Modeling the Impact of Behavior Change on the Spread of Ebola

Jessica R. Conrad, Ling Xue, Jeremy Dewar and James M. Hyman

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

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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):

$$\frac{dS}{dt} = -\lambda S \tag{1a}$$

$$= -\alpha_i I - \alpha_m M - \alpha_f F \tag{1b}$$

$$\frac{dE}{dt} = \lambda S - \gamma_{ei} E \tag{1c}$$

$$= \alpha_i I + \alpha_m M + \alpha_f F - \gamma_{ei} E \tag{1d}$$

$$\frac{dI}{dt} = \gamma_{ei} E - (\gamma_{if} + \gamma_{ib} + \gamma_{ir} + \gamma_{im}) I \tag{1e}$$

$$\frac{dM}{dt} = \gamma_{im} I - (\gamma_{mr} + \gamma_{mb}) M \tag{1f}$$

$$\frac{dF}{dt} = \gamma_{if} I - \gamma_{fb} F \tag{1g}$$

$$\frac{dB}{dt} = \gamma_{ib} I + \gamma_{mb} M + \gamma_{fb} F \tag{1h}$$

$$\frac{dR}{dt} = \gamma_{ir} I + \gamma_{mr} M. \tag{1i}$$

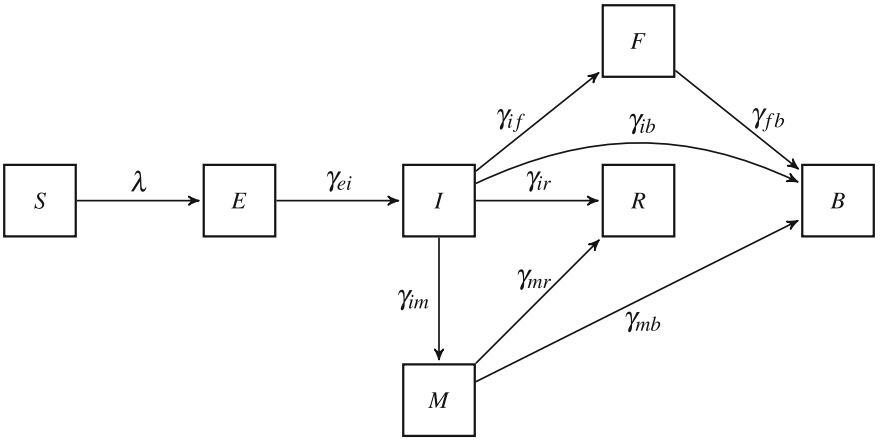

Fig. 1 When susceptible people (S) are infected, they progress to the exposed, but not infectious, state (E). From there, they become infectious (I) to the susceptible population. An infected person either enters a medical facility (M), or does not. If they do not enter a medical facility, they may recover (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 λ 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 γ_{ei}). An infectious person can recover, R, (at rate γ_{ir}), go to a medical treatment facility (at rate γ_{im}), or, if they die, the person either as a traditional funeral, F, (at rate γ_{if}), or is safely buried, B, (at rate γ_{ib}). The people in a medical facility can recover, R, at an adjusted rate γ_{mr}, or die and be safely buried (at rate γ_{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*, λ, 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*, α_*, represents the rate that an infectious person in compartment $* = I,\ M$, 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 λ and α_* 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 γ_{i*} is the progression from state I to another state $*$, where $*$ is M, F, B, or R. Similarly, the rates γ_{e*} and γ_{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, α_*, rather than the traditional force of infection, λ.

2.1.1 Force of Infection

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

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

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 β_*. There are a total of $c_s S$ contacts per day by people in the susceptible population out of $C_{tot}(t) = c_s S + c_e E + c_i I + c_m M + c_f F + c_r R + c_b B$ 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 α as the force of infection *from* the infectious population. This force (α_i, α_m, and α_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

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

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 $P_s(t) = c_s S(t)/C_{tot}(t)$ and $P_s = 1$ early in the epidemic.

