

The basic reproductive number of Ebola and the effects of public health measures: the cases of Congo and Uganda

G. Chowell^{a,d,*}, N.W. Hengartner^b, C. Castillo-Chavez^{a,d}, P.W. Fenimore^a, J.M. Hyman^c

^a Center for Nonlinear Studies (MS B258), Los Alamos National Laboratory, Los Alamos, NM 87545, USA

^b Statistical Science (MS F600), Los Alamos National Laboratory, Los Alamos, NM 87545, USA

^c Mathematical Modeling and Analysis (MS B284), Los Alamos National Laboratory, Los Alamos, NM 87545, USA

^d Department of Biological Statistics and Computational Biology, Cornell University, Warren Hall, Ithaca, NY 14853, USA

Received 4 December 2003; received in revised form 5 March 2004; accepted 8 March 2004

Abstract

Despite improved control measures, Ebola remains a serious public health risk in African regions where recurrent outbreaks have been observed since the initial epidemic in 1976. Using epidemic modeling and data from two well-documented Ebola outbreaks (Congo 1995 and Uganda 2000), we estimate the number of secondary cases generated by an index case in the absence of control interventions (R_0). Our estimate of R_0 is 1.83 (SD 0.06) for Congo (1995) and 1.34 (SD 0.03) for Uganda (2000). We model the course of the outbreaks via an SEIR (susceptible-exposed-infectious-removed) epidemic model that includes a smooth transition in the transmission rate after control interventions are put in place. We perform an uncertainty analysis of the basic reproductive number R_0 to quantify its sensitivity to other disease-related parameters. We also analyse the sensitivity of the final epidemic size to the time interventions begin and provide a distribution for the final epidemic size. The control measures implemented during these two outbreaks (including education and contact tracing followed by quarantine) reduce the final epidemic size by a factor of 2 relative the final size with a 2-week delay in their implementation.

© 2004 Elsevier Ltd. All rights reserved.

Keywords: Ebola; Reproductive number; Congo; Uganda; Outbreak; Interventions

1. Introduction

Ebola hemorrhagic fever is a highly infectious and lethal disease named after a river in the Democratic Republic of the Congo (formerly Zaire) where it was first identified in 1976 (CDC, 2003a). Twelve outbreaks of Ebola have been reported in Congo, Sudan, Gabon, and Uganda as of September 14, 2003 (CDC, 2003b; WHO, 2003a). Two different strains of the Ebola virus (Ebola-Zaire and the Ebola-Sudan) have been reported in those regions. Despite extensive search, the reservoir of the Ebola virus has not yet been identified (Bremann et al., 1999; Leirs et al., 1999). Ebola is transmitted by physical contact with body fluids, secretions, tissues or semen from infected persons (CDC, 2003a; WHO,

2003b). Nosocomial transmission (transmission from patients within hospital settings) has been typical as patients are often treated by unprepared hospital personnel (barrier nursing techniques need to be observed). Individuals exposed to the virus who become infectious do so after a mean incubation period of 6.3 days (1–21 days) (Bremann et al., 1977). Ebola is characterized by initial flu-like symptoms which rapidly progress to vomiting, diarrhea, rash, and internal and external bleeding. Infected individuals receive limited care as no specific treatment or vaccine exists. Most infected persons die within 10 days of their initial infection (Birmingham and Cooney, 2002) (50%–90% mortality (WHO, 2003b)).

Using a simple SEIR (susceptible-exposed-infectious-removed) epidemic model (Fig. 1) and data from two well-documented Ebola outbreaks (Congo 1995 and Uganda 2000), we estimate the number of secondary cases generated by an index case in the absence of control interventions (R_0). Our estimates of R_0 are 1.83

*Corresponding author. Department of Biological Statistics and Computational Biology, Cornell University, Warren Hall, Ithaca, NY 14853, USA.

E-mail address: gc82@cornell.edu (G. Chowell).

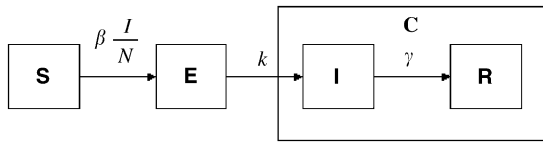


Fig. 1. A schematic representation of the flow of individuals between epidemiological classes. $\beta I/N$ is the transmission rate to susceptibles S from I ; E is the class of infected (not yet infectious) individuals; k is the rate at which E -individuals move to the symptomatic and infectious class I ; Infectious individuals (I) either die or recover at rate γ . C is not an epidemiological state but keeps track of the cumulative number of cases after the time of onset of symptoms.

(SD 0.06) for Congo (1995) and 1.34 (SD 0.03) for Uganda (2000). We model the course of the outbreaks via an SEIR epidemic model that includes a smooth transition in the transmission rate after control interventions are put in place. We also perform an uncertainty analysis on the basic reproductive number R_0 to account for its sensitivity to disease-related parameters and analyse the model sensitivity of the final epidemic size to the time at which interventions begin. We provide a distribution for the final epidemic size. A 2-week delay in implementing public health measures results in an approximated doubling of the final epidemic size.

