Effects of Population Density on the Spread of Disease*

Hasan Sumdani†, Samuel Frickle†, Matthew Le†, Martin Tran†; Christopher Kribs Zaleta‡

ABSTRACT

A new coronavirus, MERS-CoV (Middle East Respiratory Syndrome-Coronavirus) which is related to the coronavirus that caused the SARS outbreak 10 years ago, has been discovered in Saudi Arabia and observed in several other countries since 2012. A mathematical model is constructed in order to theorize possible patterns of the spread of this emerging disease which seems to require an extended contact time for transmission to occur. In order to better understand the role of population density on the spread of disease, the population is split into two groups, one with contact rates that are independent of population density and another group that has contact rates that are dependent on population density. Conditions under which the disease will spread are analyzed, and specifically, we note how population density affects the observed, theoretical dynamics and transmission characteristics predicted by the epidemiology model.

INTRODUCTION

Over the past fifteen years, outbreaks of various viruses in isolated regions have kept the global community vigilant due to the possibility of a global epidemic. The increase in global infrastructure and international travel has led to a greater threat of viruses such as H1N1 (swine flu), H7N9 (bird flu), and SARS [1]. Preventative restrictions on international travel can contain such a disease to avoid a global epidemic, but even an isolated outbreak in a country can have negative effects on the globe as a whole.

One such virus that has recently caught the attention of many disease-control organizations is the one responsible for Middle East Respiratory Syndrome (MERS). Since June of 2012, when a businessman from the Bisha area of Saudi Arabia died from a severe respiratory illness, the World Health Organization has been closely monitoring the spread of this disease [1]. As of current, there have been 180 confirmed cases with 43% mortality rate [14]. The geographically distribution of these confirmed cases consists of sparse detection (~3) in various countries in the Middle East and Europe with all other cases (n=142) occurring in Saudi Arabia [6].

This virus is similar to the coronavirus responsible for the severe acute respiratory syndrome (SARS) outbreak in 2003, and has proven to be just as dangerous with, as a majority of cases result in pneumonia, renal failure and death [4]. MERS has proven to be quite fatal, but since the spread of the disease is much slower than that of SARS, preventative measures such as quarantines do not yet seem necessary [5]. It has been confirmed that MERS can spread by

* This research was supported by an NSF UBM-Institutional grant, DUE#0827136, as part of the UTTER program at UT Arlington (http://www.uta.edu/math/utter/).
† Department of Biology, The University of Texas at Arlington, P.O. Box 19498, Arlington, TX 76019-0498
‡ Department of Mathematics, The University of Texas at Arlington, P.O. Box 19408, Arlington, TX 76019-0408

human-to-human contact, but it is still not clear where it originated from. It is believed to be zoonotic though the animal vector is still unknown. However, recent isolation and screening of viruses present in bat dropping in *Taphozous perforatus* have found nearly identical viral sequences to that of MERS-CoV, suggesting that bats may be the natural reservoir [6].Further, it has been speculated that an extended period of contact is also required for transmission of the virus from an infected individual to a susceptible individual to take place [2].

The SARS outbreak that occurred about 10 years ago was studied thoroughly for its patterns of spreading, but the preventative measure that was most successful in Hong Kong for preventing disease spread is still debated. Some argue that it was the reduced contact rate of infectious and susceptible individuals [9]. If that indeed is the case, then studying the effects of population density on the spread of disease is a logical next step to gaining more insight on how the spread of disease can possibly be minimized.

At this stage, theoretical research is very valuable since little is known about the new coronavirus that causes MERS, especially in light of the location of many of the infected cases—Saudi Arabia—which just so happens to also be the site of the Hajj pilgrimage made by millions of Muslims from all around the world.

There are two proposed models that have been classically used to describe epidemiology dynamics. The first model, mass action incidence, is a density-dependent model that assumes that the individuals' daily encountering patterns are related to the size of the infected population. The momentum or drive of mass action incidence requires an extended exposure time and a threshold of individuals with the disease. This model is appropriately used to describe a small population size. An example of such is of a teacher and his or her class. When observing such a small size and extended time, a mass action incidence approach describes how this type of interaction will yield a nearly complete infection of the entire classroom.

The other model, standard incidence, is density-independent. This model depends on the proportion of uninfected hosts relative to the total population. When the number of contacts per infected individuals is constant, there exists a threshold of infectivity that is only dependent on the contact number or basic reproduction number in order to determine whether the disease persists, but not the susceptible population. Typically, the disease will persist when infected individuals have enough contact time with susceptible individuals during their infectious period. That is, that the number of new cases increases along with the number of adequate contacts of infected individuals with susceptible individuals. This occurs due to the infectivity level of the disease. Since this level is constant, an increase of infectivity following the increase in susceptible population is not observed [12].

Our study attempts to note the consequences of both mass action and standard incidence on the control of the disease. Since there has been limited study on MERS, we wanted to simulate both conditions and the interactions between these populations to determine to what extent MERS can

affect the population. Ultimately, we study what conditions would optimally prevent this emerging viral disease from persisting.

This study follows the standard compartmentalized modeling technique while adding a degree of originality by splitting the population into two groups based on dependency on population density: independent and dependent. The model also takes into account the necessity of a prolonged contact rate to transmit the infection. The paper uses qualitative analysis to show the general effect of a prolonged contact and also shows numerical analyses which utilize the most accurate parameter values available.

In order to see the effects of population density we chose two cities that are described by high and low population densities. These exaggerated values of population density will help us observe population density's effect on the spread of disease. We focus our studies on the two cities Zarqa and Sakib which are both located in Jordan. Zarqa was chosen as one of the focuses of our research because many cases of MERS had been reported in the city. Zarqa also is a large city with a high population density which fits well with our objective for this research. Sakib is a city located near Zarqa and is characterized by a much smaller population density. Other parameter values are based on the characteristics that describe the two cities.

MODEL OVERVIEW

In a conventional *SIRS* model, the individuals in the population are separated into three classes: susceptible individuals (S), infected individuals (I), and recovered individuals (R). The system is cyclic in nature as one individual starting in the susceptible class can become infected and move to the infected class, then can recover from the disease and, after a period of immunity, returns to the susceptible class once again.

The simple, traditional *SIRS* model is modified in this paper in order to better see the effects of population density on epidemiological dynamics, but still holds the key principles of the traditional *SIRS* model as described before. The most notable modification that was introduced was the splitting of the population into two different groups (cf. Figure 0): one whose contacts with other individuals are independent of population density ($N_1=S_1+I_1+R_1$, Group 1), and one that has a contact rate that depends on population density ($N_2=S_2+I_2+R_2$, Group 2).

We include a population whose contact rate is dependent on population density (Group 2) as well as a population whose contact rate is independent of population density (Group 1) to better illustrate the differences between them, and since the differential equations that describe the dynamics of each group are identical in every qualitative regard besides the inclusion of a multiplicative population density factor, we are better able to attribute the differences that we see in the dynamics of each group to the population density factor than if that were not the case. The model and details about its construction follow.

