to have a small subset of the population

in which they make the most contacts. Similarly, those refusing vaccination may tend to cluster in groups. Another restriction is that herd immunity is possible only for infections that have person to person transmission, or when humans are an important reservoir for the infection [9].

There are several important results of herd immunity. The first is that it protects those who cannot, for medical reasons, receive live-attenuated vaccines such as MMR, which contain the live pathogen. These immunocompromised individuals may be protected indirectly by vaccination with herd immunity if the rest of the population is vaccinated. Another result is that it is then possible to achieve disease eradication with less than 100% of the population vaccinated. This is especially important to note, due the fact that 100% vaccination cannot be achieved with the existence of the immunocompromised. However, there are possible drawbacks to herd immunity, for it has been noted that herd immunity may increase the average age of infection [9]. For some infections, this may be positive due to strengthened immune systems at a later age, and thus greater success in fighting infection. However, some infections present with much stronger symptoms when infected at an older age and thus there may be greater clinical consequences to herd immunity. For example, Rubella (German measles) may result in severe birth defects for pregnant women that become infected and Mumps often causes secondary infection in the testicles of adult males who become infected, where they may be at risk for infertility [16,23]. These risks, however, appear be low enough to continue to pursue disease eradication through vaccination programs.

Critical Vaccination Level

Above, herd immunity was achieved at a certain proportion of immune individuals. However, the proportion vaccinated is not always equivalent to the proportion immune as vaccines are usually not 100% effective. If this is the case, we recall that the

proportion of immune individuals is $v * v_e$ where v is the proportion vaccinated and v_e is the proportional vaccine effectiveness (the proportion of vaccinations in which immunity is successful). Thus we describe the proportion vaccinated needed to achieve herd immunity – the “critical vaccination level” – as

$$v_c = \frac{1 - 1/R_0}{v_e}. \quad (2.2)$$

It can be seen from this equation that infection elimination would not be possible, even with 100% vaccination, if $v_e < 1 - 1/R_0$ because v_c must be less than or equal to 1. In the case of measles, a large value for R_0 results in a high vaccination level needed for herd immunity. If we assume that every vaccinated individual has received two doses of the MMR vaccine, $v_e = 0.98$, then for $12 \leq R_0 \leq 18$, the estimation of critical vaccination level is $0.9354 \leq v_c \leq 0.9637$. We will refer to the lower value of v_c calculated from $R_0 = 12$ as “ $v_c(low)$ ” and the higher value calculated from $R_0 = 18$ as “ $v_c(high)$ ”. Thus, if all vaccinated individuals received both doses of the MMR vaccine, $v_c(low) = 0.9354$ and $v_c(high) = 0.9637$.

It is possible, however, that some individuals in the population have missed or skipped their second dose of vaccination. The vaccine success rate for receiving only one dose of MMR is $v_e = 0.95$. We derive an equation for v_c which accounts for varying levels of vaccine effectiveness, where some individuals have received both doses and some have received only one. We do this by calculating the average vaccine effectiveness using a weighted average, as

$$v_e = \frac{e_1 v_1 + e_2 v_2}{v_1 + v_2} \quad (2.3)$$

where e_1 and e_2 are the proportional effectiveness of one and two doses of the vaccine (0.95 and 0.98 for measles), and v_1 and v_2 are the proportions of the population that are vaccinated once and twice, respectively. We have that $v_1 + v_2 = v$, and therefore

these weights do not usually add to 1. This will result in a critical vaccination level estimate of

$$v_c = \left(1 - \frac{1}{R_0}\right) * \frac{v_1 + v_2}{e_1 v_1 + e_2 v_2}. \tag{2.4}$$

With this formula, we are unable to estimate a single threshold for critical vaccination level, due to the fact that the critical vaccination level v_c is dependent upon the population vaccination level v . However, we may set v to be constant and calculate v_c for varying combinations of v_1 and v_2 . In this way, we may estimate the impact that increased levels of v_1 will have on the critical vaccination level. We begin with the calculations under the assumption that all vaccinated individuals have received both doses. Set v to be 0.9354 for the case in which R_0 is 12 and v to be 0.9637 for the case in which R_0 is 18. Table 4 provides selected results from varying levels of v_1 and their effects on v_c .

v_1	$v_c(low)$	$v_c(high)$
0	0.9354	0.9637
0.02	0.936	0.9643
0.04	0.9366	0.9649
0.06	0.9372	0.9656
0.08	0.9378	0.9662
0.1	0.9384	0.9668
1	0.9649	0.9941

Table 4: Resulting critical vaccination levels for varied levels of vaccinated once individuals when total vaccinated, $v_1 + v_2$, is set to be 0.9354 for $v_c(low)$ and 0.9637 for $v_c(high)$. v_2 can be calculated from $v - v_1$ for each v_1 .

Note that $v_1=1$ means that $v_2=0$, and thus is the calculation of equation 2.2 with only one vaccination level, where $v_e = 0.95$. The change in v_1 appears to have a linear relationship with the change in v_c , with an increase in v_c of 0.0003 for an increase in v_1 of 0.01. This linearity can be seen from a derivation of equation 2.4, as the difference between e_1 and e_2 is constant for the MMR vaccine. While a difference of 0.0003 is quite small proportionally, it results in a large number of individuals

when we refer to a large population size. For example, the most recent estimate for the population of the United States is 323 million [18]. This means that a 1% change in vaccinated once individuals will require approximately 92 thousand more individuals to become vaccinated. However, it is important to note that the change in v_1 is significantly larger than the change in v_c ; a 1% increase in v_1 relates to 3.2 million individuals moving from being vaccinated twice to being in the vaccinated once category. Instead, smaller steps of v_1 would likely be more realistic to the actual vaccination situation. However, data can only be found on the total proportion of the population who have received either 1 or 2 doses of the vaccine; it does not indicate the levels of v_1 or v_2 individually. A larger difference in vaccine effectiveness between multiple vaccine doses would result in more significant critical vaccination level changes. The change may also be amplified by the possibility of clustering of unvaccinated or vaccinated once individuals. Studying these effects with the use of more complex contact theory may produce more important results.

2.3 Contacts

Contacts play an important role in outbreaks, especially in infectious diseases transmitted by person-to-person contacts. They are, by definition, essential for disease spread in this case. There are specific characteristics of contacts and their patterns which affect outbreaks in different ways. These characteristics may be hard to define and implement in models, given the complexity of human behavior and thus, contact patterns. However, recent efforts have been made to find methods to do so, given that the assumption of homogeneous mixing in the population is not accurate. In a homogeneous mixing model, each individual has the same probability of being contacted and the probability of contacting anyone in the population is independent of any previous contacts. The only occasion in which this assumption may be somewhat reasonable is for data from the pre-vaccination era, where infection was

widespread [19]. However, it still does not account for the tendency of populations to be clustered in groups within which most contacts occur.

