1 **Early projections of Ebola outbreak size and duration with and without**
2 **vaccine use in Équateur, Democratic Republic of Congo, as of May 21, 2018**
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Authors
J. Daniel Kelly (a, f)*
Lee Worden (a, f)
Rae Wannier (a)
Nicole A. Hoff (b)
Patrick Mukadi (b, e)
Cyrus Sinai (b)
Sarah Ackley (a)
Xianyun Chen (c)
Daozhou Gao (c)
George W. Rutherford (a)
Thomas M. Lietman (a, f)
Jean Jacques Muyembe-Tamfum (d)
Anne W. Rimoin (b)
Travis C. Porco (a, f)
19
Institutions
a. School of Medicine, University of California, San Francisco (UCSF), San
Francisco, CA, USA
b. School of Public Health, University of California, Los Angeles, Los Angeles,
CA, USA
c. Mathematics and Science College, Shanghai Normal University, Shanghai,
China
d. Institut National de Recherche Biomédicale, Kinshasa, Democratic Republic of
Congo
e. Faculté de Médecine, Université de Kinshasa, Kinshasa, Democratic Republic
of Congo
f. F.I. Proctor Foundation, UCSF, San Francisco, CA, USA
32
Corresponding author:
J. Daniel Kelly, MD, MPH
Department of Medicine – Infectious Diseases
University of California, San Francisco
513 Parnassus Ave., S-384
San Francisco, CA 94143
Phone: (415) 476-6393
Fax: (415) 476-9364
dan.kelly@ucsf.edu

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Abstract

As of May 21, 2018, 58 cases of Ebola virus disease (EVD) were reported in

Équateur Province, Democratic Republic of Congo. We used reported case

counts and time series from prior outbreaks to estimate outbreak size and

duration using a stochastic branching process model with and without vaccine

use and using a regression model. With the stochastic transmission model, we

projected a median outbreak size of 206 EVD cases (95% credible interval: 109,

424), 265 cases (95% credible interval: 116.4, 683), and 849 cases (95%

credible interval: 166, 3691.5), using high, low, and zero estimates of vaccine

coverage. With the regression model, we estimated a median size of 96.7 cases

(95% prediction interval: 60, 265). This outbreak has the potential to be the

largest outbreak in DRC since 2007. Vaccines are projected to substantially limit

outbreak size and duration but are only part of prevention, control, and care

strategies.

Introduction

On May 8, 2018, the World Health Organization (WHO) announced the

occurrence of an outbreak of Ebola virus disease (EVD) in the Democratic

Republic of Congo (DRC).[1] From April 4 through May 7, 21 suspected EVD

cases were reported in Ikoko-Impenge and Bikoro, Équateur Province. On May

7, blood samples from five hospitalized patients had been sent to Kinshasa for

Ebola-PCR testing, and two were confirmed PCR-positive.[2] By May 21, there

were 58 suspected, probable and confirmed EVD cases, including four confirmed

cases in Mbandaka, the provincial capital of Equateur.[3] On the same day,

vaccination of healthcare workers started.[4]

This outbreak has several high-risk features. Cases have been reported

over a widespread, 168-kilometer distance. Mbandaka is a city of over 700,000

inhabitants situated on the Congo River and bordering the Republic of Congo.[5]

Moreover, travel to Kinshasa is frequent from Mbandaka. Given these risk factors,

early epidemic growth profiles, and historical outbreaks,[6] the risk of a

substantially larger outbreak cannot be ignored.

The factors causing epidemic growth to peak are debated. Delayed

detection and resulting widespread distributions of EVD have significantly

contributed to epidemic growth.[7] Unreported cases occurred at higher rates

during the early period of the 2013-2016 West Africa outbreak,[8] and urban

transmission may also occur at a higher rate than rural transmission.[9] Change to

subcritical transmission (reproduction number below 1) tends to occur when

Ebola response organizations deploy control, prevention and care measures,[10,11]

communities adopt more protective behaviors,[12,13] and/or transmission

decreases in a social network.[14,15] In the current Ebola outbreak in DRC,

scientific advances with rapid diagnostics and vaccines from the West Africa

outbreak has the potential to limit Ebola virus transmission as they are being

deployed.[16-18]

We used reported case counts from the current outbreak and/or time

series from 18 prior outbreaks to estimate the total outbreak size and duration

with and without the use of vaccines. These projections are intended to help

organizations anticipate and allocate sufficient resources to the 2018 Ebola

outbreak in DRC.

