Potential impact of sexual transmission of Ebola virus on the epidemic in West Africa

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Abstract

Ebola virus RNA can persist in seminal fluids of male convalescent patients after they recover from Ebola virus disease (EVD). We used a compartmental EVD transmission model, Monte Carlo simulations, and performed sensitivity analyses to assess the potential impact of sexual transmission on the epidemic dynamics. The rate of sexual transmission and the period during which convalescent men can transmit sexually both affect the number of excess EVD cases, while the latter also influences the duration of the epidemic. Assuming an average convalescent period of 3 months, and a per sex act transmission probability of 0.1%, we found that sexual transmission could extend the EVD epidemic in Sierra Leone by 134 days (95% CI: 121–146 days). These results show the importance of ongoing surveillance efforts in West Africa and call for a better understanding of the persistence and infectivity of Ebola virus RNA in convalescent patients.

Introduction

Recent reports suggesting the potential for sexual transmission of Ebola virus from convalescent survivors have raised a number of important questions regarding its impact on the final phase of the epidemic in West Africa [1,2]. Even once the worst hit countries of Guinea, Liberia, and Sierra Leone are declared free of Ebola virus disease (EVD), rare cases may still arise from the large number of remaining survivors. Perhaps the most crucial element for bringing the epidemic to an end is maintaining vigilance in the community and preventing new chains of transmission. Historically occurring in sparsely-populated isolated communities, often killing the vast majority of victims [3], the unprecedented number of cases – and survivors – in densely populated urban areas presents novel challenges for bringing the outbreak to an end. Although sexual transmission of EVD is likely to be rare, it is important to investigate its potential impact on the transmission dynamics in general, and on the tail of the ongoing epidemic in particular.

Follow-up studies on survivors of the 1995 outbreak in the Democratic Republic of Congo [4] and the 2000 [5] and 2007 [6] outbreaks in Uganda have raised awareness of what is now being termed "post-Ebola syndrome" (post-Ebola sequelae) – debilitating illnesses from myalgia to uveitis – which can persist for at least 21 months after the onset of symptoms. Though the virus is no longer detected in the blood after symptoms disappear, active (replicating) virus has been documented in ocular fluid, rectal fluids, vaginal fluids, and semen [4,7]. Two recent reports indicate that this is also the case for survivors of the current (2013-2015) epidemic in West Africa, having documented

58 ongoing viremia in ocular [8] and seminal [1] fluids many months after falling ill.
59 Importantly, molecular evidence from a woman who contracted EVD in Liberia after
60 unprotected vaginal intercourse with a survivor nearly 6 months after his recovery from
61 EVD supports the hypothesis that direct sexual transmission from asymptomatic
62 convalescent survivors can and does occur [2]. Transmission to sexual partners was never
63 confirmed in earlier outbreaks, but was suspected to have occurred in at least one instance
64 [4]. Similarly, cases of sexual transmission of other hemorrhagic fever infections, notably
65 by the closely related Marburg virus, have been suspected in the past [9,10].
66
67 Of particular epidemiological interest is the question of how long active Ebola virus in
68 semen, vaginal, and rectal fluids of convalescent survivors poses a threat for sexual
69 transmission. The previous studies identified active virus as late as 82 days after onset of
70 symptoms in seminal fluid from one male patient; samples positive for viral RNA were
71 identified as late as 29 days (rectal) and 33 days (vaginal) after onset of symptoms in one
72 female patient of six sampled, and 101 days after onset of symptoms in seminal fluid
73 from four out of five male patients [4,7]. The studies from the West African outbreak,
74 showing viremia in semen 4-6 months after onset of symptoms in 65% of men tested (7-9
75 months in 26%) [1] and confirming occurrence of transmission from a survivor 179 days
76 after onset of symptoms [2], suggest that sexual transmission from convalescent men may
77 pose a threat for far longer than previously anticipated.
78
79 Sexual transmission of Ebola virus from convalescent survivors is likely a rare event, but
80 researchers have warned that it is feasible and should be considered in epidemiological

models that are used to predict the trajectory of the outbreak [11]. To this end, we devised a novel mathematical model of EVD transmission and studied the epidemic dynamics in absence and presence of sexual transmission from convalescent men. We performed sensitivity analysis to understand the impact of key unknown parameters, such as the duration of the convalescent period and the transmission probability per sexual contact. We also performed Monte Carlo simulations to explore the impact of sexual transmission on the epidemic tail in Sierra Leone.