The characterization of the clustering of contacts is studied extensively within network theory, where quantitative studies investigate the social network structures of populations, such as one by Edmunds, Kretzschmar, and Wallinga [19]. Several findings have been made about the age structure of contacts, where estimations of contact rates within and between age categories find that contacts are highly structured according to age. Additionally, it seems natural to speculate that populations are structured according to many sociological factors – such as familial, professional, social, and religious – which group individuals into clusters with whom they have the most contacts. This phenomenon has been described by Edmunds et. al. with the idea of “global contacts” versus “local contacts,” using ideas which originated from a 1955 study by Rushton and Mautner [20].

Global contacts describe the relatively rare contacts between groups in the population, and local contacts describe the frequent contacts that occur within groups. In models or simulations, this idea can be investigated by dividing the population into smaller subpopulations, where each has its own transmission dynamics, with some transmission between them. This is termed a “metapopulation” or “patch” model. Edmunds et. al. have found that with this method of modeling, subpopulation dynamics can become desynchronized, where infection has faded out in some patches but is still present in others. This allows for the possibility of infection to be re-introduced into infection-free patches. Additionally, they have found that this form of transmission between local groups leads to a larger outbreak compared to a model with homogeneous mixing. This indicates that public health policy should be focused on reducing the size of local outbreaks, instead of outbreaks across the country. For example, reduced transmission within those individuals in the first generation outbreak of measles in Disneyland would have led to a smaller overall outbreak in

2014-2015.

In this paper, we do not yet include contact patterns that utilize network theory. However, we have developed a theory about decreasing contact rates in an outbreak, due to a proposed human behavior of self quarantine. This is one of the main investigations of the model and simulation.

3 Mathematical Models

Epidemic models described by several states became popular after a paper published by Kermack and McKendrick in 1927, where the population was classified into several states and then modeled with a system of differential equations. Since their work, modeling of infectious disease has become a widely studied topic, with a wide range of methods for different disease dynamics. As the field continues to develop, the more complex aspects of disease transmission such as contact patterns and vaccination methods are being tackled with the hope of obtaining more accurate models for outbreaks. These developments come both in the form of scientific discoveries about the pathogens involved in outbreaks, and in the area of mathematics where modeling variable aspects of outbreaks can be quite challenging.

At the most basic form of modeling, the population is divided into possible states in which an individual may reside. The most common states used are susceptible, infected, and recovered. Another state, exposed, is also used in several cases where infection is latent for a period of time. These states are represented as S, I, R, and E. The states used, and therefore the type of model used, depends on the pathogen and immunity to it. Some bacterial infections such as strep throat and several types of food poisoning are often modeled with an SIS model, in which susceptible individuals move to the infected stage after contracting the infection, and upon recovery from infection move back into the susceptible stage. In the SIR model, infected individ-

uals will move to the recovered state after infection, where they have no possibility of becoming re-infected. While these are commonly studied, there are few infections which truly follow these models. An SIRS model works in a similar way, except that immunity upon recovery is only temporary and thus recovered individuals eventually move back into the susceptible state. This may be a good model for infections such as flu, where immunity may be conferred for the seasonal strain; an individual then becomes susceptible to the next strain introduced into the population. The SEIR model accounts for infections, such as polio or measles, where individuals are not symptomatic immediately after contracting the infection and thus classified as exposed for a period of time. In infections with high case fatality rates, the recovered state becomes the “removed” state for those that have died, which allows for constant population size. Figure 2 shows the diagrams of some of these infection models.

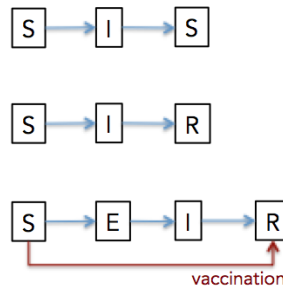


Figure 2: Common models for infectious disease outbreaks: SIS, SIR and SEIR with vaccination

While these models are widely used for certain infections, many often do not capture the full picture of the disease. They are often used, however, to simplify the model in order to make mathematical analysis easier (or even possible). While much progress has been made in learning the pathology of many of these infections, some of the infection dynamics are still unknown or are too complex to be completely modeled by these simple models.

Many models, for the sake of reducing the number of equations, will group vaccinated individuals into the recovered state. While this is a somewhat reasonable

assumption to allow for the benefits gained from doing so, it is not necessarily an accurate way to model the disease when the vaccine is less than 100% effective. It is for this reason we have made it a goal to develop a model that includes separate states for vaccination. While this works well for the simulation, it makes the equations quite complex to analyze mathematically.

3.1 Introduction to Model Equations

There are several types of equations which may be used to model outbreaks. The first distinction is between differential and difference equations, and the second distinction is between deterministic and stochastic equations. Differential equations model the change in the number in each state over continuous time, and are a function of the other state variables in addition to time. These can be represented generally as $dX_i/dt = f(X_1, X_2, \dots, X_i, \dots, X_n, t)$ where each X_i represents a state. Difference equations, however, use time as a discrete variable and model only the number in each state at time $t + \Delta t$. The state at time $t + \Delta t$ is a function of the states X_i at the previous time period, t , so that $X_i(t + \Delta t) = X_i(t) + f(X_1(t), X_2(t), \dots, X_i(t), \dots, X_n(t))\Delta t$. Using this form, a system of difference equations for an SEIR model, assuming no births and deaths, with homogeneous population mixing will be

$$\begin{cases} S(t + \Delta t) = S(t) + f(S(t), E(t), I(t), R(t))\Delta t & = S(t) - \lambda(t)S(t)\Delta t \\ E(t + \Delta t) = E(t) + g(S(t), E(t), I(t), R(t))\Delta t & = E(t) + (\lambda(t)S(t) - \gamma_1 E(t))\Delta t \\ I(t + \Delta t) = I(t) + h(S(t), E(t), I(t), R(t))\Delta t & = I(t) + (\gamma_1 E(t) - \gamma_2 I(t))\Delta t \\ R(t + \Delta t) = R(t) + k(S(t), E(t), I(t), R(t))\Delta t & = R(t) + \gamma_2 I(t)\Delta t \end{cases} \quad (3.1)$$

where $\lambda(t)$ is the force of infection, describing the number of infections which result from contacts with infected individuals per susceptible per time period [21]. It is

a function of time, as well as other variables, depending on how it is defined. The parameters γ_1 and γ_2 describe movement to the next stages, infected and recovered, respectively, and γ_2 is often called the recovery parameter. In many models, γ_1 and γ_2 are defined as having inverse relationships with their respective state lengths δ_1 and δ_2 , such that $\gamma_1 = 1/\delta_1$ and $\gamma_2 = 1/\delta_2$. Note that in difference systems, the equations together will always sum to the population size, N (as long as we are assuming constant population size). That is, $S(t) + E(t) + I(t) + R(t) = N$ for all times t . In comparison, differential equation systems will sum to 0 in constant population size models, $\frac{dS}{dt} + \frac{dE}{dt} + \frac{dI}{dt} + \frac{dR}{dt} = 0$.

