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ORIGINAL ARTICLE

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Modeling the Spread of Ebola

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Abstract

Objectives: This study aims to create a mathematical model to better understand the spread of Ebola, the mathematical dynamics of the disease, and preventative behaviors.

Methods: An epidemiological model is created with a system of nonlinear differential equations, and the model examines the disease transmission dynamics with isolation through stability analysis. All parameters are approximated, and results are also exploited by simulations. Sensitivity analysis is used to discuss the effect of intervention strategies.

Results: The system has only one equilibrium point, which is the disease-free state $(S,L,I,R,D) = (N,0,0,0,0)$. If traditional burials of Ebola victims are allowed, the possible end state is never stable. Provided that safe burial practices with no traditional rituals are followed, the endemic-free state is stable if the basic reproductive number, R_0, is less than 1. Model behaviors correspond to empirical facts. The model simulation agrees with the data of the Nigeria outbreak in 2004: 12 recoveries, eight deaths, Ebola free in about 3 months, and an R_0 value of about 2.6 initially, which signifies swift spread of the infection. The best way to reduce R_0 is achieving the speedy net effect of intervention strategies. One day's delay in full compliance with building rings around the virus with isolation, close observation, and clear education may double the number of infected cases.

Conclusion: The model can predict the total number of infected cases, number of deaths, and duration of outbreaks among others. The model can be used to better understand the spread of Ebola, educate about prophylactic behaviors, and develop strategies that alter environment to achieve a disease-free state. A future work is to incorporate vaccination in the model when the vaccines are developed and the effects of vaccines are known better.

1. Introduction

The Ebola virus was first identified in 1976 near the Ebola River infecting at least 280 people, and there were several outbreaks of Ebola virus disease (EVD) over the years. However, none of those were as serious as the current outbreak in West Africa, which started in March 2014 and is affecting the whole world.

Multiple species have been identified, but the present outbreak was caused by the Zaire species. The Centers for Disease Control and Prevention say that only mammals have shown the ability to spread and become

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infected with Ebola. The current outbreak in West Africa was started from a 2-year-old boy who was infected by a bat, and then Ebola has spread through human-to-human transmission via direct contact with bodily fluids of infected people, and with surfaces and materials contaminated with these fluids. That is why health care workers have frequently been infected while treating patients with suspected or confirmed EVD. It has not been proved that Ebola can spread among humans via airborne transmission, although Ebola goes airborne from pigs to monkeys [1].

Diagnosis of EVD without a laboratory test can be difficult. Since the symptoms start with fever, severe headache, muscle pain, and fatigue, the onset appears to be similar to that of flu. Progressed symptoms also cause misdiagnosis as malaria or typhoid, because diarrhea, vomiting, abdominal pain, and unexplained hemorrhage follow. The delay in laboratory tests for EVD multiplies secondary infections, slows quarantine or isolation, and increases fatality. Once infected, the incubation period is anywhere between 2 days and 21 days, but the average is 8−10 days [2]. The average fatality rate is around 50%, and case fatality rates vary from 25% to 90% [3].

Epidemiologists build rings around the virus to stop the spread of Ebola, which starts with the circle of people in direct contact with the patient. All the people in the circle are asked about their own circle of close contacts. With close observation and clear education, such as monitoring the symptoms and avoiding crowded public spaces among others, these rings are usually sufficient to stop the spread of EVD [4]. Isolation is absolutely necessary to bring an end to the spread of Ebola. However, it is not easy to decide whether to quarantine a person or not. According to Sankarankutty and Mekaru [5], quarantine is the separation and restriction of movement of healthy people who may have been exposed to an infected person, and isolation is the separation and restriction of movement of already infected individuals. Quarantine is a strong control strategy, but is excessive and can be counterproductive because many quarantined persons may turn out to be not infectious at all. Along the analogous reasoning, the World Health Organization does not recommend any ban on international travel or trade. Closing borders hinders the international community's ability to fight EVD. The World Health Organization and Centers for Disease Control and Prevention recommend isolation of the infected persons and self-monitoring of exposed individuals, on which our model is based.