Methods

Transmission model. We extended a SEIR (susceptible-exposed-infected-recovered) modeling framework, which has been extensively used to describe EVD transmission [12–14], by adding a component for sexual transmission from convalescent survivors who maintain active Ebola virus replication (Fig. 1). The resulting SEICR model has five states: susceptible, S, exposed, E, symptomatic and infectious, I, convalescent, C, fully recovered and immune, R, and dead, D. The model is represented by the following set of ordinary differential equations (ODEs):

$$\begin{aligned}
\frac{dS}{dt} &= -\beta(t)SI - \beta_S pC\frac{S}{N} \\
\frac{dE}{dt} &= \beta(t)SI + \beta_S pC\frac{S}{N} - \sigma E \\
\frac{dI}{dt} &= \sigma E - \gamma I \\
\frac{dC}{dt} &= (1-f)\gamma I - \alpha C \\
\frac{dR}{dt} &= \alpha C \\
\frac{dD}{dt} &= f\gamma I
\end{aligned} \tag{1}$$

where $N = S + E + I + C + R$ denotes the total population size. We assumed the non-sexual transmission rate, $\beta(t)$, to be initially constant (β_0) before it starts to decay exponentially due to the effect of control interventions and behavior change after time τ : $\beta(t) = \beta_1 + (\beta_0 - \beta_1)e^{-k(t-\tau)}$ [12]. The sexual transmission parameter, β_s, can be described as the product of two parameters ($\beta_s = \eta q$) that we will consider separately: η is the per sex act transmission probability of Ebola virus from convalescent men, and q is the daily rate at which they engage in sexual intercourse. The number of convalescent individuals are scaled by p, which is the proportion of convalescent survivors who are sexually active men. $1/\sigma$ and $1/\gamma$ represent the average durations of incubation and symptomatic infection, respectively. f is the case fatality rate. The average duration after which convalescent patients recover completely and shed no further replicating Ebola virus from their body is given by $1/\alpha$. We assumed that sexual transmission is frequency-dependent [15–17], i.e., the probability that the sexual partner of a convalescent man is susceptible is given by S/N .

Model parameters. The basic reproductive number, R_0, for the SEICR model can be calculated using the next-generation matrix method [18,19] and is given by

$$R_0 = \frac{\beta S_0}{\gamma} + \frac{(1-f)\, p\, \beta_s}{\alpha},$$

where S_0 is the initial number of susceptible individuals (see *Supplementary Material*). When α goes to infinity or either $\beta_s = 0$ or $p = 0$, the equation reduces to the basic reproductive number in absence of sexual transmission: $R_{0,N} = \frac{\beta S_0}{\gamma}$. Thus, the second

119 term represents the contribution of sexual transmission from convalescent patients to the
120 overall R_0: $R_{0,C} = \frac{(1-f)\, p\, \beta_s}{\alpha}$.
121
122 The model parameters were either based on published values from the literature or
123 adjusted to provide a good description of the EVD epidemic in Sierra Leone (Table 1).
124 We assumed that published estimates of R_0 do not include the contribution of sexual
125 transmission, i.e., the transmission rate during the early phase of the outbreak was given
126 by $\beta_0 = R_{0,N}\, \gamma/S_0$. We further assumed that the non-sexual reproductive number drops
127 below unity in the presence of partially effective control interventions [20] and set $\beta_1 =$
128 $0.5\, \gamma/S_0$. We used the weekly incidence and cumulative case counts of EVD from Sierra
129 Leone reported by the World Health Organization (WHO) Ebola Outbreak Situation
130 Reports (including updates according to the patient database) [21] as a comparison to the
131 model results.
132
133 ***Deterministic model and sensitivity analysis.*** We solved the system of ODEs
134 numerically using the function *ode* from the *deSolve* package in the R software
135 environment for statistical computing [22]. We compared the following response
136 variables of the model: the epidemic peak number of exposed, *E*, acute, *I*, and
137 convalescents, *C*, cases; the cumulative number of EVD cases, deaths, and recoveries; the
138 date at the epidemic peak; the daily and cumulative incidence of sexual transmission; and
139 the date at which the last symptomatic case either died or entered into convalescence
140 ("day of last case"). We defined the day of last case as the time when the number of
141 symptomatic and infectious individuals, *I*, dropped below 0.5. We considered the

following parameters for the sensitivity analysis: the per sex act transmission probability of Ebola virus from convalescent men (η), the proportion of convalescent survivors who are sexually active men (p), the rate at which they engage in sexual intercourse (q), and the rate at which convalescent patients recover completely and shed no further replicating Ebola virus from their body (α). The sensitivity of the response variables to changes in R_0 was explored simultaneously as a comparison. We generated 1000 parameter combinations from the uniform ranges, log-transformed [0.5x – 2x] for the parameter values for η, p, q, and α, given in Table 1 via Latin hypercube sampling using the Huntington and Lyrintzis correlation correction method (function *lhs* from R package *pse*) [23]. We then calculated partial rank correlation coefficients (PRCCs) using 50 bootstrap replicates [24].