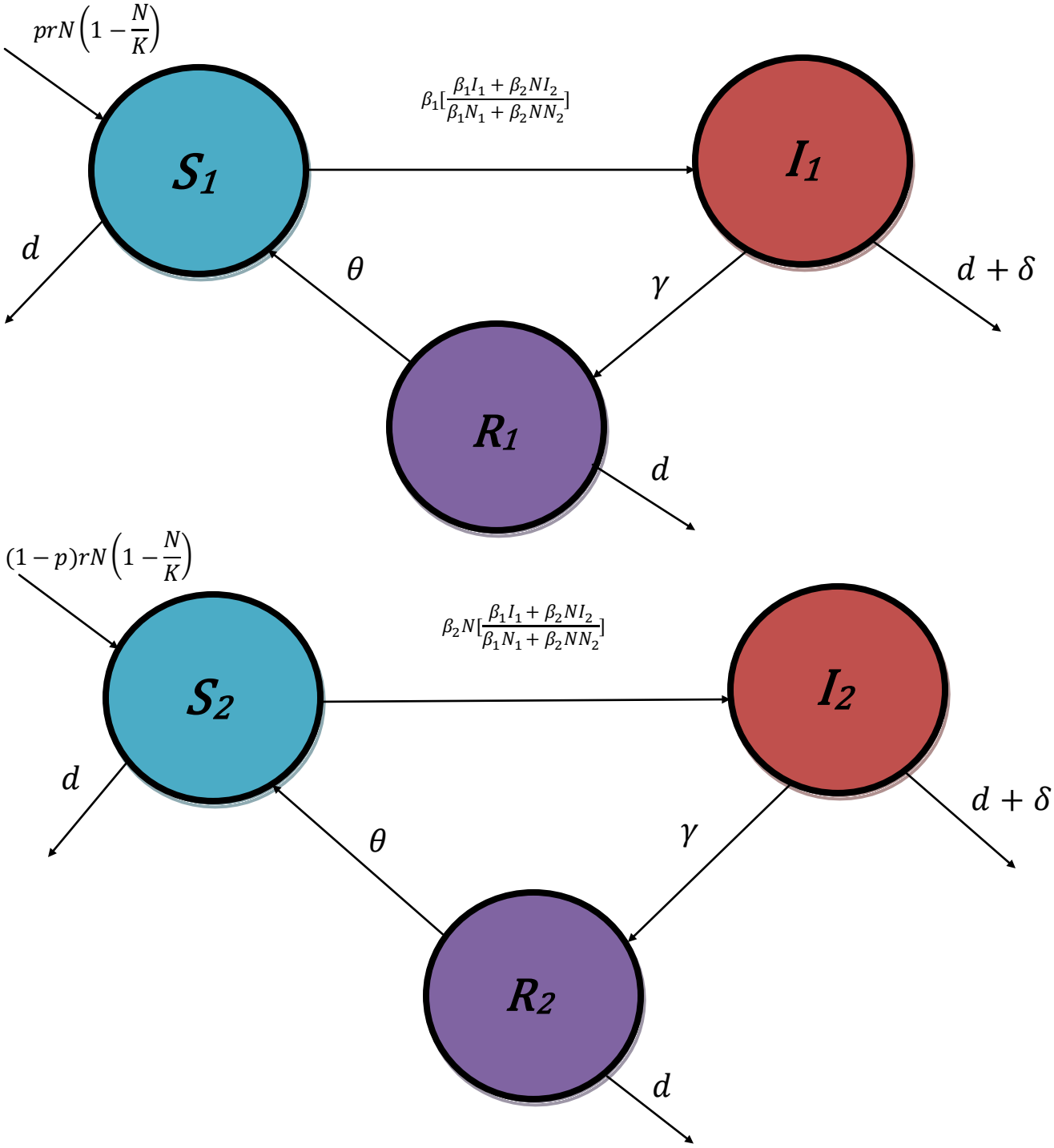

Fig. 0. Flow chart for the two-group model

MODEL CONSTRUCTION

$$\frac{dS_1}{dt} = prN\left(1-\frac{N}{K}\right) + \theta R_1 - \beta_1\left[\frac{\beta_1 N_1}{\beta_1 N_1+\beta_2 N_2 N}\left(\frac{I_1}{N_1}\right) + \left(1-\frac{\beta_1 N_1}{\beta_1 N_1+\beta_2 N_2 N}\right)\frac{I_2}{N_2}\right]S_1 - dS_1$$

$$\frac{dS_2}{dt} = (1-p)rN\left(1-\frac{N}{K}\right) + \theta R_2 - \beta_2 N\left[\frac{\beta_2 N_2 N}{\beta_1 N_1+\beta_2 N_2 N}\left(\frac{I_2}{N_2}\right) + \left(1-\frac{\beta_2 N_2 N}{\beta_1 N_1+\beta_2 N_2 N}\right)\frac{I_1}{N_1}\right]S_2 - dS_2$$

Many epidemiological models omit the births and deaths that occur in a population during an epidemic. However, we assume that these rates can be significant on the time-scale of our mathematical model, and would therefore be practical to include in the appropriate differential equations that are affected by these demographic renewal agents.

To represent the growth rate of the population due to births, we employ a modified logistic growth expression, where N is the total population ($N=N_1+N_2$), K is the carrying capacity of the area, r is the maximum per capita reproductive rate, and p is the proportion of births that become members of the population N_1. Reproduction in the N_2 class is similar except that the proportion of individuals born into the N_2 population is represented by $(1-p)$.

The expressions that represent growth due to birth only appear in the differential equations for S_1 and S_2 because of an assumption we make: immunity or infection cannot be passed to the offspring from the mother congenitally, and as a consequence, all individuals that are born during the time of this model's simulation become a part of their respective susceptible populations as opposed to infected or recovered populations.

Each susceptible population has a common per-capita death rate (d) which is multiplied by the size of the respective susceptible class to get the net decrease of the population due to natural death. This death rate, d is the same for both susceptible populations because our model has no reason to believe that population density has any effect on the natural death rate in this epidemiology study.

Both susceptible populations increase as individuals who have recovered from the disease begin to lose their immunity over time. This per-capita rate is represented by theta (θ) and is multiplied by the respective recovered class to yield the number of individuals that return to the susceptible population from the recovered class. Again, theta is assumed to be the same for both recovered populations because population density is unlikely to affect the recovery rate.

The most noteworthy difference between the differential equations for S_1 and S_2 are the expressions that represent a decrease in the susceptible population due to infection. The infection event for individuals that are a part of the first susceptible class is represented by

$$1.\ \beta_1\left[\frac{\beta_1 N_1}{\beta_1 N_1+\beta_2 N_2 N}\left(\frac{I_1}{N_1}\right) + \left(1-\frac{\beta_1 N_1}{\beta_1 N_1+\beta_2 N_2 N}\right)\frac{I_2}{N_2}\right]S_1 = \beta_1\left[\frac{\beta_1 I_1+\beta_2 I_2 N}{\beta_1 N_1+\beta_2 N_2 N}\right]S_1$$

whereas the same event for individuals that are a part of the second susceptible class is represented by

$$2.\ \beta_2 N[\frac{\beta_2 N_2 N}{\beta_1 N_1+\beta_2 N_2 N}\left(\frac{I_2}{N_2}\right)+\left(1-\frac{\beta_2 N_2 N}{\beta_1 N_1+\beta_2 N_2 N}\right)\frac{I_1}{N_1}]S_2=\beta_2 N[\frac{\beta_1 I_1+\beta_2 I_2 N}{\beta_1 N_1+\beta_2 N_2 N}]S_2.$$

In essence, these expressions are just complex forms of the general expression that is used to showcase the infection event in most epidemiological models:

$$\beta\frac{I}{N}S$$

The fractions in expression 1 that include a beta (β) term in both the numerator and the denominator are simply ratios that are utilized to show that infection of susceptible individuals from group 1 (S_1) can take place by encountering infected individuals from either group 1 (I_1) or group 2 (I_2). The ratios more accurately specify the proportion of contacts made with either group.