Systems of equations can also be classified into deterministic and stochastic systems. Deterministic systems include no randomness in the system, so that for one set of initial conditions and constant parameter values, the result will always be the same. In contrast, a stochastic system adds randomness in some form to the system. This can be done in several ways, ranging from purely stochastic systems where each state is completely randomly determined, or with Markov Chain processes which use sequences of random variables which depend, at time $t + \Delta t$, only on the state at time t . Note that both differential and difference equations can be classified as either deterministic or stochastic; see table 5 for a summary of the main categories of models.

	Differential	Difference
Deterministic	Deterministic Differential	Deterministic Difference
Stochastic	Stochastic Differential	Stochastic Difference

Table 5: General types of models

In our model, we will incorporate stochasticity by including random error terms in each equation. This can be thought of as adding “noise” to the system. It will allow for us to include some of the known variability in outbreaks. Additionally, it

will be possible that for one set of initial conditions and constant parameter values, sometimes an outbreak will occur and sometimes it will not. We add these random error terms ε_i to the system as

$$\begin{cases} S(t + \Delta t) = S(t) - \lambda(t)S(t)\Delta t + \varepsilon_1 \\ E(t + \Delta t) = E(t) + (\lambda(t)S(t) - \gamma_1 E(t))\Delta t + \varepsilon_2 \\ I(t + \Delta t) = I(t) + (\gamma_1 E(t) - \gamma_2 I(t))\Delta t + \varepsilon_3 \\ R(t + \Delta t) = R(t) + \gamma_2 I(t)\Delta t + \varepsilon_4 \end{cases} \quad (3.2)$$

where $\varepsilon_1, \varepsilon_2, \varepsilon_3$, and ε_4 are random variables determined by some probability distribution. From this point forward, we will allow Δt to be 1, so that the system becomes

$$\begin{cases} S(t + 1) = S(t) - \lambda(t)S(t) + \varepsilon_1 \\ E(t + 1) = E(t) + \lambda(t)S(t) - \gamma_1 E(t) + \varepsilon_2 \\ I(t + 1) = I(t) + \gamma_1 E(t) - \gamma_2 I(t) + \varepsilon_3 \\ R(t + 1) = R(t) + \gamma_2 I(t) + \varepsilon_4 \end{cases} \quad (3.3)$$

To analyze systems of difference equations, we find equilibrium solutions of the system. Equilibrium solutions occur when all states reach a “steady state”. The benefit of using difference equations, however, over differential equations is that they allow (in stochastic models) for the recurrence of an outbreak, even when it has nearly died out. Here is where R_e can determine the behavior of a system. When R_e is less than 1, the disease extinction equilibrium solution, $(\bar{S}, \bar{E}, \bar{I}, \bar{R}) = (N, 0, 0, 0)$, is a stable solution. This is the equilibrium we wish to reach for disease eradication.

3.2 Model for Measles

For our research, an expanded model which includes the more detailed stages of infection and vaccination has been investigated. This was done to accurately model

and simulate outbreaks of measles. It includes not only the susceptible stage but also two separate stages of vaccination – vaccinated once (V_1) and vaccinated twice (V_2). In addition, the infected stage is broken into two stages – the prodrome stage (P) and the rash stage (I). The prodrome stage of measles is the period when an individual is infectious and is experiencing some symptoms, however they have not yet developed the rash which is characteristic to measles. The reason for dividing the infected stage is to investigate the effect of self-quarantine on outbreaks, which we theorize may occur in measles. The reason is this – when individuals are in the prodrome stage, the symptoms are described as cold or flu-like. They are likely to have a similar contact rate to their normal, uninfected rate. However, when they move to the rash stage, they will have the rash which is visible on their face and body (see figure 3). At this point, we theorize that most or all individuals would be staying



Figure 3: Child with measles rash [22]

home from school or work, and only contacting family members, roommates, or a doctor. Additionally, we believe that this contact rate will decrease the longer they are in the rash state, assuming they have already gone to the doctor or have already infected any susceptible housemates. In this way, we account for a small portion of the contact patterns of humans. The other states – susceptible (S), exposed (E), and recovered (R) – remain as before. Individuals in the exposed state show no symptoms and are not infectious to others. The complete model diagram is shown in figure 4.

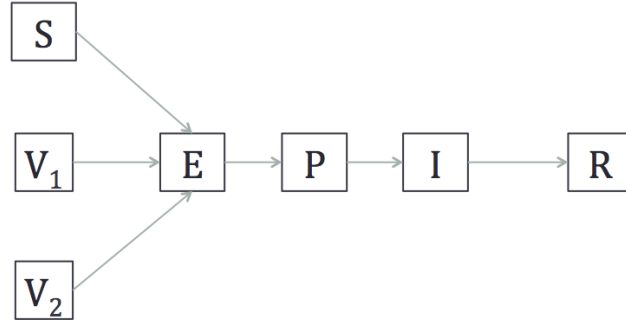


Figure 4: The model for measles

For our model, we assume constant population size, no natural births or deaths, no deaths due to infection, no new vaccinations, and homogeneous population mixing. We also note that individuals will stay permanently in the recovered category and vaccination does not have waning effectiveness. That is, there will be no movement from vaccinated states to susceptible states and vaccine effectiveness is constant. These are not exactly “assumptions,” because they are supported by scientific literature [10]. Our model represented as a system of stochastic difference equations is

$$\left\{ \begin{array}{l} S(t+1) = S(t) - \lambda_1(t)S(t) + \varepsilon_1 \\ V_1(t+1) = V_1(t) - \lambda_2(t)V_1(t) + \varepsilon_2 \\ V_2(t+1) = V_2(t) - \lambda_3(t)V_2(t) + \varepsilon_3 \\ E(t+1) = E(t) - \gamma_1 E(t) + \lambda_1(t)S(t) + \lambda_2(t)V_1(t) + \lambda_3(t)V_2(t) + \varepsilon_4 \\ P(t+1) = P(t) + \gamma_1 E(t) - \gamma_2 P(t) + \varepsilon_5 \\ I(t+1) = I(t) + \gamma_2 P(t) - \gamma_3 I(t) + \varepsilon_6 \\ R(t+1) = R(t) + \gamma_3 I(t) + \varepsilon_7 \end{array} \right. \quad (3.4)$$

The functions $\lambda_i(t)$ for $i = \{1, 2, 3\}$ are the force of infections for each un-infected state, which in our model is defined as the number of infections which result from contacts with prodrome or rash individuals per individual in state X_i per time period.