Monte Carlo simulations. We performed stochastic simulations of the SEICR model with and without sexual transmission using Gillespie's algorithm [25]. We specifically investigated the following response variables from the simulations: the cumulative number of EVD cases, the size and date of the epidemic's peak incidence (daily number of new symptomatic infections), and the date of last case (last day that symptomatic infections, I, fell below 1). Summary statistics were based on the results of 1000 simulation runs for each transmission scenario. We calculated the average of the total number of EVD cases by including all simulations runs, i.e., also the simulations that rapidly go extinct. In contrast, the date of the epidemic end was based on the simulated epidemic trajectories that lasted for at least 300 days.

Results

Contribution of sexual transmission to overall R_0. Using the baseline parameter values from Table 1, the reproductive number of a convalescent infection, $R_{0,C}$, is 0.0024. This corresponds to only 0.12% of the overall R_0 of 2.02. Increasing the convalescent period from 3 to 6 months, the contribution of $R_{0,C}$ (0.0051) to the overall R_0 rises to 0.25%. The equation for $R_{0,C}$ (see *Methods*) illustrates that doubling the per sex act transmission probability has the same impact as doubling the convalescent period. It is important to note that the relative contribution of sexual transmission to the overall reproductive number rises as the effective reproductive number drops during the epidemic due to the effects of control interventions (see *Supplementary Material,* Fig. *S1*).

Effect of sexual transmission parameters on epidemic dynamics. Simulating the deterministic transmission model using the baseline parameter values from Table 1 resulted in a good description of the EVD epidemic in Sierra Leone (see *Supplementary Material*, Fig. *S2*). The two key unknown parameters of sexual transmission are the per sex act transmission probability, η, and the rate at which convalescent survivors fully recover, α. The duration of the convalescent period has the biggest impact on the peak number of convalescent individuals, while η does not (compare Fig. 2a and Fig. 3a). Both parameters have extremely small effects on the peak number of infected or exposed patients (Fig. 2a and Fig. 3a). The total number of recovered individuals is reached more slowly the longer the convalescent period (Fig. 2b), which is not an effect caused by η (Fig. 3b). While the convalescent periods ($1/\alpha$ = [0 – 9 months]) and the low values of η (η = [0.0005 – 0.002]) we explored create very few extra cases (Fig. 2b and Fig. 3b),

sensitivity analyses revealed that a higher per sex act transmission probability, a higher proportion of sexually active convalescent individuals, p, or a higher frequency of sex acts, q, could have larger impacts on the total number of cases than would proportional increases in the convalescent period (see *Supplementary Material*, Fig. *S4a*). Sensitivity analyses also revealed that these sexual transmission parameters could produce a small delay on the epidemic peak, more so than by changes in the convalescent period (see *Supplementary Material*, Fig. *S4b*).

The number of sexual transmission events expected from the baseline scenario ($\eta = 0.001$ and $1/\alpha = 3$ months) is 31.5, the majority of which will occur around the peak of the epidemic (Fig. 2c and Fig. 3c) and thus likely go undetected. Doubling either η or $1/\alpha$ results in almost equal increases in the incidence and cumulative number of sexual transmission events (Fig. 2c, 2d and Fig. 3c, 3d), with either leading to roughly double the number of sexually transmitted cases over the course of the whole epidemic (> 60 cases). It should be noted that the total number of cases increases more than by simply the number of sexual transmission events, because each sexual transmission event results in a new potential cluster of non-sexual transmission. The day of last case is affected more by the convalescent period than the per sex act transmission probability (represented by vertical lines in Fig. 2a and Fig. 3a), a result confirmed by the sensitivity analysis (see *Supplementary Material*, Fig. *S4a*). The tail of the epidemic will depend on a small number of events that are likely to be affected by stochastic processes, thus we used Monte Carlo simulations to explore this behaviour.