Likewise, the fractions in expression 2 that include beta terms are also ratios that are necessary to illustrate the concept of infection being able to arise as a consequence of susceptible individuals from group 2 (S_2) encountering infected individuals from either group.

The term $\beta_1\left(\frac{\beta_1 N_1}{\beta_1 N_1+\beta_2 N_2 N}\right)\left(\frac{I_1}{N_1}\right)S_1$ from expression 1 represents the number of contacts of S_1 individuals and I_1 individuals that leads to transmission of the disease. In contrast, the term $\beta_1\left(1-\frac{\beta_1 N_1}{\beta_1 N_1+\beta_2 N_2 N}\right)\left(\frac{I_2}{N_2}\right)S_1$ also from expression 1 represents the number of contacts of S_1 individuals and I_2 individuals that leads to transmission of the disease. The same principles are used to construct the analogous expression for the second susceptible population.

The entire term given by 1 gives us the number of contacts of S_1 and both infectious classes that result in new cases of the disease in the N_1 population. The same is true for new cases of the disease in the N_2 population which is given by 2.

An important distinction to bear in mind about these infection events for S_1 and S_2 is that S_2's infection event is multiplied by N while S_1's infection event is independent of N. This factor N acts to put a dependency on group 2's epidemiology dynamics on population density.

Many SIRS models assume that the infection event is not affected by population density, and this assumption is common for simple models. However, in order to see the effects of population density on the spread of disease, we introduce the concept of an infection event that varies with changes as population density changes through time, and this is accomplished by our N factor.

The construction of the differential equations that model the changes in the infected populations is more intuitive after the explanation for the rationale behind the construction of the differential equations for the susceptible populations.

$$\frac{dI_1}{dt} = \beta_1 \left[\frac{\beta_1 I_1 + \beta_2 I_2 N}{\beta_1 N_1 + \beta_2 N_2 N}\right] S_1 - \gamma I_1 - (d + \delta) I_1$$

$$\frac{dI_2}{dt} = \beta_2 N \left[\frac{\beta_1 I_1 + \beta_2 I_2 N}{\beta_1 N_1 + \beta_2 N_2 N}\right] S_2 - \gamma I_2 - (d + \delta) I_2$$

The infected populations increase by the infection events that decrease the susceptible populations, with I_1 experiencing an increase with the same magnitude as the decrease experienced by S_1 due to the infection event, and I_2 experiencing an increase with the same magnitude as the decrease experienced by S_2 due to the infection event.

This class-transfer process highlights an important assumption: changing a person's class doesn't change their affiliation with the group they were initially a member of. For example, individuals that are a part of group 1, which has dynamics that are independent of population density, will remain a part of group 1 regardless of any sort of class change they experience (susceptible to infected, infected to recovered, or recovered to susceptible). The same is true for individuals that are members of group 2, which experiences epidemiological dynamics that are dependent on population density. This means that any individual will always or never be affected by the effects of population density. This exaggerated distinction between groups is important for identifying the role of population density on the spread of disease. And this biologically means that individuals will have the same type of lifestyle throughout the scope of this model because we assume that anyone's dependency or independency of population density on contact rates is a result of their profession which is unlikely to change over the time of this model.

The infection event is the only event that increases the size of the infected pool of individuals. There are two events that have a decreasing effect on the infected class: recovery and death.

Unfortunate individuals that happen to contract the disease still have the chance to undergo full recovery. The rate of recovery is symbolized by gamma (γ), and this per-capita recovery rate is multiplied by the total population size of the infected class to measure the theoretical amount of individuals that will recover in a specified amount of time. Gamma is the same for both infected classes, as the recovery rate will most likely be constant across the entire population N, regardless of which group an individual is categorized into.

The death rate of the infected populations is different from all the other classes. While the other classes have a death rate quantified by the per capita rate d, the infected classes have death rates that are quantified by $d + \delta$, and this is rationalized by the idea that infected individuals will most likely have a death rate that is higher than the natural death rate if the disease has severe symptoms, which indeed is the case with MERS. In the case that a disease does not have lethal

effects, delta will be 0. Like many of the other per-capita rates, this elevated death rate for the infected classes is the same for both infected classes since population density will likely have little effect on the death rate of individuals.

The differential equations that describe the dynamics of the recovered classes are much simpler because they have dynamics that do not directly depend on the complicated infection event. The changes in the recovered classes are only due to the simple, non-changing per-capita rates for recovery, death, and re-susceptibility or loss of immunity.

$$\frac{dR_1}{dt} = \gamma I_1 - \theta R_1 - dR_1$$

$$\frac{dR_2}{dt} = \gamma I_2 - \theta R_2 - dR_2$$

The recovered class experiences an increase in their population as infected individuals recover, but decrease as recovered individuals lose their immunity and as recovered individuals die.

After a certain period of time, individuals become susceptible to the disease again since their immunity to the disease is only temporary, as is the case with the related disease, SARS.

Recovered individuals are also vulnerable to death, and they experience the same death rate, d as susceptible individuals. When an infected individual recovers, he or she will lose their disease related symptoms, one of them being the elevated death rate. Recovered individuals have no advantage over susceptible individuals for escaping natural death and therefore share the same per-capita death rate, d.

MODEL SYMBOLS

There are quite a few symbols that were used in the construction of this epidemiology model. The tables that follow offer a concise overview of their role in the model.

Table 1 offers a brief description of the details concerning the differential equations that constitute the mathematical model for this study.

Symbol	Description	Units	Notes
$\frac{dS_1}{dt}, \frac{dI_1}{dt}, \frac{dR_1}{dt}$	Change in class (S_1, I_1, or R_1) population density over time	$\frac{\#\ people\ in\ class}{km^2 * day}$	Group 1 – Contacts are independent of population density
$\frac{dS_2}{dt}, \frac{dI_2}{dt}, \frac{dR_2}{dt}$	Change in class(S_2, I_2, or R_2) population density over time		Group 2 – Contacts are dependent on population density

Table 1. Condensed explanation of differential equations

In order to condense the mathematical equations that were used in this model, some variables were grouped, and Table 2 shows the groupings that are made for this model. The subscript of each variable denotes the group number of which that class is a part.

Symbol	Description	Units
N_1	$S_1 + I_1 + R_1$	$\frac{\#\ people}{km^2}$
N_2	$S_2 + I_2 + R_2$	
N	$N_1 + N_2$	

Table 2. Shorthand for class groups

There are several parameters that are used in this model, and Table 3 provides a description, as well as an estimation for their numerical value, for all the parameter symbols that are used in the differential equations that comprise the epidemiology model.