Our objective is to better understand the spread of the Ebola virus, the mathematical dynamics of the disease, and preventative behaviors by creating a mathematical model. We create an epidemiological model with a system of nonlinear differential equations, and the model examines the dynamics of the system analytically and numerically. To see how closely our model describes an outbreak of EVD, we approximate all parameter values of the system. Since the model is applied to the recent outbreak in Nigeria, the data set from Nigeria is used to estimate parameter values. The first Ebola case in Nigeria appeared in July 2014, and Nigeria was declared Ebola free in October 2014 [6]. Discussions and conclusions follow with the combination of analytical stability analysis and simulation of the model in the last section.

2. Materials and methods

Our model is composed of five compartments, dividing the population studied into the following classes: S, L, I, R, and D; $S(t)$ is the number of susceptible individuals at time t; the class L is consisted of latent individuals, who are infected but not infectious yet, or individuals with symptoms but misdiagnosed by a doctor or the patient; I denotes the class of infected, infectious, and isolated individuals; R is the group of recovered individuals; and $D(t)$ represents the number of individuals who died of EVD at time t. Since the outbreaks and durations of the EVD epidemics are usually short time periods, we assume that the total population:

$$N(t) = S(t) + L(t) + I(t) + R(t) + D(t)$$

is constant, i.e., the number of births and deaths due to factors that are unrelated to Ebola is negligible in our study.

Transmission rates are expressed as the mass action terms:

$$\beta(1-p)S/N$$

where p denotes the proportion of susceptible professional health care workers to general susceptible individuals;

$$\beta = (p_\beta)(c_\beta),$$

where p_β is the probability of getting successfully infected when contacted with an infected person and c_β is the per capita contact rate. Once an Ebola patient is confirmed, the spread can be stopped systematically by activating control strategies such as identifying and following up contacts, setting up isolation units, training health care providers, providing protective clothing and gear, educating public about how Ebola spreads, prohibiting traditional burials of Ebola victims among others. Since the intervention takes time, the transmission rates are reduced gradually; hence, β is defined as a piecewise function of time. The contagion from latent individuals and isolated patients often occurs to health care providers. In the expression:

$$(\alpha_L L + \alpha_I I)pS/N,$$

α_L and α_I are the probabilities of getting positively infected when a healthcare provider comes into contact

with an individual from classes L and I, respectively, and these are also described by a piecewise function. In our study, γ models the infectivity rate between S and D; when a traditional burial ritual occurs, γ increases fast. The rate at which an asymptomatic infected individual is isolated and treated before a death occurs is represented by ϕ. Some Ebola patients recover from and some die of Ebola, which are modeled by ξ and τ, respectively. Researchers believe that individuals who have recovered from Ebola do not contract the EVD again in the same epidemic, although microscopic strands of a virus remain in sperm for 2 months after recovery. Hence, recovered individuals remain in class R, i.e., do not become susceptible. The rate at which an L class individual dies of Ebola without being confirmed and isolated is denoted by ψ. All transition rates are *per capita* rates on average. Figure 1 summarizes the model in a schematic form.

We can now write a system of nonlinear differential equations, and the governing compartmental model is the following:

$$\frac{dS}{dt} = -\beta(1-p)S\frac{L}{N} - p(\alpha_L L + \alpha_I I)\frac{S}{N} - \gamma S\frac{D}{N}$$

$$\frac{dL}{dt} = \beta(1-p)S\frac{L}{N} + p(\alpha_L L + \alpha_I I)\frac{S}{N} + \gamma S\frac{D}{N} - \phi L - \psi L$$