2. Methods

We fit data from Ebola hemorrhagic fever outbreaks in Congo (1995) and Uganda (2000) to a simple deterministic (continuous time) SEIR epidemic model (Fig. 1). The least-squares fit of the model provides estimates for the epidemic parameters. The fitted model can then be used to estimate the basic reproductive number R_0 and quantify the impact of intervention measures on the transmission rate of the disease. Interpreting the fitted model as an expected value of a Markov process, we use multiple stochastic realizations of the epidemic to estimate a distribution for the final epidemic size. We also study the sensitivity of the final epidemic size to the timing of interventions and perform an uncertainty analysis on R_0 to account for the high variability in disease-related parameters in our model.

2.1. Epidemic model

Individuals are assumed to be in one of the following epidemiological states (Fig. 1): susceptibles (at risk of contracting the disease), exposed (infected but not yet infectious), infectives (capable of transmitting the disease), and removed (those who recover or die from the disease).

2.1.1. Differential equation model

Susceptible individuals in class S in contact with the virus enter the exposed class E at the per-capita rate $\beta I/N$, where β is transmission rate per person per day, N is the total effective population size, and I/N is the probability that a contact is made with a infectious individual (i.e. uniform mixing is assumed). Exposed individuals undergo an average incubation period (assumed asymptomatic and uninfected) of $1/k$ days before progressing to the infectious class I . Infectious individuals move to the R -class (death or recovered) at the per-capita rate γ (see Fig. 1). The above transmission process is modeled by the following system of nonlinear ordinary differential equations (Anderson and May, 1991; Brauer and Castillo-Chavez, 2000):

$$\begin{aligned} \dot{S}(t) &= -\beta S(t)I(t)/N, \\ \dot{E}(t) &= \beta S(t)I(t)/N - kE(t), \\ \dot{I}(t) &= kE(t) - \gamma I(t), \\ \dot{R}(t) &= \gamma I(t), \\ \dot{C}(t) &= kE(t), \end{aligned} \tag{1}$$

where $S(t)$, $E(t)$, $I(t)$, and $R(t)$ denote the number of susceptible, exposed, infectious, and removed individuals at time t (the dot denotes time derivatives). $C(t)$ is not an epidemiological state but serves to keep track of the cumulative number of Ebola cases from the time of onset of symptoms.

2.1.2. Markov chain model

The analogous stochastic model (continuous time Markov chain) is constructed by considering three events: *exposure*, *infection* and *removal*. The transition rates are defined as

Event	Effect	Transition rate
Exposure	$(S, E, I, R) \rightarrow (S - 1, E + 1, I, R)$	$\beta(t)SI/N$
Infection	$(S, E, I, R) \rightarrow (S, E - 1, I + 1, R)$	kE
Removal	$(S, E, I, R) \rightarrow (S, E, I - 1, R + 1)$	γI

The event times $0 < T_1 < T_2 < \dots$ at which an individual moves from one state to another are modeled as a renewal process with increments distributed exponentially,

$$P(T_k - T_{k-1} > t | T_j, j \leq k - 1) = e^{-t\mu(T_{k-1})},$$

where $\mu(T_{k-1}) = (\beta(T_{k-1})S(T_{k-1})I(T_{k-1})/N + kE(T_{k-1}) + \gamma I(T_{k-1}))^{-1}$.

The final epidemic size is $Z = C(T)$ where $T = \min\{t > 0, E(t) + I(t) = 0\}$, and its empirical distribution can be computed via Monte Carlo simulations (Renshaw, 1991).

2.2. The transmission rate and the impact of interventions

The intervention strategies to control the spread of Ebola include surveillance, placement of suspected cases in quarantine for 3 weeks (the maximum estimated length of the incubation period), education of hospital personnel and community members on the use of strict barrier nursing techniques (i.e. protective clothing and equipment, patient management), and the rapid burial or cremation of patients who die from the disease (WHO, 2003b). Their net effect, in our model, is to reduce the transmission rate β from β_0 to $\beta_1 < \beta_0$. In practice, the impact of the intervention is not instantaneous. Between the time of the onset of the intervention to the time of full compliance, the transmission rate is assumed to decrease gradually from β_0 to β_1 according to

$$\beta(t) = \begin{cases} \beta_0 & t < \tau, \\ \beta_1 + (\beta_0 - \beta_1)e^{-q(t-\tau)} & t \geq \tau, \end{cases}$$

where τ is the time at which interventions start and q controls the rate of the transition from β_0 to β_1 . Another interpretation of the parameter q can be given in terms of $t_h = \ln(2)/q$, the time to achieve $\beta(t) = (\beta_0 + \beta_1)/2$.

2.3. Epidemiological data

The data for the Congo (1995) and Uganda (2000) Ebola hemorrhagic fever outbreaks include the identification dates of the causative agent and data sources. The reported data are (t_i, y_i) , $i = 1, \dots, n$ where t_i denotes the i th reporting time and y_i the cumulative number of infectious cases from the beginning of the outbreak to time t_i (Fig. 4).