The *probability of transmission per contact*, β_*, 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

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

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, $P_*, * = i,\ m,\ f$. 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,

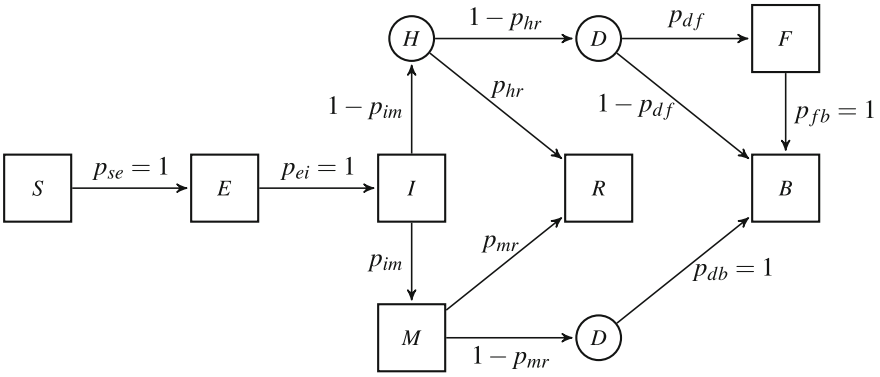

Fig. 2 The probabilities that an individual progresses from one state to the next, denoted as p_{jk}, where j is the state they are leaving and k is the state they are entering. In the branching diagram, the nodes for staying at home, the *circled* H, and dead, the *circled* D, are branching points, and are not compartments of the model

Ⓗ, and dying, Ⓓ, are not compartments in the model. They represent nodes in the branching process that are useful when defining the probabilities of going from one state to another.

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 τ_e, τ_i, and τ_f and the time that entering the medical facility can reduce the time to recovery, t_r days. For example, τ_e is the average time it takes an infected person to become infectious, and τ_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, γ_{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:

$$\gamma_{ei} = p_{ei}/\tau e = 1/\tau_e \qquad \gamma_{ib} = p_{ib}/\tau_f$$
$$\gamma_{if} = p_{if}/\tau_f \qquad \gamma_{ir} = p_{ir}/\tau_i$$

Table 1 The baseline values are chosen selected so that the model is consistent with the Montserrado EVD epidemic incidence data [6, 7, 10, 23, 38]

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

The basic reproductive number for the baseline case is $\mathbb{R}_0 = 2.64$

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

where γ_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 $c_*(t)$ 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, $c_*(t)$ 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 $c_*(t)$ is a piecewise constant function that changes t_c days after the first (index) case when the epidemic starts. That is,

$$c_*(t) = \begin{cases} c_*^- & \text{if } t < t_c \\ c_*^+ & \text{if } t \geq t_c. \end{cases} \tag{3}$$

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:

$$p_{im}(t) = \begin{cases} p_{im}^- & \text{if } t < t_m \\ p_{im}^+ & \text{if } t \geq t_m \end{cases} \quad \text{and} \quad p_{df}(t) = \begin{cases} p_{df}^- & \text{if } t < t_f \\ p_{df}^+ & \text{if } t \geq t_f. \end{cases} \tag{4}$$

3 Reproduction Numbers

The effective reproductive number, $\mathbb{R}_e(t)$, is the expected number of new infections that a newly infected person will create [12]. Thus, $\mathbb{R}_e(t)$ depends upon the state of the entire system at the time when a susceptible person is infected, $\mathbb{R}_e(t) = \mathbb{R}_e(t, S, E, I, M, F, B, R)$. The basic reproduction number, $\mathbb{R}_0$, 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 $\mathbb{R}_0$ 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 $\mathbb{R}_e$ into a sum of the compartmental basic reproductive numbers for each state:

$$\mathbb{R}_e = \mathbb{R}_e^i + \mathbb{R}_e^m + \mathbb{R}_e^f,$$

where $\mathbb{R}_e^*$ is the average number of new infections caused by an infectious person, while in state $*$, ($* = i, m$ and f). Each of these reproduction numbers can be factored into three terms:

$$\mathbb{R}_e^* = P_* \tau_* \alpha_*(t) = \begin{pmatrix} \text{Probability an} \\ \text{infected person} \\ \text{enters state } * \end{pmatrix} \begin{pmatrix} \text{Time a} \\ \text{person is} \\ \text{in state } * \end{pmatrix} \begin{pmatrix} \text{Force from infectious} \\ \text{for a person} \\ \text{in state } * \end{pmatrix}.$$