In the system,

$$\lambda_i(t) = \left(\left(\sum_{q=0}^{P_t-1} \phi_{1,q,t} \right) + \left(\sum_{r=0}^{I_t-1} \phi_{2,r,t} \right) \right) \left(\frac{1}{N-1} \right) (\beta_i) \quad (3.5)$$

where q is individual j such that they are in the prodrome state and r is individual j such that they are in the rash state. ϕ_1 is the beginning contact rate for prodrome individuals and ϕ_2 is the beginning contact rate for rash individuals. So, $\phi_{1,q,t}$ is the contact rate for prodrome individual j at time t and $\phi_{2,r,t}$ is the contact rate for rash individual j at time t . These are summed for all individuals in prodrome and rash, respectively, and thus the first expression is the total contacts made by infectious individuals at time t . When this expression is divided by the $N - 1$, it describes the average number of contacts made at time t . We divide by $N - 1$, instead of N , because an individual may not contact themselves. The final parameter is β_i , which is the probability for transmission of infection upon contact with a infected individual. β_i for susceptible individuals is $\beta_1 = 0.9$, because about 9 in 10 contacts with infected individuals will result in infection for unvaccinated susceptible individuals, according to the CDC [10]. β_i for vaccinated once individuals is assumed to be $\beta_2 = 0.05$, the complement of the immunity success rate of being vaccinated once, which is 0.95. β_i for vaccinated twice individuals is assumed to be $\beta_3 = 0.02$, the complement of the immunity success rate of being vaccinated twice, which is 0.98. It is important to note that we are assuming that all vaccinations are given at the recommended intervals; if the first dose of the MMR vaccine is given before 1 year of age, instead of after, there is only a 0.85 immunity success rate [10].

In the equations of system 3.4, each $\lambda_i(t)$ term is multiplied by the corresponding state, X_i . Thus, the expression $\lambda_i(t)X_i$ is

$$\lambda_i(t)X_i = \left(\left(\sum_{q=0}^{P_t-1} \phi_{1,q,t} \right) + \left(\sum_{r=0}^{I_t-1} \phi_{2,r,t} \right) \right) \left(\frac{X_i}{N-1} \right) (\beta_i) \quad (3.6)$$

Now, the second expression is the probability that a contact was with an individual in state X_i . Together, we can summarize the expression as $\lambda_i(t)X_i = (\text{total contacts}) \cdot \text{P}(\text{contacting individual in } X_i) \cdot \text{P}(\text{transmission to individual in state } X_i)$, and from this see that $\lambda_i(t)X_i$ is the total number of contacts with individuals in X_i which result in infection. For now, the parameters γ_i will be defined as they were above, as having inverse relationships with their state length δ_i such that $\gamma_i = 1/\delta_i$.

Note that $R(t)$ is non-decreasing, and $S(t)$, $V_1(t)$ and $V_2(t)$ are strictly non-increasing functions, for all t . Because the population size is constant, $S(t) + V_1(t) + V_2(t) + E(t) + P(t) + I(t) + R(t) = N$ for all t . All λ_i are non-negative functions and $0 < \gamma_i \leq 1$ because δ_i are positive integers. Because this is a system of seven equations, the equilibrium solutions would be quite difficult to find and analyze. Therefore, we investigate this model and the effects of self-quarantine using a simulation of measles outbreaks.

4 Simulation

The simulation was created as an HTML website, using JavaScript to simulate a population through arrays and the production of events using random number generation. Other programs may be more efficient in producing such simulations, which is something to investigate as further research. However, we possessed limited programming skills and thus HTML and JavaScript were useful to build the simulation as we learned about the programming. One benefit of doing it with JavaScript is that it provides a public application that can be easily run by uninformed users. The idea to build the simulation began when we noticed most other simple epidemic simulations were run through Java, and thus were more difficult to run on devices such as tablets.

This simulation should run well on most internet browsers and operating systems.

The simulation runs as follows. Users enter information on the percentage beginning in each state, as well as the population size and the contact rates for prodrome and rash individuals, as shown in figure 5. These variables are all taken into the program run function, and used to calculate the initial number in each state, $X_i(0)$. We assume that $X_7(0) = R(0) = 0$. These are used to set up the state array, which is a two-dimensional matrix that contains information on the entire population. In the array, each row represents an individual in the population, and the columns retain different variables for each individual. The first column is the current state of the

Not Vaccinated	12.995	%
Vaccinated 1	0	%
Vaccinated 2	87	%
Exposed	0	%
In Prodrome	0.005	%
In Rash	0	%
Population Size	20000	
Contact Rate for Prodrome	10	per day
Max Contact Rate for Rash	5	per day

Figure 5: Screenshot of sample program inputs

individual, $X_i(t)$, the second column is the duration of the current state, γ_i , the third column is the number of days they have been in the state, and the fifth column stores the state in which they started, $X_i(0)$. The fourth column stores the number of times they have been contacted by prodrome or rash individuals before infection occurs, so that we may observe information on the outbreak such as average number of contacts before infection resulted. Thus, the state array will appear as

$$S_{N,5} = \begin{pmatrix} s_{0,0} & s_{0,1} & s_{0,2} & s_{0,3} & s_{0,4} \\ s_{1,0} & s_{1,1} & s_{1,2} & s_{1,3} & s_{1,4} \\ \vdots & \vdots & \vdots & \vdots & \vdots \\ s_{N-1,0} & s_{N-1,1} & s_{N-1,2} & s_{N-1,3} & s_{N-1,4} \end{pmatrix}. \quad (4.1)$$

Since the index for arrays in JavaScript begins at 0, we will do the same here with

$j = \{0, 1, \dots, N - 1\}$ being the row index and $m = \{0, 1, \dots, 4\}$ being the column index. The states are coded into numerical variables as

$$X_1(t) = S(t) \rightarrow 1$$

$$X_2(t) = V_1(t) \rightarrow 2$$

$$X_3(t) = V_2(t) \rightarrow 3$$

$$X_4(t) = E(t) \rightarrow 4$$

$$X_5(t) = P(t) \rightarrow 5$$

$$X_6(t) = I(t) \rightarrow 6$$

$$X_7(t) = R(t) \rightarrow 7.$$

At time $t = 0$, the states are assigned as 1 for $0 \leq j < S(0) - 1$, as 2 for $S(0) \leq j < S(0) + V_1(0) - 1$, and so on. These are stored temporarily in $s_{j,0}$ and permanently stored in $s_{j,4}$. For those initially in the exposed, prodrome, or rash states, their state duration δ_i is determined. According to the CDC, the average length of these states are 10-12 days for exposed, 2-4 days for prodrome, and 5-6 days for rash [10]. A random number is generated within these ranges for each respective state according to a uniform distribution (where each have equal probabilities). This process contributes to the random error terms $\varepsilon_4, \varepsilon_5, \varepsilon_6$ and ε_7 in system 3.4. These stage duration parameters, now $\delta_{i,j}$ for each individual j , are then stored as $s_{j,1} = \delta_{i,j}$ where $i = s_{j,0} - 3 = \{1, 2, 3\}$.