Congo 1995: This outbreak began in the Bandundu region, primarily in Kikwit, located on the banks of the Kwilu River. The first case (January 6) involved a 42-year old male charcoal worker and farmer who died on January 13. The Ebola virus was not identified as the causative agent until May 9. At that time, an international team implemented a control plan that involved active surveillance (identification of cases) and education programs for infected people and their family members. Family members were visited for up to 3 weeks (maximum incubation period) after their last identified contact with a probable case. Nosocomial transmission occurred in Kikwit General Hospital but it was halted through the institution of strict barrier nursing techniques that included the use of protective equipment and special isolation wards. A total of 315 cases of Ebola were identified (81% case fatality). Daily

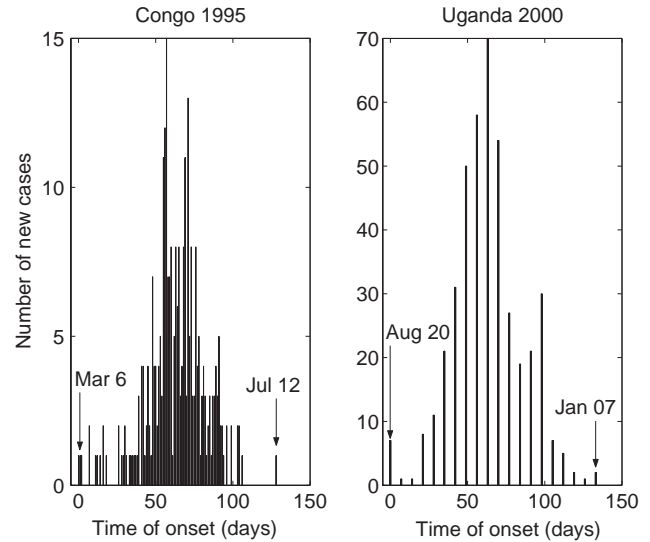


Fig. 2. On the left, we have the *daily* number of cases by date of symptom onset during the Ebola outbreak in Congo 1995 (Mar 6–Jul 12). On the right, we have the *weekly* number of cases by date of symptom onset during the Ebola outbreak in Uganda 2000 (Aug 20–Jan 07). Data has been taken from Refs. (Khan et al., 1995; WHO, 2001).

Ebola cases by date of symptom onset from March 1 through July 12 are available (Fig. 2) (Khan et al., 1995).

Uganda 2000: A total of 425 cases (53% case fatality) of Ebola were identified in three districts of Uganda: Gulu, Masindi and Mbarra. The onset of symptoms for the first reported case was on August 30, but the cause was not identified as Ebola until October 15 by the National Institute of Virology in Johannesburg (South Africa). Active surveillance started during the third week of October. A plan that included the voluntary hospitalization of probable cases was then put in place. Suspected cases were closely followed for up to three weeks. Other control measures included community education (avoiding crowd gatherings during burials) and the systematic implementation of protective measures by health care personnel and the use of special isolation wards in hospitals. Weekly Ebola cases by date of symptom onset are available from the WHO (World Health Organization) (WHO, 2001) (from August 20, 2000 through January 7, 2001) (Fig. 2).

2.4. Parameter estimation

Empirical studies in Congo suggest that the incubation period is less than 21 days with a mean of 6.3 days (Bremner et al., 1977) and the infectious period is between 3.5 and 10.7 days. The model parameters $\Theta = (\beta_0, \beta_1, k, q, \gamma)$ are fitted to the Congo (1995) and Uganda (2000) Ebola outbreak data by least-squares fit to the cumulative number of cases $C(t, \Theta)$ in Eq. (1). We used a computer program (Berkeley Madonna,

Berkeley, CA) and appropriate initial conditions for the parameters ($0 < \beta < 1$, $0 < q < 100$, $1 < 1/k < 21$ (Breman et al., 1977), $3.5 < 1/\gamma < 10.7$ (Piot et al., 1977)). The optimization process was repeated 10 times (each time the program is fed with two different initial conditions for each parameter) before the “best fit” was chosen. The asymptotic variance-covariance $AV(\hat{\theta})$ of the least-squares estimate is

$$AV(\hat{\theta}) = \sigma^2 \left(\sum_{i=1}^n \nabla C(t_i, \theta_0) \nabla C(t_i, \theta_0)^T \right)^{-1}$$

which we estimate by

$$\hat{\sigma}^2 \left(\sum_{i=1}^n \hat{\nabla} C(t_i, \hat{\theta}) \hat{\nabla} C(t_i, \hat{\theta})^T \right)^{-1},$$

where n is the total number of observations, $\hat{\sigma}^2 = 1/(n - 5) \sum (y_i - C(t_i, \hat{\theta}))^2$ and $\hat{\nabla} C$ are numerical derivatives of C .

For small samples, the confidence intervals based on these variance estimates may not have the nominal coverage probability. For example, for the case of Zaire 1995, the 95% confidence interval for q based on asymptomatic normality is $(-0.26, 2.22)$. It should be obvious that this interval is not “sharp” as it covers negative values whereas we know $q \geq 0$. The likelihood ratio provides an attractive alternative to build confidence sets (Fig. 3). Formally, these sets are of the form

$$\left\{ \theta : \frac{\sum (y_i - C(t_i, \theta))^2}{\sum (y_i - C(t_i, \hat{\theta}))^2} \leq A_x \right\},$$

where A_x is the $1 - \alpha$ quantile of an F distribution with appropriate degrees of freedom. Parameter estimates are given in Table 1.

