Modeling the Impact of Behavior Change on the Spread of Ebola

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Abstract We create a compartmental mathematical model to analyze the role of behavior change in slowing the spread of the Ebola virus disease (EVD) in the 2014–2015 Western Africa epidemic. Our model incorporates behavior change, modeled as decreased contact rates between susceptible and infectious individuals, the prevention of traditional funerals, and/or increased access to medical facilities. We derived the basic reproductive number for the model, and approximated the parameter values for the spread of the EVD in Monrovia. We used sensitivity analysis to quantify the relative importance of the timing, and magnitude, of the population reducing their contact rates, avoiding the traditional burial practices, and having access to medical treatment facilities. We found that reducing the number of contacts made by infectious individuals in the general population is the most effective intervention method for mitigating an EVD epidemic. While healthcare interventions delayed the onset of the epidemic, healthcare alone is insufficient to stop the epidemic in the model.

Keywords Ebola virus disease · EVD · Mathematical model · Reproductive number · Behavior changes · Epidemic model · Differential equations · Western Africa
1 Introduction

Ebola virus disease (EVD) is a zoonotic tropical disease [36] with an average fatality rate of 50% and a range of 25–90% in past outbreaks. It was first identified in 1976 in Yambuku, Zaire and Nzara, South Sudan [34]. While its circulation among humans is rare, around 30 outbreaks occurred since EVD was first identified, causing less than 1,600 deaths before 2014 [36]. However, the current West Africa 2014 outbreak has led to more than 28,600 probable cases and 11,300 deaths [32].

Typical symptoms of the disease include fever, weakness, and diarrhea. Bleeding complications occur in less than half of all infectious people, and heavy bleeding is relatively rare. EVD’s incubation period, i.e. the time from infection of the virus to onset of symptoms, is typically between five and seven days, but can range from 2 to 21 days. Humans are not infectious until they develop symptoms [34]. Blood samples usually start to show positive results by PCR one day before the symptoms appear [36], which have been used to confirm 15,216 cases since the onset of the West Africa 2014 EVD epidemic [32]. Early supportive care with rehydration, symptomatic treatment improves survival rate, but no licensed treatments proven to neutralize the virus are available yet, though blood, immunological, and drug therapies are under development [34].

Although the reservoir for EVD is in the animal population, once a human is infectious it can be sustained through person to person transmission until the conditions change. The infection spreads through direct contact with bodily fluids such as blood, vomit, urine, or sweat. Transmission can also occur through contact with objects contaminated by bodily fluids. EVD can persist for several hours after the death of an infectious person and traditional burial practices, which involve bathing the bodies contributes to the spread of infection, thus accelerating the early spread of the infection [36]. The primary transmission routes are through individuals in close contact with the infectious person, such as health workers and family members.

Prior to the current West African 2014 EVD outbreak, the epidemics were in rural areas. These outbreaks were quickly controlled with contact tracing and isolation and quarantine of the patients to break the chain of transmission. The previous epidemics were mitigated by combining the active isolation of people who came in contact with infected individuals, an effective community response, and preventative education programs [36]. The community support is important for identifying and isolating infectious people and stopping traditional funerals where people can come in contact with infectious postmortem bodily fluids.

Early EVD models were developed to quantify transmission in different settings (illness in the community, availability of medical care, and traditional burial) [8, 21]. These models simulated the 1995 EVD outbreak in the Democratic Republic of the Congo, the 2000 outbreak in Uganda, and the current outbreak in Liberia and Sierra Leone. Although the models took into account common places where infection spreads, they failed to consider different specialized medical care and funeral settings, such as EVD Treatment Centers, local EVD Community Centers, and home-based medical care respectively. These subclasses were considered by Lofgren et al. [22]
to identify where healthcare-only interventions would be the most effective. They found that healthcare initiatives can decrease the burden of the disease significantly on a community, making it a key role in mitigating the EVD epidemic.

Recent models forecasted disease progression in Sierra Leone and Liberia during the epidemic to compare the potential impact of some other common interventions, such as contact tracing, medical care access, as well as pharmaceutical intervention [10]. Rivers et al. adapted Legrand et al.’s EVD epidemic model, and determined that increased contact tracing in addition to infection control could have a substantial impact on the number of EVD cases, though they also predicted that this would not be sufficient to halt the progression of the epidemic [10].

Most models for the recent West Africa EVD are based on ordinary differential equation (ODE) compartmental models [5, 8–10, 10, 14, 16, 17, 27, 28, 28], network-models [2, 13, 18, 26, 39], or individual based models (IBMs) [24, 29, 33]. The ODE compartmental models are the easiest to analyze and estimate threshold conditions for an epidemic. The network models can capture the complexity of human contact interactions, but are usually static and don’t account for the rapid change in the contact patterns of an infectious person. The large-scale IBMs usually require synthetic population data that is not yet available for this epidemic.

In past EVD epidemics, behavior change has been the primary method to bring epidemics under control [15]. These behavior changes, coupled with community support and prevention education, are key to mitigating ebola outbreaks. Most of the existing models do not directly account for behavior change, and therefore cannot accurately reproduce, or forecast, the transmission pathways. In our model, we account for behavior changes as they affect the contact rates between susceptible and infectious individuals, the prevention of traditional funerals, and/or increased access to medical facilities.

