Ebola virus disease outbreak in Nigeria: lessons to learn

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ABSTRACT

International air travel has already spread Ebola virus disease (EVD) to major cities as part of the unprecedented epidemic that started in Guinea in December 2013. An infected airline passenger arrived in Nigeria on July 20, 2014 and caused an outbreak in Lagos and then Port Harcourt. After a total of 20 reported cases, including 8 deaths, Nigeria was declared EVD free on October 20, 2014. We quantified the impact of early control measures in preventing further spread of EVD in Nigeria and calculated the risk that a single undetected case will cause a new outbreak. We fitted an EVD transmission model to data from the outbreak in Nigeria and estimated the basic reproduction number $R_0 = 9.0$ (95% confidence interval [CI]: 5.2–15.6). We also found that the net reproduction number $R_t$ fell below unity 15 days (95% CI: 11–21 days) after the arrival of the index case. Using the estimated value of $R_0$ in Nigeria, we calculated that the risk of an outbreak from a single undetected case was 89% (95% CI: 81–94%). Even though $R_0$ in Nigeria was high, EVD outbreaks caused by infected air travelers can be successfully contained if control measures are rapidly implemented.

Keywords: Ebola virus disease, outbreak, basic reproduction number, mathematical model, Nigeria

INTRODUCTION

Air travel allows Ebola virus disease (EVD) to spread internationally (Gomes et al., 2014; Bogoch et al., 2014). Nigeria experienced an outbreak of EVD with the arrival of an infected air traveler at the international airport in Lagos on July 20, 2014 (Shuaib et al., 2014; Fasina et al., 2014). The traveler had been exposed to EVD in Liberia, had symptoms during his journey, and died on July 25, 2014, after being admitted to a private hospital in Lagos. Although authorities responded to the outbreak rapidly, there were an additional 19 EVD cases in Lagos and a large city in the south of Nigeria, Port Harcourt. The World Health Organization (2014c) declared Nigeria EVD free on October 20, 2014, after no new cases had been detected for 42 days.

Analyses of data from the EVD outbreak in Nigeria can provide important information about the impact of the sudden introduction of EVD in large cities and on the control measures needed to stop such outbreaks. The basic reproduction number $R_0$ is defined as the average number of secondary infections generated by an infectious index case at the beginning of an outbreak (Heffernan et al., 2005). The aim of control interventions is to reduce the net reproduction number $R_t$ during an outbreak (also called effective
or instantaneous reproduction number) below unity so the outbreak eventually ends. Studying the change in $R_t$ during the course of an outbreak provides useful information on the effectiveness of the control measures that were implemented (Chowell et al., 2004; Althaus, 2014; Camacho et al., 2014).

In this study, we fitted an EVD transmission model to the reported daily numbers of incident cases and deaths during the outbreak in Nigeria. This allowed us to estimate the basic reproduction number $R_0$, and to describe how the net reproduction number $R_t$ changed after control interventions were implemented. We then compare the risks of an outbreak from a single undetected case in Nigeria and the other West African countries with ongoing EVD transmission.

**METHODS**

**Model**

We applied an EVD transmission model that we used to estimate the reproduction number of EVD in Guinea, Sierra Leone and Nigeria (Althaus, 2014). EVD transmission follows SEIR (susceptible-exposed-infectious-recovered) dynamics (Figure 1) and can be described by the following set of ordinary differential equations (ODEs):