211

212 ***Impact of sexual transmission on the epidemic tail.*** We performed stochastic
213 simulations of the EVD transmission model to investigate the epidemic dynamics when
214 the number of new cases becomes small, i.e, during the tail of the epidemic. Comparing
215 model simulations while assuming a convalescent period of 3 months to without sexual
216 transmission confirmed the deterministic results that sexual transmission from
217 convalescent survivors does not lead to a significant increase in the cumulative number of
218 infected cases (non-STI: 12,933 +/- 686 cases; STI: 12,802 +/- 669 cases; $t = 0.137$, df =
219 1996.7, p = 0.89; *Supplementary Material*, Fig. *S3*), nor the size (non-STI: 99 +/- 5.1
220 new cases per day; STI: 97 +/- 4.9 new cases per day) or timing (non-STI: day 199 +/-
221 0.7; STI: day 198 +/- 1.0) of the epidemic peak incidence (Fig. 4a, 4b, 4c). Strikingly,
222 this conservative period of potential sexual transmission, which has recently been shown
223 to extend well beyond 3 months in at least 65% of patients [1], extended the average date
224 on which the last active case could be detected by over four months (non-STI: 504 +/- 2.6
225 days; STI: 638 +/- 6.0 days; difference: 134 days [95% CI: 121-147 days], $t = -20.5$, df =
226 666.29, $p < 0.0001$; Fig. 4d, 4e, 4g, 4h). The width of the tail (s.d. = 132 days) was such
227 that 27% of the 492 simulated epidemics that had not ended by day 300 still had
228 symptomatic cases 700 days (nearly two years) after the start of the epidemic (Fig. 4h).
229 When the convalescent period was extended from 3 months to 6 months, the projected
230 length of the epidemic increased to a mean of 1095 days (+/- 15.1), with 87% of these
231 simulated epidemics taking over two years to end (Fig. 4i). Importantly, there is greater
232 variance in the tail of the epidemic when sexual transmission is considered, and this
233 uncertainty grows with the length of the convalescent period (Fig. 4g, 4h, 4i).

Discussion

Our study shows that sexual transmission of Ebola virus from convalescent men could have a profound effect on the duration of the epidemic in Sierra Leone. Using a mathematical transmission model, we found that an average duration of the convalescent period of 3 months, and a per sex act transmission probability of 0.1% could extend the EVD epidemic in Sierra Leone by 134 days (95% CI: 121–147 days). Such a scenario would be consistent with the occurrence of a small number of sexual transmission events during the end-phase of the epidemic. So far, the reported cases of sexual transmission of EVD remain rare [1,2]. Hence, the per sex act transmission probability of Ebola virus from male convalescent survivors is unlikely to be higher than 0.1%, but might well be below this value. Our sensitivity analysis indicates that the duration of the EVD epidemic is heavily influenced by the period during which convalescent men can transmit sexually, calling for a better understanding of the persistence and duration of infectivity of Ebola virus RNA in convalescent patients.

To our knowledge, this is the first study using mathematical modeling to assess the potential impact of sexual transmission of Ebola virus on the epidemic in West Africa. We extended an accepted modeling framework that has been widely used to describe the epidemic trajectories of EVD outbreaks and epidemics [12–14]. Our baseline model provides a good description of the EVD epidemic in Sierra Leone and we performed sensitivity analysis to account for the considerable uncertainty in key unknown parameters regarding sexual transmission. Given that chance will play a crucial role in

257 sexual transmission of Ebola virus, we used stochastic simulations to explore the
258 expected variability in the tail of the epidemic. In the absence of a better understanding of
259 sexual transmission of EVD, mathematical modeling currently remains the only tool to
260 explore its potential impact on the epidemic trajectory.
261
262 Our study provides a preliminary picture of the potential epidemiological consequences
263 of sexual transmission of Ebola virus on the epidemic in West Africa. Consequently,
264 there are a number of limitations that should be considered when interpreting the results.
265 First, we limited our analysis to sexual transmission from convalescent men who remain
266 infectious through the presence of Ebola virus in their semen. However, our modeling
267 framework could be easily extended to account for transmission by other routes, e.g.,
268 through infectious vaginal secretions from female survivors. Second, we assumed a
269 homogeneously mixing population to describe both non-sexual and sexual transmission
270 of EVD. Spatial structure might play an important role in the spread of EVD [26] as close
271 contact with infected bodily fluids is typically required even for non-sexual transmission.
272 In particular, close contact limited to family or community members during the
273 convalescence period, often accompanied by decreased activity levels due to post-Ebola
274 sequelae, may help limit the chances of sexual transmission. Third, asymptomatic
275 infection may occur [27], and is predicted to lower epidemic projections due to increased
276 levels of immunity in the population [28]. Fourth, the model does not incorporate
277 potential heterogeneity in sexual behavior [15], and we assumed that all sexually active
278 male survivors have the same average numbers of sex acts per month. The assumed
279 frequency of sex acts (8.3 sex acts per month) came from a study of heterosexual couples