We found that the most effective intervention method for mitigating an EVD epidemic is reducing the number of contacts made by infectious individuals in the general population. While increasing medical care access delayed the onset of the epidemic, this form of intervention failed to prevent or stop the epidemic overall. One way to measure the impact of behavior changes or medical interventions dynamic effects on the transmission rate is to measure the resulting change in the effective reproductive number of how many new infections that add a single new infected person would create.

After describing the mathematical model and the parameters, we derive the basic and effective reproduction numbers and use sensitivity analysis to quantify the relative importance of the behavior changes and availability of medical facilities in stopping the epidemic. We find that the effective reproduction number is most sensitive to the number of contacts that an infected person has with the susceptible population.
2 Mathematical Model

This model in Fig. 1 can be expressed as the system of ordinary differential equations (ODEs):

\[
\begin{align*}
\frac{dS}{dt} &= -\lambda S \\
&= -\alpha_i I - \alpha_m M - \alpha_f F \\
\frac{dE}{dt} &= \lambda S - \gamma_{ei} E \\
&= \alpha_i I + \alpha_m M + \alpha_f F - \gamma_{ei} E \\
\frac{dI}{dt} &= \gamma_{ei} E - (\gamma_{if} + \gamma_{ib} + \gamma_{ir} + \gamma_{im}) I \\
\frac{dM}{dt} &= \gamma_{im} I - (\gamma_{mr} + \gamma_{mb}) M \\
\frac{dB}{dt} &= \gamma_{ib} I + \gamma_{mb} M + \gamma_{fb} F \\
\frac{dR}{dt} &= \gamma_{ir} I + \gamma_{mr} M.
\end{align*}
\]

\(F\)  
\(M\)  
\(I\)  
\(B\)  
\(S\)  
\(E\)  
\(R\)  
\(\lambda\)  
\(\gamma_{ei}\)  
\(\gamma_{if}\)  
\(\gamma_{ib}\)  
\(\gamma_{ir}\)  
\(\gamma_{im}\)  
\(\gamma_{mr}\)  
\(\gamma_{mb}\)  
\(\gamma_{fb}\)

Fig. 1 When susceptible people \((S)\) are infected, they progress to the exposed, but not infectious, state \((E)\). From there, they become infectious \((I)\) to the susceptible population. An infected person either enters a medical facility \((M)\), or does not. If they do not enter a medical facility, they may recover \((R)\) or die. When they die, they may have a traditional funeral \((F)\), where others can be infected, or a ‘safe’ burial \((B)\). People in a medical facility are more likely to recover and if they die that have a safe burial. The dynamics are described by differential equations \((1)\).
The susceptible population, $S$, is infected at a rate $\lambda$ and progresses to an infected, but not infectious, exposed ($E$) state. Then they advance to an infectious state in the general population, $I$, (at rate $\gamma_{ei}$). An infectious person can recover, $R$, (at rate $\gamma_{ir}$), go to a medical treatment facility (at rate $\gamma_{im}$), or, if they die, the person either as a traditional funeral, $F$, (at rate $\gamma_{if}$), or is safely buried, $B$, (at rate $\gamma_{ib}$). The people in a medical facility can recover, $R$, at an adjusted rate $\gamma_{mr}$, or die and be safely buried (at rate $\gamma_{mb}$). In this simplified model, because of the short duration of the epidemic, we do not include natural birth, death, or migration into, or out of, our population.

We have included two formulations for rates that people are infected, $\lambda S = \alpha_i I + \alpha_m M + \alpha_f F$. The more traditional formulation is expressed in terms of the susceptible viewpoint where the force of infection, $\lambda$, represents the rate that the susceptible population is being infected. The other formulation is expressed in terms of the infectious viewpoint where the force from infectious, $\alpha_*$, represents the rate that an infectious person in compartment $* = I, M, \text{ or } F$ infects the susceptible population. The mathematical models are equivalent when $\lambda = (\alpha_i I - \alpha_m M - \alpha_f F)/S$.

We include the force from infectious viewpoint because it clarifies the mathematical analysis, such as computing the basic reproductive number, and has advantages in estimating the model parameter values when only a small fraction of the population is infected.

The model parameters $\lambda$ and $\alpha_*$ are nonlinear functions of other variables and time. To simplify the notation, we will not explicitly list all of the parameters unless doing so clarifies the analysis. In particular, the time variable, $t$, will be listed when we want to emphasize that contact rates or healthcare availability, can change in time. A description of the parameters used and the baseline values are in Table 1. The rate $\gamma_{*}$ is the progression from state $I$ to another state $*$, where $* = M, F, B$, or $R$. Similarly, the rates $\gamma_{e*}$ and $\gamma_{m*}$ are the progressions out of states $E$ and $M$ respectively into other states $*$.

We use the model to investigate the impact of behavior changes and the availability of medical facilities on the spread of the 2014–2015 EVD epidemic in Western Africa. We ignored the natural birth-death cycle in the model because of the short duration of the epidemic. We did not include the migration of people in, and out, of the modeled population, as would need to be included if this local population model is used as the local community in a larger networked model. These effects can be easily added to the model and would not affect the conclusions of our study.