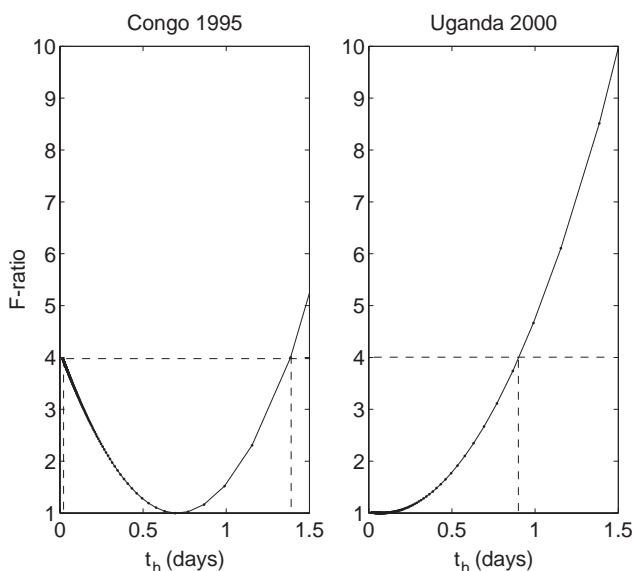


Fig. 3. Ninety-five percent confidence intervals for t_h ($t_h = \log(2)/q$), the time to achieve a transmission rate of $(\beta_0 + \beta_1)/2$, obtained from the likelihood ratio as described in the text.

2.5. The reproductive number

The basic reproductive number R_0 measures the average number of secondary cases generated by a primary case in a pool of mostly susceptible individuals (Anderson and May, 1991; Brauer and Castillo-Chavez, 2000) and is an estimate of the epidemic growth at the start of an outbreak if everyone is susceptible. That is, a primary case generates $R_0 = \beta_0/\gamma$ new cases on the average where β_0 is the pre-interventions transmission rate and $1/\gamma$ is the mean infectious period. The effective reproductive number at time t , $R_{eff}(t) = (\beta(t)/\gamma)x(t)$, measures the average number of secondary cases per infectious case t time units after the introduction of the initial infections and $x(t) = S(t)/N \approx 1$ as the population size is much larger than the resulting size of the outbreak (Table 2). Hence, $R_{eff}(0) = R_0$. In a closed population, the effective reproductive number $R_{eff}(t)$ is non-increasing as the size of the susceptible population decreases. The case $R_{eff}(t) \leq 1$ is of special interest as it highlights the crossing of the threshold to eventual control of the outbreak. An intervention is judged successful if it reduces the effective reproductive number to a value less than one. In our model, the post-intervention reproductive number $R_p = \beta_1/\gamma$ where β_1 denotes the post-intervention transmission rate. In general, the smaller β_1 , the faster an outbreak is extinguished. By the delta method (Bickel and Doksum, 1977), the variance of the estimated basic reproductive number \hat{R}_0 is approximately

$$V(\hat{R}_0) \approx \hat{R}_0^2 \left\{ \frac{V(\hat{\beta}_0)}{\hat{\beta}_0^2} + \frac{V(\hat{\gamma})}{\hat{\gamma}^2} - \frac{2Cov(\hat{\beta}_0, \hat{\gamma})}{\hat{\beta}_0 \hat{\gamma}} \right\}.$$

2.6. The effective population size

A rough estimate of the population size in the Bandundu region of Congo (where the epidemic developed) in 1995 is computed from the population size of the Bandundu region in 1984 (The World Gazetteer, 2003) and annual population growth rates (UN-HABITAT, 2003) (Table 2). For the case of Uganda (2000), we adjusted the population sizes of the districts of Gulu, Masindi and Mbarra in 1991 and annual population growth rates (UBOS, 2003) (Table 2). These estimates are an upper bound of the effective population size (those at risk of becoming infected) for each region. Estimates of the effective population size are essential when the incidence is modeled with the pseudo-mass-action assumption $(\beta(t)SI)$ which implies that transmission grows linearly with the population size and hence the basic reproductive number $R_0(N) = \beta_0 N/\gamma$. In our model, we use the true mass-action assumption $(\beta(t)SI/N)$ which makes the model parameters (homogeneous system of order 1) independent of

Table 1

Parameter definitions and baseline estimates obtained from the best fit of the model equations (1) to the epidemic-curve data of the Congo 1995 and Uganda 2000 outbreaks (Fig. 5)

Parameter	Definition	Congo 1995		Uganda 2000	
		Estim.	SD	Estim.	SD
β_0	Pre-interventions transmission rate (days ⁻¹)	0.33	0.06	0.38	0.24
β_1	Post-interventions transmission rate (days ⁻¹)	0.09	0.01	0.19	0.13
t_h	Time to achieve $\frac{\beta_0 + \beta_1}{2}$ (days)	0.71	(0.02, 1.39) ^a	0.11	(0,0.87) ^a
$1/k$	Mean incubation period (days)	5.30	0.23	3.35	0.49
$1/\gamma$	Mean infectious period (days)	5.61	0.19	3.50	0.67

The parameters were optimized by a computer program (Berkeley Madonna, Berkeley, CA) using a least-squares fitting technique and appropriate initial conditions for the parameters ($0 < \beta < 1$, $0 < q < 100$, $1 < 1/k < 21$ (Bremam et al., 1977), $3.5 < 1/\gamma < 10.7$ (Piot et al., 1977)). The optimization process was repeated 10 times (each time the program is fed with two different initial conditions for each parameter) before the “best fit” was chosen.

