BIOLOGY LETTERS

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Cite this article: Vinson JE, Drake JM, Rohani P, Park AW. 2016 The potential for sexual transmission to compromise control of Ebola virus outbreaks. *Biol. Lett.* **12**: 20151079. http://dx.doi.org/10.1098/rsbl.2015.1079

Received: 24 December 2015
Accepted: 16 May 2016

Subject Areas:
ecology, health and disease and epidemiology

Keywords:
Ebola virus, sexual transmission, mathematical model, epidemic, population dynamics

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Electronic supplementary material is available at http://dx.doi.org/10.1098/rsbl.2015.1079 or via http://rsbl.royalsocietypublishing.org.

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Population ecology

The potential for sexual transmission to compromise control of Ebola virus outbreaks

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Recent evidence suggests that sexual contact may give rise to transmission of Ebola virus long after infection has been cleared from blood. We develop a simple mathematical model that incorporates contact transmission and sexual transmission parametrized from data relating to the 2013–2015 West African Ebola epidemic. The model explores scenarios where contact transmission is reduced following infection events, capturing behaviour change, and quantifies how these actions reducing transmission may be compromised by sexual transmission in terms of increasing likelihood, size and duration of outbreaks. We characterize the extent to which sexual transmission operates in terms of the probability of initial infection resolving to sexual infectiousness and the sexual transmission rate, and relate these parameters to the overall case burden. We find that sexual transmission can have large effects on epidemic dynamics (increasing attack ratios from 25% in scenarios without sexual transmission but with contact-transmission-reducing behaviour, up to 80% in equivalent scenarios with sexual transmission).

1. Introduction

The recent Ebola virus outbreak in West Africa posed a global threat and came at significant morbidity (approx. 30 000 cases) and mortality costs (case fatality rate 40–70%) [1,2]. Owing to the rapid and concerted local and international intervention, focused on breaking the chain of direct transmission, the epidemic was eventually brought under control. Recent evidence suggests that the virus can persist in semen for several months [3] and genomic evidence has identified at least one instance of sexual transmission from male to female [4]. Here, we use a mathematical model to study the extent to which sexual transmission may compromise interventions and seed future epidemics. Our model comprised both direct-contact and sexual transmission modes, parametrized using recent data on Ebola virus transmission and shedding in semen. Uncertain parameters, such as the probability of becoming sexually infectious, are varied through plausible ranges and metrics of epidemic impact; specifically increase in outbreak size, duration and probability are attributed to the degree to which sexual transmission is assumed to be in operation. We find that sexual transmission can dramatically affect the course of the outbreak and that the probability of becoming sexually infectious is a key parameter determining outbreak size.

2. Model and analysis

To parametrize the dynamics of the sexually infectious class, we used recently published data from a convenience survey of men who recovered from Ebola

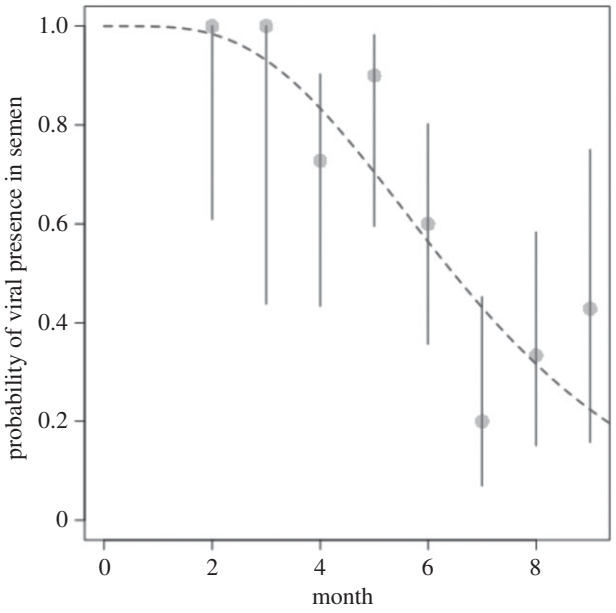

Figure 1. Probability of semen containing Ebola virus RNA as a function of month post-recovery (with 95% binomial confidence intervals), adapted from [3]. The dashed line is a fitted gamma distribution with shape parameter $\alpha = 5$ and rate parameter $\eta = 0.722$ with a mean of 6.925 months.

virus infection during the 2013–2015 epidemic [3], which suggested that virus can remain present in the semen for a considerable time (figure 1).