## 2.1 Rates of Infection

Although both the susceptible and infectious viewpoint models are identical, the model parameters that determine the rates of infection are different. When there are only a few people infectious, as in the EVD epidemic, then there are advantages to estimating the parameters that define the force from infectious, $\alpha_*$, rather than the traditional force of infection, $\lambda$. 
2.1.1 Force of Infection

The force of infection, \( \lambda \), can be decomposed into sum of three terms, \( \lambda = \lambda_i + \lambda_m + \lambda_f \), where each term is factored into

\[
\lambda_* = c_s \beta_* P_* = \begin{pmatrix}
\text{Number of contacts a susceptible has per day} \\
\text{Probability of transmission per contact with someone in } *
\end{pmatrix}
\begin{pmatrix}
\text{Probability the contact is with someone in state } *
\end{pmatrix}
\]

Here the subscript \( * = i, m, f \) refers to one of the infectious states, \( I, M, \) or \( F \). A susceptible person has \( c_s \) contacts per day and the probability of transmission per contact with an infected person is \( \beta_* \). There are a total of \( c_s S \) contacts per day by people in the susceptible population out of \( C_{tot}(t) = c_s S + c_e E + c_i I + c_m M + c_f F + c_t R + c_b B \) total contacts in the entire population. The probability that a random contact by a susceptible is with a person in state \( I \) is \( P_i(t) = c_i I(t)/C_{tot}(t) \) and changes exponentially early in the epidemic. The formulas for the other states are similar.

2.1.2 Force from Infectious

To consider how infection spreads from the perspective of the infectious individuals, we define \( \alpha \) as the force of infection from the infectious population. This force (\( \alpha_i, \alpha_m, \) and \( \alpha_f \)) depends upon what state the infectious population is in. Here we assume that the exposed population is not infectious, \( \alpha_e = 0 \). The rate that the susceptible population is being infected is the sum of the product of each of these forces times the people who are in that state, (1a).

Each force from the infectious states \( I, M, \) and \( F \) can be decomposed into three factors

\[
\alpha_* = c_* \beta_* P_* = \begin{pmatrix}
\text{Number of contacts an infectious person in state } * \text{ has per day} \\
\text{Probability of transmission per contact from someone in } *
\end{pmatrix}
\begin{pmatrix}
\text{Probability the contact is with a susceptible}
\end{pmatrix}
\]

The number of contacts per day, \( c_* \), a person in state * has depends upon the state. A contact is defined as an interaction between two individuals where the disease transmission could take place. We assume that the infectious populations, \( I \) and \( M \), have fewer contacts per day than the susceptible and exposed populations. The contacts for the people in a traditional funeral, \( F \), are averaged over the length of time for the funeral. In this model, we treat every contact as an independent event and do not explicitly account for repeated contacts between the two same individuals.

The probability that contact by an infectious person is with a susceptible person, \( P_s \), depends on how the infectious person mixes with the current population. These
contacts are not random and, to be accurate, the model should include a mixing matrix between people in each of the states [11, 19]. For simplicity, we assume that the mixing is random and will investigate the importance of this assumption in a later analysis of this model. The probability that a random contact will be with a susceptible person is $P_s(t) = \frac{c_s S(t)}{C_{tot}(t)}$ and $P_s = 1$ early in the epidemic.

The probability of transmission per contact, $\beta_s$, depends on the state that the infectious person is in. We assume that contacts with an infectious individual, who is not under medical care, are more likely to transmit the disease than contact with a person using protective measures at a medical facility.

In summary, the forces from each of the infectious states are

$$\alpha_i(t) = c_i \beta_i \frac{c_s S(t)}{C_{tot}(t)}, \quad \alpha_m(t) = c_m \beta_m \frac{c_s S(t)}{C_{tot}(t)}, \quad \alpha_f(t) = c_f \beta_f \frac{c_s S(t)}{C_{tot}(t)}.$$  \hspace{1cm} (2)

Model forecasts are sensitive to accurately modeling the contacts of an infected person. This is complicated when considering behavior change since an infected person is more likely to change their behavior than the general susceptible population. An advantage of the infectious viewpoint is that it is formulated in terms of these infectious contacts, not the susceptible's contacts. That is, in the susceptible viewpoint, the first factor, $c_s$, in the force of infection is the average number of contacts that a susceptible person has, while in the infectious viewpoint the first factor, $c_i$, is the number of contacts that an infectious person has. If disease changes behavior, as it does in EVD, then $c_i$ is likely to change more than $c_s$, and changes in $c_i$ have a greater impact on the spread of an infection than do changes in $c_s$. It is especially important when investigating the impact of behavior changes.

Another advantage is that the infected viewpoint is formulated based on estimating the probability that a random contact is with a susceptible person, which is in the early stages of an epidemic $P_s(t) \approx 1$, since nearly every contact is with a susceptible person. In the susceptible viewpoint, the model is based on estimating the probability that a random contact is with an infectious person, which is changing rapidly. That is, from the susceptible viewpoint, we must estimate the probability for a susceptible person that a random contact is with an infectious person, $P_s, = i, m, f$. This can be a difficult parameter to estimate when there are few infectious people and the behavior is changing quickly early in the epidemic.