^a95% CI (Fig. 3)

Table 2

Population parameters and estimated R_0 for the Congo 1995 and the Uganda 2000 Ebola outbreaks

Outbreak	Eff. pop. size (N)	Start of interv.	Fatality rate (%)	Estim. R_0	SD R_0
Congo 1995	5,364,500 ^a	May 9, 1995 (Khan et al., 1995)	81% (Khan et al., 1995)	1.83	0.06
Uganda 2000	1,867,200 ^b	Oct 22, 2000 (WHO, 2001)	53% (WHO, 2001)	1.34	0.03

Notice that even though our expression for R_0 is independent of N , our model is not independent of N and hence the corresponding population sizes for Congo and Uganda are used in the least-squares estimation of the parameters.

^aAdjusted from population size of the Bandundu region in 1984 (The World Gazetteer, 2003) using the annual population growth rates (UN-HABITAT, 2003).

^bAdjusted from the population sizes of the districts of Gulu, Masindi and Mbarra (where the outbreak developed) in 1991 using the annual population growth rates (UBOS, 2003).

N and hence the basic reproductive number can be estimated by $R_0 = \beta_0/\gamma$ (Castillo-Chavez et al., 1994). In fact, comparisons between the pseudo-mass-action and the true mass-action assumptions with experimental data have concluded in favor of the later (De Jong et al., 1995). The model assumption that N is constant is not critical as the outbreaks resulted in a small number of cases compared to the size of the population.

2.7. Uncertainty analysis on R_0

Log-normal distributions seem to model well the incubation period distributions for a large number of diseases (Sartwell, 1966). Here, a log-normal distribution is assumed for the incubation period of Ebola in our uncertainty analysis. Log-normal distribution parameters are set from empirical observations (mean incubation period is 6.3 and the 95% quantile is 21 days Bremam et al., 1977). The infectious period is assumed to be uniformly distributed in the range (3.5–10.7) days (Piot et al., 1977).

A formula for the basic reproductive number R_0 that depends on the initial per-capita rate of growth r in the number of cases (Fig. 4), the incubation period ($1/k$) and the infectious period ($1/\gamma$) can be obtained by linearizing equations \dot{E} and \dot{I} of system (1) around the disease-free equilibrium with $S = N$. The corresponding

Jacobian matrix is given by

$$J = \begin{pmatrix} -k & \beta \\ k & -\gamma \end{pmatrix},$$

and the characteristic equation is given by

$$r^2 + (k + \gamma)r + (\gamma - \beta)k = 0,$$

where the early-time and per-capita free growth r is essentially the dominant eigenvalue. By solving for β in terms of r , k and γ , one can obtain the following expression for R_0 using the fact that $R_0 = \beta/\gamma$:

$$R_0 = 1 + \frac{r^2 + (k + \gamma)r}{k\gamma}.$$

Our estimate of the initial rate of growth r for the Congo 1995 epidemic is $r = 0.07 \text{ day}^{-1}$, obtained from the time series $y(t)$, $t < \tau$ of the cumulative number of cases and assuming exponential growth ($y(t) \propto e^{rt}$). The distribution of R_0 (Fig. 4) lies in the interquartile range (IQR) (1.66–2.28) with a median of 1.89, generated from Monte Carlo sampling of size 10^5 from the distributed epidemic parameters ($1/k$ and $1/\gamma$) for fixed r (Blower and Dowlatabadi, 1994). We give the median of R_0 as the resulting distribution of R_0 from our uncertainty analysis is skewed to the right.

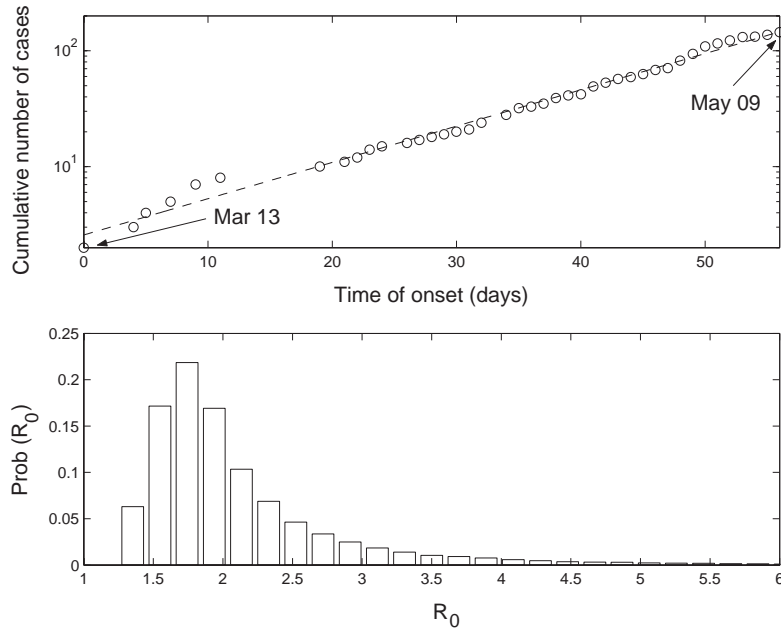


Fig. 4. (Top) cumulative number of cases (log–lin scale) during the exponential growth phase of the Congo 1995 epidemic as identified by the date of start of interventions (09 May 1995 (Khan et al., 1995)). The model-free initial growth rate of the number of cases for Congo 1995 is 0.07 (linear regression); (bottom) estimated distribution of R_0 from our uncertainty analysis (see text). R_0 lies in the interquartile range (IQR) (1.66–2.28) with a median of 1.89. Notice that 100% of the weight lies above $R_0 = 1$.