Additionally, we assume that individuals in exposed, prodrome, and rash stages may not be in their first day of that state for day 1 ($t = 0$) of the outbreak. For example, if the program is to model an outbreak which was caused by a single infected traveler entering the population at $t = 0$, the traveler may be in the middle of the prodrome stage, experiencing flu-like symptoms, at that time. Thus a random number within the appropriate range is generated for individuals in E, P, and I at

$t = 0$, according to a uniform distribution, and are stored in $s_{j,2}$ for individual j . For individuals in the susceptible and vaccinated stages, we let $s_{j,1} = 0$ and $s_{j,2} = 0$, given that they will not be moving on to other states after any specific period of time – only contact and subsequent infection will cause this. This concludes the population set-up for $t = 0$.

Beginning on day 2 ($t = 1$), several things occur. The first process is updating the days in state ($s_{j,2}$) for exposed, prodrome and rash individuals. This is done by simply incrementing the values of $s_{j,2}$ by one. If, after this update we have $s_{j,2} > s_{j,1}$ for individual j , then they will be moved into the next state because they have completed their stay in that state. Because of this, the simulation is unique from the mathematical model in that we have accurate descriptions of the movement parameters γ_i . Instead of an average movement from exposed to prodrome to rash to recovered states, we can track and calculate the actual movement for each at time t . When an individual moves to states of prodrome or rash, a value for $s_{j,1}$ is generated randomly according to the respective range, and $s_{j,2} = 1$ because it is now their first day in the new state. If, however, the new state is recovered, $s_{j,1} = 0$ and $s_{j,2} = 0$ because recovered individuals will stay in that state for the remainder of the outbreak.

The second process that will occur each day is the generation of contacts for prodrome and rash individuals. In this simulation, we are using assumptions of self quarantine as mentioned above. The first theory was that contact rates will be lower for rash individuals than for prodrome individuals, and this is the reason that the user may input different contact rates for each of these. The second theory was that within the rash state, contact rates will decrease as their time in the state increases. Additionally, contact rates for prodrome individuals may decrease, because as the outbreak develops and individuals in the population become infected, the outbreak will be reported by the news, schools, and so on. Thus, those in prodrome experiencing mild symptoms may be more conscious of their sickness and have reduced activity.

Recall that $\phi_{1,q,t}$ is the contact rate for prodrome individual j and $\phi_{2,r,t}$ is the contact rate for rash individual j at time t . Contacts are generated as follows: if an individual is in the prodrome stage, we generate $\phi_{1,q,t}$ random numbers in the range of $[0, j) \cup (j, N]$ and store them in a contact vector,

$$C_{\phi_{1,q,t}} = \begin{pmatrix} c_0 \\ c_1 \\ \vdots \\ c_{\phi_{1,q,t}-1} \end{pmatrix}.$$

For each of these contacts, we then generate a random number $\tau \in [0, 1]$, and if $\tau < \beta_i$ then the individual will contract the infection, and move to the exposed state where a state duration is then generated. Recall that $\beta_1 = 0.9$, $\beta_2 = 0.05$, and $\beta_3 = 0.02$ for S , V_1 , and V_2 . These β_i are constant because, as mentioned, the MMR vaccine does not experience waning immunity over time. For a simulation of an infection other than measles, with a vaccine different from the MMR, β_i may be a decreasing function of time. Similarly to those in prodrome, a contact vector $C_{\phi_{2,r,t}} = \{c_0, c_1, \dots, c_{\phi_{2,r,t}-1}\}$ for rash individuals is generated, but only for those whose $s_{j,2} \leq 4$, because rash individuals are only infectious for the first four days of the rash [10]. This process of random generation of contacts and transmission contributes, through $\lambda_i(t)$, to the random error terms $\varepsilon_1 - \varepsilon_4$ in the equations of system 3.4. This process is repeated each day, until there are no individuals in the rash, prodrome, or exposed state ($E(t) + P(t) + I(t) = 0$) at which time t we say the outbreak has ended. It is easy to program calculations for variables such as percent infected over the outbreak, percent of each state infected, and average contacts made until infection occurs. The use of JavaScript makes it easy to also include calculations such as, for each day, the percentage of contacts which resulted in infections for each state. Over an entire outbreak, these should average to the values of β_i for each state. Figure 6 shows a

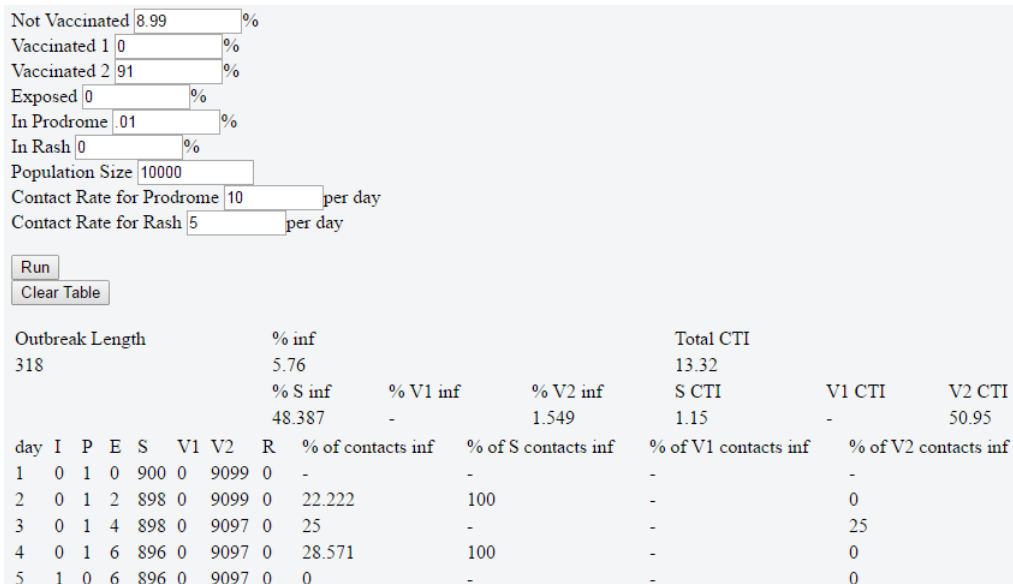


Figure 6: Screenshot of program output

screenshot of the program output.