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

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

The third term in $\mathbb{R}_e^*$ is the force from infectious for person in state $*$, α_* as defined in (2). Combining these terms, we can express the effective reproductive number as

$$\begin{aligned} \mathbb{R}_e(t) &= \mathbb{R}_e^i(t) + \mathbb{R}_e^m(t) + \mathbb{R}_e^f(t) \\ &= p_{ei}\tau_i\alpha_i(t) + p_{em}\tau_m\alpha_m(t) + p_{ef}\tau_f\alpha_f(t) \\ &= \frac{1}{\gamma_i} c_i \frac{c_s S(t)}{C_{tot}(t)} \beta_i + \frac{\gamma_{im}}{\gamma_i}\frac{1}{\gamma_i} c_m \frac{c_s S(t)}{C_{tot}(t)} \beta_m + \frac{\gamma_{if}}{\gamma_i}\frac{1}{\gamma_{fb}} c_f \frac{c_s S(t)}{C_{tot}(t)} \beta_f. \end{aligned}$$

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, $\mathbb{R}_0 = \mathbb{R}_e^*(0, S, 0, 0, 0, 0, 0, 0) = \mathbb{R}_e(0)$ and represents the number of new infections that would be caused by a single infected person being introduced into the population. $\mathbb{R}_0 = 2.64$ 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 $\alpha_*(0) = c_*\beta_* P_s(0) = c_*\beta_*$. Hence,

$$\begin{aligned} \mathbb{R}_0 &= \mathbb{R}_0^i + \mathbb{R}_0^m + \mathbb{R}_0^f \\ &= p_{ei}\tau_i c_i \beta_i + p_{em}\tau_m c_m \beta_m + p_{ef}\tau_f c_f \beta_f \\ &= \frac{1}{\gamma_i} c_i \beta_i + \frac{\gamma_{im}}{\gamma_i}\frac{1}{\gamma_i} c_m \beta_m + \frac{\gamma_{if}}{\gamma_i}\frac{1}{\gamma_{fb}} c_f \beta_f \end{aligned} \tag{5}$$

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

The next generation matrix algorithm [12, 37] can be used to explicitly define $\mathbb{R}_0$ 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 $\frac{dx}{dt} = \mathscr{F} - \mathscr{V}$ by defining the vectors $\mathscr{F}$ and $\mathscr{V}$ so that $\mathscr{F}_i$ is the rate new infections are introduced into state i, and $\mathscr{V}_i$ is the rate of transfer out of state i;

$$\mathscr{F} = \begin{bmatrix} \alpha_i I + \alpha_m M + \alpha_f F \\ 0 \\ 0 \\ 0 \end{bmatrix}, \quad \mathscr{V} = \begin{bmatrix} \gamma_{ei} E \\ -\gamma_{ei} E + (\gamma_{if} + \gamma i b + \gamma_{ir} + \gamma_{im}) I \\ -\gamma_{im} I + (\gamma_{mr} + \gamma_{mb}) M \\ -\gamma_{if} I + \gamma_{fb} F. \end{bmatrix} \tag{6}$$

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

$$J_{\mathscr{F}} = \begin{bmatrix} 0 & \beta_i c_i & \beta_m c_m & \beta_f c_f \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}, \tag{7}$$

$$J_{\mathscr{V}} = \begin{bmatrix} \tau_e^{-1} & 0 & 0 & 0 \\ -\gamma_{ei} & \tau_i^{-1} & 0 & 0 \\ 0 & -\gamma_{im} & \tau_m^{-1} & 0 \\ 0 & -\gamma_{if} & 0 & \tau_f^{-1} \end{bmatrix} = \begin{bmatrix} \tau_e^{-1} & 0 & 0 & 0 \\ -\tau_e^{-1} & \tau_i^{-1} & 0 & 0 \\ 0 & -p_{im}/\tau_m & \tau_m^{-1} & 0 \\ 0 & -p_{if}/\tau_f & 0 & \tau_f^{-1} \end{bmatrix} \tag{8}$$