### 2.2 Progression Rates

The rates that people advance between the model compartments depends upon the disease progression rates and branching probabilities among the next possible compartments where a person could go. We find that using a branching diagram (Fig. 2) greatly simplifies the complexity of having multiple pathways among the model components. The branching probability, $p_{jk}$, is defined as the fraction of people who progress from state $j$ to state $k$. The nodes in the diagram for staying at home,
The probabilities that an individual progresses from one state to the next, denoted as $p_{jk}$, where $j$ is the state they are leaving and $k$ is the state they are entering. In the branching diagram, the nodes for staying at home, the circled H, and dead, the circled D, are branching points, and are not compartments of the model.

In our model, we define four progression rates in terms of the probability of going from one state to another, $p_{im}$, $p_{mr}$, $p_{hr}$, and $p_{df}$ (Table 1). The other branching probabilities are defined in terms of these four probabilities. For example, the probability that an infectious person, I, will have a traditional funeral, F, is $p_{if} = p_{ih} p_{hd} p_{df} = (1 - p_{im})(1 - p_{hr}) p_{df}$. Similarly, $p_{ib} = p_{im} p_{md} p_{db} + p_{ih} p_{hd} p_{df}$ and $p_{ir} = p_{ih} p_{hr} + p_{im} p_{mf}$. When describing the meaning of terms that arise in defining the basic reproductive number, we also find it useful to define probabilities that a person will progress through multiple states, such as $p_{ijk} = p_{ij} p_{jk}$ is the probability of going from state $i$ to state $j$ and then to state $k$.

In addition to the branching probabilities, the transition rates are defined in terms of the average time (in days) spent in a state $\tau_e$, $\tau_i$, and $\tau_f$ and the time that entering the medical facility can reduce the time to recovery, $\tau_r$ days. For example, $\tau_e$ is the average time it takes an infected person to become infectious, and $\tau_i$ is the time that would be spent in state $I$ for someone not going to the medical facility.

The branching probabilities and average times for the disease progression are then used to define the compartment progression rates, $\gamma_{jk}$ from compartment $j$ to compartment $k$. That is, instead of directly defining the progression rates, we define them in terms of parameters that can be directly measured or are easier to interpret.

From these parameters, we define the progression rates as:

- $\gamma_{ei} = p_{ei}/\tau_e = 1/\tau_e$
- $\gamma_{ib} = p_{ib}/\tau_f$
- $\gamma_{if} = p_{if}/\tau_f$
- $\gamma_{ir} = p_{ir}/\tau_i$
### Table 1
The baseline values are chosen so that the model is consistent with the Montserrado EVD epidemic incidence data [6, 7, 10, 23, 38]

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Parameter description</th>
<th>Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>$c_s^-$</td>
<td>Number of contacts per day when $t &lt; t_c$</td>
<td>$c_s^- = 30$, $c_f^- = 30$, $c_i^- = 8.1657$, $c_m^- = 5$, $c_r^- = 20$, $c_e^- = 30$</td>
</tr>
<tr>
<td>$c_s^+$</td>
<td>Number of contacts per day when $t \geq t_c$</td>
<td>$c_s^+ = 30$, $c_f^+ = 30$, $c_i^+ = 3.0311$, $c_m^+ = 5$, $c_r^+ = 20$, $c_e^+ = 30$</td>
</tr>
<tr>
<td>$\beta_e$</td>
<td>Probability of transmission per contact with state $*$</td>
<td>$\beta_i = 0.017$, $\beta_m = 0.0005$, $\beta_f = 0.05$</td>
</tr>
<tr>
<td>$\tau_e$</td>
<td>Average days spent in exposed state</td>
<td>7</td>
</tr>
<tr>
<td>$\tau_i$</td>
<td>Average days spent in $I$</td>
<td>20</td>
</tr>
<tr>
<td>$\tau_f$</td>
<td>Average days spent in funeral state</td>
<td>1</td>
</tr>
<tr>
<td>$p_{hr}$</td>
<td>Probability an infectious person recovers (at home)</td>
<td>0.55</td>
</tr>
<tr>
<td>$p_{mr}$</td>
<td>Probability an infectious person recovers (medical care)</td>
<td>0.75</td>
</tr>
<tr>
<td>$p_{df}_-$</td>
<td>Probability a person dying at home has a traditional burial $t &lt; t_f$</td>
<td>0.9</td>
</tr>
<tr>
<td>$p_{df}_+$</td>
<td>Probability a person dying at home has a traditional burial $t \geq t_f$</td>
<td>0.18</td>
</tr>
<tr>
<td>$p_{im}$</td>
<td>Probability an infected goes to a medical facility $t &lt; t_m$</td>
<td>0.1</td>
</tr>
<tr>
<td>$p_{im}$</td>
<td>Probability an infected goes to a medical facility $t \geq t_m$</td>
<td>0.71</td>
</tr>
<tr>
<td>$t_c$</td>
<td>Date (days) when people change their contact rates</td>
<td>122</td>
</tr>
<tr>
<td>$t_m$</td>
<td>Date (days) when medical facilities become more available</td>
<td>140</td>
</tr>
<tr>
<td>$t_f$</td>
<td>Date (days) when number of traditional funerals drops</td>
<td>84</td>
</tr>
<tr>
<td>$\gamma_{jk}$</td>
<td>Rate of going from state $j$ to state $k$ (derived from $p_<em>$ and $\tau_</em>$)</td>
<td></td>
</tr>
<tr>
<td>$P_*$</td>
<td>Probability of random contact with state $<em>$, e.g. $P_</em> = c_0S/C_{tot}$</td>
<td></td>
</tr>
</tbody>
</table>