$$\frac{dS}{dt} = -\beta(t)SI, \quad (1)$$

$$\frac{dE}{dt} = \beta(t)SI - \sigma E, \quad (2)$$

$$\frac{dI}{dt} = \sigma E - \gamma I, \quad (3)$$

$$\frac{dR}{dt} = (1 - f)\gamma I, \quad (4)$$

$$\frac{dD}{dt} = f\gamma I. \quad (5)$$

After infection, susceptible individuals $S$ enter the exposed class $E$ before they become infectious individuals $I$ and either recover ($R$) or die ($D$). The average durations of incubation and infectiousness are given by $1/\sigma$ and $1/\gamma$, respectively. $f$ is the case fatality rate. The transmission rate before the introduction of control interventions was assumed to be constant, i.e., $\beta(t) = \beta_0$. Upon the implementation of control measures at time $\tau$, the transmission rate was assumed to decay exponentially: $\beta(t) = \beta_0 e^{-k(t-\tau)}$ (Lekone and Finkenstädt, 2006). The basic and net reproduction numbers are given by $R_0 = \beta_0 S(0)/\gamma$ and $R_t = \beta(t)S(t)/\gamma$, respectively.

We assumed the outbreak started with a single infected case in a large susceptible population ($I(0) = 1$ and $S(0) = 10^6$). As long as the number of cases is small compared to the total population size, the exact number of susceptible individuals does not need to be known to estimate the model parameters. The ODEs were solved numerically in the R software environment for statistical computing (R Development Core Team, 2014) using the function `ode` from the package `deSolve`.

We assumed the observed daily numbers of incident cases and deaths to be Poisson distributed to derive maximum likelihood estimates (MLEs) of the following model.
Figure 1. Schematic illustration of the EVD transmission model. Susceptible individuals $S$ become infected by infectious individuals $I$ at rate $\beta$. They then move through an incubation period ($E$) at rate $\sigma$ before they become infectious individuals $I$. Infectious individuals $I$ recover or die at rate $\gamma$. The case fatality rate is given by $f$.

parameters (Bolker, 2008): the baseline transmission rate $\beta_0$, the rate $k$ at which control measures reduce transmission, and the case fatality rate $f$. The average durations of incubation ($1/\sigma$) and infectiousness ($1/\gamma$) were fixed to values obtained from other data sets (see Data). We also set $\tau = 3$ days as the implementation of control measures began on July 23, 2014 (Shuaib et al., 2014). We used the optimization algorithm by Nelder & Mead, which is implemented in the function \textit{optim}.

We derived simulation based 95% confidence intervals (CIs) for the model curve making use of the asymptotic normality of MLEs (Mandel, 2013). We also constructed 95% prediction intervals (PIs) for the cumulative number of cases and deaths. The algorithm was as follows:

1. Simulate $n = 10,000$ values, $\theta_1, \ldots, \theta_n \sim N(\hat{\theta}, \Sigma)$, where $\hat{\theta}$ is the MLE of the unknown model parameters with associated variance-covariance matrix $\Sigma$, using the function \textit{rmvnorm} from the package \textit{mvtnorm}.
2. For each $\theta_i$, solve the system of ODEs to obtain the model curves for the cumulative number of infected cases and deaths. For each time-point $t$, use the 2.5% and 97.5% quantiles from these bootstrap samples to construct the point-wise CIs for the model.
3. For each epidemic trajectory, simulate a vector of daily incident cases from the sampling model, assuming they are Poisson distributed. For each time-point $t$, use the resulting bootstrap sample of the cumulative number of cases to construct the 95% PI. Proceed similarly for the number of deaths.

Data

Daily incidence of symptom onset and death were derived from the published reports about confirmed ($n = 19$) and probable ($n = 1$) EVD cases (Shuaib et al., 2014; Fasina et al., 2014). We extended the data set from the time of death of the last case to the date that WHO declared Nigeria EVD free (Oct 20, 2014) with zero counts for the number of incident cases and deaths.

The mean incubation period of EVD was based on the reported cases from the EVD outbreak in Zaire in 1976 (Breman et al., 1978; Breman and Johnson, 2014). We only used the time of symptom onset after person-to-person contact ($n = 109$, range: 2–21 days). Fitting a gamma distribution to the data resulted in a mean incubation period of 9.31 days (shape: 3.04; rate: 0.33).