Methods

We used the following methods to generate projections: a stochastic

branching process model,[19] statistical regression based on prior outbreaks, and

Gott's Law.[20] On May 21, 58 EVD cases were reported in three locations (Ikoko-

Impenge, Bikoro, and Mbandaka) (**Figure 1**). Based on EVD situation reports

from DRC, we assumed the ring vaccination campaign would start on May 26.

Stochastic branching process model

We modeled Ebola virus transmission using a stochastic branching

process model, parameterized by transmission rates estimated from the

dynamics of prior Ebola outbreaks, and conditioned on agreement with reported

case counts from the current outbreak to date. We incorporated high and low

estimates of vaccination coverage into this model. Then we generated a set of

probabilistic projections of the size and duration of simulated outbreaks in the

current setting.

To estimate the reproduction number R as a function of the number of

days from the beginning of the outbreak, we included reported cases by date

from thirteen prior outbreaks and excluded the first historical outbreak reported in

those countries (e.g., 1976 outbreak in Yambuko, DRC) (**Supplement 1**).[21-28] As

there is a difference in the Ebola response system as well as community

sensitization to EVD following a country's first outbreak, we employed this

inclusion criterion to reflect the Ebola response system in DRC during what is

now its ninth outbreak. We used the Wallinga-Teunis technique to estimate R for

each case and therefore for each reporting date in the outbreak.[29] The serial

interval distribution used for this estimation was a gamma distribution with a

mean of 14.5 days and a standard deviation of 5 days, with intervals rounded to

the nearest whole number of days, consistent with the understanding that the

serial interval of EVD cases ranges from 3 to 36 days with mean 14 to 15 days.

We fit a curve $R = R_0\,e^{-\tau d}$ to each outbreak's estimates of R by day d, initial

reproduction number R_0 and quenching rate τ (**Supplement 2**).

We modeled transmission using a stochastic branching process model in

which the number of secondary cases caused by any given primary case is

drawn from a negative binomial distribution whose mean is the reproduction

number R, and variance is controlled by a dispersion parameter k.[30,31] All

transmission events were assumed to be independent. The interval between date

of detection of each primary case and that of each of its secondary cases is

assumed gamma distributed with mean 14.5 days and standard deviation 5 days,

rounded to the nearest whole number of days, as above. The pair of

parameters R_0 and τ estimated for the different past outbreaks used, and

dispersion parameter k, were used in all possible combinations

(with R_0 and т taken as a unit) to simulate outbreaks.

This model generated randomly varying simulated outbreaks with a range

of case counts per day. The outbreak was assumed to begin on April 4 with a

single case. The simulation process occurs as follows: proposed epidemic

trajectories are generated in an initial step based on the above branching

process, and these are then subsequently filtered by discarding all but those

whose cumulative case counts match the known counts of the current DRC

outbreak on known dates (**Table 1**). The filtration accepts epidemics within a

range of 3 cases more or less than each recorded value. This one-step particle

filtering technique produced an ensemble of model outbreaks, filtered on

agreement with the recorded trajectory of the outbreak to date. This filtered

ensemble is then used to generate projections of the eventual outcome of the

outbreak.[14]

To model vaccination coverage with respect to total transmission

(unreported and reported), we multiplied the estimate of vaccine effectiveness by

low and high estimates of reported cases. In a ring vaccination study at the end

of the West Africa outbreak, the overall estimated rVSV-vectored vaccine efficacy

was 100% and vaccine effectiveness was 64.6% in protecting all contacts and

contacts of contacts from EVD in the randomized clusters, including

unvaccinated cluster members.[17] We designed the stochastic model using

vaccine effectiveness. Then, we used past estimates of the proportion of

unreported cases to estimate the proportion of exposed individuals not covered

by the vaccination process. Based on a Sierra Leonean study from the 2013-

2016 outbreak,[8] we estimated that the proportion of reported cases in DRC

would rise over time from a low of 68% to a high of 96%. Given these low and

high estimates of reported cases and the estimate of vaccine effectiveness, a low

estimate of vaccination program coverage was 44% (68% * 64.6%) and a high

estimate of vaccination program coverage was 62% (96% * 64.6%). We modeled

the course of the outbreak with and without the vaccination program, with the

program beginning on May 26, based on dates available from situation reports.[3]

In the 2013-2016 West Africa outbreak, the mean time from symptom

onset to reporting was found to be approximately 4 days.[32] Based on that

estimate, we assumed a four-day period of transmission, with mean time of a

transmission event falling two days before reporting. Based on this, we modeled

transmission from a primary case to a secondary case using the value

of R corresponding to two days before the reporting date of the primary case.