$$\frac{dI}{dt} = \phi L - \xi I - \tau I$$

$$\frac{dR}{dt} = \xi I$$

$$\frac{dD}{dt} = \psi L + \tau I$$

$$N = S + L + I + R + D$$

$$(1)$$

We find that the only equilibrium point of the system is the endemic-free equilibrium (EFE) $(N,0,0,0,0)$, by setting each of the derivatives of the system (Eq. 1) equal to zero. Applying stability analysis to the Jacobian of the system (Eq. 1) at EFE, we see that the end-state EFE is always unstable as long as γ is positive; i.e., if the traditional burial rituals such as touching corpses are

allowed, the system can never achieve an endemic-free state. Hence, for the rest of analysis, we assume that $\gamma = 0$, which reflects the reality in Africa: to stop the spread of Ebola, touching the dead from Ebola is prohibited; cremation of Ebola victims is required, but some family and friends of victims bribe officials to have traditional funerals.

The basic reproductive number R_0 is the average number of secondary cases caused by a typical single infected individual; hence, the disease spreads if $R_0 > 1$ and it dies out if $R_0 < 1$. To calculate R_0, we used the next generation matrix method, which was discussed by Diekmann, Heesterbeek and Metz [7,8]. We find that:

$$R_0 = \frac{1}{2}\left[\frac{\beta(1-p)+\alpha p}{\phi+\psi}\right.$$

$$\left. + \sqrt{\left(\frac{\beta(1-p)+\alpha p}{\phi+\psi}\right)^2 + \frac{4p\alpha\phi}{(\xi+\tau)(\phi+\psi)}}\right]$$

In order to interpret R_0 in terms of the dynamics of Ebola spread, we rewrite (Eq. 2) as follows:

$$\frac{\beta(1-p)+\alpha p}{\phi+\psi} < R_0$$

$$< \frac{\beta(1-p)+\alpha p}{\phi+\psi} + \sqrt{\frac{p\alpha\phi}{(\xi+\tau)(\phi+\psi)}}$$

$$(2)$$

The expression $1/\phi+\psi$ represents the average time an infected person stays in class L, so the first sum of the basic reproductive number is the proportion of susceptible individuals who become infected. Recall that once a patient is isolated, only health care givers have the possibility of getting infected from the isolated patient. That is why β does not appear in the second fraction, which shows the fraction of health providers who become infected. The product $(\tau+\xi)(\phi+\psi)$ indicates entering I after entering L. Since R_0 is an indicator of how fast a disease spreads or whether it dies out, Ebola control strategies should aim to reduce the value of the basic reproductive number when an outbreak occurs. Therefore, we find a parameter to which the system is
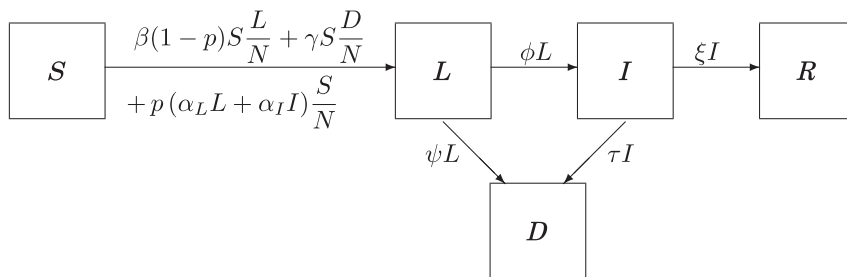

Figure 1. A schematic diagram of the model.

most sensitive using sensitivity indices of R_0 with respect to all parameters that can be controlled by intervention policies in a later section.

Assuming that $\gamma = 0$, the Routh−Hurwitz criteria [9] show that EFE is locally asymptotically stable only if the follwoing threshold condition is met:

$$T = \frac{(\xi + \tau)(\beta(1-p) + \alpha p) + \alpha p \phi}{(\xi + \tau)(\phi + \psi)} < 1 \qquad (3)$$