The mean duration of the infectious period of EVD was calculated from the reported
cases in the early transmission chain of the outbreak in Guinea. Baize et al. (2014) described the dates of onset of symptoms and death in 17 patients. We assumed that the infectious period was the difference between these two dates (range: 4–17 days). Fitting a gamma distribution to the data resulted in an average infectious period of 7.41 days (shape: 5.29; rate: 0.71).

RESULTS

Fitting the transmission model to the data illustrates the variation around the expected number of cases and deaths for a small EVD outbreak as observed in Nigeria (Figure 2). The model provides a good description of the cumulative number of deaths. However, the model shows an earlier and slower increase in the cumulative number of cases, compared to the rapid rise in cases that were observed between 8 and 13 days after the arrival of the index case in Lagos. This discrepancy could be a result of stochastic effects or our assumptions about the transmissibility of EVD (see Discussion). The maximum likelihood estimate (MLE) of the baseline transmission rate $\beta_0$ was $1.22 \times 10^{-6}$ per individual per day (95% CI: $0.70 \times 10^{-6}$–$2.10 \times 10^{-6}$ per individual per day). This corresponds to a basic reproduction number $R_0 = 9.01$ (95% CI: 5.22–15.55). The rate at which control measures reduce transmission was estimated at $k = 0.19$ per day (95% CI: 0.10–0.38 per day), and the case fatality rate at $f = 0.39$ (0.14–0.71).

Figure 2. Dynamics of Ebola virus disease (EVD) outbreak in Nigeria. Symbols represent reported cases (red) and deaths (black). The best-fit model (solid lines) is given together with the 95% confidence intervals (dashed lines). The shaded areas correspond to the 95% prediction intervals. Note that the model was fit to the daily and not cumulative numbers of incident cases and deaths.

The Nigerian Federal Ministry of Health, the Lagos State government and international partners activated an Ebola Incident Management Center on July 23, 2014 (Shuaib et al., 2014). We assumed that this led to a reduction of the transmission rate $\beta(t)$. Based on our estimates of the baseline transmission rate $\beta_0$ and the rate $k$ at which control interventions reduce transmission, we calculated the decrease of the net reproduction number $R_t$ following the introduction of control measures that included case isolation, contact tracing and surveillance (Figure 2). We estimated that $R_t$ dropped below unity 12 days (95% CI: 8–18 days) after the control measures were implemented. This is about one serial interval after the index case arrived at the airport in Lagos (WHO Ebola
Response Team, 2014) and explains the small number of secondary and tertiary cases that were observed in this outbreak (Shuaib et al., 2014; Fasina et al., 2014).

Figure 3. Net reproduction number $R_t$ during the Ebola virus disease (EVD) outbreak in Nigeria. The maximum likelihood estimates of the net reproduction number $R_t$ (solid line) are shown together with the 95% confidence intervals (dashed lines). The black dot denotes the time at which $R_t$ dropped below unity (12 days after control measures were implemented).

Figure 4 shows the relation between the basic reproduction number $R_0$ and the probability $P = 1 - 1/R_0$ that a single infected case that remains undetected causes a subsequent outbreak (Antia et al., 2003). Using the estimated value of $R_0$ in Nigeria, we calculated that the risk of an outbreak from a single undetected case was 89% (95% CI: 81%–94%). Our previous estimates of $R_0$ for Guinea, Sierra Leone and Liberia are lower than for Nigeria and range between 1.51 and 2.53 (Althaus, 2014). This corresponds to an outbreak probability of 34%–60%, which is substantially lower than in Nigeria.

DISCUSSION

We fitted a dynamic transmission model to data about reported cases and deaths of EVD during a small urban outbreak in Nigeria. We estimated that the basic reproduction number $R_0$ for the infected airline traveler arriving in Lagos was 9.01 (95% CI: 5.22–15.55). The rapid implementation of control measures reduced the net reproduction number $R_t$ below unity 15 days (95% CI: 11–21 days) after the arrival of the index case. Using the estimated value of $R_0$, we calculated that the risk of an outbreak from a single undetected case was 89% (95% CI: 81%–94%).