Symbol	Description	Numerical Value	Units
β_1	Contact rate of an individual in Group 1 and someone else	.1	$\frac{1}{day}$
$\beta_2 N$	Contact rate of an individual in Group 2 and someone else	(.000035)N	$\frac{km^2}{day * \#people}$
r	Reproductive factor	1	$\frac{1}{day}$
k	Carrying capacity	High – 13500 Low – 400	$\frac{\#people}{km^2}$
d	Natural death rate	.00003731	$\frac{1}{day}$
δ	Increased risk of death due to infection	.048	$\frac{1}{day}$
γ	Recovery rate	.036	$\frac{1}{day}$
θ	Re-susceptibility or loss of immunity rate	.0009132	$\frac{1}{day}$
p	Proportion of individuals born into Group 1	.5	N/A
1 – p	Proportion of individuals born into Group 2	.5	N/A

Table 3. Parameter list

The parameter that describes the per-capita reproduction rate, r is given a numerical value of 1 $\frac{1}{day}$. The positive value of r indicates that the population is growing, which follows the pattern

observed for the population size of the areas of interest in Jordan [9]. The exact value of r seemed a bit arbitrary though since extreme values of r didn't seem to affect the qualitative or even quantitative dynamics of the populations much.

The areas (Zarqa and Sakib) that are under study with this model have populations that are steadily increasing, but at a low percentage. We therefore deemed it to be appropriate to give the population a carrying capacity that was near, but greater than its initial population size.

β_1 is a parameter that represents the contact rate of an individual from Group 1 with another person in the population, independent of which group the other person belongs, while $\beta_2 N$ is another parameter that describes the contact rate of an individual from Group 2 with anyone else in the population, regardless of group affiliation.

There isn't much useful research available to quantify the numerical value of the β_1 parameter, but using the value of $.1 \frac{1}{day}$ in conjunction with the numerical value of β_2 gives us interesting epidemiology dynamics while other values do not.

β_2 is given a numerical value that is much lower than that of β_1 in order to counteract the factor of N. Since N is multiplied only to β_2 and not to β_1, we gave β_2 a smaller value so that $\beta_2 N$ and β_1 are somewhat comparable. Otherwise, dynamics would be greatly exaggerated for the populations described with $\beta_2 N$. For this reason, β_2 is given a value that is on the order of 3 magnitudes lower than β_1, which corresponds to the magnitude of increase that the N factor for population density provides. After this balancing of values, we observe what values of β_2 give the most interesting epidemiology dynamics and we settle on a numerical value of $.000035 \frac{1}{day}$.

The natural death rate ($\frac{1}{day}$) was calculated to be the inverse of the life expectancy of the average person in days. Since our study is focused on areas located in Jordan, the inverse of the life expectancy of the average citizen of Jordan was taken and applied to the natural death rate [7].

There is little data in the scientific literature about MERS since it has only been discovered recently. As a consequence of the limited amount of research that has been done on MERS, many parameter values had to be estimated. Following the idea that MERS is a coronavirus and is related to SARS, another coronavirus, estimates were based off of the data that was able to be gathered from the research that had been done on SARS. The elevated death rate due to infection (δ), recovery rate (γ), and re-susceptibility rate (θ) were estimated based on data from SARS research, and these rates are all measured in units of $\frac{1}{day}$.

It was observed that individuals that had died due to SARS, died within a period of approximately 3 weeks [8]. This time was inverted then converted into days to get the daily rate of death for infected individuals ($d + \delta$). Delta was calculated by subtracting the natural death rate from this infected death rate that was just calculated

It was also seen that full recovery from SARS was able to take place, but only after a period of time that was longer than the average time for SARS to cause a death [8]. This model used the inverse of 28 days (1 week longer than the elevated death rate for SARS) to approximate the value for the daily rate of recovery (γ). This recovery rate and the elevated death rate correspond well with each other and give us a mortality rate that is about 60%, as observed from the literature.

It was observed that, antibodies specific for SARS were retained in the body for a long period of time, and other specific immune response factors persisted for a period of about 3 years. We therefore proposed a small, but significant daily rate of loss of immunity (θ) which is the inverse of 3 years, after being converted to days.

In order to quantify the value for p (and thus the value for 1-p), we first assume that the proportion of individuals of N_1 to individuals of N_2 (N_1/N_2) would remain unchanged over the course of the epidemic, which isn't unreasonable considering the time-scope of the model. Under this assumption, we observe that p would be equal to the size of N_1 divided by the size of the total population, N. But in order to keep the model simple, we make p equal to the *initial* value of N_1 divided by the initial size of the entire population, N (N_1+N_2). This avoids the problem of introducing more variables into the already complex model. This method also allows the increase experienced by each susceptible population by births to be an increase that is weighted by their initial population size.

Quantifying the specific numeric values of p (p corresponds to proportion of births in Group 1, while (1-p) corresponds to proportion of births in Group 2) include estimating the proportion of the population whose contact rate is unaffected by population density, and in order to estimate the numeric value for p, we must take into account how the people in the total population spend their time. After some thought and deliberation, we speculate that p could likely be .5, although we will offer situations in which the value of p is changed in order to see the effects of a shifted proportion on disease dynamics. Even if p is significantly different from .5, the numerical value of .5 for the proportion is useful in better distinguishing the effects of population density on disease dynamics because this gives both populations equal weight in their growth due to reproduction and their initial population size.

MODEL ANALYSIS

Equilibria—When observing population dynamic trends in a mathematical model, researchers generally search for states of no change, called equilibria. Equilibrium values of each population can be calculated by setting their respective differential equations to zero and solving for the variable of interest.

Disease-free equilibria:

In the case of having no disease present, infected and recovered individuals become zero, and all terms being multiplied by those variables become zero as a consequence. In this special situation, our model becomes more simplified since there are no non-susceptible individuals, and the differential equations describing the susceptible individuals become simpler as well:

$$\frac{dS_1}{dt} = prN\left(1 - \frac{N}{K}\right) - \mathrm{d}S_1 = pr(S_1 + S_2)\left(1 - \frac{S_1 + S_2}{K}\right) - \mathrm{d}S_1 = 0$$

$$\frac{dS_2}{dt} = (1-p)rN\left(1 - \frac{N}{K}\right) - \mathrm{d}S_2 = (1-p)r(S_1 + S_2)\left(1 - \frac{S_1 + S_2}{K}\right) - \mathrm{d}S_2 = 0$$

and since the entire population N is comprised only of susceptible individuals, we can replace N with $S_1 + S_2$. After equating these new expressions to zero, we solve for S_1 in the first differential equation and S_2 in the second differential equation to get equilibria expressions for the two populations:

$$S_1 = pK\left(1 - \frac{d}{r}\right), \; S_2 = (1-p)K\left(1 - \frac{d}{r}\right)$$

Endemic equilibria:

The scenario of endemic equilibria restricts us from making the simplifications that we were able to make when calculating the disease-free equilibria. This is because both groups have non-negligible population sizes for the infected and recovered classes which prohibit us from ignoring their contributions in the differential equations in which they appear. Furthermore, the complex nature of the differential equations prevents us from being able to find an analytical expression for any of the populations in terms of parameters. However, graphical and numerical evaluations provide evidence for the existence of endemic equilibrium.