3. Results

Using our parameter estimates (Table 1), we estimate an R_0 of 1.83 (SD 0.06) for Congo (1995) and 1.34 (SD 0.03) for Uganda (2000). The effectiveness of interventions is often quantified in terms of the reproductive number R_p after interventions are put in place. For the case of Congo $R_p = 0.51$ (SD 0.04) and $R_p = 0.66$ (SD 0.02) for Uganda allowing us to conclude that in both cases, the intervention was successful in controlling the epidemic. Furthermore, the time to achieve a transmission rate of $(\beta_0 + \beta_1)/2$ (t_h) is 0.71 (95% CI (0.02, 1.39)) days and 0.11 (95% CI (0, 0.87)) days for the cases of Congo and Uganda respectively after the time at which interventions begin.

We use the estimated parameters to simulate the Ebola outbreaks in Congo (1995) and Uganda (2000) via Monte Carlo simulations of the stochastic model of Section 2.1 (Renshaw, 1991). There is very good agreement between the mean of the stochastic simulations and the reported cases despite the “wobble” captured in the residuals around the time τ of the start of interventions (Fig. 5). The empirical distribution of the final epidemic sizes for the cases of Congo 1995 and Uganda 2000 are given in Fig. 6.

The final epidemic size is sensitive to the start time of interventions τ . Numerical solutions (deterministic model) show that the final epidemic size grows exponentially fast with the initial time of interventions

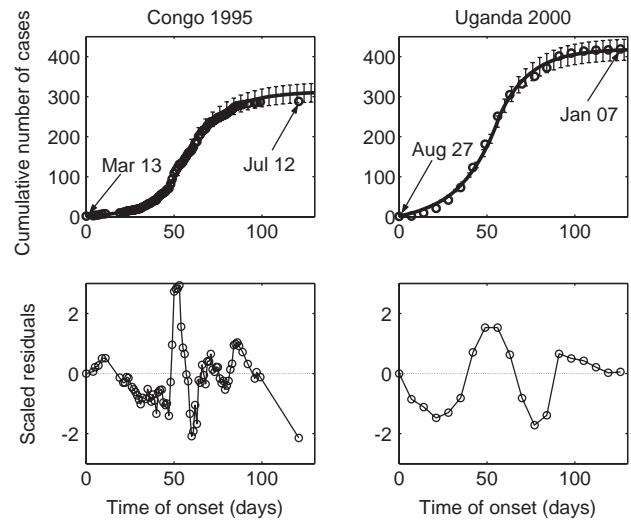


Fig. 5. (Top) Comparison of the cumulative number of Ebola cases during the Congo 1995 and Uganda 2000 Ebola outbreaks, as a function of the time of onset of symptoms. Circles are the data. The solid line is the average of 250 Monte Carlo replicates and the error bars represent the standard error around the mean from the simulation replicates using our parameter estimates (Table 1). For the case of Congo 1995, simulations were begun on 13 Mar 1995. A reduction in the transmission rate β due to the implementation of interventions occurs on 09 May 1995 (day 56) (Khan et al., 1995). For the case of Uganda 2000, simulations start on 27 August 2000 and interventions take place on 22 October 2000 (day 56) (WHO, 2001); (bottom) comparison of the residuals (difference between the data and the model best fit) scaled by the standard deviation for the cases of Congo and Uganda.

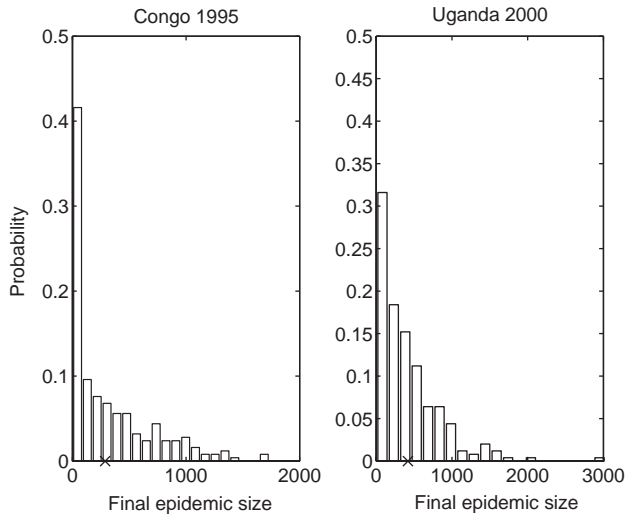


Fig. 6. The final epidemic size distributions for the cases of Congo 1995 and Uganda 2000 obtained from 250 Monte Carlo replicas. Crosses (X) represent the final epidemic size from data.