We can express the inverse of $J_{\mathscr{V}}$ in terms of the transition probabilities as

$$J_{\mathscr{V}}^{-1} = \begin{bmatrix} \tau_e & 0 & 0 & 0 \\ p_{ei}\tau_i & \tau_i & 0 & 0 \\ p_{im}\tau_m & p_{im}\tau_i & \tau_m & 0 \\ p_{ei}p_{if}\tau_f & p_{if}\tau_i & 0 & \tau_f \end{bmatrix} = \begin{bmatrix} \tau_e & 0 & 0 & 0 \\ p_{ei}\tau_i & \tau_i & 0 & 0 \\ p_{em}\tau_m & p_{im}\tau_i & \tau_m & 0 \\ p_{ef}\tau_f & p_{if}\tau_i & 0 & \tau_f \end{bmatrix}$$

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

The next generation matrix is $\mathscr{N} = J_{\mathscr{F}} J_{\mathscr{V}}^{-1} =$

$$\begin{bmatrix} p_{ei}\tau_i c_i \beta_i + p_{em}\tau_m c_m \beta_m + p_{ef}\tau_f c_f \beta_f & \tau_i c_i \beta_i + p_{if}\tau_i c_f \beta_f + p_{im}\tau_i c_m \beta_m & c_m \beta_m \tau_m & c_f \beta_f \tau_f \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{bmatrix}$$

The basic reproduction number can be defined as the spectral radius of $\mathscr{N}$. In this case, the matrix is upper triangular, so the eigenvalues are on the diagonal, and the

largest eigenvalue, $\mathscr{N}(1,1) = p_{ei}\tau_i c_i \beta_i + p_{em}\tau_m c_m \beta_m + p_{ef}\tau_f c_f \beta_f$, 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 approximations 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 inappropriate 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 *fmincon*.

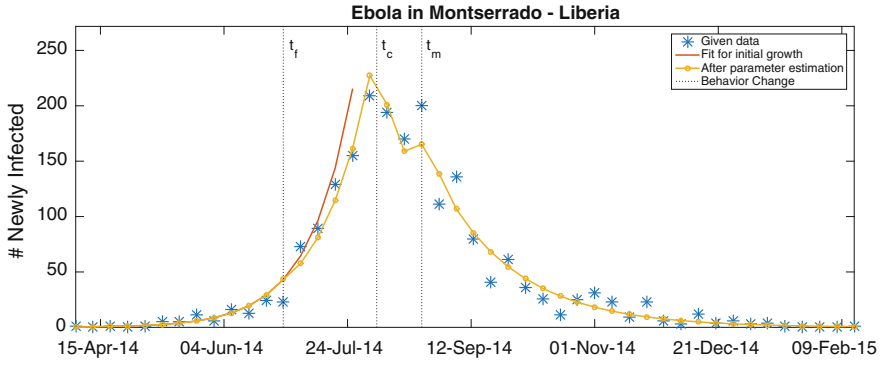

Fig. 3 The weekly EVD cases [31] for Montserrado ($*$) are fit with the model (*solid line*) by varying: (1) the behavior change in the infected population, c_i^+; (2) the fraction of infected people who go to a medical facility, p_{im}; and (3) the fraction of people who have a traditional funeral p_{if}

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 (POI), 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 $q = q(\hat{p} + \theta_p^q \hat{p})$ where $\theta_q := \theta_p \frac{\hat{p}}{\hat{q}} \frac{\partial q}{\partial p}$. The

