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Ebola Virus Disease in West Africa — The First 9 Months of the Epidemic and Forward Projections

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ABSTRACT

BACKGROUND

On March 23, 2014, the World Health Organization (WHO) was notified of an outbreak of Ebola virus disease (EVD) in Guinea. On August 8, the WHO declared the epidemic to be a "public health emergency of international concern."

METHODS

By September 14, 2014, a total of 4507 probable and confirmed cases, including 2296 deaths from EVD (Zaire species) had been reported from five countries in West Africa — Guinea, Liberia, Nigeria, Senegal, and Sierra Leone. We analyzed a detailed subset of data on 3343 confirmed and 667 probable Ebola cases collected in Guinea, Liberia, Nigeria, and Sierra Leone as of September 14.

RESULTS

The majority of patients are 15 to 44 years of age (49.9% male), and we estimate that the case fatality rate is 70.8% (95% confidence interval [CI], 69 to 73) among persons with known clinical outcome of infection. The course of infection, including signs and symptoms, incubation period (11.4 days), and serial interval (15.3 days), is similar to that reported in previous outbreaks of EVD. On the basis of the initial periods of exponential growth, the estimated basic reproduction numbers (R_0) are 1.71 (95% CI, 1.44 to 2.01) for Guinea, 1.83 (95% CI, 1.72 to 1.94) for Liberia, and 2.02 (95% CI, 1.79 to 2.26) for Sierra Leone. The estimated current reproduction numbers (R) are 1.81 (95% CI, 1.60 to 2.03) for Guinea, 1.51 (95% CI, 1.41 to 1.60) for Liberia, and 1.38 (95% CI, 1.27 to 1.51) for Sierra Leone; the corresponding doubling times are 15.7 days (95% CI, 12.9 to 20.3) for Guinea, 23.6 days (95% CI, 20.2 to 28.2) for Liberia, and 30.2 days (95% CI, 23.6 to 42.3) for Sierra Leone. Assuming no change in the control measures for this epidemic, by November 2, 2014, the cumulative reported numbers of confirmed and probable cases are predicted to be 5740 in Guinea, 9890 in Liberia, and 5000 in Sierra Leone, exceeding 20,000 in total.

CONCLUSIONS

These data indicate that without drastic improvements in control measures, the numbers of cases of and deaths from EVD are expected to continue increasing from hundreds to thousands per week in the coming months.

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As of September 14, 2014, a total of 4507 confirmed and probable cases of Ebola virus disease (EVD), as well as 2296 deaths from the virus, had been reported from five countries in West Africa — Guinea, Liberia, Nigeria, Senegal, and Sierra Leone. In terms of reported morbidity and mortality, the current epidemic of EVD is far larger than all previous epidemics combined. The true numbers of cases and deaths are certainly higher. There are numerous reports of symptomatic persons evading diagnosis and treatment, of laboratory diagnoses that have not been included in national databases, and of persons with suspected EVD who were buried without a diagnosis having been made.[1]

The epidemic began in Guinea during December 2013,[2] and the World Health Organization (WHO) was officially notified of the rapidly evolving EVD outbreak on March 23, 2014. On August 8, the WHO declared the epidemic to be a "public health emergency of international concern."[3] By mid-September, 9 months after the first case occurred, the numbers of reported cases and deaths were still growing from week to week despite multinational and multisectoral efforts to control the spread of infection.[1] The epidemic has now become so large that the three most-affected countries — Guinea, Liberia, and Sierra Leone — face enormous challenges in implementing control measures at the scale required to stop transmission and to provide clinical care for all persons with EVD.

Because Ebola virus is spread mainly through contact with the body fluids of symptomatic patients, transmission can be stopped by a combination of early diagnosis, contact tracing, patient isolation and care, infection control, and safe burial.[1] Before the current epidemic in West Africa, outbreaks of EVD in central Africa had been limited in size and geographic spread, typically affecting one to a few hundred persons, mostly in remote forested areas.[4] The largest previous outbreak occurred in the districts of Gulu, Masindi, and Mbarara in Uganda.[5] This outbreak, which generated 425 cases over the course of 3 months from October 2000 to January 2001,[6] was controlled by rigorous application of interventions to minimize further transmission — delivered through the local health care system, with support from international partners.[5,7,8]

We now report on the clinical and epidemiologic characteristics of the epidemic in Guinea, Liberia, Nigeria, and Sierra Leone during the first 9 months of the epidemic (as of September, 14, Senegal had reported only a single case). We document trends in the epidemic thus far and project expected case numbers for the coming weeks if control measures are not enhanced.