280 in sub-Saharan Africa [29], and is on the high end of estimates gathered from studies of
281 other populations (e.g., [29–31], but see the wide range in individual frequencies in [32]);
282 the sexual activity of convalescent Sierra-Leonean EVD survivors has not been reported.
283 Fifth, EVD is known to exhibit superspreading characteristics [33,34], and we did not
284 include this in our model. Superspreading events could lead to explosive regrowth of the
285 epidemic after the occurrence of a new case through sexual transmission [33]. On the
286 other hand, 72% of infected individuals in transmission chains in Guinea did not generate
287 further cases [33], suggesting that some cases of sexual transmission of EVD might not
288 be detected at all. Sixth, we assumed a single compartment for convalescent survivors
289 with an exponentially distributed period of convalescence. Recent data indicates that the
290 time during which convalescent men remain positive for Ebola virus RNA could be better
291 described by a unimodal distribution [1]. Seventh, it remains to be determined whether
292 the virus found in semen of male convalescent survivors is replication competent, and the
293 time window during which these men remain infectious could be shorter than the duration
294 they remain positive for Ebola virus RNA. Finally, like other negative-sense single-
295 stranded RNA ((-)ssRNA) viruses [35], the species currently circulating in West Africa
296 has been estimated to have high substitution rates [36–38]. This rapid evolution detected
297 throughout the current outbreak zone suggests that within- or between-host adaptation of
298 the virus leading to pro-longed persistence in the seminal fluids is possible.
299
300 Awareness of the potential for sexual transmission has led to WHO issuing
301 recommendations that ask convalescent men to abstain from sexual activity as much as
302 possible and to use condoms for up to 6 months after the onset of symptoms [39].

303 Condom use and social awareness of the risks of sexual transmission during
304 convalescence should have an impact on the per sex act transmission probability (η) and
305 the frequency of sex acts (q), respectively. Our results show that condom use should
306 reduce the number of sporadic sexual transmission events during the tail of the epidemic
307 and after discharge of all remaining symptomatic individuals. However, the time during
308 which the public health community must stay vigilant is not reduced because these
309 interventions will not affect the time during which convalescent survivors can shed
310 infectious virus ($1/\alpha$). This is especially poignant since adherence to these
311 recommendations will never be 100%. Better knowledge about the rate at which
312 convalescent survivors recover completely and shed no further replicating Ebola virus
313 from their body is thus urgently needed to plan continued surveillance efforts.
314
315 The EVD epidemic in Sierra Leone was declared to be over on 7 November 2015 [40].
316 Our modeling results show that sporadic events of sexual transmission of Ebola virus –
317 potentially leading to small transmission clusters – could continue to occur in the months
318 to come. Sexual transmission of EVD is likely to be rare, but recent events such as the
319 suspected infection of a 16-year-old girl through sexual transmission in Makeni, Sierra
320 Leone, during September 2015 exemplify the continued risks [41]. In addition, the
321 considerable uncertainty around the infectivity of convalescent men who test positive for
322 Ebola virus RNA, and the duration of this period, asks us to remain vigilant. We must
323 monitor and quantify this phenomena in order to help us better prepare health networks,
324 and to provide convalescent survivors with sound advice that balances protection of the
325 community with the harm that could come from unnecessary stigmatization [42–44]. As

more data about the convalescent survivors of EVD becomes available, this and future mathematical modeling studies will help to better understand the potential epidemiological consequences of sexual transmission on the EVD epidemic in West Africa.

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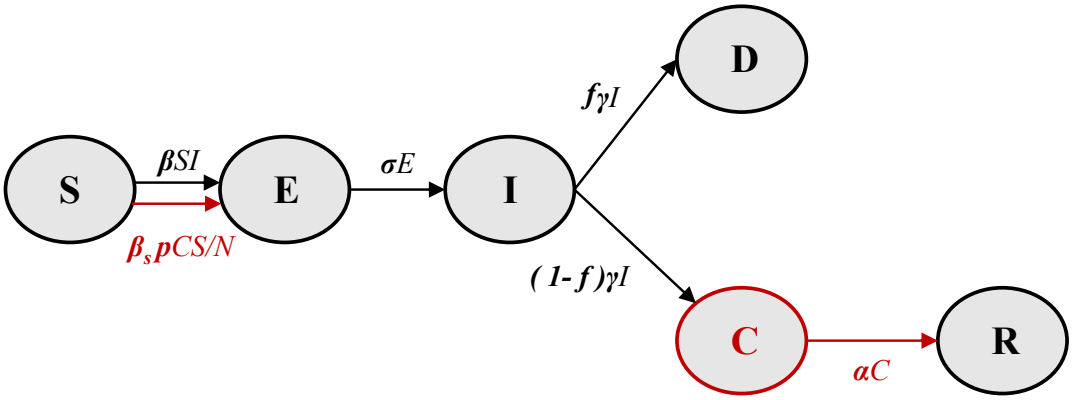
481 **Table 1: Model parameters describing EVD transmission in Sierra Leone.** The
482 indicated parameter ranges are used for the sensitivity analysis (partial rank correlation
483 coefficients, PRCC) only.