This study adds to the epidemiological descriptions of the EVD outbreak in Nigeria and benefited from the detailed published data about the reported dates of onset of symptoms and death (Shuaib et al., 2014; Fasina et al., 2014). We estimated $R_0$ from the data by extending the modeling approach that provided the first estimates of $R_0$ for the 2014 EVD epidemics in Guinea, Sierra Leone and Liberia (Althaus, 2014). Our estimates of the average periods of incubation and infectiousness, which were based on historical data from the 1976 outbreak in Zaire (Breman et al., 1978) and the first cases of the 2013/2014 outbreak in Guinea (Baize et al., 2014), are in good agreement with other estimates (Eichner et al., 2011; Chowell and Nishiura, 2014). In particular, the
estimated generation time, the sum of the incubation and infectious periods (16.7 days), is consistent with the serial interval reported by the WHO Ebola Response Team (2014) (15.3 days).

There are two main limitations related to the model structure. First, we did not distinguish between transmission in health-care settings and in the community so we could not examine their separate contributions, as in some other studies (Legrand et al., 2007; Fasina et al., 2014). Second, we did not distinguish between different interventions such as case isolation, personal protective equipment for healthcare workers and contact tracing. We considered all control measures together and assumed that their implementation led to an exponential reduction in the transmission rate. Third, we assumed that EVD cases are equally infectious throughout their infectious period. However, transmissibility could increase with disease progression due to higher viral loads (Yamin et al., 2014). This could explain the sudden increase in cases during the second week as most of these were probably infected shortly before the index case died.

The $R_0$ in this outbreak in Nigeria shows the transmission potential of an index patient arriving in a major urban area with symptomatic EVD. Our estimate of $R_0$ in Nigeria was substantially higher than the values of around 1.5 to 2.5 estimated for the countries first affected in 2014 (Althaus, 2014; Fisman et al., 2014; Nishiura and Chowell, 2014; Towers et al., 2014; WHO Ebola Response Team, 2014; Stadler et al., 2014). Our model estimate of $R_0$ is consistent with the epidemiological contact data describing 12 or 13 secondary cases directly linked to the index case (Shuaib et al., 2014; Fasina et al., 2014) and the 95% CI (5.22–15.55) included the observed values. Superspreading events are also suspected to have happened at funerals during the early spread of EVD in Sierra Leone (Gire et al., 2014; Volz and Pond, 2014). These episodes contribute to the overall estimate of $R_0$, which is the average number of secondary infections for a particular country.

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**Figure 4.** Risk of an Ebola virus disease (EVD) outbreak from a single undetected case. The curve depicts the relation between the basic reproduction number $R_0$ and the probability of an outbreak. The red dots correspond to values of $R_0$ estimated in this study and previously (Althaus, 2014). The gray areas correspond to the 95% confidence intervals for Nigeria.
Modeling studies and epidemiological analyses of the outbreak in Nigeria provide important information about the infectiousness of EVD transmission due to international travel. In Nigeria, although the infected case had prominent symptoms whilst he was traveling, no secondary cases occurred in passengers (Fasina et al., 2014). Most of the secondary cases were healthcare workers in the hospital who presumably had direct contact with infected body fluids. EVD has also spread in September and October 2014 through international air travel to the USA (World Health Organization, 2014a), where two healthcare workers became infected. Patients with EVD also travelled by road to Senegal (World Health Organization, 2014d) and Mali (World Health Organization, 2014b). In Senegal there were no secondary cases and it is not yet known whether further cases will occur in Mali. The EVD outbreak in Nigeria shows that $R_0$ can be very high, but that early diagnosis and rapid and intensive control interventions can stop transmission.

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