We now need to estimate the values of model parameters in order to establish model predictions. We are also very interested in examining how closely our model activity agrees with the behavior of Nigeria's recent Ebola epidemic, i.e., comparing the model behaviors with observed data. Since the epidemic in Nigeria started in July 2013 and Nigeria was declared "Ebola free" in 3 months, we test our model against the Nigerian case. Although a good set of data is available from the Nigeria epidemic, which we use to estimate parameter values in this section, the data set is very small, so we can obtain only rough approximations for some of the parameters. It is also due to the absence of precise data, especially when we use the information from West Africa's epidemic. To estimate the following parameter values, we use data from cases in Nigeria [6] and West Africa [3] in 2014:

$\phi = (1/9)(p_I)/$d: The incubation period varies between 2 days and 21 days; the average incubation time is 8−10 days; the onset of symptoms occurs 9 days on average after infection; p_I is the proportion of infected and isolated patients to the patients who are infected but neither confirmed nor isolated; p_I varies depending on which area. As soon as the first case was confirmed, an Ebola incident management center was activated and a very high isolation rate was achieved in Nigeria, close to 90% (1 probable, 19 confirmed cases, and the 1st case was not confirmed fast enough), which was the main reason why the epidemic was stopped so fast; p_I was much less in West Africa in 2014.

$\xi = (1/18)(p_R)/$d: Generally, a patient requires a few weeks of recovery time; the average recovery time is 18 days; p_R denotes the probability of recovery; 60% of 20 Ebola patients from Nigeria had beaten the virus, although about 50% of Ebola patients have survived in general in the present epidemic in West Africa.

$\tau = (1/8.5)(1 - p_R)/$d: Death, if it occurs, takes typically 6−16 days from the start of symptoms, between 8 days and 9 days on average; $1 - p_R$ was 0.4 in Nigeria; $1 - p_R = 0.5$ in West Africa.

$\psi = 1/(9 + 7)(1 - p_I)/$d: The average incubation period plus days of suffering before death is 9 days plus 7 days on average; when patients are not isolated and symptoms are not tended appropriately, death, when it happens, occurs a bit sooner than when patients are isolated and tended, i.e., 7 days rather than 8.5 days on

average; $1 - p_I$ was about 10% in Nigeria and much higher in West Africa in 2014.

$p = 0.1$: Professional health care providers are about 10% of the contact population.

$\alpha_L = \alpha_I = \alpha = 1.5*\beta$: Twelve of Nigeria's 20 patients were exposed in two health facilities in Lagos; two nurses were infected while providing care to one Ebola patient in Texas; many doctors, nurses, and hospital aides were infected in West Africa; only 10% of the contact population is health care providers. It is clear that α is greater than β, so we will use $\alpha = 1.5\beta$.

$$\beta = \beta(t) = \begin{cases} \beta_i & t \leq \eta \\ \beta_l + (\beta_i - \beta_l)e^{-q*(t-\eta)} & t > \eta \end{cases}$$

is defined as a piecewise function. Once an Ebola patient is confirmed, stopping the spread should be methodically organized by following contacts and self-monitoring of the contacted persons. Hence, the crucial point is the beginning of the outbreak of the L class, and the effect of the intervention is gradual, i.e., the transmission rates are reduced gradually. Chowell et al [10] assume that the transmission rate decreases from β_i to β_l according to the function similar to $\beta(t)$ above; η is the time at which the effect of interventions start and q controls the transmission from β_i to β_l. The first patient of the Nigerian outbreak showed symptoms on July 17, 2013 and arrived in Nigeria on July 20, 2013 and Nigeria's Ebola Incident Emergency started on July 23, 2013. Hence, we choose $\eta = 7$, so $q = ln(2)/7$. Since the outbreak starts with a constant number of patients, often just one, and the incubation period is 9 days on average, for the first 9 days or so, we may assume that $dI/dt \approx 0$ and $S \approx N$. The expression:

$$dI/dt = \phi L - \xi I - \tau I = 0$$

implies that $I = \phi L/(\xi + \tau)$. If we substitute $I = \phi L/(\xi + \tau)$ and $S/N = 1$ into the second equation of the system (Eq. 1), we have:

$$dL/dt = \{\beta_i(1-p) + \alpha p[1 + \phi(\xi + \tau)] + \gamma - \phi - \psi\}L,$$

where β_i is the value of β when an outbreak occurs. When the daily infection figure is given, the cumulative of the daily infection, L, is obtained:

$$L(t) = L(0)exp\{[\beta(1-p) + \alpha p[1 + \phi(\xi + \tau)] + \gamma - \phi - \psi]t\};$$

$$ln[L(t)] = L(0)\{\beta(1-p) + \alpha p[1 + \phi(\xi + \tau)] + \gamma - \phi - \psi\}t.$$

