

Ebola virus disease outbreak in Nigeria: transmission dynamics and rapid control

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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 can be high, our study illustrates the time window for successful containment of EVD outbreaks caused by infected air travelers.

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 (WHO) declared Nigeria EVD free on October 20, 2014, after no new cases had been detected for 42 days (World Health Organization, 2014c).

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

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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 the effective or instantaneous reproduction number) below unity so that 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 Liberia (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 τ , 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*.

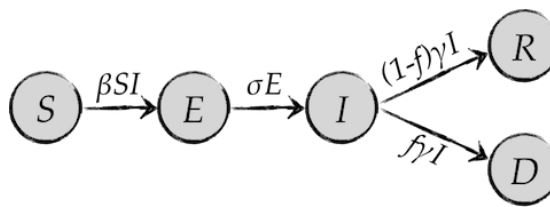


Figure 1. Schematic illustration of the EVD transmission model. Susceptible individuals S become infected by infectious individuals I at rate β . They then move through an incubation period (E) at rate σ before they become infectious individuals I . Infectious individuals I recover or die at rate γ . The case fatality rate is given by f .

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 parameters (Bolker, 2008): the baseline transmission rate β_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 *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, $\theta_1, \dots, \theta_n \sim N(\hat{\theta}, \Sigma)$, where $\hat{\theta}$ is the MLE of the unknown model parameters with associated variance-covariance matrix Σ , using the function *rmvnorm* from the package *mvtnorm*.
2. For each θ_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 was 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 β_0 was 1.22×10^{-6} per individual per day (95% CI: 0.70×10^{-6} – 2.10×10^{-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 $f = 0.39$ (95% CI: 0.14–0.71).

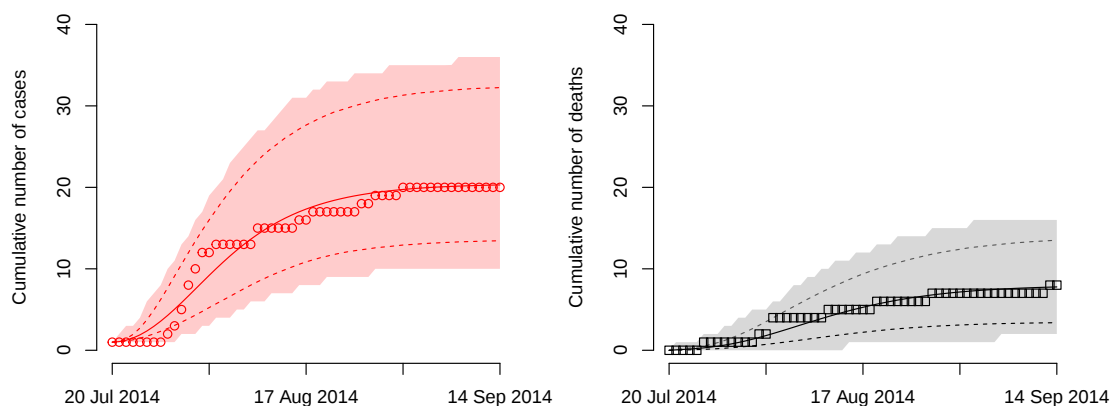


Figure 2. Dynamics of Ebola virus disease (EVD) outbreak in Nigeria. Symbols represent reported cases (red) and deaths (black). The best-fit model (solid lines) is given together with the 95% confidence intervals (dashed lines). The shaded areas correspond to the 95% prediction intervals. Note that the 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). Based on our estimates of the baseline transmission rate β_0 and the rate k at which control interventions reduce transmission, we calculated the decrease in 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 15 days (95% CI: 11–21 days) after the arrival of the index case, that is, 12 days after 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 was observed in this outbreak (Shuaib et al., 2014; Fasina et al., 2014).

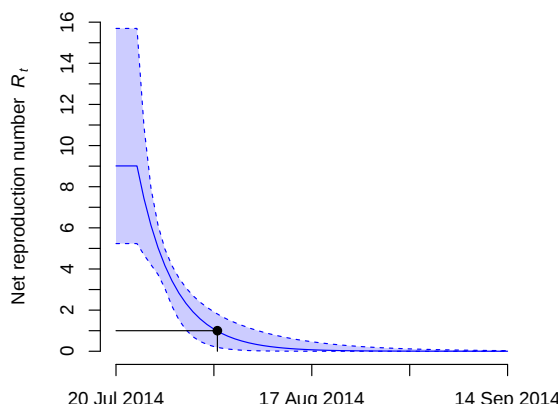


Figure 3. Net reproduction number R_t during the Ebola virus disease (EVD) outbreak in Nigeria. The maximum likelihood estimates of the net reproduction number R_t (solid line) are shown together with the 95% confidence intervals (dashed lines). The black dot denotes the time at which R_t dropped below unity (15 days after the arrival of the index case).