The four-month lag before the probability of virus detection in semen drops below 100% suggests a gamma distribution rather than an exponential distribution to describe the probability of remaining sexually infectious over time. Accordingly, we fitted the gamma probability density function

$$\frac{\eta^{\alpha}}{\Gamma(\alpha)} t^{\alpha-1} e^{-\eta t} \tag{2.1}$$

to the data using maximum likelihood (details in the electronic supplementary material).

We used the method of stages [5] to produce a gamma distributed residence time in the sexually infectious class, with mean duration $\tau = \alpha/\eta$ and corresponding recovery rate $\omega = 1/\tau$. After fitting the model, we recast α to its nearest integer and refitted η. The results of the fitting exercise show that the optimal model contains $\alpha = 5$ sexually infectious pseudo-stages with a pseudo-stage transition rate of 0.722 months^{-1} (alternative plausible parametrizations, $\alpha = 4,6$, are explored in the electronic supplementary material).

We developed a Susceptible-Infectious-Sexually Infectious-Recovered (*SIYR*) model to describe the dynamics of the epidemic in a population of size N ($N = S + I + \sum_{j=1}^{5} Y_j + R$). Susceptible individuals (S) may transition to the symptomatic infectious state (I) via two modes of virus transmission: direct- or sexual contact with infectious (I and Y, respectively) individuals. The parameter β_C is the transmission rate for infection that occurs through density-dependent direct-contact, which is scaled by the function $e^{-\phi I}$. Here $\phi \geq 0$ acts to reduce direct-contact transmission when the number of cases is high, reflecting behaviour and intervention changes that reduce transmission (one of several ways to model outbreaks brought under control). The parameter β_S is the transmission rate of the virus that occurs through frequency-dependent sexual contact.

Table 1. Parameter values used in *SIYR* model. These parameter values result in an $R_0 = 2.0$ in the absence of sexual transmission. Time unit is months (correspondingly months^{-1} for rates).

	description	value
N	total population size	1000
γ	mean recovery rate from symptomatic infection	2
ϕ	degree of intervention to current incidence	0.054
β_C	transmission rate through direct-contact	0.01334
α	scaling parameter of gamma distribution/ number of sexually infectious pseudo-stages	5
η	rate parameter of gamma distribution/pseudo-stage transition rate	0.722
ω	mean recovery rate from sexually infectious phase (η/α)	0.144
p	proportion of directly infectious individuals who become sexually infectious	0.0–0.5
β_S	transmission rate through sexual contact	0.0–0.5
ψ	probability of disease-induced mortality	0.7

Individuals transition out of the directly infectious class at rate γ, or die due to infection with probability ψ. After transitioning from class I, a proportion of individuals (p) become sexually infectious and transition through the five equally infectious pseudo-stages, with pseudo-stage transition rate η. Individuals who transition from the last pseudo-stage (Y_5) or did not become sexually infectious are then recovered (R) and are immune to reinfection.

$$\left.\begin{aligned} \dot{S} &= -\beta_C e^{-\phi I} SI - \beta_S \frac{\sum_{j=1}^{5} Y_j}{N} S, \\ \dot{I} &= \beta_C e^{-\phi I} SI + \beta_S \frac{\sum_{j=1}^{5} Y_j}{N} S - \frac{1}{1-\psi}\gamma I, \\ \dot{Y}_1 &= p\gamma I - \eta Y_1, \\ \dot{Y}_2 &= \eta(Y_1 - Y_2), \\ \dot{Y}_3 &= \eta(Y_2 - Y_3), \\ \dot{Y}_4 &= \eta(Y_3 - Y_4), \\ \dot{Y}_5 &= \eta(Y_4 - Y_5) \\ \text{and} \quad \dot{R} &= (1-p)\gamma I + \eta Y_5 \end{aligned}\right\} \tag{2.2}$$

Using the next generation matrix method [6], the basic reproductive ratio of virus in the system is

$$\begin{aligned} R_0 &= (1-\psi)\left(\frac{\beta_C N}{\gamma} + \frac{p\beta_S}{\omega}\right) \\ &= R_0^C + R_0^S, \end{aligned} \tag{2.3}$$

i.e. the sum of the basic reproductive ratios associated with contact transmission, R_0^C, and sexual transmission, R_0^S. We set R_0^C to 2.0, consistent with data-derived estimates, which include the common assumption of a two week infectious period [7]. Parameter ϕ was determined by selecting an attack ratio of 25% in the absence of sexual transmission (assuming that an Ebola outbreak may affect as many as one in four individuals even with behaviour change;