METHODS

SURVEILLANCE

Full details of the methods, along with sensitivity and uncertainty analyses, are provided in Supplementary Appendix 1, available with the full text of this article at NEJM.org; a summary is provided here. Case definitions for EVD have been reported previously by the WHO.[9] In brief, a suspected case is illness in any person, alive or dead, who has (or had) sudden onset of high fever and had contact with a person with a suspected, probable, or confirmed Ebola case or with a dead or sick animal; any person with sudden onset of high fever and at least three of the following symptoms: headache, vomiting, anorexia or loss of appetite, diarrhea, lethargy, stomach pain, aching muscles or joints, difficulty swallowing, breathing difficulties, or hiccupping; or any person who had unexplained bleeding or who died suddenly from an unexplained cause. A probable case is illness in any person suspected to have EVD who was evaluated by a clinician or any person who died from suspected Ebola and had an epidemiologic link to a person with a confirmed case but was not tested and did not have laboratory confirmation of the disease. A probable or suspected case was classified as confirmed when a sample from the person was positive for Ebola virus in laboratory testing.

Clinical and demographic data were collected with the use of a standard case investigation form (see Supplementary Appendix 1) on confirmed, probable, and suspected EVD cases identified through clinical care, including hospitalization, and through contact tracing in Guinea, Liberia, Nigeria, and Sierra Leone. To create the fullest possible picture of the unfolding epidemic, these data were supplemented by information collected in informal case reports, by data from diagnostic laboratories, and from burial records. The data recorded for each case included the district of residence, the district in which the disease was reported, the patient's age, sex, and signs

and symptoms, the date of symptom onset and of case detection, the name of the hospital, the date of hospitalization, and the date of death or discharge. A subgroup of case patients provided information on potentially infectious contacts with other persons who had Ebola virus disease, including possible exposure at funerals. We present here the results from analyses of detailed data on individual confirmed and probable cases recorded by each country in databases provided to the WHO as of September 14, 2014; analyses of confirmed and probable cases, together with suspected cases, are provided in Supplementary Appendix 1.

ETHICAL CONSIDERATIONS

This study is based on data collected during surveillance and response activities for EVD in Guinea, Liberia, Nigeria, and Sierra Leone. All information on individual patients has been anonymized for presentation.

CLINICAL MANIFESTATIONS AND CASE FATALITY RATE

We report on the frequency of symptoms in patients with confirmed and probable EVD cases overall and by country. We evaluated potential risk factors for a fatal outcome, including sex, age group (<15 years, 15 to 44 years, and ≥45 years), general and hemorrhagic symptoms, and occupation (whether the patient was or was not a health care worker). We performed the analysis using logistic-regression models, with data on patients for whom there was a definitive outcome (death or recovery) by August 17, 2014.

The case fatality rate was calculated as the percentage of fatal EVD cases among reported cases with a known definitive clinical outcome (see Supplementary Appendix 1). For comparison, we also calculated a case fatality rate that was based only on the ratio of reported deaths to reported cases, including in the denominator cases for which the clinical outcome is unknown.

KEY TIME PERIODS

We investigated five key time periods that characterize the progression of infection, the detection, care, and recovery or death of a person with Ebola virus disease, and the transmission of infection: the incubation period, which is the time between infection and the onset of symptoms (information that is relevant for assessing the length of time that case contacts have to be followed up); the interval from symptom onset to hospitalization (which is indicative of the infectious period in the community); the interval from hospital admission to death and the interval from hospital admission to discharge (both of which are relevant to assessing the demand for beds in relation to hospital capacity); the serial interval, which is defined as the interval between disease onset in an index case patient and disease onset in a person infected by that index case patient; and the generation time, which is the time between infection in an index case patient and infection in a patient infected by that index case patient (required to estimate the reproduction number, or R, of the epidemic).