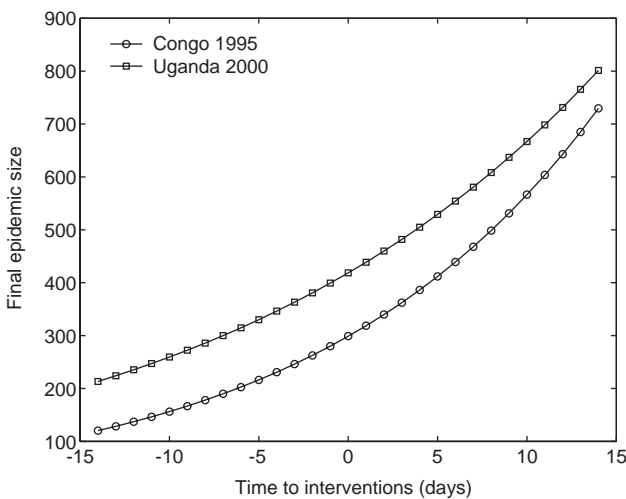


Fig. 7. Sensitivity of the final epidemic size to the time of start of interventions. Here negative numbers represent number of days before the actual reported intervention date (Table 2) and positive numbers represent a delay after the actual reported intervention date ($\tau = 0$). All other parameters have been fixed to their baseline values (Table 2). The final epidemic size grows exponentially as expected with the time of interventions with a rate of 0.06 for the case of Congo and 0.05 for the case of Uganda.

(not surprising as the initial epidemic growth is driven by exponential dynamics). For instance, for the case of Congo, our model predicts that there would have been 20 more cases if interventions had started one day later (Fig. 7).

4. Discussion

Using epidemic-curve data from two major Ebola hemorrhagic fever outbreaks (Khan et al., 1995; WHO,

2001), we have estimated the basic reproductive number (R_0) (Table 2). Our estimate of R_0 (median is 1.89) obtained from an uncertainty analysis (Blower and Dowlatabadi, 1994) by simple random sampling (Fig. 4) of the parameters k and γ distributed according to empirical data from the Zaire (now the Democratic Republic of Congo) 1976 Ebola outbreak (Bremner et al., 1977; Piot et al., 1977) is in agreement with our estimate of $R_0 = 1.83$ from the outbreak in Congo 1995 (obtained from least-squares fitting of our model (1) to epidemic curve data).

The difference in the basic reproductive numbers R_0 between Congo and Uganda is due to our different estimates for the infectious period ($1/\gamma$) observed in these two places. Their transmission rates β_0 are quite similar (Table 1). Our estimate for the infectious period for the case of Congo (5.61 days) is slightly larger than that of Uganda (3.50 days). Clearly, a larger infectious period increases the likelihood of infecting a susceptible individual and hence increases the basic reproductive number. The difference in the infectious periods might be due to differences in virus subtypes (Niikura et al., 2003). The Congo outbreak was caused by the Ebola-Zaire virus subtype (Khan et al., 1995) while the Uganda outbreak was caused by the Ebola-Sudan virus subtype (WHO, 2001).

The significant reduction from the basic reproductive number (R_0) to the post-intervention reproductive number (R_p) in our estimates for Congo and Uganda shows that the implementation of control measures such as education, contact tracing and quarantine will have a significant effect on lowering the effective reproductive rate of Ebola. Furthermore, estimates for the time to achieve $(\beta_0 + \beta_1)/2$ have been provided (Table 1).

We have explored the sensitivity of the final epidemic size to the starting time of interventions. The exponential increase of the final epidemic size with the time of start of interventions (Fig. 7) supports the idea that the rapid implementation of control measures should be considered as a critical component in any contingency plan against disease outbreaks specially for those like Ebola and SARS for which no specific treatment or vaccine exists. A 2-week delay in implementing public health measures results in an approximated doubling of the final outbreak size. Because the existing control measures cut the transmission rate to less than half, we should seek and support further improvement in the effectiveness of interventions for Ebola. A mathematical model that considers basic public health interventions for SARS control in Toronto supports this conclusion (Chowell et al., 2003; Chowell et al., 2004). Moreover, computer simulations show that small perturbations to the rate q at which interventions are put fully in place do not have a significant effect on the final epidemic size. The rapid identification of an outbreak, of course,

remains the strongest determinant of the final outbreak size.

Field studies of Ebola virus are difficult to conduct due to the high risk imposed on the scientific and medical personnel (Nabel, 1999). Recently, a new vaccine that makes use of an *adenovirus technology* has been shown to give cynomolgus macaques protection within 4 weeks of a single jab (Sullivan et al., 2003; Clarke and Knight, 2003). If the vaccine turns out to be effective in humans, then its value should be tested. A key question would be “What are the conditions for a successful target vaccination campaign during an Ebola outbreak?” To address questions of this type elaborate models need to be developed.