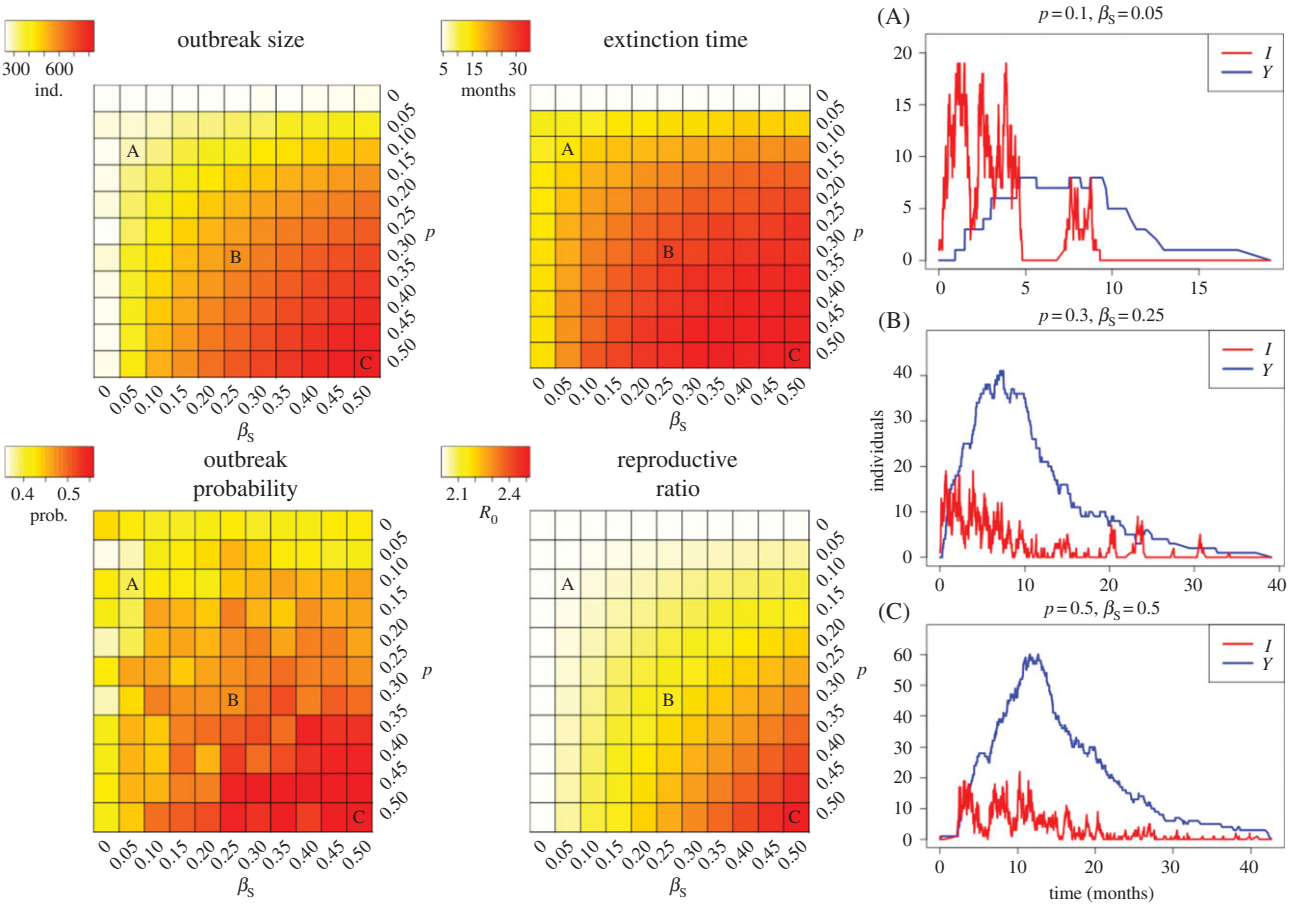

Figure 2. Heat maps of the average outbreak size, average extinction time of a large outbreak (time until last infectious individual recovers or dies), probability of a large outbreak, all determined from simulations and calculated reproductive ratio (R_0). For simulation-based estimates, 1000 stochastic simulations are used for each parameter set. Panels (a–c) are example outbreaks that can occur with the specified parameter combinations.

electronic supplementary material). Without such behaviour change ($\phi = 0$) attack ratios are typically 80% in this model. Parameter values are listed in table 1.