This simulation may be changed in multiple ways, to account for more states or to include contact networks. It should be relatively straightforward to program this to become a patch model, where the population is split into smaller subpopulations. Additionally, we can add age structure to the population, as it is known that contacts tend to be assortative with respect to age [19]. We wish to do such things in future work.

5 Results

Given that the simulation has stochastic elements, the results are variable for any set of initial conditions and contact rates. For this reason, we must run multiple trials for each that we investigate, to see the average behavior that results. For example, having 0% of the population infected (no outbreak) in one trial of the simulation, does not mean that an outbreak can't occur in another trial with the same initial conditions. While we have a wide range of variables we can measure with the simulation, the main

measurement is average percent infected over the entire time period. Additionally, the challenge exists of having a large number of combinations of initial conditions that we could study. There are more than 90,000 combinations, when we only include integer values of percentages, for which multiple trials could be run. For this reason, we have run and presented here a selection of these results at both individual and summary levels.

Individual Results. First, it is interesting to see the nature of individual trials. The figures below plot the number in each state over time, for one outbreak simulation, and show that the results appear to follow patterns similar to figures plotted using deterministic difference equations. In figure 7, an outbreak of larger size occurred when the contact rate for rash individuals was $\phi_2 = 10$ instead of $\phi_1 = 5$. As

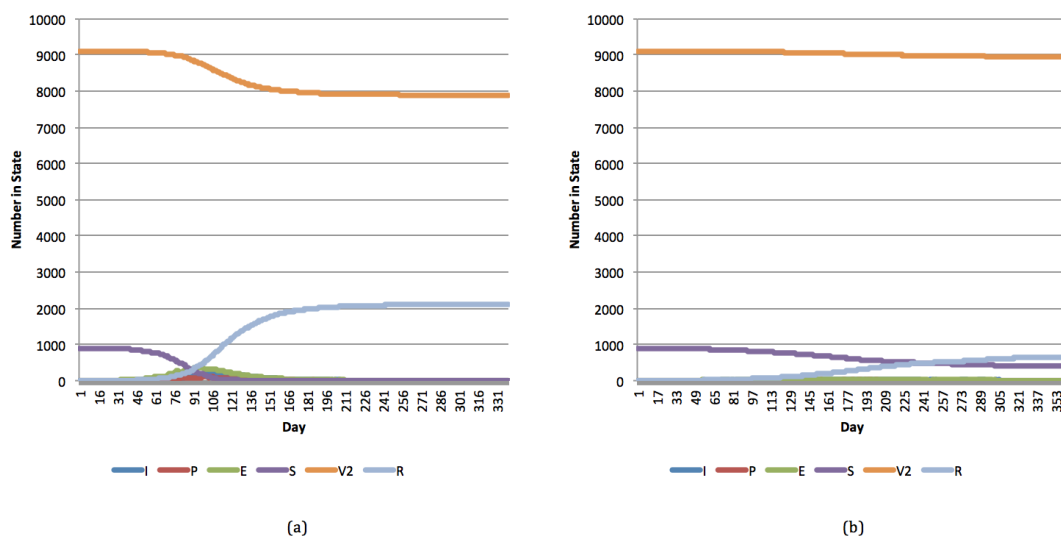


Figure 7: Single simulation trial for vaccination at 91% with variable contact rates. (a) $N = 10000$, $S(0) = 899$, $V_1(0) = 0$, $V_2(0) = 9100$, $E(0) = 0$, $P(0) = 1$, $I(0) = 0$, $\phi_1 = 10$, $\phi_2 = 10$. Percent infected = 21.5. (b) Initial conditions as in (a), with $\phi_2 = 5$. Percent infected = 6.42.

the number in vaccinated twice is quite larger than all of the other states, it can enlarge the scale so that the behaviors of some of the states are hidden. If we remove vaccinated twice from the graph, we can see in greater detail how the others behave.

Figure 8 displays the results of the same trial as in figure 8, however, we can see some of the behavior of recovered and susceptible individuals. In plot (a) of figure 8, the number of recovered individuals passes the number of susceptible individuals at a point relatively early in the outbreak. It takes a while for the outbreak to completely

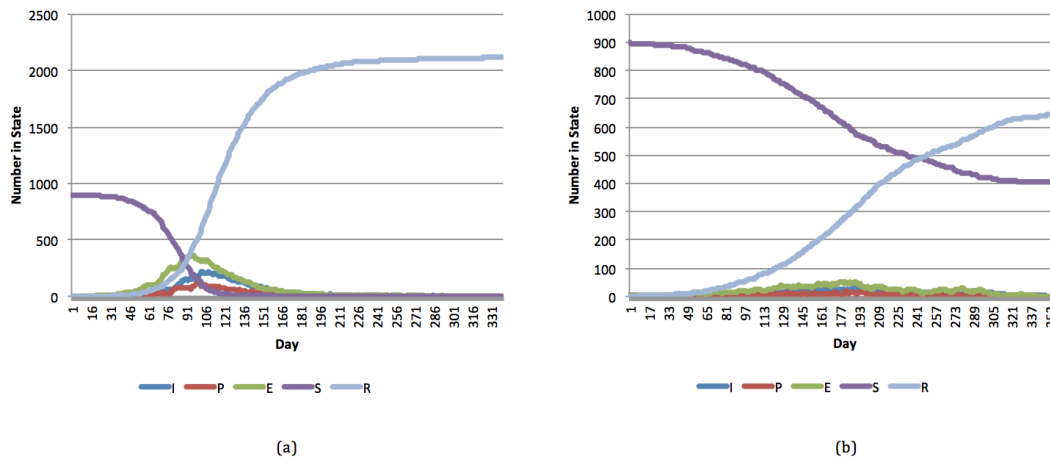


Figure 8: The simulation trial from figure 7, with vaccinated twice removed from plot.

die out in the population, even though it is effectively over at around day 210. In plot (b) of figure 8, the infection proceeds at a slower rate, where the number of recovered individuals does not pass the number of susceptible individuals until much later in the outbreak than (a). It does not persist at a low level near the end of the outbreak, instead effectively ending when it should. This could be a unique result for this trial, or it could be a characteristic of the lower contact rate for rash individuals.