The incubation period was estimated retrospectively (by having patients with confirmed cases recall the likely source of infection), with a distinction made between persons with single exposures and those with multiple exposures. In the case of multiple exposures, all the times of exposure were used to fit a parametric distribution (see Supplementary Appendix 1 for a sensitivity analysis). The interval from symptom onset to hospitalization is summarized as the mean, rather than the median, number of days to reflect the average person-days of infectiousness in the community. The mean duration of hospitalization was estimated as the average number of days from hospitalization to discharge and the average number of days from hospitalization to death, weighted by the proportion of patients who died. For each statistic we calculated the mean, median, and interquartile range and fitted a gamma probability distribution to model the variation among persons (see the results in Supplementary Appendix 1). Separate estimates were obtained for health care workers and for all other adults. The serial interval was estimated from a subgroup of patients for whom information was available on the time of symptom onset in known or suspected chains of transmission. For EVD, we expect the generation time distribution to be nearly identical to the serial interval distribution (result derived in Supplementary Appendix 1).

QUANTIFICATION OF THE SPREAD OF INFECTION AND PROJECTION OF FUTURE CASES

The basic reproduction number (R_0) is the average number of secondary cases that arise when one primary case is introduced into an uninfect-

ed population. These secondary cases arise after a period measured by the serial interval or by the generation time. When R_0 is greater than 1, infection may spread in the population, and the rate of spread is higher with increasingly high values of R_0. The doubling time (the time required for the incidence to double) was estimated on the basis of the reproduction number and the serial interval.[11] After the early phase of exponential growth in case numbers, once infection has become established, the number of people still at risk declines, so the reproduction number falls from its maximum value of R_0 to a smaller, net reproduction number, R_t. When R_t falls below 1, infection cannot be sustained. Estimates of R_0 and R_t help in evaluating the magnitude of the effort required to control the disease, the way in which transmission rates have fluctuated through time, and the effectiveness of control measures as they are implemented.

We estimated R_t over time from the time series of incidence of cases (i.e., a plot of the number of new cases per week over the course of the epidemic) and from our estimate of the serial interval distribution.[12] We then estimated R_0 for the early stages of the epidemic, when transmission rates were at their highest, on the basis of the date of symptom onset. As described in Supplementary Appendix 1, average estimates of R_t for the period from July 28 to September 7, 2014, which were made on the basis of the date of report to facilitate comparison with future cases, were used to project future cases, allowing for both uncertainty in the estimates of R_t and stochastic variability in the transmission process.

RESULTS

SCALE OF THE EPIDEMIC

An animated map with timeline is available at NEJM.org

A total of 4507 confirmed and probable EVD cases were reported to the WHO between December 30, 2013, and September 14, 2014 — a 37-week period. A total of 718 confirmed and probable cases and 289 deaths were reported in the week of September 8 through September 14 alone. The numbers of confirmed and probable cases reported by each country over time are shown in Figures 1 and 2. Detailed information was available on 3343 confirmed and 667 probable cases; these cases were used in all our analyses, with the exception of projections (results of analyses based on confirmed, probable, and suspected cases are provided in Supplementary Appendix 1). The median age of persons with EVD was 32 years (interquartile range, 21 to 44), and there were no significant differences in the age distribution of persons with EVD among countries. The majority of persons with EVD (60.8%) were between 15 and 44 years of age (this age group makes up only 44% of the population) (Table 1). There were also no significant differences among countries in the total numbers of male and female persons with EVD reported (49.9% of the total were male patients; within-country differences have not yet been fully investigated). EVD has taken a heavy toll among health care workers in Guinea, Liberia, and Sierra Leone. By September 14, a total of 318 cases, including 151 deaths, had been reported among health care workers.

GEOGRAPHIC ORIGIN AND THE SPREAD OF INFECTION

In December 2013, the first cases occurred in Guéckédou and Macenta districts, the focus of the epidemic in Guinea. During March 2014, a rise in the numbers of cases in these two districts, in addition to the first reports from Lofa and other districts in Liberia, was followed by the discovery of cases in the capital, Conakry. A second increase in case incidence in Guinea — first in Guéckédou and Macenta and then in the capital — occurred in May and June.