Because some parameters relating to sexual transmission (p, β_S) are uncertain, these were varied through plausible ranges: $\beta_S \in \{0, 0.05, \ldots, 0.5\}$, $p \in \{0, 0.05, \ldots, 0.5\}$ with maximum values increasing overall R_0 up to 2.5. Baseline epidemic metrics (probability, size and duration) in the absence of sexual transmission are discerned by including $p = 0$ and $\beta_S = 0$ in simulations. Models were implemented as stochastic simulations using Gillespie's direct method [8] to link parameter values with increases in average outbreak size, average duration of the outbreak and the probability of an outbreak. Replication was at the scale of 1000 outbreaks per parameter set and each simulation began with one symptomatically infectious individual ($I_0 = 1$), with all other individuals assumed susceptible. Simulations ran until there were no infectious individuals ($I = Y = 0$).

Probability of large outbreaks was established by seeking the relative size of the second, large mode for outbreak sizes from the appropriate histogram [9]. For each parameter set a histogram of the size of outbreaks was generated (breaks occurring at every 50 individuals). All sets exhibited a U-shaped distribution, from which we found the outbreak size that separated the two modes of the distribution (local minimum of the distribution function). Additionally, extinction time (time until last infectious individual, I or Y, recovers) and size were calculated only from the set of large outbreaks (i.e. conditional on a large outbreak occurring).

3. Results

The average outbreak size, extinction time and outbreak probability increased with sexual transmission rate, β_S, and the proportion of individuals that become sexually infectious, p (figure 2). When there is no sexual transmission ($p = 0$, $\beta_S = 0$), outbreak size and outbreak probability are at their minimum. Extinction time is shortest for $p = 0$, and only longer for $\beta_S = 0$, $p > 0$ because individuals can enter the sexually infectious phase (Y) without transmitting, and extinction time is measured as the time they recover from class Y.

The three panels A, B, and C in figure 2 are example outbreaks that occur with each denoted parameter pairing. When both β_S and p are small (A), outbreaks that occur have lower sizes and happen over a shorter time. Intermediate values of β_S and p (B), result in slightly longer outbreak duration with larger sizes. With the largest values of β_S and p (C), the outbreaks have similar duration to those associated with (B) and have the largest outbreak sizes. In each example, the direct-contact chain breaks (red curves showing incidence of symptomatic cases at 0) and is rescued by sexually infectious individuals.

4. Discussion

Adding sexual transmission to a direct-transmission compartment model increases parasite fitness by augmenting the possible ways in which the parasite may achieve onward transmission. The parasite basic reproductive ratio is the sum of the direct and sexual transmission basic reproductive ratios, similar to the sum of direct and environmental transmission ratios derived for avian influenza viruses [10] and waterborne pathogens [11]. The degree to which sexual transmission compromises mitigation of an outbreak that is waning due to behaviour change reducing direct-contact transmission depends on the probability that regular infections resolve to a sexually infectious state, the duration of that state and the sexual transmission rate. The inclusion of sexual transmission increases the probability of outbreaks occurring partly by repairing broken transmission chains, which augments the reproductive ratio used in the stochastic threshold theorem for epidemic probability derived using a birth–death model [12].

The study explores the possibility that Ebola virus outbreaks could be reignited by sexual transmission post-convalescence. Our model provides a way to evaluate the extent to which this transmission mode may increase outbreak size and duration, as well as its ability to repair broken, or stuttering, direct-transmission chains. The probability that individuals become sexually infectious is key to this process and is a relatively unknown parameter. The ongoing advice and counselling to Ebola survivors aimed at preventing sexual transmission [13], when translated to a reduced probability of being sexually infectious, could have a striking impact even if it is hard to measure in practice. The aim of the model presented is to provide a timely, broad perspective on the potential role of sexual transmission and an appreciation of which controllable parameters have the largest effect on outbreaks. Available data [3] were invaluable in enabling the model to describe non-exponentially distributed residence times in the sexually infectious class. Future data sources are likely to further improve on basic compartment models, such as data on the disproportionate role that individuals may play based on partner exchange rates [14], and the network structure of sexual contacts [15]. These enhancements may ultimately refine predictions on the role of sexual transmission in otherwise direct-contact contagious processes like Ebola.

Data accessibility. The research uses only previously published data. Details of certain methods are explained in the electronic supplementary material.

Authors' contributions. J.E.V., J.M.D., P.R. and A.W.P. participated in the design of the study and drafted the manuscript; J.E.V and A.W.P. performed the mathematical analysis and numerical simulation; all authors gave final approval for publication and agree to be held accountable for the content therein.

Competing interests. We declare we have no competing interests.

Funding. We acknowledge funding from the National Institute of General Medical Sciences of the National Institutes of Health under Award number U01GM110744 and funding from the National Science Foundation under Rapid Award number 1515194.

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