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). These estimates correspond to an outbreak probabilities between 34% and 60%, which are 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 $R_0 = 9.01$ was unusually high (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

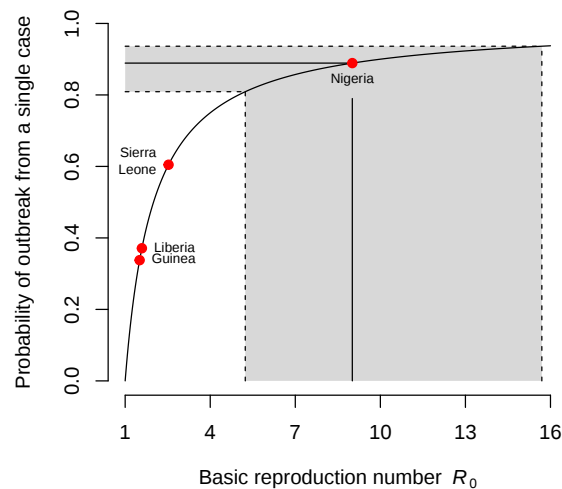


Figure 4. Risk of an Ebola virus disease (EVD) outbreak from a single undetected case. The curve depicts the relation between the basic reproduction number R_0 and the probability of an outbreak. The red dots correspond to values of R_0 estimated in this study and previously (Althaus, 2014). The gray areas correspond to the 95% confidence intervals for Nigeria.

estimates of the average periods of incubation and infectiousness, which were based on historical data from the 1976 outbreak in Zaire (Bremner 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 (15.3 days) reported by the WHO Ebola Response Team (2014).

There are three 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 estimated R_0 is consistent with the epidemiological contact data describing 12 (Fasina et al., 2014) or 13 (Shuaib et al., 2014) secondary cases directly linked to the index case and the 95% CI (5.22–15.55) includes the observed values. The high number of infections during the early phase of the outbreak could be attributed to the setting where they took place: a health facility where people had direct exposure to highly infectious body fluids such as blood. The observed challenges around patient compliance could also have contributed to the high level of transmission seen. In this context, it is worth noting that the decision of the index case to obtain medical care in a private

instead of a public health facility might have limited further spread. The socio-economic status of individuals in Nigeria weighs heavily on their health seeking behavior and the decision to obtain medical care in public or private facilities is influenced by their need to get prompt and consistent high quality health services. Those in the upper strata are more likely to seek initial care in the latter rather than the former. Thus, it is not unexpected that the index case, who was a diplomat, opted to attend a private health facility. Notwithstanding that there was a strike action in government hospitals, it is likely that the first point of call would still have been a private health facility.

Despite the large number of secondary cases, no transmissions occurred while the index case traveled from Liberia to Lagos. Because he provided support to his sister who subsequently died from EVD, it is possible that the index case was aware of his infection and took precautions to minimize contact with other passengers. This may also explain why an already sick secondary contact of the index case who evaded contact tracers and traveled by air from Lagos to Port Harcourt, was able to initiate another EVD cluster in Port Harcourt without infecting other airline passengers.

Our estimate of R_0 in Nigeria should not be confused with the lower 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). Those estimates are based on a larger number of cases and represent the average number of secondary cases for a particular country as whole. In contrast, the early phase of the EVD outbreak in Nigeria can be considered a superspreading event, similarly to the funerals that are suspected to have contributed to the early spread of EVD in Sierra Leone (Gire et al., 2014; Volz and Pond, 2014). Another difference is the availability of complete data on the numbers of people infected during the Nigeria outbreak compared to that of other countries. In the outbreaks in Guinea, Sierra Leone and Liberia, which started in the community, it is likely that not all infected individuals were documented, which might influence the estimation of R_0 .