During May, the focus of the epidemic in Guinea expanded to the neighboring districts of Kenema and Kailahun in Sierra Leone, and in June further cases were reported in Lofa district in Liberia. These five districts have remained the focus of transmission in the border areas of the three countries. From July onward, there were sharp increases in case numbers at the epidemic foci in all three countries, at other sites away from the epicenter, and in the capital cities of Conakry, Freetown, and Monrovia (Fig. 1, and animated map and timeline at NEJM.org). However, although EVD has spread to many parts of Guinea, Liberia, and Sierra Leone, it has not been reported in all districts in the countries: among the total of 67 districts in the three countries, only 43 have reported one or more confirmed, probable, or suspected cases, and more than 90% of cases have been reported from just 14 districts.

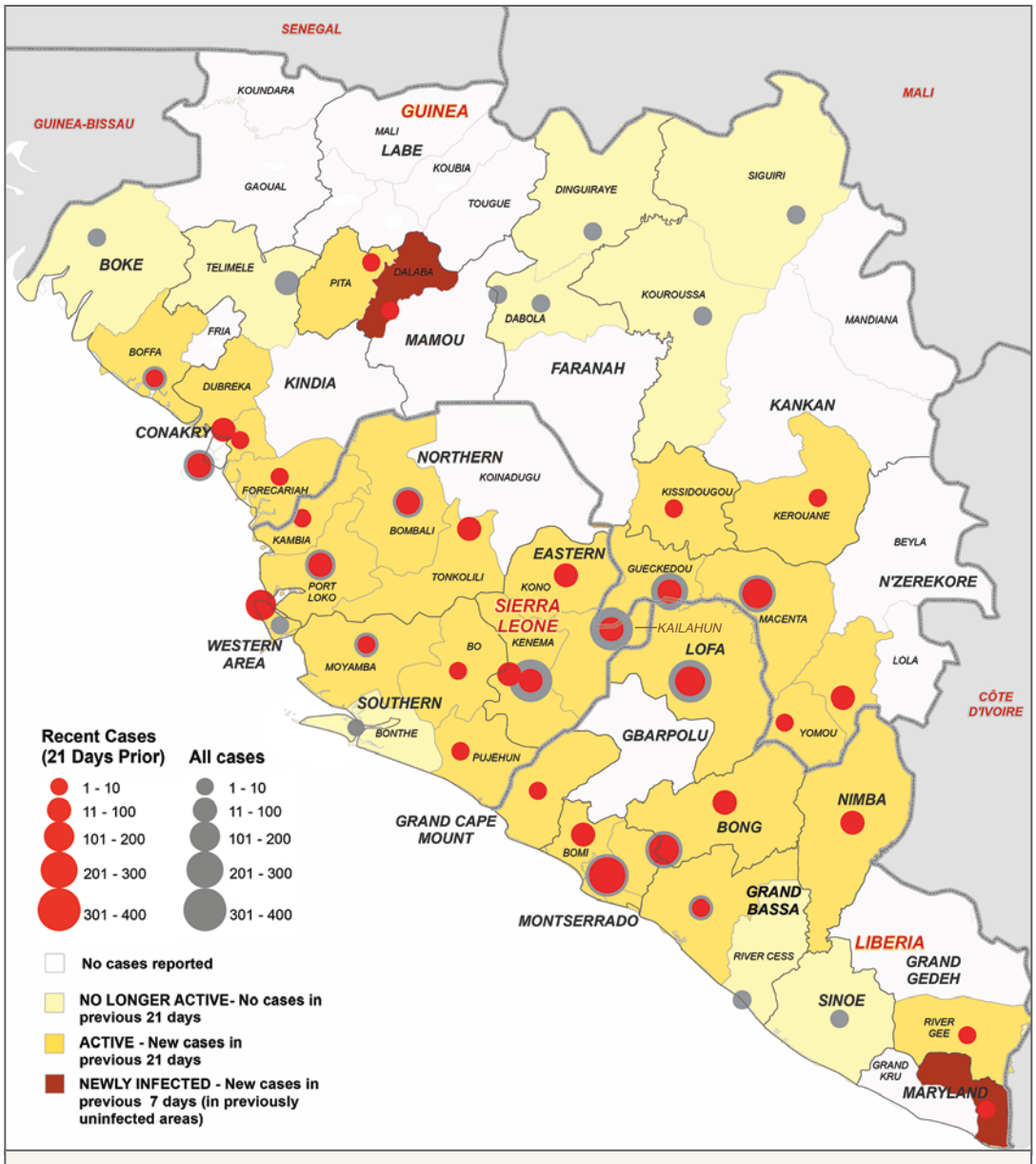

Figure 1. Districts Affected by Ebola Virus Disease in Three Countries in Africa.