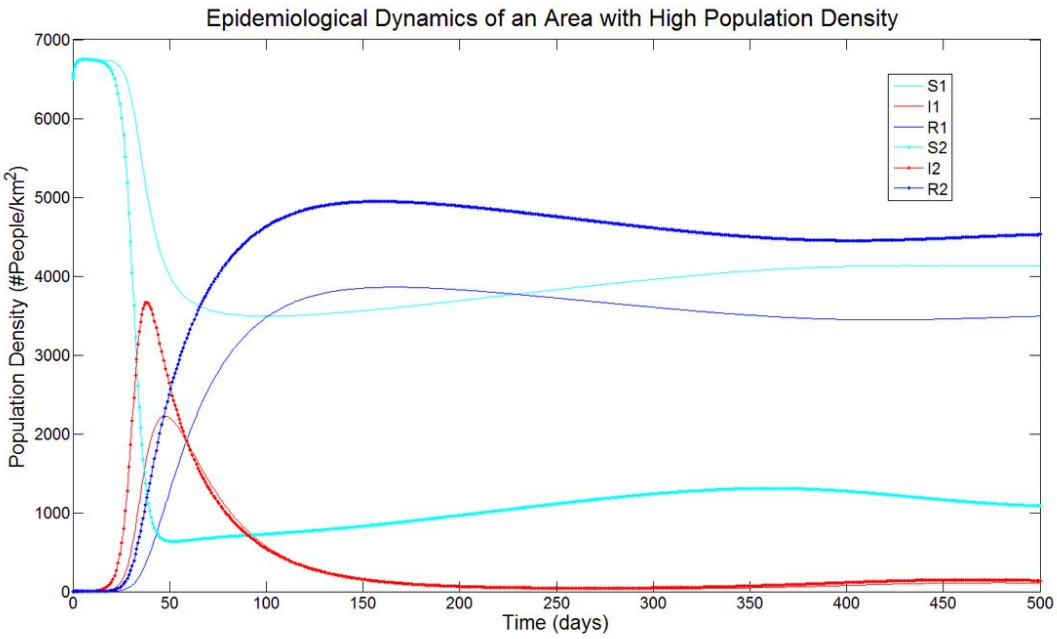

Fig. 1 Illustrates the theoretical dynamics of disease in a region of high population density

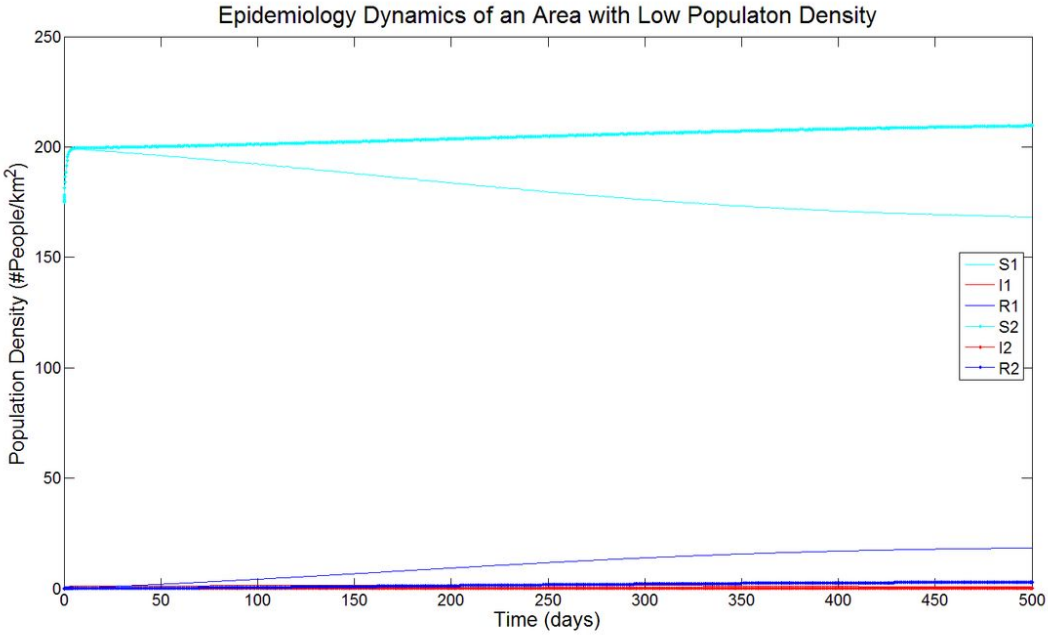

Fig. 2 Depicts the theoretical dynamics of disease in a region of low population density

Some of the populations are still changing near the end of the graphs, but if time is extended farther, equilibrium is established.

As seen in Fig. 1, it appears that group 2, the group that has contact rates that are dependent on population density, experiences dynamics that are similar to that of group 1, but are exaggerated. The corresponding increases and decreases taking place in the first group happen sooner and occur to a higher degree in the second group.

Equilibrium values for each group correspond to this observation with the susceptible population in group 2 being lower than the susceptible population in group 1 and both the infected and recovered populations from group 1 being lower than the infected and recovered populations in group 2.

The higher equilibrium value for the susceptible population in group 1 (compared with the equilibrium value for the susceptible population in group 2) correlates well with the idea that the populations from group 2, which had contact rates that were dependent on population density are affected to a higher degree than the populations that had contact rates that were not dependent on population density.

The same logic follows for the observations for the other groups. $I_{1,eq} < I_{2,eq}$ is observed and also contributes to the idea formulated from the relationship between $S_{1,eq}$ and $S_{2,eq}$ ($S_{1,eq} > S_{2,eq}$), that group 2 has exaggerated dynamics because it has contact rates that are dependent on population density, given the setting of a high population density. $R_{1,eq} < R_{2,eq}$ is true since there are more infected individuals in group 2 that can recover.

In contrast, Fig. 2 shows the opposite pattern evidenced in Fig. 1: group 1 has dynamics that vary more than group 2 in a low population density setting, and equilibrium relationships between corresponding groups are reversed: $S_{1,eq} < S_{2,eq}$, $I_{1,eq} > I_{2,eq}$, and $R_{1,eq} > R_{2,eq}$. The reversal of the patterns observed from Fig. 1 in Fig. 2 can be attributed to the small population density used in the model since all other parameter values were held constant.