Even with vaccinated twice removed from the plot, it is still difficult to see the dynamics of the exposed, prodrome, and rash states at this level. Figure 9 shows the plots with susceptible and recovered states also removed, from the same simulation trial as in figures 7 and 8 above. Here, we can truly see the stochastic nature of the simulation, where the numbers in the states will fluctuate at each time period. These states indicate similar patterns that emerged from figure 8. In figure 9(a), the epidemic increases very quickly, with a strong peak at around day 100. Then, it will

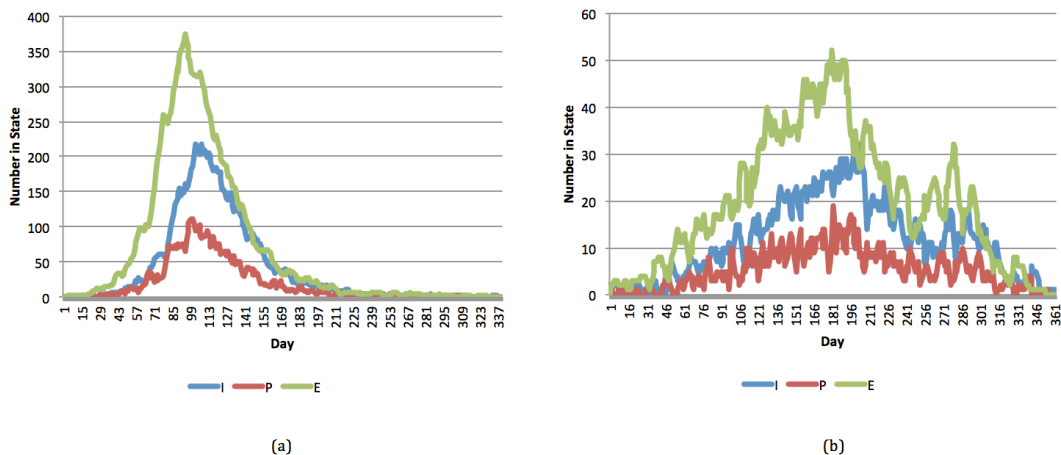


Figure 9: The simulation trial from figure 7, showing only exposed, prodrome, and rash states.

persist at very low levels for a while before it completely dies out. In figure 9(b), the outbreak, which is smaller overall, will proceed at a much slower rate over the entire time period. Of course, these three states, in both (a) and (b), should be related to each other. Because individuals proceed from exposed to prodrome to rash, the prodrome and rash states should be similar to exposed but occur at a delay. Indeed, we can see that the peak for prodrome in (a) is later than that of the exposed, and the peak for rash is later than that of the prodrome state. The peaks have slightly different shapes due to the fact that each state has a different duration.

Summary Results. We begin the investigation of vaccination levels by first assuming that all vaccinations have been received with two doses. Our goal was to find the vaccination level at which herd immunity might be achieved. Recall that above, our estimation for the critical vaccination level for herd immunity for measles, with all receiving two doses of the vaccination, was $0.9354 \leq v_c \leq 0.9637$ when we varied R_0 between 12 and 18. Figure 10 shows the average percent infected with varying levels of initial percent vaccinated. This figure shows that as the initial vaccination level reaches 94%, the average percent infected in an outbreak will decrease to very low levels. We say that this is the critical vaccination level estimated by the simulation,

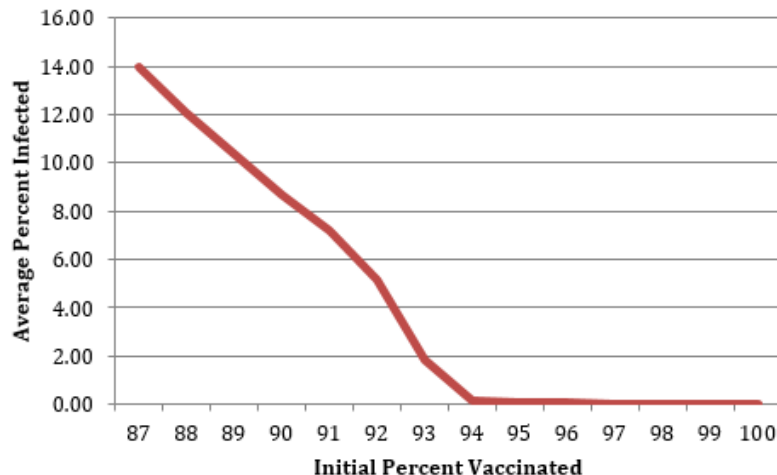


Figure 10: Average percent infected for varying levels of initial percent vaccinated ($V_2(0)$). The initial conditions for all were $N = 10,000$, $S(0) = 9,999 - V_2(0)$, $V_1(0) = 0$, $E(0) = 0$, $P(0) = 1$, $I(0) = 0$, $\phi_1 = 10$, $\phi_2 = 5$.

for all being vaccinated twice with contact rates of $\phi_1 = 10$ and $\phi_2 = 5$. These contact rates were chosen as part of our self-quarantine assumption. While studies have been done on contact rates in European countries, we have found no contact rate for the United States in the literature. We chose the general contact rate to be 10, as this is close to several European countries [24]. We chose the rash contact rate to be 5 because, as mentioned above, we theorize that contact rates will be limited to family members and housemates once the rash occurs. As our resulting v_c was found to be 94%, which is close to that estimated when $R_0 = 12$, this may be an indication that these contact rates were accurately chosen.

Now, if we let our total vaccination level be 94%, what is the effect of some of these vaccinated individuals having received only one dose of the vaccine? We keep the contact rates and initial infected conditions the same as above, but vary the levels of V_1 and V_2 . In figure 11 there is no strong trend in the average percent infected. Here, we would want to run more trials of each, to see if we get any clearer results. However, it would not be surprising if the vaccinated once level does not have a large

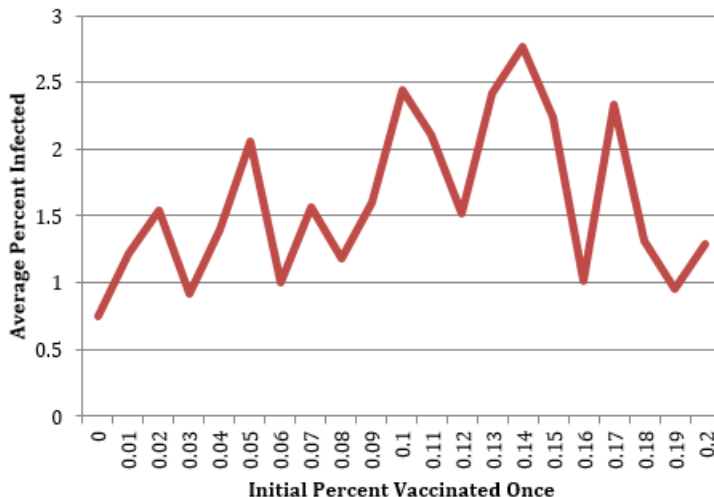


Figure 11: Average percent infected for varying levels of vaccinated once $V_1(0)$ and twice $V_2(0)$, when total vaccination level is set at 94%. The initial conditions for all were $N = 10,000$, $S(0) = 599$, $E(0) = 0$, $P(0) = 1$, $I(0) = 0$, $\phi_1 = 10$, $\phi_2 = 5$.