Employing the data of Nigeria's case for the first 12 days and using PolynomialFit of Maple, we estimated that the slope is about 0.167. Now we can solve the equation:

$$\beta_i(1-p) + 1.5*\beta_i p[1 + \phi(\xi + \tau)] + \gamma - \phi - \psi = 0.167$$

to obtain the value of β_i, since all values of model parameters were estimated earlier. In result, $\beta_i \approx 0.221/$
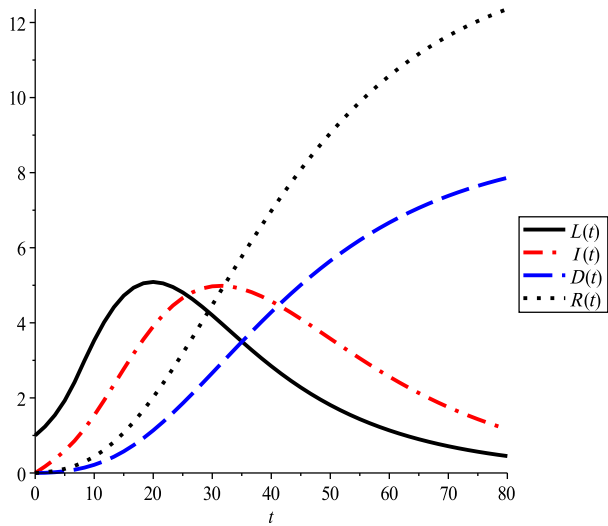
Figure 2. Nigeria case

The parameters to which our system is most sensitive are β over all and then α, which can be influenced by intervention strategies. (Sensitivity indices are discussed in Section 4.) We can use the model to better understand the spread of Ebola, educate about prophylactic behaviors, and develop strategies that alter environment to achieve disease free state.

4. Discussion

To examine how closely our model behavior describes the Nigeria case, we run simulations using the parameter values that we estimated in the previous section with the initial condition:

$$[L(0), I(0), R(0), D(0)] = (1, 0, 0, 0).$$

We varied N and $S(0) = N - 1$ accordingly; i.e., our assumption has been that Ebola starts with one infected person, which was the case in Nigeria. Since a total of 894 contacts were made, we tried $N = 894$ and $N = 10,000$ among others. The overall numbers of infections, recoveries, and deaths over about 3 months are consistent regardless of values of N, and are shown in Figure 2.