From 30,670,848 simulated outbreaks, 7,684 were retained after filtering

on approximate agreement with DRC case counts. The simulated outbreaks that

were retained after filtering were continued until they generated no further cases.

We used this ensemble to derive a distribution of outbreak sizes and durations.

We calculated mean and median values and 95% credible intervals using the 2.5

and 97.5 percentiles of simulated outbreak size and duration. We conducted the

analyses using R 3.4.2 (R Foundation for Statistical Computing, Vienna, Austria).

Regression model

For contrast with the stochastic model above, we conducted a simple

regression forecast based solely on outbreaks of size 10 or greater. Time series

for all 18 such prior outbreaks were obtained, including seven prior ones from

DRC, dating back to 1976 (**Supplement 1 & 3**).[3,21-28,33-39] No exclusions were

made; no attempt to model specific features of this outbreak was conducted. The

regression model predicted the outbreak size based on values of the outbreak

size at a specific earlier time. The beginning of each outbreak was not reliably

characterized; therefore, all time series were aligned on the day they reached 10

cases. In the current outbreak, we observed cases over the period from April 4 to

May 21 (day 0 to day 47). May 21 corresponded to day 28 since reaching 10

reported cases. For the prior 18 outbreaks, we used linear interpolation to obtain

the number of cases on day 28 (after reaching 10 cases). To reduce the

influence of outliers and high leverage points, and to improve linearity, we

calculated the pseudologarithm transform $f(x)=\text{arcsinh}(x/2)$, asymptotically

logarithmic but well-behaved at 0. We used non-parametric Theil-Sen regression

(R-package *mblm*) followed by calculation of the resulting prediction interval for a

new observation.[40,41] Finally, we reported the median and 95% central coverage

intervals for the prediction distribution conditional on the value being no smaller

than the observed value on day 28. Sensitivity analysis was conducted using

ordinary least squares regression. We conducted these analyses using R 3.4.2

(R Foundation for Statistical Computing, Vienna, Austria).

Gott's Law

We applied Gott's Law to estimate the outbreak size using data from early in the

current outbreak period.[20] With Gott's Law, we assume we have no special

knowledge of our position on the epidemic curve. If we assume a non-informative

uniform prior for the portion of the epidemic that still remains, the resulting

probability distribution for the remaining number of cases y is $P(Y=y)= Y_0/y^2$. We

estimated the median outbreak size, along with the two-sided 95% confidence

interval.

Results

As of May 21, 2018, there were 58 EVD cases (**Table 1, Figure 1**). Bikoko

had ten confirmed cases and 19 probable cases. Iboko had 14 confirmed cases,

two probable cases, and six suspected cases. Mbandaka had four confirmed

cases and three suspected cases. In addition to cases, there have been 628

contacts (361 contacts in Bikoro, 120 contacts in Iboko, 117 contacts in

Mbandaka, and 30 contacts in Ntondo). Twenty-seven (47%) of 58 EVD cases

have died.[3]

In the absence of any vaccination program, the projected median outbreak

size based on the stochastic model was 849 cases (mean 1231.6; 95% credible

interval: 166, 3691.5). Median duration of projected outbreaks was 235 days

(mean 220.9; 95% credible interval: 136, 295). Using a lower estimate of 44%

vaccination coverage, the median outbreak size was 265 cases (mean 312.0;

95% credible interval: 116.4, 683) and median duration was 151 days (mean

152.2; 95% credible interval: 101, 209). Using a higher estimate of 62%

vaccination coverage, the median size was 206 EVD cases (mean 227.4; 95%

credible interval: 109, 424), and the median duration was 127 days (mean 128.9;

95% credible interval: 90, 175) (**Figure 2**).

With the regression based on past outbreaks, the median outbreak size

was estimated to be 96.7 cases (95% prediction interval: 60, 265). Removal of

data from the 2013-2016 West Africa outbreak from the regression yielded a

median size of 80.6 cases (95% central coverage interval for outbreak size

distribution: 59, 149), while use of ordinary least squares produced a median size

of 141 cases (95% central coverage interval: 65, 372). One (5.6%) of the 18 prior

outbreaks in our sample (the 2013-2016 West Africa outbreak) achieved a large

size (over 28,000 cases).

Gott's Law suggests that given 58 EVD cases, the median estimate of

outbreak size was 116 EVD cases (95% CI: 59, 2320).