The basic reproductive number for the baseline case is $R_0 = 2.64$

\[
\gamma_{im} = p_{im}/\tau_m \quad \gamma_{imr} = p_{imr}/\tau_m = p_{im}p_{mr}/\tau_m \\
\gamma_{imb} = p_{imb}/\tau_m = p_{im}(1 - p_{mr})/\tau_m \quad \gamma_i = \gamma_{if} + \gamma_{ib} + \gamma_{ir} + \gamma_{im}
\]

where $\gamma_i$ is the total rate that people exit from the $I$ compartment.

### 2.3 Behavior Change, Healthcare Availability, and Traditional Funerals

The number of contacts $c_s(t)$ per day for someone in compartment $*$ can change as the epidemic progresses to avoid being infected or to avoid infecting others. We realize that, in general, $c_s(t)$ is a complex function of time. Our goal is to analyze the relative importance of the behavior changes and we make the simplifying assumption that $c_s(t)$ is a piecewise constant function that changes $t_c$ days after the first (index) case when the epidemic starts. That is,
This simplified form of the behavior change makes it easy to quantify the importance of the time the behavior change takes place and the magnitude of the change.

As medical treatment units become available and traditional funerals become less frequent, we change the probabilities that an infected person will go to the medical facility $p_{im}$ and the probability that a person dying at home will have a traditional funeral $p_{df}$ as step functions:

\[
\begin{align*}
p_{im}(t) &= \begin{cases} 
p_{im}^- & \text{if } t < t_m \\
p_{im}^+ & \text{if } t \geq t_m \end{cases} \\
p_{df}(t) &= \begin{cases} 
p_{df}^- & \text{if } t < t_f \\
p_{df}^+ & \text{if } t \geq t_f \end{cases}
\end{align*}
\]  

3 Reproduction Numbers

The effective reproductive number, $R_e(t)$, is the expected number of new infections that a newly infected person will create [12]. Thus, $R_e(t)$ depends upon the state of the entire system at the time when a susceptible person is infected, $R_e(t) = R_e(t, S, E, I, M, F, B, R)$. The basic reproduction number, $R_0$, measures the average number of secondary cases produced by introducing one infected individual into the disease free equilibrium (DFE).

We will first derive the reproductive numbers from the viewpoint of a stochastic Markov Chain process. It is natural to define the transition probabilities from perspective and to connect relationship between the effective and basic reproductive numbers. We will then use the next generation approach to derive $R_0$ based on a mathematical analysis of the differential equations.

3.1 Branching Process Derivation of the Reproductive Numbers

We can view the model (1) as a stochastic Markov Chain branching process where the progression rates are defined in terms of a probability per day that a person will progress to another state. This viewpoint has the advantage that each step in the process has a natural epidemiological interpretation.

The reproductive number is derived by estimating the probable number of new infections that would be created by a single individual in each of the infectious states. Since all the new infections must come from one of the three infectious states, we can decompose $R_e$ into a sum of the compartmental basic reproductive numbers for each state:

\[
R_e = R_e^l + R_e^m + R_e^f,
\]
where $R_e^*$ is the average number of new infections caused by an infectious person, while in state $\ast, (\ast = i, m$ and $f)$. Each of these reproduction numbers can be factored into three terms:

$$R_e^* = P_e \tau_e \alpha_e(t) = \left( \begin{array}{c}
\text{Probability an infected person enters state } \ast \\
\text{Time a person is in state } \ast \\
\text{Force from infectious for a person in state } \ast \end{array} \right).$$

We define $P_e$ as the probability that an infected person ever enters state $\ast$. In a large infectious population, $P_e$ is also the fraction of the infected people that will eventually enter state $\ast$. This is determined by the progression rates of all the possible paths someone can enter state $\ast$.

Since all infected people enter state $I$, $p_{ei} = 1$. The probability that an infected person goes to a medical facility is $p_{em} = p_{im} = \gamma_m / \gamma_i = \gamma_m \tau_i$. Similarly, the probability that an infected person will have a traditional funeral can be expressed as $p_{ef} = p_{if} = \gamma_f / \gamma_i = \gamma_f \tau_i$.

The third term in $R_e^*$ is the force from infectious for person in state $\ast, \alpha_e$ as defined in (2). Combining these terms, we can express the effective reproductive number as

$$R_e(t) = R^i_e(t) + R^m_e(t) + R^f_e(t)$$

$$= p_{ei} \tau_i \alpha_i(t) + p_{em} \tau_m \alpha_m(t) + p_{ef} \tau_f \alpha_f(t)$$

$$= \frac{1}{\gamma_i} c_i S(t) \beta_i + \frac{\gamma_m}{\gamma_i} \frac{1}{\gamma_m} c_m S(t) \beta_m + \frac{\gamma_f}{\gamma_f} \frac{1}{\gamma_f} c_f S(t) \beta_f.$$

If at $t = 0$, the population is at the DFE where everyone in the population is susceptible, then the effective reproductive number is also called the basic reproductive number, $R_0 = R_e^*(0, S, 0, 0, 0, 0, 0, 0, 0) = R_e(0)$ and represents the number of new infections that would be caused by a single infected person being introduced into the population. $R_0 = 2.64$ in this model for the baseline parameter values.