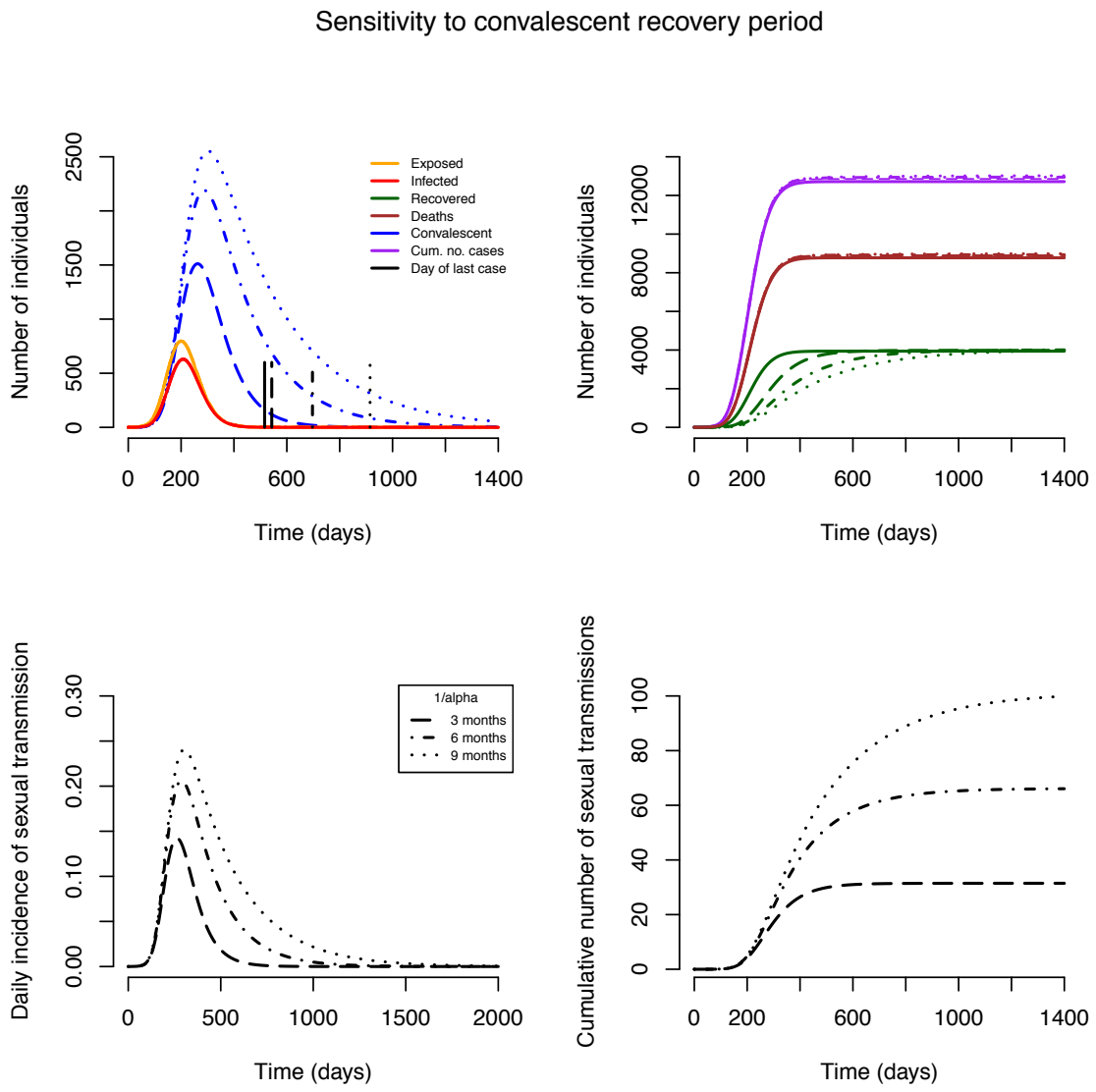
Parameter		Value (Range)	Comments and References
Basic reproductive number	$R_{0,N}$	2.02 (1.26 – 2.53)	Non-sexual transmission only [45] Range explores estimates from [13] and [46]
Date of onset of symptoms in index case		April 6, 2014	WHO epidemic day 92, epidemic week 14 [21]
Rate at which transmission rate decays	k	0.0098 d^{-1}	Results in a good description of the EVD epidemic in Sierra Leone
Time at which transmission rate starts to decay	τ	90 d	We assume that control measures were not effectively deployed country-wide until three months following the first detected case ($R_{0,N}$ estimates began to fall in August 2014 [45]).
Initial population size	N_0	6.316×10^6	Based on 2014 estimate [47]
Incubation period	$1/\sigma$	9.31 d	[14]
Case fatality rate	f	0.69	[45]
Infectious period	$1/\gamma$	7.41 d	[14]
Sexual transmission probability (per coital act)	η	0.001 (0.0005 – 0.002)	Roughly based on sexual transmission probability of HIV per coital act from infected men [48]
Frequency of sex acts	q	0.272 d^{-1} (0.136 – 0.544)	8.27 coital acts per month [29]
Proportion of convalescent survivors who are infectious and sexually active	p	0.347 (0.1725-0.694)	Of 47.4% male survivors, 73.1% are aged 15-45 [45].
Rate at which convalescent survivors recover completely	α	1/83.84 d^{-1} (1/168 – 1/42)	3 months after onset of symptoms [4,39] and assuming an infectious period of 7.41 days

484

Figure 1. Schematic illustration of EVD transmission model including sexual transmission from convalescent patients. The elements in black form the base model without sexual transmission [12–14]. The red elements (convalescent individuals and additional transmission term) were added to account for sexual transmission.