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. 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 traveled by road to Senegal (World Health Organization, 2014d) and Mali (World Health Organization, 2014b). In Senegal there were no secondary cases but further cases have occurred in Mali. For the outbreak in Nigeria, we found that the net reproduction number R_t dropped below unity 15 days after the arrival of the index case at the international airport in Lagos. This suggests that the number of additional infections will be limited if transmission can be stopped within one serial interval of the infection, and illustrates the time window for successful containment of new EVD outbreaks caused through international travel.

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REFERENCES

- Althaus, C. L. (2014). Estimating the reproduction number of Ebola virus (EBOV) during the 2014 outbreak in West Africa. *PLoS Curr*, 6.
- Antia, R., Regoes, R. R., Koella, J. C., and Bergstrom, C. T. (2003). The role of evolution in the emergence of infectious diseases. *Nature*, 426(6967):658–61.
- Baize, S., Pannetier, D., Oestereich, L., Rieger, T., Koivogui, L., Magassouba, N., Soropogui, B., Sow, M. S., Keita, S., De Clerck, H., Tiffany, A., Dominguez, G., Loua, M., Traoré, A., Kolié, M., Malano, E. R., Heleze, E., Bocquin, A., Mély, S., Raoul, H., Caro, V., Cadar, D., Gabriel, M., Pahlmann, M., Tappe, D., Schmidt-Chanasit, J., Impouma, B., Diallo, A. K., Formenty, P., Van Herp, M., and Günther, S. (2014). Emergence of Zaire Ebola virus disease in Guinea. *N Engl J Med*, 371(15):1418–25.
- Bogoch, I. I., Creatore, M. I., Cetron, M. S., Brownstein, J. S., Pesik, N., Miniota, J., Tam, T., Hu, W., Nicolucci, A., Ahmed, S., Yoon, J. W., Berry, I., Hay, S., Anema, A., Tatem, A. J., MacFadden, D., German, M., and Khan, K. (2014). Assessment of the potential for international dissemination of Ebola virus via commercial air travel during the 2014 west African outbreak. *The Lancet*, pages –.
- Bolker, B. M. (2008). *Ecological Models and Data in R*. Princeton University Press, Princeton, NJ. ISBN: 0691125228.
- Breman, J., Piot, P., Johnson, K., White, M., Mbuyi, M., Sureau, P., Heymann, D., Van Nieuwenhove, S., McCormick, J., Ruppel, J., et al. (1978). The epidemiology of Ebola hemorrhagic fever in Zaire, 1976. *Ebola virus haemorrhagic fever*, pages 103–124.
- Breman, J. G. and Johnson, K. M. (2014). Ebola Then and Now. *N Engl J Med*.
- Camacho, A., Kucharski, A., Funk, S., Breman, J., Piot, P., and Edmunds, W. (2014). Potential for large outbreaks of Ebola virus disease. *Epidemics*, (0):–.
- Chowell, G., Hengartner, N. W., Castillo-Chavez, C., Fenimore, P. W., and Hyman, J. M. (2004). The basic reproductive number of Ebola and the effects of public health measures: the cases of Congo and Uganda. *J Theor Biol*, 229(1):119–26.
- Chowell, G. and Nishiura, H. (2014). Transmission dynamics and control of Ebola virus disease (EVD): a review. *BMC Med*, 12(1):196.
- Eichner, M., Dowell, S. F., and Firese, N. (2011). Incubation period of ebola hemorrhagic virus subtype zaire. *Osong Public Health Res Perspect*, 2(1):3–7.
- Fasina, F., Shittu, A., Lazarus, D., Tomori, O., Simonsen, L., Viboud, C., and Chowell, G. (2014). Transmission dynamics and control of Ebola virus disease outbreak in Nigeria, July to September 2014. *Euro Surveill*, 19(40).
- Fisman, D., Khoo, E., and Tuite, A. (2014). Early Epidemic Dynamics of the West African 2014 Ebola Outbreak: Estimates Derived with a Simple Two-Parameter Model. *PLoS Curr*, 6.
- Gire, S. K., Goba, A., Andersen, K. G., Sealfon, R. S. G., Park, D. J., Kanneh, L., Jalloh, S., Momoh, M., Fullah, M., Dudas, G., Wohl, S., Moses, L. M., Yozwiak, N. L., Winnicki, S., Matranga, C. B., Malboeuf, C. M., Qu, J., Gladden, A. D., Schaffner, S. F., Yang, X., Jiang, P.-P., Nekoui, M., Colubri, A., Coomber, M. R., Fonnies, M.,