At the DFE, the probability that a contact will be with susceptible person is $P_s(0) = 1$, and the transmission rates simplify to $\alpha_s(0) = c_s \beta_s P_s(0) = c_s \beta_s$. Hence,

$$R_0 = R^i_0 + R^m_0 + R^f_0$$

$$= p_{ei} \tau_i c_i \beta_i + p_{em} \tau_m c_m \beta_m + p_{ef} \tau_f c_f \beta_f$$

$$= \frac{1}{\gamma_i} c_i \beta_i + \frac{\gamma_m}{\gamma_i} \frac{1}{\gamma_m} c_m \beta_m + \frac{\gamma_f}{\gamma_f} \frac{1}{\gamma_f} c_f \beta_f.$$

### 3.2 Next Generation Method Derivation of the Basic Reproductive Number

The next generation matrix algorithm [12, 37] can be used to explicitly define $R_0$ by computing the number of new infections that are generated from the infected
states. We define the vector \( x = [E, I, M, F, ]^T \) and write the equations for these variables as \( \frac{dx}{dt} = \mathcal{F} - \mathcal{V} \) by defining the vectors \( \mathcal{F} \) and \( \mathcal{V} \) so that \( \mathcal{F}_i \) is the rate new infections are introduced into state \( i \), and \( \mathcal{V}_i \) is the rate of transfer out of state \( i \);

\[
\mathcal{F} = \begin{bmatrix}
\alpha_i I + \alpha_m M + \alpha_f F \\
0 \\
0 \\
0
\end{bmatrix}, \quad \mathcal{V} = \begin{bmatrix}
\gamma_{ei} E \\
-\gamma_{ei} E + (\gamma_{if} + \gamma_{ib} + \gamma_{ir} + \gamma_{im})I \\
-\gamma_{im} I + (\gamma_{mr} + \gamma_{mb})M \\
-\gamma_{if} I + \gamma_{fb} F
\end{bmatrix}
\]  

(6)

The Jacobian matrices \( J_{\mathcal{F}} \) and \( J_{\mathcal{V}} \) for this system of differential equations at the DFE have the property that the \((i, j)\)th element of the matrix, \( J_{\mathcal{F}}(i, j) = \frac{\partial \mathcal{F}_i}{\partial x_j} \), is the rate at which infected individuals in state \( j \) produce new infections in state \( i \). Similarly, \( J_{\mathcal{V}}(j, k) = \frac{\partial \mathcal{V}_j}{\partial x_k} \), is the rate at which individuals in compartment \( k \) transfer to compartment \( j \).

At the DFE \( \alpha_*(0) = c_* \beta_* \) and the Jacobian matrices of \( \mathcal{F} \) and \( \mathcal{V} \) are:

\[
J_{\mathcal{F}} = \begin{bmatrix}
0 & \beta_i c_i & \beta_m c_m & \beta_f c_f \\
0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0
\end{bmatrix}, \quad J_{\mathcal{V}} = \begin{bmatrix}
\tau_e^{-1} & 0 & 0 & 0 \\
-\gamma_{ei} & \tau_i^{-1} & 0 & 0 \\
0 & -\gamma_{im} & \tau_m^{-1} & 0 \\
0 & -\gamma_{if} & 0 & \tau_f^{-1}
\end{bmatrix}
\]  

(7)

We can express the inverse of \( J_{\mathcal{V}} \) in terms of the transition probabilities as

\[
J_{\mathcal{V}}^{-1} = \begin{bmatrix}
\tau_e & 0 & 0 & 0 \\
p_e i \tau_i & \tau_i & 0 & 0 \\
p_i m \tau_m & p_i m \tau_i & \tau_m & 0 \\
p_e i p_f \tau_f & p_i f \tau_i & 0 & \tau_f
\end{bmatrix} = \begin{bmatrix}
\tau_e & 0 & 0 & 0 \\
p_e i \tau_i & \tau_i & 0 & 0 \\
p_e m \tau_m & p_i m \tau_i & \tau_m & 0 \\
p_e f \tau_f & p_i f \tau_i & 0 & \tau_f
\end{bmatrix}
\]  

(8)

Note that each row of \( J_{\mathcal{V}}^{-1} \) is the probability of going from state \( i \) to state \( j \) scaled by the time in state \( j \).

The next generation matrix is \( \mathcal{N} = J_{\mathcal{F}} J_{\mathcal{V}}^{-1} = \)

\[
\begin{bmatrix}
p_e i c_i \beta_i + p_e m c_m \beta_m + p_e f c f \beta_f \tau_i c_i \beta_i + p_i f \tau_i c f \beta_f + p_i m \tau_i c_m \beta_m c_m \beta_m \tau_m c_f \beta_f \tau_f \\
0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0
\end{bmatrix}
\]

The basic reproduction number can be defined as the spectral radius of \( \mathcal{N} \). In this case, the matrix is upper triangular, so the eigenvalues are on the diagonal, and the
largest eigenvalue, \( \mathcal{N}(1, 1) = p_{ei} \tau_i c_i \beta_i + p_{em} \tau_m c_m \beta_m + p_{ef} \tau_f c_f \beta_f \), which agrees with the previous calculation (5).