Stability of equilibria—
Stability of disease-free equilibrium:

The disease-free equilibrium that was found earlier can be tested for stability mathematically by setting up an appropriate Jacobian matrix, and finding the corresponding eigenvalues. The Jacobian matrix we constructed has the structure

$$\begin{bmatrix} \frac{\partial}{\partial S_1}(\frac{dS_1}{dt}) & \frac{\partial}{\partial S_2}(\frac{dS_1}{dt}) & \frac{\partial}{\partial I_1}(\frac{dS_1}{dt}) & \frac{\partial}{\partial I_2}(\frac{dS_1}{dt}) & \frac{\partial}{\partial R_1}(\frac{dS_1}{dt}) & \frac{\partial}{\partial R_2}(\frac{dS_1}{dt}) \\ \frac{\partial}{\partial S_1}(\frac{dS_2}{dt}) & \frac{\partial}{\partial S_2}(\frac{dS_2}{dt}) & \frac{\partial}{\partial I_1}(\frac{dS_2}{dt}) & \frac{\partial}{\partial I_2}(\frac{dS_2}{dt}) & \frac{\partial}{\partial R_1}(\frac{dS_2}{dt}) & \frac{\partial}{\partial R_2}(\frac{dS_2}{dt}) \\ \frac{\partial}{\partial S_1}(\frac{dI_1}{dt}) & \frac{\partial}{\partial S_2}(\frac{dI_1}{dt}) & \frac{\partial}{\partial I_1}(\frac{dI_1}{dt}) & \frac{\partial}{\partial I_2}(\frac{dI_1}{dt}) & \frac{\partial}{\partial R_1}(\frac{dI_1}{dt}) & \frac{\partial}{\partial R_2}(\frac{dI_1}{dt}) \\ \frac{\partial}{\partial S_1}(\frac{dI_2}{dt}) & \frac{\partial}{\partial S_2}(\frac{dI_2}{dt}) & \frac{\partial}{\partial I_1}(\frac{dI_2}{dt}) & \frac{\partial}{\partial I_2}(\frac{dI_2}{dt}) & \frac{\partial}{\partial R_1}(\frac{dI_2}{dt}) & \frac{\partial}{\partial R_2}(\frac{dI_2}{dt}) \\ \frac{\partial}{\partial S_1}(\frac{dR_1}{dt}) & \frac{\partial}{\partial S_2}(\frac{dR_1}{dt}) & \frac{\partial}{\partial I_1}(\frac{dR_1}{dt}) & \frac{\partial}{\partial I_2}(\frac{dR_1}{dt}) & \frac{\partial}{\partial R_1}(\frac{dR_1}{dt}) & \frac{\partial}{\partial R_2}(\frac{dR_1}{dt}) \\ \frac{\partial}{\partial S_1}(\frac{dR_2}{dt}) & \frac{\partial}{\partial S_2}(\frac{dR_2}{dt}) & \frac{\partial}{\partial I_1}(\frac{dR_2}{dt}) & \frac{\partial}{\partial I_2}(\frac{dR_2}{dt}) & \frac{\partial}{\partial R_1}(\frac{dR_2}{dt}) & \frac{\partial}{\partial R_2}(\frac{dR_2}{dt}) \end{bmatrix}$$

The characteristics (sign and complexity) of the applicable eigenvalue (λ) will determine the stability of the disease-free equilibrium.

$$\det\begin{bmatrix} \frac{\partial}{\partial S_1}(\frac{dS_1}{dt}) - \lambda & \frac{\partial}{\partial S_2}(\frac{dS_1}{dt}) & \frac{\partial}{\partial I_1}(\frac{dS_1}{dt}) & \frac{\partial}{\partial I_2}(\frac{dS_1}{dt}) & \frac{\partial}{\partial R_1}(\frac{dS_1}{dt}) & \frac{\partial}{\partial R_2}(\frac{dS_1}{dt}) \\ \frac{\partial}{\partial S_1}(\frac{dS_2}{dt}) & \frac{\partial}{\partial S_2}(\frac{dS_2}{dt}) - \lambda & \frac{\partial}{\partial I_1}(\frac{dS_2}{dt}) & \frac{\partial}{\partial I_2}(\frac{dS_2}{dt}) & \frac{\partial}{\partial R_1}(\frac{dS_2}{dt}) & \frac{\partial}{\partial R_2}(\frac{dS_2}{dt}) \\ \frac{\partial}{\partial S_1}(\frac{dI_1}{dt}) & \frac{\partial}{\partial S_2}(\frac{dI_1}{dt}) & \frac{\partial}{\partial I_1}(\frac{dI_1}{dt}) - \lambda & \frac{\partial}{\partial I_2}(\frac{dI_1}{dt}) & \frac{\partial}{\partial R_1}(\frac{dI_1}{dt}) & \frac{\partial}{\partial R_2}(\frac{dI_1}{dt}) \\ \frac{\partial}{\partial S_1}(\frac{dI_2}{dt}) & \frac{\partial}{\partial S_2}(\frac{dI_2}{dt}) & \frac{\partial}{\partial I_1}(\frac{dI_2}{dt}) & \frac{\partial}{\partial I_2}(\frac{dI_2}{dt}) - \lambda & \frac{\partial}{\partial R_1}(\frac{dI_2}{dt}) & \frac{\partial}{\partial R_2}(\frac{dI_2}{dt}) \\ \frac{\partial}{\partial S_1}(\frac{dR_1}{dt}) & \frac{\partial}{\partial S_2}(\frac{dR_1}{dt}) & \frac{\partial}{\partial I_1}(\frac{dR_1}{dt}) & \frac{\partial}{\partial I_2}(\frac{dR_1}{dt}) & \frac{\partial}{\partial R_1}(\frac{dR_1}{dt}) - \lambda & \frac{\partial}{\partial R_2}(\frac{dR_1}{dt}) \\ \frac{\partial}{\partial S_1}(\frac{dR_2}{dt}) & \frac{\partial}{\partial S_2}(\frac{dR_2}{dt}) & \frac{\partial}{\partial I_1}(\frac{dR_2}{dt}) & \frac{\partial}{\partial I_2}(\frac{dR_2}{dt}) & \frac{\partial}{\partial R_1}(\frac{dR_2}{dt}) & \frac{\partial}{\partial R_2}(\frac{dR_2}{dt}) - \lambda \end{bmatrix} = 0$$

Basic Reproduction Number (R_0)—The value of R_0 in an epidemiological model can be thought of as the average number of new cases one infected individual can create when placed in a population of susceptible individuals. The next generation operator approach developed by Diekmann*et al. (1990)* was used to determine the value of R_0 [10]. This method involves creating a Jacobian matrix using equations representative of the infectious classes and manipulating the result into the next generation matrix with the form of $A=MD^{-1}$ where M>1 and D>1. In our case the next generation matrix is a two-by-two matrix where the eigenvalues can be found using the quadratic formula in the following form:

$$\lambda = \frac{(\mathrm{a}+\mathrm{d}) \pm \sqrt{(a+d)^2 - 4(ad-bc)}}{2}$$

Where values of a, b, c and d correspond to the entries of matrix A.

$$A = \begin{pmatrix} a & b \\ c & d \end{pmatrix}$$

The analysis showed that det(A)=0. Since the det(A) is the same as the product of the eigenvalues, the positive, non-zero eigenvalue is equal to tr(A)(the sum of the eigenvalues). Therefore,

$$R_0 = \left[\frac{\beta_1(\beta_1 P) + \beta_2 N(\beta_2 N(1-P))}{\beta_1 P + \beta_2 N(1-P)}\right]\left(\frac{1}{\delta+\gamma+\theta}\right)$$

This value of R_0 consists of the average rate of infectivity weighted by each group's number of contacts, multiplied bythe average amount of time that an individual spends in the infected class. Through this value we can determine whether the disease-free equilibrium will be locally stable with a given set of parameter values.