The map shows the districts that have been affected by Ebola virus disease in Guinea, Liberia, and Sierra Leone. Gray circles indicate the total numbers of confirmed and probable Ebola cases reported in each affected district, and red circles the number reported during the 21 days leading up to September 14, 2014.

CLINICAL MANIFESTATIONS AND CASE FATALITY RATE

Table 1 provides information on demographic characteristics and symptom frequency in patients with confirmed or probable EVD with a definitive outcome in Guinea, Liberia, Nigeria, and Sierra Leone. The most common symptoms reported between symptom onset and case detection included fever (87.1%), fatigue (76.4%), loss of appetite (64.5%), vomiting (67.6%), diarrhea (65.6%), headache (53.4%), and abdominal pain (44.3%). Specific hemorrhagic symptoms were rarely reported (in <1% to 5.7% of patients). "Unexplained bleeding," however, was reported in 18.0% of cases. These patterns are similar in each country (see Supplementary Appendix 1).

Assessing the case fatality rate during this

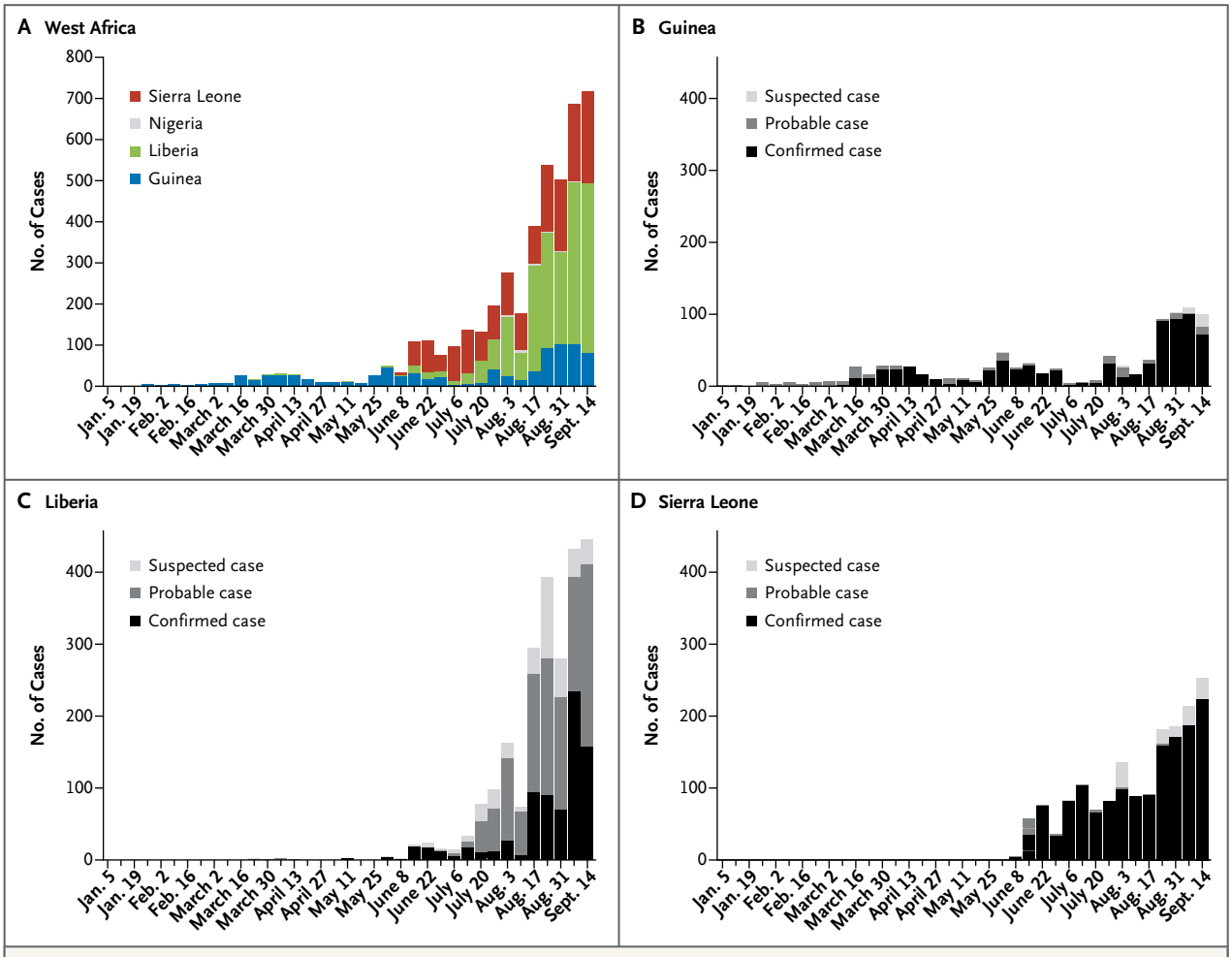

Figure 2. Weekly Incidence of Confirmed, Probable, and Suspected Ebola Virus Disease Cases.

Shown is the weekly incidence of confirmed, probable, and suspected EVD cases, according to actual or inferred week of symptom onset. A suspected case is illness in any person, alive or dead, who has (or had) sudden onset of high fever and had contact with a person with a suspected, probable, or confirmed Ebola case or with a dead or sick animal; any person with sudden onset of high fever and at least three of the following symptoms: headache, vomiting, anorexia or loss of appetite, diarrhea, lethargy, stomach pain, aching muscles or joints, difficulty swallowing, breathing difficulties, or hiccupping; or any person who had unexplained bleeding or who died suddenly from an unexplained cause. A probable case is illness in any person suspected to have EVD who was evaluated by a clinician or any person who died from suspected Ebola and had an epidemiologic link to a person with a confirmed case but was not tested and did not have laboratory confirmation of the disease. A probable or suspected case was classified as confirmed when a sample from the person was positive for Ebola virus in laboratory testing.