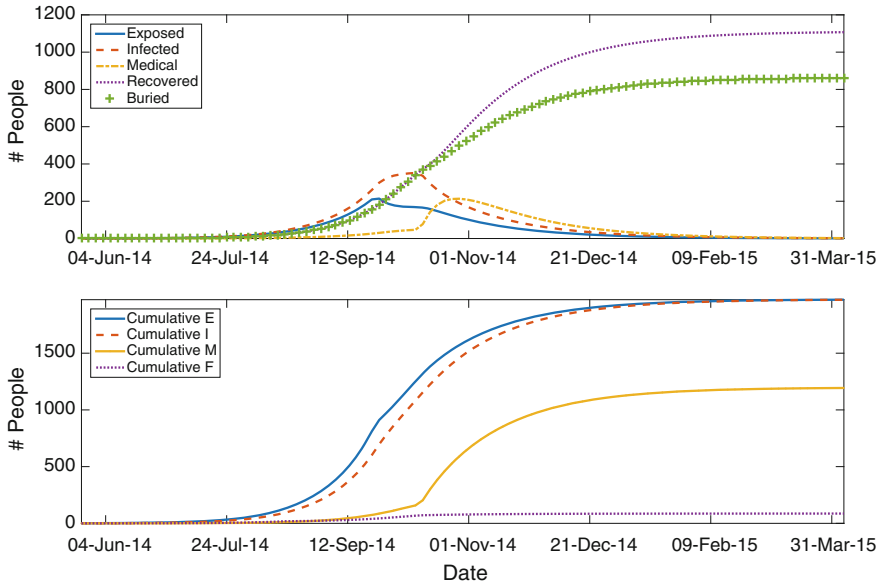

Fig. 4 The baseline solution of the model (1) using the fitted parameters (Table 1) has a noticeable jump in the number of people receiving medical treatment at time $t_m = 22 - Oct - 2014$

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

$$\mathsf{S}_p^q := \frac{\hat{p}}{\hat{q}} \times \left.\frac{\partial q}{\partial p}\right|_{p=\hat{p}} = \frac{\theta_q}{\theta_p}. \tag{9}$$

That is, this local normalized relative sensitivity index S_p^q 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 $\mathsf{S}_p^q x\%$. 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 $\mathbb{R}_0$ with respect to the model parameters for the baseline case (Table 1)

Total	c_s	c_e	c_i	c_m	c_f	c_r	p_{df}	$\frac{c_i^+}{c_i^-}$	p_{im}
Exposed	0.0015	– 0.00047	9.5	0.048	1	– 0.00086	0.12	1.2	–0.4
Dead	0.0014	– 0.00045	9.3	0.044	1	– 0.00079	0.12	1.1	–0.44

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 %

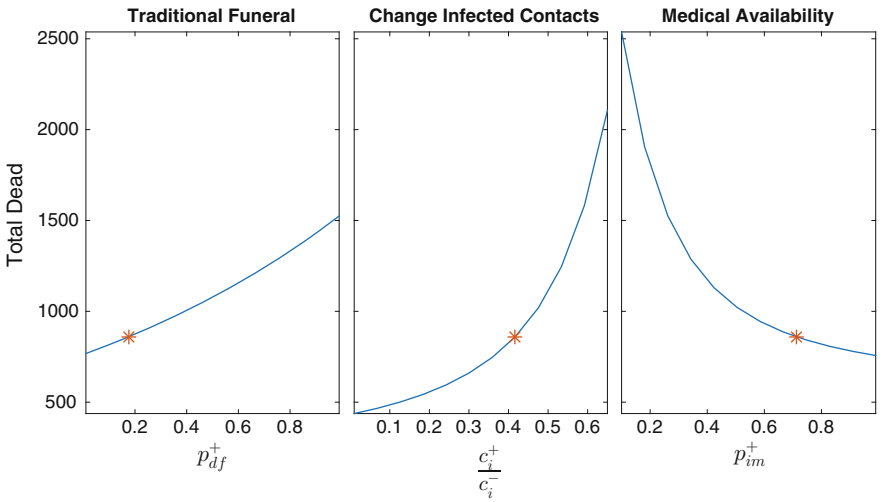

Fig. 5 The baseline case in these extended sensitivity analysis plots is indicated by an $*$. The y-axis for the total number of people dying is plotted as a function of p_{df}^+, c_i^+/c_i^-, and p_{df}^+ over a wide range of possible values. Notice that in the center figure, reducing the number of 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 they had cut 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