In order to see where the two R_0 values are derived from, we re-write the original R_0 equation:

$$R_0 = \left(\frac{\beta_1}{\delta+\gamma+\theta}\right)\left[\frac{\beta_1 P}{\beta_1 P+\beta_2 N(1-P)}\right]+\left(\frac{\beta_2 N}{\delta+\gamma+\theta}\right)\left[\frac{\beta_2 N(1-P)}{\beta_1 P+\beta_2 N(1-P)}\right]$$

Since the expressions in the square brackets are known to just be proportionality terms for contacts, we know that the expressions $\left(\frac{\beta_1}{\delta+\gamma+\theta}\right)$ and $\left(\frac{\beta_2 N}{\delta+\gamma+\theta}\right)$ symbolize R_{01} and R_{02}, respectively.

In some interesting cases we may also be able to observe situations where the individual R_0 in one group is greater than one while the other group's R_0 is less than one. This situation can arise by analyzing the respective R_0 values for each population, R_{01} for Group 1 and R_{02} for Group 2.

If analyzed graphically, it would be clear that the group with R_0 greater than one would have an endemic equilibrium numerically greater than that of the other group. However, since individuals in both groups can contact one another, the disease would still persist in the group where R_0 is less than one, even if the numerical value of the endemic equilibrium is miniscule.

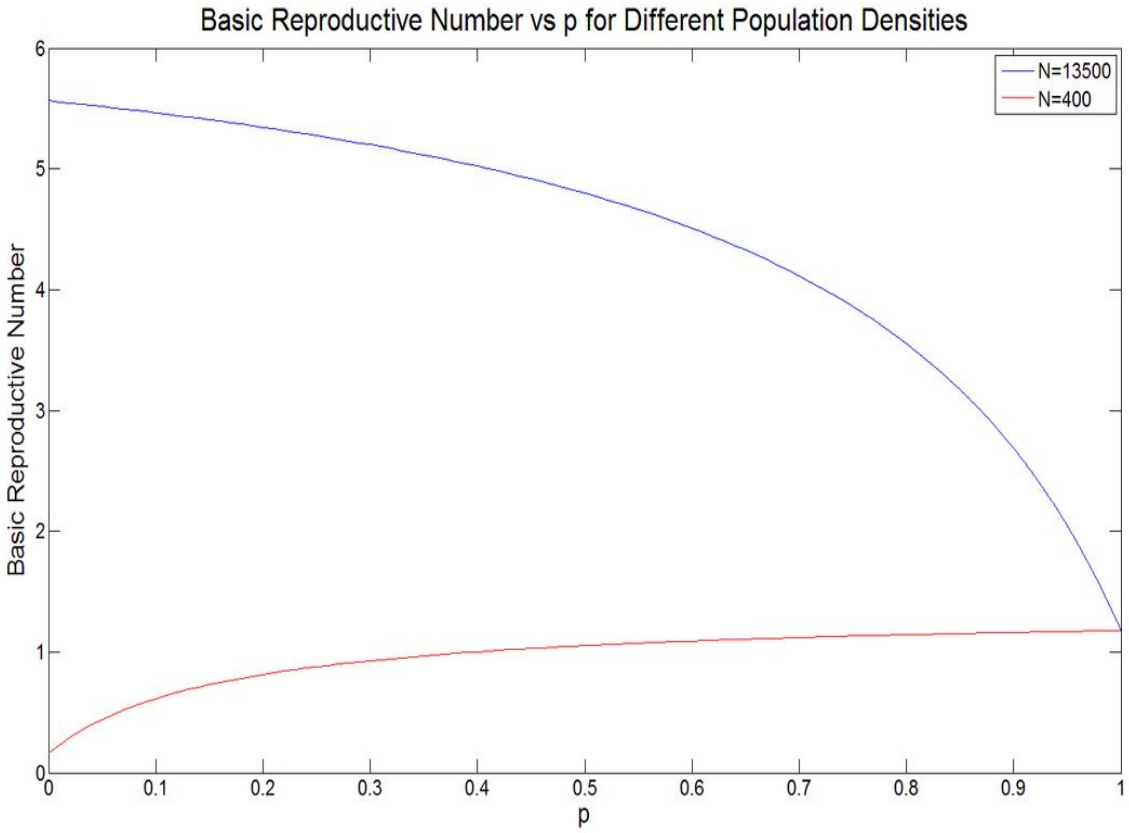

Fig. 3 Shows how R_0 varies as a function of p for different values of N

With the given set of parameter values, a threshold value of N was discovered where, above this threshold and regardless of the value of p, $R_0 > 1$. Mathematically, this is caused by higher values of N increasing the numerator more than they increase the denominator (N is squared in the numerator), and also because the value of β_1 is great enough to cause an assignment of p=1 to yield an $R_0 > 1$.

When N is less than the threshold value, values of p exist where $R_0 < 1$. This refers to instances where the density dependent group's contribution to R_0 is small enough that when $p < 0.5$, the total R_0 is less than one. However, when p=1 for any value of N, $R_0 > 1$ with the current value of β_1.

Further analysis reveals a mathematical phenomena in which R_0 shoots up as N approaches zero with the limit being the constant R_0 value when p=1. Figure 4 shows this interesting result by comparing the relationship between R_0, N, and p.

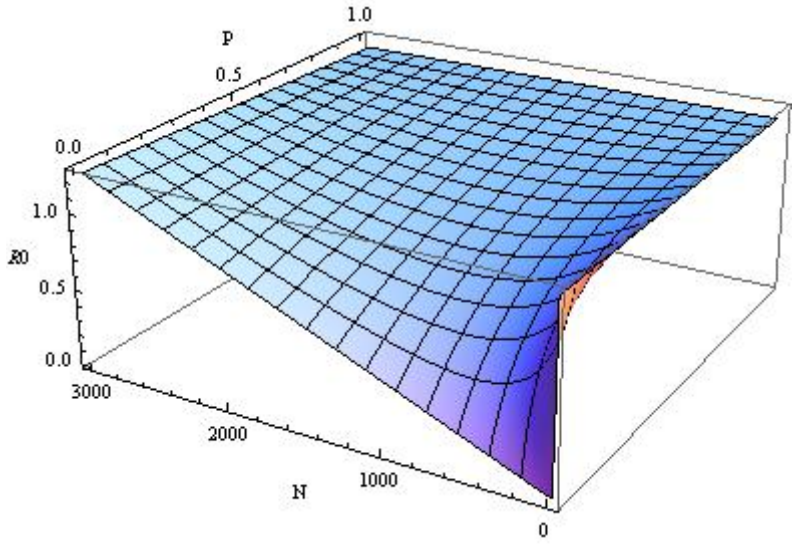

Fig. 4: Relationship between R_0, N, and p.

This occurs because as N approaches 0, the ratio of contacts occurring are all in group 1 with other individuals in group 1, that is, the R_0 for group 2 is almost 0. Therefore, nearly all contacts rely on the contact rate of group 1 which is the constant value R_{01}. Consider R_0 as separate values again. As N approaches 0, R_{02} goes to 0 while R_{01} remains constant.