- Moigboi, A., Gbakie, M., Kamara, F. K., Tucker, V., Konuwa, E., Saffa, S., Sellu, J., Jalloh, A. A., Kovoma, A., Koninga, J., Mustapha, I., Kargbo, K., Foday, M., Yillah, M., Kanneh, F., Robert, W., Massally, J. L. B., Chapman, S. B., Bochicchio, J., Murphy, C., Nusbaum, C., Young, S., Birren, B. W., Grant, D. S., Scheiffelin, J. S., Lander, E. S., Happi, C., Gevao, S. M., Gnirke, A., Rambaut, A., Garry, R. F., Khan, S. H., and Sabeti, P. C. (2014). Genomic surveillance elucidates Ebola virus origin and transmission during the 2014 outbreak. *Science*, 345(6202):1369–72.
- Gomes, M. F. C., y Piontti, A. P., Rossi, L., Chao, D., Longini, I., Halloran, M. E., and Vespignani, A. (2014). Assessing the International Spreading Risk Associated with the 2014 West African Ebola Outbreak. *PLoS Curr*, 6.
- Heffernan, J. M., Smith, R. J., and Wahl, L. M. (2005). Perspectives on the basic reproductive ratio. *J R Soc Interface*, 2(4):281–293.
- Legrand, J., Grais, R. F., Boelle, P. Y., Valleron, A. J., and Flahault, A. (2007). Understanding the dynamics of Ebola epidemics. *Epidemiol Infect*, 135(4):610–21.
- Lekone, P. E. and Finkenstädt, B. F. (2006). Statistical inference in a stochastic epidemic SEIR model with control intervention: Ebola as a case study. *Biometrics*, 62(4):1170–7.
- Mandel, M. (2013). Simulation-Based Confidence Intervals for Functions With Complicated Derivatives. *The American Statistician*, 67(2):76–81.
- Nishiura, H. and Chowell, G. (2014). Early transmission dynamics of Ebola virus disease (EVD), West Africa, March to August 2014. *Euro Surveill*, 19:36.
- R Development Core Team (2014). *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing, Vienna, Austria.
- Shuaib, F., Gunnala, R., Musa, E. O., Mahoney, F. J., Oguntimehin, O., Nguku, P. M., Nyanti, S. B., Knight, N., Gwarzo, N. S., Idigbe, O., Nasidi, A., and Vertefeuille, J. F. (2014). Ebola virus disease outbreak - Nigeria, july-september 2014. *MMWR Morb Mortal Wkly Rep*, 63(39):867–72.
- Stadler, T., Kühnert, D., Rasmussen, D., and du Plessis, L. (2014). Insights into the Early Epidemic Spread of Ebola in Sierra Leone Provided by Viral Sequence Data. *PLoS Curr*, 6.
- Towers, S., Patterson-Lomba, O., and Castillo-Chavez, C. (2014). Temporal Variations in the Effective Reproduction Number of the 2014 West Africa Ebola Outbreak. *PLoS Curr*, 6.
- Volz, E. and Pond, S. (2014). Phylodynamic Analysis of Ebola Virus in the 2014 Sierra Leone Epidemic. *PLoS Curr*, 6.
- WHO Ebola Response Team (2014). Ebola virus disease in West Africa—the first 9 months of the epidemic and forward projections. *N Engl J Med*, 371(16):1481–95.
- World Health Organization (2014a). Ebola virus disease – United States of America. <http://www.who.int/csr/don/01-october-2014-ebola/en/>.
- World Health Organization (2014b). Mali confirms its first case of Ebola. <http://www.who.int/mediacentre/news/ebola/24-october-2014/en/>.
- World Health Organization (2014c). Nigeria is now free of Ebola virus transmission. <http://www.who.int/mediacentre/news/ebola/20-october-2014/en/>.
- World Health Organization (2014d). The outbreak of Ebola virus disease in Senegal is over. <http://www.who.int/mediacentre/news/ebola/17-october-2014/en/>.
- Yamin, D., Gertler, S., Ndeffo-Mbah, M. L., Skrip, L. A., Fallah, M., Nyenswah, T. G.,

Altice, F. L., and Galvani, A. P. (2014). Effect of Ebola Progression on Transmission and Control in Liberia. *Ann Intern Med*.