1. All Africa.: Liberia: Ellen Enforces Cremation as Measure Against Ebola (2014). Available from: http://allafrica.com/stories/201408051276.html
2. Arino, J., Van den Driessche, P.: A multi-city epidemic model. Math. Popul. Stud. **10**(3), 175–193 (2003)
3. Arriola, L., Chowell, G., Hyman, J.M., Bettencourt, L.M.A., Castillo-Chavez, C.: Sensitivity Analysis for Quantifying Uncertainty in Mathematical Models (2009)
4. Arriola, L.M., Hyman, J.M.: Being sensitive to uncertainty. Comput. Sci. Eng. **9**(2), 10–20 (2007)
5. Browne, C., Huo, X., Magal, P., Seydi, M., Seydi, O., Webb, G.: A Model of the 2014 Ebola Epidemic in West Africa (2014). arXiv:1410.3817 [q-bio.PE]
6. Bwaka, M.A., Bonnet, M.J., Calain, P., Colebunders, R., De Roo, A., Guimard, Y., Katwiki, K.R., Kibadi, K., Kipasa, M.A., Kuvula, K.J. et al.: Ebola Hemorrhagic Fever in Kikwit, Democratic Republic of the Congo: Clinical Observations in 103 Patients. J. Infect. Dis. **179**(Supplement 1), S1–S7 (1999)
7. Camacho, A., Kucharski, A.J., Funk, S., Breman, J., Piot, P., Edmunds, W.J.: Potential for large outbreaks of ebola virus disease. Epidemics **9**, 70–78 (2014)
8. Chowell, G., Hengartner, N.W., Castillo-Chavez, C., Fenimore, P.W., Hyman, J.M.: The basic reproductive number of ebola and the effects of public health measures: the cases of congo and uganda. J. Theor. Biol. **229**(1), 119–126 (2004)

9. Althaus, C.L.: Estimating the reproduction number of ebola virus (EBOV) during the 2014 outbreak in West Africa. PLOS Curr. Outbreaks (2014)
10. Rivers, C.M., Lofgren, E.T., Marathe, M., Eubank, S., Lewis, B.L.: Modeling the impact of interventions on an epidemic of ebola in sierra leone and liberia. PLOS Curr. Outbreaks (2014)
11. Valle, S.Y.D., Hyman, J.M., Hethcote, H.W., Eubank, S.G.: Mixing patterns between age groups in social networks. Soc. Netw. **29**(4), 539–554 (2007)
12. Diekmann, O., Heesterbeek, J.A.P., Metz, J.A.J.: On the definition and the computation of the basic reproduction ratio r 0 in models for infectious diseases in heterogeneous populations. J. Math. Biol. **28**(4), 365–382 (1990)
13. Eubank, S., Guclu, H., Kumar, V.S.A., Marathe, M.V., Srinivasan, A., Toroczkai, Z., Wang, N.: Modelling disease outbreaks in realistic urban social networks. Nature **429**(6988), 180–184 (2004)
14. Tuite, A., Fisman, D., Khoo, E.: Early epidemic dynamics of the West African 2014 ebola outbreak: Estimates derived with a simple two-parameter model. PLOS Curr. Outbreaks (2014)
15. Garrett, L.: Ebola: Story of an Outbreak. Hachette Books, New York (2014)
16. Gomes, M.F.C., Piontti, A.P., Rossi, L., Chao, D., Longini, I., Halloran, M.E., Vespignani, A.: Assessing the international spreading risk associated with the 2014 West African ebola outbreak. PLOS Curr. Outbreaks (2014)
17. Thomas House. Epidemiological Dynamics of Ebola Outbreaks. eLife (September 2014)
18. Hyman, J.M., LaForce, T.: Modeling the spread of influenza among cities. Bioterrorism Math. Model. Appl. Homel. Secur. 211–236 (2003)
19. Hyman, J.M., Li, J.: Disease transmission models with biased partnership selection. Appl. Numer. Math. **24**(2), 379–392 (1997)
20. Hyman, J.M., Li, J., Stanley, E.A.: The initialization and sensitivity of multigroup models for the transmission of HIV. J. Theor. Biol. **208**(2), 227–249 (2001)
21. Legrand, J., Grais, R.F., Boelle, P.Y., Valleron, A.J., Flahault, A.: Understanding the dynamics of ebola epidemics. Epidemiol. Infect. **135**(04), 610–621 (2007)
22. Lofgren, E.T., Rivers, C.M., Marathe, M.V., Eubank, S.G., Lewis, B.L.: The Potential Impact of Increased Hospital Capacity to Contain and Control Ebola in Liberia (2014). arXiv:1410.8207
23. Maganga, G.D., Kapetshi, J., Berthet, N., Ilunga, B.K., Kabange, F., Kingebeni, P.M., Mondonge, V., Muyembe, J.-J.T., Bertherat, E., Briand, S., et al.: Ebola virus disease in the democratic republic of congo. N. Engl. J. Med. **371**(22), 2083–2091 (2014)
24. Manore, C., McMahon, B., Fair, J., Hyman, J.M., Brown, M., LaBute, M.: Disease properties, geography, and mitigation strategies in a simulation spread of rinderpest across the United States. Vet. Res. **42**(1), 1–12 (2011)
25. Manore, C.A., Hickmann, K.S., Xu, S., Wearing, H.J., Hyman, J.M.: Comparing dengue and chikungunya emergence and endemic transmission in a. aegypti and a. albopictus. J. Theor. Biol. **356**, 174–191 (2014)
26. McMahon, B., Manore, C., Hyman, J., LaBute, M., Fair, J.: Coupling Vector-host Dynamics with Weather, Geography and Mitigation Measures to Model Rift Valley Fever in Africa. Submitted (2014)
27. Martin, I.M., Atkins, C.Y., Santibanez, S., Knust, B., Petersen, B.W., Ervin, E.D., Nichol, S.T., Damon, I.K., Washington, M.L.: Estimating the future number of cases in the ebola epidemicliberia and sierra leone, 2014–2015. MMWR Surveill Summ **63**(suppl 3), 1–14 (2014)
28. Nishiura, H., Chowell, G.: Early transmission dynamics of ebola virus disease (EVD), West Africa, March to August 2014. Eurosurveillance, **19**(36) (2014)
29. University of Pittsburg MIDAS National Center of Excellence. Framework for Reconstructing Epidemiological Dynamics (2012). https://midas.pitt.edu/index.php?option=com_content&view=article&id=78&Itemid=72
30. World Health Organization. Ebola Epidemic Liberia, Marchoctober 2014 (2014). Available from: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm63e1114a4.htm
31. World Health Organization. Who Ebola Data and Statistics (2016). Available from: http://time.com/3478238/ebola-liberia-burials-cremation-burned