4 Parameter Estimation from Montserrado EVD Cases

Most of the model parameters, such as the number of contacts per day, are approxima-
tions for the expected value of stochastic events with broad probability distribution. Some model parameters, such as the probability of transmission per contact, independent of the region where the epidemic is taking place. Others, such as the behavior change of the local community in reducing their number of contacts, depend upon the specific region we are studying. Our goal is to define the baseline parameters for our best guess at what actually happened during the epidemic in a specific region. We will then use sensitivity analysis to ask “what if” questions and quantify the relative importance of the mitigation efforts, such as the how sensitive the course of the epidemic will be to the time that the Ebola treatment units are established, or to the time it takes to stop traditional funerals.

To illustrate our approach, we used the EVD incidence from Montserrado, Liberia (Fig. 3). This data can be easily fit with a three, or four parameter spline. It is inap-
propriate to fit any model using more than the degrees of freedom evident in the data, and therefore we limit our fits to 3 or 4 parameters. In fitting the data, we first defined all the parameters in Table 1 based on our best estimate from the published literature [1, 6, 7, 10, 23, 30, 35, 38]. The dates for the ban of traditional funerals, and increase in medical availability were obtained by press releases [1, 35]. We then identified the parameters that are most likely to vary from region to region and used these to fit the model to the data using the sequential quadratic programming (SQP) MATLAB program \textit{fmincon}.

![Ebola in Montserrado - Liberia](image)

Fig. 3 The weekly EVD cases [31] for Montserrado (*) are fit with the model (solid line) by varying: (1) the behavior change in the infected population, \( c_i^+ \); (2) the fraction of infected people who go to a medical facility, \( p_{im} \); and (3) the fraction of people who have a traditional funeral \( p_{if} \).
The first step in initializing a multicompartmental model is to create balanced initial conditions for the number of people in each compartment that is consistent with a real epidemic [20]. We achieved this balanced initial state by starting the epidemic with a small (0.001 %) infected population, and letting the epidemic advance until there is one person infected. We then reset the integration time to zero as the time of the first index case.

Starting with the balanced initial conditions, we varied the single parameter $c_i$ to match the early growth of the epidemic based on the difference between the model predictions and the WHO data for the number of weekly cases [31]. That is, we started by fitting the model with a single parameter match to the initial growth of the epidemic in the first four months of the epidemic, before there were significant behavior changes or new medical facilities available. We then verified that our fitted parameter, $c_i^- = 8.2$, was relatively insensitive to the four month window. The fit is shown as the solid red line in Fig. 3 and would continue growing exponentially unless we account for the decreased contact rates, reduced traditional funerals, and availability of medical treatment facilities.

Once we have the model agreeing with the initial growth, we then varied the:

- magnitude, $c_i^+$, and time, $t_c$, that the infected population changed behavior,
- increase in the fraction of people receiving medical treatment $p_{im}$, and
- reduction in the fraction of people having a traditional funeral $p_{if}$. The fitted values are given in Table 1.

The resulting baseline solution of the model (Fig. 4) is in good agreement with the published incidence data.

5 Sensitivity Analysis

In local sensitivity analysis [3, 4], we perturb our reference (baseline) solution to quantify how quantities of interest (QOIs), such as the reproductive numbers or size of the infected population, change in response to small changes in the parameters of interest (POIs), such as the time people change their behavior ($t_c$) or the probability that an infected person will be treated at a medical facilities ($p_{im}$). The sensitivity indices tell us the relative importance of each parameter to the QOIs and how sensitive they are to changes in parameters, such as the magnitude of the behavior change. The sign of the index indicates the direction of the response, and its magnitude tells us the relative importance of each parameter in our model predictions. Because the analysis is based on a linearization of the solution with the baseline parameters, the local sensitivity analysis indices are only valid in a small neighborhood of the baseline parameter values.

We define $\hat{q} = q(\hat{p})$ as the value of the QOI when the model is solved with the baseline parameter values $\hat{p}$. If the POI, $\hat{p}$, is perturbed by a small amount, $p = \hat{p}(1 + \theta_p)$, then the QOI will change by $q = q(\hat{p} + \theta_p \hat{p})$ where $\theta_q := \theta_p \frac{\partial q}{\partial p}$. The
Fig. 4 The baseline solution of the model (1) using the fitted parameters (Table 1) has a noticeable jump in the number of people receiving medical treatment at time \( t_m = 22 \text{ Oct} 2014 \).

The ratio of the change in \( q \) with respect to a change in \( p \) is defined as the dimensionless relative sensitivity index as

\[
S^q_p := \left. \frac{\hat{q}}{\hat{\theta} q} \times \frac{\partial q}{\partial p} \right|_{p=\hat{p}} = \frac{\theta_q}{\theta_p}.
\]  

That is, this local normalized relative sensitivity index \( S^q_p \) is the percent change in the output given the percent change in an input parameter. If the \( \hat{p} \) changes by \( x \% \), then \( \hat{q} \) will change by \( S^q_p x \% \). Note that the sign of the sensitivity index indicates whether the QOI increases (\( > 0 \)) or decreases (\( < 0 \)) with the POI.