References

- Anderson, R.M., May, R.M., 1991. *Infectious Diseases of Humans*. Oxford University Press, Oxford.
- Bickel, P., Doksum, K.A., 1977. *Mathematical Statistics*. Holden-Day, Oakland, CA.
- Birmingham, K., Cooney, S., 2002. Ebola: small, but real progress (news feature). *Nature Med.* 8, 313.
- Blower, S.M., Dowlatabadi, H., 1994. Sensitivity and uncertainty analysis of complex models of disease transmission: an HIV model, as an example. *Int. Stat. Rev.* 2, 229–243.
- Brauer, F., Castillo-Chavez, C., 2000. *Mathematical Models in Population Biology and Epidemiology*. Springer, New York.
- Breman, J.G., Piot, P., Johnson, K.M., et al., 1977. The epidemiology of Ebola hemorrhagic fever in Zaire, 1976. Proceedings of the International Colloquium on Ebola Virus Infections held in Antwerp, Belgium, 6–8 December 1977.
- Breman, J.G., Johnson, K.M., van der Groen, G., et al., 1999. A search for Ebola virus in animals in the Democratic Republic of the Congo and Cameroon: ecologic, virologic, and serologic surveys 1979–1980. *J. Inf. Dis.* 179, S139–S147.
- Castillo-Chavez, C., Velasco-Hernandez, J.X., Fridman, S., 1994. Modeling contact structures in biology. In: Levin, S.A. (Ed.), *Frontiers of Theoretical Biology, Lecture Notes in Biomathematics*, Vol. 100. Springer, Berlin, Heidelberg, New York, pp. 454–491.
- Chowell, G., Fenimore, P.W., Castillo-Garsow, M.A., et al., 2003. SARS outbreaks in Ontario, Hong Kong and Singapore: the role of diagnosis and isolation as a control mechanism. *J. Theor. Biol.* 24, 1–8.
- Chowell, G., Castillo-Chavez, C., Fenimore, P.W., et al., 2004. Implications of an uncertainty and sensitivity analysis for SARS’s basic reproductive number for general public health measures, *Emerging Infectious Diseases*, to appear.
- Clarke, T., Knight, J., 2003. Fast vaccine offers hope in battle with Ebola. *Nature* 424, 602.
- Centers for Disease Control (CDC), 2003a. Ebola hemorrhagic fever. (<http://www.cdc.gov/ncidod/dvrd/spb/mnpages/dispages/ebola.htm>), accessed on August 24, 2003.
- Centers for Disease Control (CDC), 2003b. Ebola hemorrhagic fever: table showing known cases and outbreaks, in chronological order. (<http://www.cdc.gov/ncidod/dvrd/spb/mnpages/dispages/ebotabl.htm>), accessed on August 24, 2003.
- De Jong, M.C.M., Diekmann, O., Heesterbeek, H., 1995. How does transmission of infection depend on population size? In: Mollison, D. (Ed.), *Epidemic Models: Their Structure and Relation to Data*. Cambridge University Press, Cambridge, pp. 84–94.
- Khan, A.S., Tshioko, F.K., Heymann, D.L., et al., 1995. The reemergence of Ebola hemorrhagic fever, Democratic Republic of the Congo, 1995. *J. Inf. Dis.* 179, S76–S86.
- Leirs, H., Mills, J.N., Krebs, J.W., et al., 1999. Search for the Ebola virus reservoir in Kikwit, Democratic Republic of the Congo: reflections on a vertebrate collection. *J. Inf. Dis.* 179, S155–S163.
- Nabel, G.J., 1999. Surviving Ebola virus infection (news feature). *Nature* 4, 373–374.
- Niikura, M., Ikegami, T., Saijo, M., et al., 2003. Analysis of linear B-cell epitopes of the nucleoprotein of Ebola virus that distinguish Ebola virus subtypes. *Clin. Diagn. Lab. Immunol.* 10, 83–87.
- Piot, P., Bureau, P., Breman, G.D., Heymann, et al., 1977. Clinical aspects of Ebola virus infection in Yambuku Area, Zaire, 1976. Proceedings of the International Colloquium on Ebola Virus Infections held in Antwerp, Belgium, 6–8 December 1977.
- Renshaw, E., 1991. *Modelling Biological Populations in Space and Time*. Cambridge University Press, Cambridge.
- Sartwell, P.E., 1966. The distribution of incubation periods and the dynamics of infectious disease. *Am. J. Epidem.* 83, 204–216.
- Sullivan, N.J., Geisbert, T.W., Geisbert, J.B., et al., 2003. Accelerated vaccination for Ebola virus haemorrhagic fever in non-human primates. *Nature* 424, 681–684.
- The World Gazetteer, 2003. Democratic Republic of the Congo. (<http://www.world-gazetteer.com/fr/fr.cd.htm>), accessed on August 24, 2003.
- Uganda Bureau of Statistics (UBOS), 2003. Website: (<http://www.ubos.org/>), accessed on August 24, 2003.
- UN-HABITAT (United Nations Human Settlements Programme), 2003. Republic of Congo. Website: (<http://www.unhabitat.org/habrdd/conditions/midafrika/zaire.html>), accessed on August 24, 2003.
- World Health Organization (WHO), 2001. Outbreak of Ebola hemorrhagic fever, Uganda, August 2000–January 2001. *Weekly Epidemiol. Record* 76, 41–48.
- World Health Organization (WHO), 2003a. Ebola hemorrhagic fever: disease outbreaks. (<http://www.who.int/disease-outbreak-news/disease/A98.4.htm>), accessed on October 17, 2003.
- World Health Organization (WHO), 2003b. Ebola hemorrhagic fever. (<http://www.who.int/inf-fs/en/fact103.html>), accessed on August 24, 2003.