epidemic is complicated by incomplete information on the clinical outcomes of many cases, both detected and undetected. Estimates of the case fatality rate (Table 2) derived by calculating the ratio of all reported deaths to all reported cases to date are low in comparison with historical outbreaks and are highly variable among the affected countries. However, estimating the case fatality rate using only the 46% of cases with definitive recorded clinical outcomes gives higher estimates that show no significant variation among countries (Table 2). This analysis shows that by September 14, a total of 70.8% (95% confidence interval [CI], 68.6 to 72.8) of case patients with definitive outcomes have died, and this rate was consistent among Guinea, Liberia, and Sierra Leone (Table 2). The case fatality rate in Nigeria was lower (45.5%), though this estimate is based on only 11 recent cases. The case fatality rate among hospitalized case

patients was 64.3% (95% CI, 61.5 to 67.0) lower than that among all patients with definitive outcomes and was consistent among countries. The case fatality rate among health care workers ranged from 56.1% (95% CI, 41.0 to 70.1) in Guinea to 80.0% (95% CI, 68.7 to 87.9) in Liberia (Table 2). Risk factors for a fatal outcome, after adjustment for country, are provided in Table 1. Significant risk factors for death include an age of 45 years or older as compared with 44 years of age or younger (odds ratio, 2.47; 95% CI, 1.79 to 3.46) and a number of general symptoms (diarrhea, conjunctivitis, difficulty breathing or swallowing, confusion or disorientation, and coma) and hemorrhagic symptoms (unexplained bleeding, bleeding gums, bloody nose, bleeding at the injection site, and bleeding from the vagina) (odds ratios and 95% confidence intervals for these factors are provided in Table 1).

KEY TIME PERIODS

The mean incubation period was 11.4 days (Table 2 and Fig. 3A), and did not vary by country (Fig. 3B, 3C, and 3D). Approximately 95% of the case patients had symptom onset within 21 days after exposure (Fig. 3A), which is the recommended period for follow-up of contacts. The estimated mean (±SD) serial interval was 15.3±9.3 days (Table 2 and Fig. 3E), which is the same as the estimated mean generation time (see Supplementary Appendix 1). The mean time from the onset of symptoms to hospitalization, a measure of the period of infectiousness in the community, was 5.0±4.7 days (Table 2), and was no shorter for health care workers than for other case patients. The mean time to death after admission to the hospital was 4.2±6.4 days, and the mean time to discharge was 11.8±6.1 days. The mean length of stay in hospital was 6.4 days in Guinea, Liberia, and Sierra Leone (Table 2).