490 **Figure 2. Effect of convalescent period on EVD epidemics.** The average duration of
491 the convalescent period ($1/\alpha$) is varied between 3 and 9 months. (a, b): Epidemic
492 trajectories in presence (broken lines) and absence of sexual transmission (solid lines).
493 Vertical lines mark the day of last symptomatic case. (c) Daily incidence of sexual
494 transmission. (d) Cumulative number of sexual transmission events. Note that the vertical
495 axes vary across panels.



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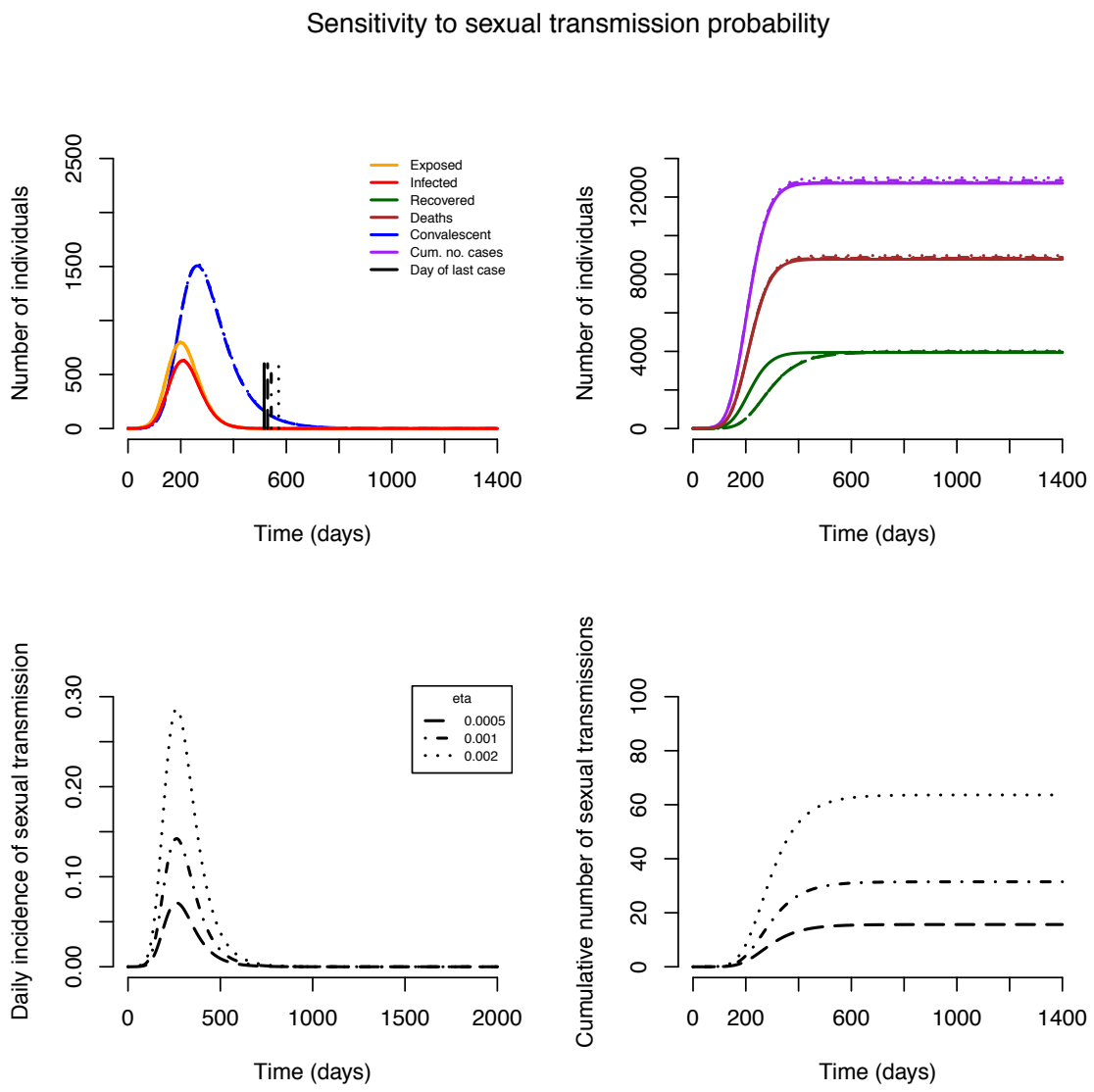
497

498 **Figure 3. Effect of per sex act transmission probability on EVD epidemics.** The per
499 sex act transmission probability (η) is varied between 0.05% and 0.2%. (a, b): Epidemic
500 trajectories in presence (broken lines) and absence of sexual transmission (solid lines).
501 Vertical lines mark the day of last symptomatic case. (c) Daily incidence of sexual
502 transmission. (d) Cumulative number of sexual transmission events. Note that the vertical
503 axes vary across panels.