Discussion

We estimated that EVD cases in Équateur Province have been growing at

a rate consistent with supercritical transmission and that this outbreak has the

potential to become the largest outbreak in DRC since 2007, even with vaccine

use. Introduction of Ebola virus into Mbandaka with its over 700,000-person

population resulted in multiple transmission chains and redoubles the importance

of an adequate influx of support for response team efforts to implement

interventions that control and prevent the spread of EVD. While real-time

modeling projections historically overestimate outbreak size and duration,[42,43] this

study exemplifies how simple mathematical models can be useful for advising

real-time decision making because they provide rapid projections and similar

estimates of *R* as compared to complex models.[44]

Vaccine use, regardless of high or low coverage levels, is projected to

substantially limit the magnitude of this outbreak but is only part of prevention,

control, and care strategies. Thus far, there has been a strong local and

international response, and deployment of vaccines and rapid diagnostic tests

(RDT) occurred early in response efforts.[3] RDTs are being used to screen Ebola

suspects while the vaccines are being administered to high-risk groups for EVD,

including healthcare workers, contacts, and contacts of contacts. To limit

epidemic growth from unreported cases, particularly those who have non-specific

symptoms but are screened negative by the WHO case definition, more

decentralized use of RDTs should be considered. We estimate that this EVD

outbreak will peak soon, if it is indeed still growing, and encourage evaluations of

vaccine use and coverage on transmission reduction.

There are limitations to our projections. Projection distributions are right-

skewed, with long tails (and we therefore report the median instead of the mean).

While there have been 22 observed EVD outbreaks with a case count greater

than ten cases, we were unable to include all prior outbreaks in our estimates

due to data availability.[39,45] Note that the simple regression projection is based

entirely on past outbreaks of Ebola virus disease (measured and reported in

different ways), and cannot account for the improved control measures and

vaccination in the way that a mechanistic model does. We included, however, as

much real-time information into our estimates as possible, but situations such as

the introduction of EVD into a large urban population and implementation of

RDTs and vaccines are new to DRC. A strength of our approach was the use of

multiple methods to estimate the outbreak size, even though Gott's Law has not

been validated for outbreak projections. We did not include vaccination of

healthcare workers in the stochastic model. Our estimates of vaccination

effectiveness, reported cases, and mean time from symptom onset to reporting

were obtained from West Africa not DRC studies.

This EVD outbreak has been growing and entered an urban setting, but

we do not believe this outbreak will be a repeat of the 2013-2016 West African

one. Introduction of vaccines will limit transmission, even with lower levels of

vaccination coverage, and DRC has the significant experience of eight prior

outbreaks. As vaccine coverage is scaled up, an influx of support is warranted to

support and bolster the evolving rapid response and be continued during the

post-outbreak period. Stronger surveillance, preparedness, and health systems

are needed to detect EVD cases before transmission threatens an even larger

populace during future outbreaks.

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298   Authors' contributions

J.D.K. contributed to concept and design, analysis, interpretation, drafting,

revising, and final approval; L.W. contributed to concept and design, analysis,

interpretation, drafting, revising, and final approval; R.W. contributed to

acquisition, analysis, interpretation, revising, and final approval; N.A.H.

contributed to interpretation, revising, and final approval; P.M. contributed to

interpretation, revising, and final approval; C.S. contributed to acquisition,

revising, and final approval; S.A. contributed to interpretation, revising, and final

approval; X.C. contributed to acquisition, revising, and final approval; D.G.

contributed to acquisition, revising, and final approval; G.W.R. contributed to

concept and design, interpretation, revising, and final approval; T.L. contributed

to concept and design, analysis, interpretation, revising, and final approval;

J.J.M. contributed to interpretation, revising, and final approval; A.W.R.

contributed to concept and design, interpretation, revising, and final approval;

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Table 1.

Cumulative case counts used in filtering stochastic model.

May 7 (day 33)	21
May 12 (day 38)	32
May 13 (day 39)	39
May 14 (day 40)	41
May 15 (day 41)	42
May 16 (day 42)	44
May 21 (day 47)	58

Figure 1. Map of cases of Ebola virus disease per health zone in Equateur
Province, Democratic Republic of Congo

Figure 2. Distribution of outbreak projections from stochastic branching process model. **a.** Mean and credible interval of cumulative case count by day in model projections, by proportion of vaccine coverage. Target case numbers and dates are marked with + signs. **b.** Mean and credible interval of weekly average of per-day case count in model projections. **c.** Distribution of outbreak size over all model projections. **d.** Distribution of outbreak duration over all model projections.

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