effect on herd immunity. In the above section on herd immunity, we saw that the increase in critical vaccination level was lower than the change in vaccinated once level. These results may indicate that including two separate levels of vaccination in our model may not be necessary, and that we could simply include one level without losing a great deal of accuracy. This would be a step towards making mathematical analysis more reasonable.

Now we would like to investigate the effect of contact rates on the size and probability of an outbreak. As mentioned earlier, in infections with person-to-person transmission routes, contacts are necessary and thus should obviously have a large effect on outbreaks. Figure 12 shows the average percent infected for varying contact rates, when we assume that $\phi_1 = \phi_2$. Here, the result is as expected. The average percent infected in an outbreak increases almost linearly as the contact rate is increased. This increase is quite large, which shows the significant effect that contact rates have on an outbreak, as a contact rate of 15 will result in outbreaks upwards of 35% of the population infected. It is possible that this is due to our assumption of homogeneous

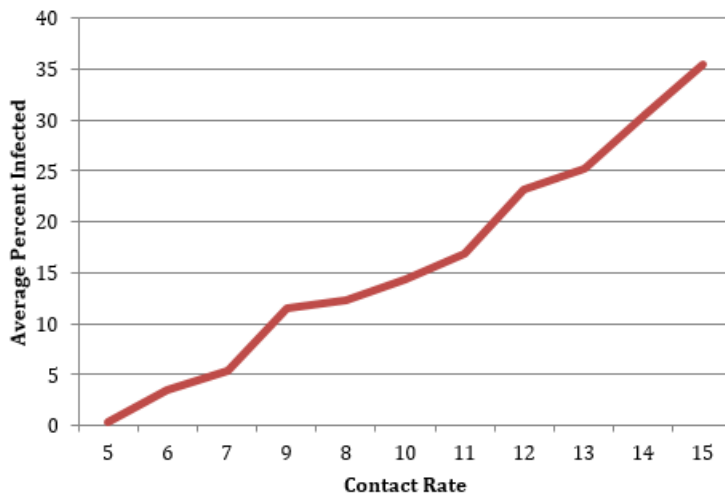


Figure 12: Average percent infected for varying contact rates ($\phi_1 = \phi_2$). The initial conditions for all were $N = 10,000, S(0) = 599, V_1(0) = 0, V_2(0) = 9,400, E(0) = 0, P(0) = 1, I(0) = 0$.

population mixing, or because a relatively small population size was used. An outbreak size of 35% of the population infected seems much larger than reports indicate should occur. In the California outbreak, where contact rates are high, the average percent infected from the first generation of infection (who visited the park) was approximately $39/44,000 = 0.09$ percent [6]. Nevertheless, reducing contact rates of infected persons is likely to have a significant effect on reducing outbreaks of measles.

In our simulation, it appears that rash contacts have a greater impact on outbreaks than prodrome contacts do. For the set of initial conditions as in figure 12, we vary first the prodrome contact rate and then the rash contact rate. For $5 \leq \phi_1 \leq 15$, when $\phi_2 = 5$, the average percent infected in the outbreaks is in the range of $[0.747, 2.915]$. This indicates that the prodrome contact rate has a small effect. It is also interesting to note that $\phi_1 = 5$ resulted in the highest average percent infected value. More trials should be run, to see if this result is consistent. However, if we let $\phi_1 = 5$ and vary the rash contact rate as $5 \leq \phi_2 \leq 15$, we will see average percent infected in outbreaks in the range of $[2.915, 37.068]$. This is likely a result of how we programmed the simulation. As mentioned above, another contact hypothesis was that the contact

rates for rash will decrease for each individual j over time, because they may have already contacted everyone in their home the first day they were in the rash stage, or even during the prodrome stage. This was one way to account for some of the contact patterns in a population. Thus, increasing the rash contact rates, in contrast to our assumption about self-quarantine, will result in very large outbreaks. While, again, these average percent infected rates may be higher than truly seen in outbreaks, they are indications of the strength of self-quarantine and what might happen when individuals do not behave in this way.

These results are a very small selection of what we might investigate with the simulation. We would like to continue to study these past the timeline of this research, and see if we can obtain more significant results.

6 Discussion and Further Research

For possible future work, there are many things that could be done, some of which were already mentioned. Contact patterns may be incorporated into the simulation by the use of a patch model, where we split the population into subpopulations. The population may also be characterized by age, according to current age distribution data. Contacts could then be sorted by age, as research indicates occurs. Several other assumptions that we made might be removed. Vital dynamics could be included, which are the natural births and deaths in a population, even with keeping the population size constant. New vaccinations could also be included in the model, especially given that the outbreaks for measles last for long periods of time. It is reasonable to believe that new vaccinations might occur. Some data also indicates that the MMR vaccine, received after infection, might help with preventing the progression of infection [10]. If this is further supported, it may be important to include in the model.

Another major adjustment to the simulation would be to make it run more efficiently. Currently, the run time is very slow and thus our population size is effectively limited to about 20,000. Even at this level, the simulation takes a long time to run, which compounds our issue of multiple combinations of initial conditions with multiple trials. To make the simulation faster would allow us to increase the population size, while also running more trials. We would like to investigate further levels of vaccination and contact rates. Also, different beginning levels of infection should be studied. Because of the limiting factor of time to run the simulation, we began all of the outbreaks with one person in the prodrome state, with none in the exposed or rash state. Instead, we may begin with individuals in the exposed or rash states, or combinations of the three infected states.

Another use of the simulation would be parameter estimation. If we can use results of the program to estimate parameters such as the $\lambda_i(t)$'s, these estimations might be used in the mathematical models. This would allow us to study outbreaks further in a more efficient manner. Contact rate estimations for infected individuals would also greatly contribute to the modeling process. This is something that could be done with an observational study with individuals in the United States. Given that contact rates and patterns are crucial aspects of the modeling process, this should be an area of focus for mathematical and sociological research in future years.

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