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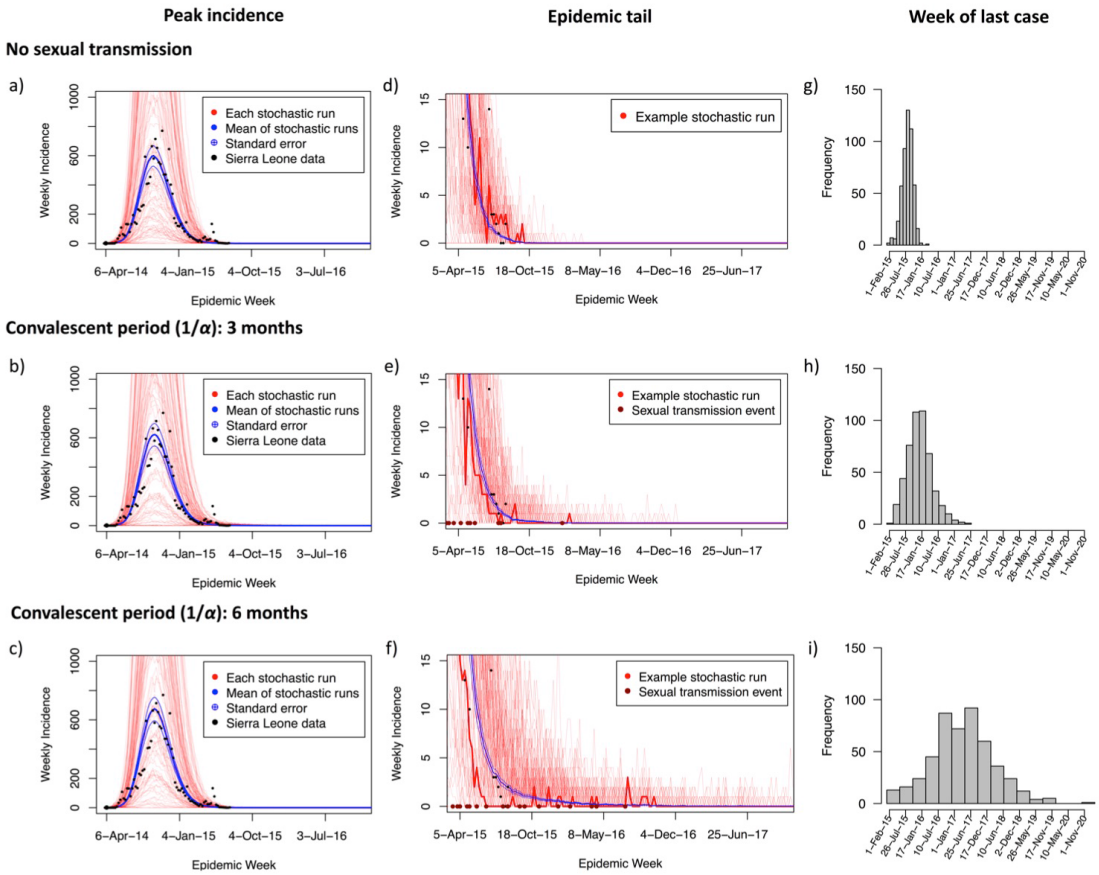
Figure 4. Impact of convalescent period on the tail of the EVD epidemic. Monte Carlo simulations of the weekly incidence of new cases (a, b, c) and the sporadic occurrence of sexual transmission events at the epidemic tail (d, e, f), assuming no sexual transmission (a, d), and sexual transmission with a 3 (b, e) and 6 months (c, f) convalescent period. Thin red lines show the result of 200 simulated trajectories, with corresponding mean (thick blue line) and standard errors (thin blue lines). Black dots denote incident cases in Sierra Leone as reported by the WHO [49]. The thick red lines in d, e, and f highlight a single representative trajectory, and the dark red dots along the horizontal axis indicate a sexual transmission event. Histograms of the day of the last EVD case from 1,000 simulated epidemics in absence of sexual transmission (g) and for a convalescent period of 3 (h) and 6 (i) months.