The sensitivity indices in the Table 2 show that, by far, the most efficient way for slowing the epidemic is to reduce the number of contacts that an infectious person has in state \( I \). The impact of the general susceptible public \( S \) reducing their contacts \( c_s \) has a much smaller effect since the vast majority of these contacts are with other susceptible people that have little impact on the epidemic. This suggests that the emphasis of mitigation efforts should be focused on urging the infected people to isolate themselves, rather than have everyone reduce all their contacts.

In extended sensitivity analysis [25], we vary the POIs over a wide range of values. In Fig. 4, the total number of people dying increases with the fraction \( p_{df}^+ \) of people not in medical care who continued to have a traditional funeral after the funeral restrictions went into effect. Note that the epidemic would have been over three times worse if everyone continued to have a traditional funeral (\( p_{df}^+ = 1 \)) compared to
Table 2 The sensitivity indices of $R_0$ with respect to the model parameters for the baseline case (Table 1)

<table>
<thead>
<tr>
<th>Total</th>
<th>$c_s$</th>
<th>$c_e$</th>
<th>$c_i$</th>
<th>$c_m$</th>
<th>$c_f$</th>
<th>$c_r$</th>
<th>$p_{df}$</th>
<th>$c_i^+ / c_i^-$</th>
<th>$p_{im}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposed</td>
<td>0.0015</td>
<td>–</td>
<td>9.5</td>
<td>0.048</td>
<td>1</td>
<td>–</td>
<td>0.12</td>
<td>1.2</td>
<td>–0.4</td>
</tr>
<tr>
<td>Dead</td>
<td>0.0014</td>
<td>–</td>
<td>9.3</td>
<td>0.044</td>
<td>1</td>
<td>–</td>
<td>0.12</td>
<td>1.1</td>
<td>–0.44</td>
</tr>
</tbody>
</table>

Note that the sensitivity index for the total dead with respect to $c_i$ is 9.3 meaning that if the infected population reduced their contacts by 1%, then the number of people who died would be reduced by 9.5%.

![Fig. 5](image_url) The baseline case in these extended sensitivity analysis plots is indicated by an *. The y-axis for the total number of people dying is plotted as a function of $p_{df}^+$, $c_i^+ / c_i^-$, and $p_{df}^+$ over a wide range of possible values. Notice that in the center figure, reducing the number of contacts an infectious person has after the behavior change has begun has the greatest impact on slowing the epidemic.

<table>
<thead>
<tr>
<th>Traditional Funeral</th>
<th>Change Infected Contacts</th>
<th>Medical Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image_url" alt="Plot" /></td>
<td><img src="image_url" alt="Plot" /></td>
<td><img src="image_url" alt="Plot" /></td>
</tr>
</tbody>
</table>

Fig. 5 The baseline case in these extended sensitivity analysis plots is indicated by an *. The y-axis for the total number of people dying is plotted as a function of $p_{df}^+$, $c_i^+ / c_i^-$, and $p_{df}^+$ over a wide range of possible values. Notice that in the center figure, reducing the number of contacts an infectious person has after the behavior change has begun has the greatest impact on slowing the epidemic.

completely stopping the funerals ($p_{df}^+ = 0$). The center plot illustrates the sensitivity of the epidemic growth as a function of the relative reduction ($c_i^+ / c_i^-$) in the number of contacts that an infectious person has after the behavior change begins. The baseline case is that infected people reduce their contacts to 40% of what they were before time $t_c$. The model predicts that the death toll would have been cut in half if they had reduced their contacts to 10% of $c_i^-$. The plot on the right shows the dramatic effect that increasing the fraction $p_{if}$ of infected people who are admitted to a medical treatment unit can have on reducing the total number of people dying in the epidemic. Without the availability of medical treatment ($p_{if} = 0$) the model predicts that the epidemic would have been far worse (Fig. 5).
6 Summary and Conclusions

Our simulations indicate that reducing the contacts that infectious people have with the general public is the most important mitigation strategy of those considered in the model. These contacts include both the contacts with an infected person at home, under medical care, and in a traditional funeral. Reducing the number of contacts that the general susceptible population has per day by the same factor is a more difficult task to have the same impact on the epidemic. The simulations predict that medical care intervention alone would have been insufficient to stop this epidemic from spreading through a population.

We acknowledge that ordinary differential equations, such as this model, are best used to simulate large epidemics and may not be valid in representing how the infection would spread through small rural communities. Also, our simple model also fails to account for the important role that family structure had in the EVD epidemic where infectious individuals are more likely to infect family members than people in the general community. Even though it would be inappropriate to use a simple model, such as this one, for forecasting an epidemic where so few people are infected, these models can provide insights into the relative importance of mitigation strategies, such as the effectiveness of behavior change and the availability of medical interventions in stopping the epidemic.

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References

17. Thomas House. Epidemiological Dynamics of Ebola Outbreaks. eLife (September 2014)


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