32. Parpia, A.S., Ndeffo-Mbah, M.L., Wenzel, N.S., Galvani, A.P.: Effects of response to 2014–2015 ebola outbreak on deaths from malaria, HIV/AIDS, and tuberculosis, West Africa. Emerg. Infect. Dis. **22**(3), 433–441 (2016)
33. Stroud, P., Del Valle, S., Sydoriak, S., Riese, J., Mniszewski, S.: Spatial dynamics of pandemic influenza in a massive artificial society. J. Artif. Soc. Soc. Simul. **10**(4), 9 (2007)
34. WHO Ebola Response Team. Ebola virus disease in west africathe first 9 months of the epidemic and forward projections. N. Engl. J. Med. **371**(16), 1481–1495 (2014)
35. Time. Liberia burns its bodies as ebola fears run rampant (2014). Available from: http://apps.who.int/gho/data/node.ebola-sitrep
36. Troncoso, A.: Ebola outbreak in West Africa: a neglected tropical disease. Asian Pac. J. Tropical Biomed. **5**(4), 255–259 (2015)
37. Van den Driessche, P., Watmough, J.: Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission. Math. Biosci. **180**(1), 29–48 (2002)
38. Van Kerkhove, M.D., Bento, A.I., Mills, H.L., Ferguson, N.M., Donnelly, C.A.: A review of epidemiological parameters from ebola outbreaks to inform early public health decision-making. Sci. Data, **2** (2015)
39. Xue, L., Scott, H.M., Cohnstaedt, L.W., Scoglio, C.: A network-based meta-population approach to model Rift Valley fever epidemics. J. Theor. Biol. (2012)

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