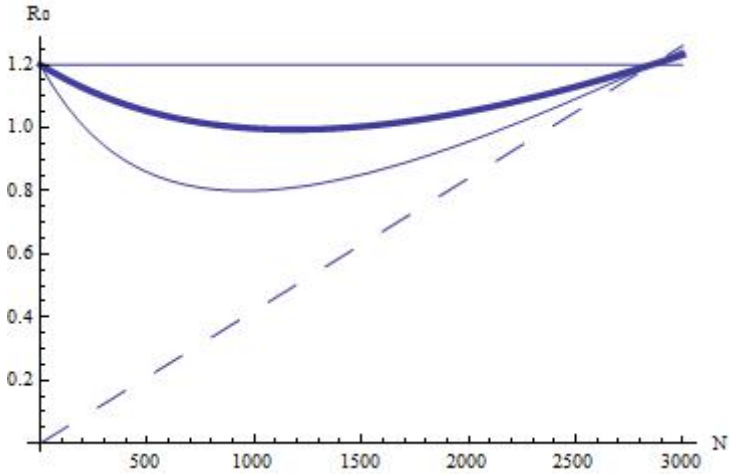

Fig. 5: Effects of population Density on R_0 for different values of p. Straight solid line: p=1; dashed line: p=0; thick curve: p=0.5; thin curve: p=0.25.

A more biologically relevant result of this model is represented in Figure 5. The horizontal straight line and the straight dashed line in this figure represent trends where p=1 and p=0 respectively. Any p value between 0 and 1 will produce a curve that lies between the two straight lines and will have a shape close to the two example curves where p=0.5 (thicker line) and p=0.25 (thin line). The significance of these curves is that there are local minima at certain

values of N where $R_0<1$. In the examples shown, the curve where p=0.25 has a local minima where the population density is around 950 people.

Discussion

After analyzing the theoretical patterns of development of the disease in two sub-populations in two areas of different population densities, we can make some general conclusions.

Because of the significant differences in the dynamics of each group in the two scenarios explored (high and low population densities—Fig. 1 and 2 respectively), and because the main difference between those groups can be attributed to their contact rates' dependency (or lack thereof) on population density, population density does seem to have a noticeable effect on the dynamics of disease spread, and accounts for the difference in the disease dynamics for the different groups in either city.

Groups that are dependent on population density are more affected by the disease when population density is high, but when population density is low, groups that are independent of population density are more affected. This is just another supporting factor for the large role that population density seems to play in epidemiological models that are constructed to be dependent on population density.

The value of the basic reproductive number (R_0) is very dependent on both p and N as evidenced by Fig. 3, though, the stability of the disease free equilibrium seems that it would be more dependent on the value of N first-and-foremost.

Future Directions

Future efforts to progress this model involve calculation of the endemic equilibrium and full stability analysis for all equilibria discussed. Also, more revisions and adjustments can be made to parameter values as more data becomes available for MERS to make our model more accurate and useful.

More detailed analysis of R_0 can help us better understand the effect of population density on the spread of disease. The variables that are most likely to vary in different settings–whether urban, suburban, or rural–is the population density (N) and the proportion of people in each group (p), and this idea could be explored more.

To give our model a broader scope, we can modify this model to predict patterns of interest for a wider demographic and possibly create a more global view of the spread of this disease instead of a localized study. In addition, we can note the effects of population density on other diseases instead of just MERS.

Going the other direction, we can also narrow our scope and take into account special event circumstances by seeing the effects of temporary but significant events like mass gathering proceedings such as the Hajj pilgrimage.

REFERENCES

1. Tatem A, Rogers D, Hay S. 2006. Global Transport Networks and Infectious Disease Spread: Adv Parasitol [Internet]. [Cited 2013 July 7]; 62: 293-343. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3145127/
2. Alwan A, Mahjour J, Memish Z. 2013. Novel coronavirus infection: time to stay ahead of the curve: EMHJ [Internet]. [cited 2013 July 1]; 19: 3-4. Available from: http://applications.emro.who.int/emhj/v19/Supp1/EMHJ_2013_19_Supp1_S3_S4.pdf
3. 2013 June 3. Deadly MERS virus spreads to Italy. Foxnews.com [Internet]. [cited 2013 July 1]. Available from: http://www.foxnews.com/health/2013/06/03/deadly-mers-virus-spreads-to-italy/
4. Hijawi B, Abdallat M, Sayaydeh A, Alqasrawi S, Haddadin A, Jaarour N, Alsheikh S, Alsanouri T. 2013. Novel coronavirus infections in Jordan, April 2012: epidemiological findings from a retrospective investigation. EMHJ [Internet]. [cited 2013 July 2]; 19: 12-18. Available from: http://applications.emro.who.int/emhj/v19/Supp1/EMHJ_2013_19_Supp1_S12_S18.pdf
5. Seto W, Conly J, Pessoa-Silva C, Malik M, Eremin S. 2013. Infection prevention and control measures for acute respiratory infections in healthcare settings: an update: EMHJ [Internet]. [cited 2013 July 2]; 19: 39-47. Available from: http://applications.emro.who.int/emhj/v19/Supp1/EMHJ_2013_19_Supp1_S39_S47.pdf
6. Abdel-Moneim A. 2014January 16. Middle East respiratory syndrome coronavirus (MERS-CoV): evidence and speculations. Arch Virol. [Internet]. [cited 2014 March 3]. Available from: http://link.springer.com/article/10.1007%2Fs00705-014-1995-5
7. evidence and speculations [Internet]. Medilexicon: [cited 2013 July 2]. Available from: http://www.medicalnewstoday.com/articles/261803.php
8. The World Bank [Internet]. c2013. The World Bank Group; [cited 2013 July 2]. Available from http://data.worldbank.org/indicator/SP.DYN.LE00.IN
9. 2003 May 7. Update 49-SARS case fatality ratio, incubation period. World Health Organization [Internet]. World Health Organization; [cited 2013 July 2]. Available from: http://www.who.int/csr/sarsarchive/2003_05_07a/en/
10. Dye C, Gay N. 2003 June 20. Modeling the SARS Epidemic. SCIENCE [Internet]. Published online 23 May 2003; 10.1126/science.108692. [cited 2013 July 2]; 300 1884-1885. Available from: http://www.vcu.edu/csbc/bbsi/inst/courses/courses-2004/Modeling/ModelingTheSARSEpidemic.pdf

11. The Demographic Profile of Jordan [Internet]. United Nations; [cited 2013 July 2]. Available from: http://www.escwa.un.org/popin/members/Jordan.pdf
12. Diekmann O, Heesterbeek J, Metz J. 1990. On the definition and the computation of the basic reproductive ratio R0 in models for infectious diseases in heterogeneous populations. J. Math. Biol. [Internet]. [cited 2013 July 2]; 28: 365-382. Available from: http://link.springer.com/content/pdf/10.1007%2FBF00178324.pdf
13. Ryder, Jonathan J., et al. "Host-parasite population dynamics under combined frequency-and density-dependent transmission." Oikos 116.12 (2007): 2017-2026. Available from: http://www.macs.hw.ac.uk/~awhite/Ryder_etal07b.pdf
14. 2014 January 27. Middle East respiratory syndrome coronavirus (MERS-CoV)-update. World Health Organization [Internet]. World Health Organization; [cited 2014 March 5]. Available from: http://www.who.int/csr/don/2014_01_27mers/en/