The numbers of infections, recoveries, and deaths in Figure 2 are a bit greater than, but very close to, the real data in Nigeria. $R(t)$ and $D(t)$ in the model agree with the data very well—12 patients were recovered from, and eight died of, Ebola in Nigeria. The figure shows a couple of more Ebola patients at the end of the model time line. Note that the first patient did not arrive in Nigeria until July 20, 2013 although the patient showed symptoms on July 17, 2013, and multiple contagions that occurred before his arrival were not part of the data of the Nigerian case. This also explains the following: it took longer to be free of Ebola in Figure 2—Nigeria was declared Ebola free on September 24, 2013; new cases in the model
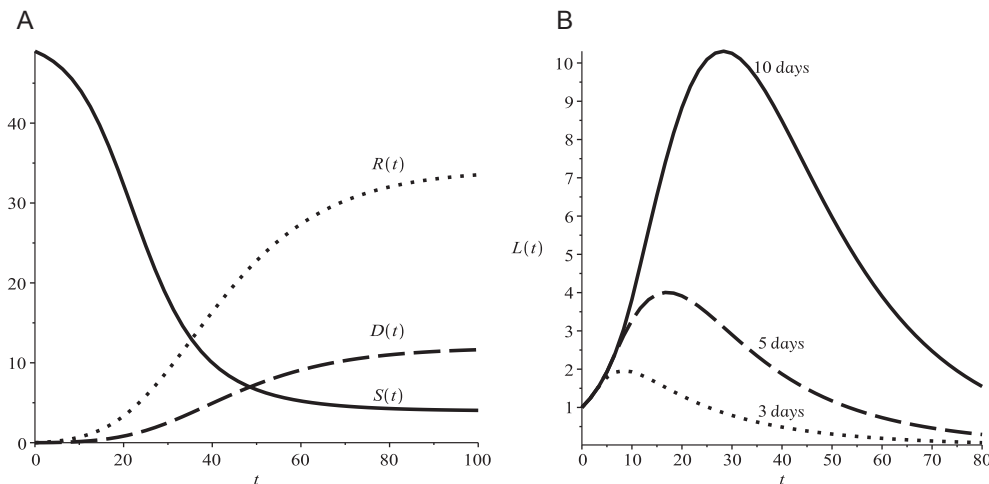
d and the initial value of α is $\alpha_i \approx 0.332/d$. To find β_l, we use the threshold condition (3),

$$\frac{(\tau + \xi)[\beta_l(1 - p) + 1.5 * \beta_l p] + 1.5 * \beta_l p\, \phi}{(\tau + \xi)(\phi + \psi)} = \frac{1}{2}$$

Solving for β_l using other values of model parameters, we obtain $\beta_l = 0.043$ and $\alpha_l = 0.065$.

3. Results

The basic reproductive number is provided in Section 2.

Our model behaviors correspond with empirical facts. The model can predict the total number of infected, number of deaths and duration of outbreaks among others (see Discussions below).

Figure 3. Controlling infection rates. (A) No ring. (B) Threshold days.

figure were confirmed a bit later—confirmations of new cases were most active around August 1, 2013 in Nigeria.

Since our model behaviors correspond to empirical facts, we can predict the number of infections and durations of the spread, and develop control strategies using the model. The basic reproduction number R_0 measures and provides a point at which a stable system turns into an unstable one or vice versa. With β_i, we obtain that $R_0 \approx 2.57$, which is much greater than 1, so the disease spreads fast unless control policies are applied urgently. Let us assume that a small remote village has an infected person, who is isolated and symptoms are treated, but no ring is built to stop the spread of Ebola; in this case, Ebola infects almost 90% of villagers, as shown in Figure 3A, which used parameter values obtained from West Africa cases and the initial condition:

$$[S(0), L(0), I(0), R(0), D(0)] = (50, 1, 0, 0, 0).$$

To see how a small perturbation made to a parameter q affects the basic reproductive number R, we define the sensitivity index of R for q as follows:

$$S_q = \frac{\partial R}{\partial q}\frac{q}{R}$$

In order to determine parameters to which our system is most sensitive, we find the sensitivity indices of R_0 for all parameters that can be influenced by intervention strategies; the system is most sensitive to β and then to α. Since decreasing the transmission rate β means to reach β_l from β_i as soon as possible, the time between the outbreak of Ebola and the start of the intervention should be minimized. Training staff and being equipped with medical supplies should be in place before an outbreak. Emory University Hospital in Atlanta, GA, USA, is an excellent example. Figure 3B shows the dynamics of infected cases depending on the days of full compliance. Lingering Ebola in West Africa implies that control policies are not fully complied.

The best way to eradicate Ebola is to develop a vaccine and vaccinate people. Since vaccines are being developed, although only in a trial phase, the future work of this research is to incorporate vaccination in the model and answer who should be vaccinated and when by studying the dynamics of the disease.

Conflicts of interest

The authors have no conflicts of interest to declare.

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