QUANTIFICATION OF THE SPREAD OF INFECTION AND PROJECTION OF FUTURE CASES

Estimates of the basic reproduction number, R_0, were 1.71 (95% CI, 1.44 to 2.01) for Guinea, 1.83 (95% CI, 1.72 to 1.94) for Liberia, 1.20 (95% CI, 0.67 to 1.96) for Nigeria, and 2.02 (95% CI, 1.79 to 2.26) for Sierra Leone (Table 2, and Fig. S7 in Supplementary Appendix 1). Although R_0 reflects the maximum potential for growth in case incidence, Figure S7 in Supplementary Appendix 1 shows the variation in the estimated net reproduction number, R_t, during the course of the epidemic. Between March and July 2014, the R_t for Guinea fluctuated around the threshold value of 1 but appeared to increase again in August, reflecting the rise in case incidence in Macenta district. In Sierra Leone, the value of R_t dropped between June and August as the case incidence stabilized in Kenema and Kailahun. In Liberia, the R_t remained above 1 for most of the period between March and August, reflecting the consistent increase in case incidence (Fig. S9) in that country.

The growing numbers of cases reported from Guinea, Liberia, and Sierra Leone in August and early September suggest that the R_t remains above 1 in a still-expanding epidemic (reliable estimates of R_t could be obtained only to early September owing to reporting delays). As of September 14, the doubling time of the epidemic was 15.7 days in Guinea, 23.6 days in Liberia, and 30.2 days in Sierra Leone (Table 2). We estimate that, at the current rate of increase, assuming no changes in control efforts, the cumulative number of confirmed and probable cases by November 2 (the end of week 44 of the epidemic) will be 5740 in Guinea, 9890 in Liberia, and 5000 in Sierra Leone, exceeding 20,000 cases in total (Fig. 4, and Table S8 in Supplementary Appendix 2). The true case load, including suspected cases and undetected cases, will be higher still.

DISCUSSION

Although the current epidemic of EVD in West Africa is unprecedented in scale, the clinical course of infection and the transmissibility of the virus are similar to those in previous EVD outbreaks. The incubation period, duration of illness, case fatality rate, and R_0 are all within the ranges reported for previous EVD epidemics.[7,13-18] Our estimates of R_0 are similar to other recent estimates for this West Africa epidemic.[19-23] The combination of signs and symptoms recorded between symptom onset and clinical presentation is also similar to that in other reports.[14,17,24-26] We infer that the present epidemic is exceptionally large, not principally because of the biologic characteristics of the virus, but rather because of the attributes of the affected populations and because control efforts have been insufficient to halt the spread of infection.

Certain characteristics of the affected populations may have led to the rapid geographic dissemination of infection. The populations of Guinea, Liberia, and Sierra Leone are highly interconnected, with much cross-border traffic at the epicenter and relatively easy connections by road between rural towns and villages and between densely populated national capitals. The large intermixing population has facilitated the spread of infection, but a large epidemic was not inevitable. In Nigeria, the number of cases has so far been limited, despite the introduction of infection into the large cities of Lagos (approximately 20 million people) and Port Harcourt (>1 million people). The critical determinant of epidemic size appears to be the speed of implementation of rigorous control measures.

Previous experience with EVD outbreaks, though they have been limited in size and geographic spread, suggests that transmission can

Table 1. Demographic Characteristics and Signs and Symptoms in Confirmed and Probable Ebola Case Patients with a Definitive Clinical Outcome in Guinea, Liberia, Nigeria, and Sierra Leone.*

Variable	All Patients	Patients Who Died	Patients Who Recovered	Odds Ratio (95% CI)†
		no./total no. (%)		
Demographic characteristics				
Male sex	685/1415 (48.4)	515/1056 (48.8)	170/359 (47.4)	0.93 (0.73–1.19)
Age group				
<15 yr	190/1378 (13.8)	145/1021 (14.2)	45/357 (12.6)	1.18 (0.83–1.71)
15–44 yr	838/1378 (60.8)	577/1021 (56.5)	261/357 (73.1)	0.48 (0.36–0.62)
≥45 yr	350/1378 (25.4)	299/1021 (29.3)	51/357 (14.3)	2.47 (1.79–3.46)
Health care worker	158/1429 (11.1)	112/1067 (10.5)	46/362 (12.7)	0.86 (0.60–1.27)
Signs and symptoms				
General symptoms				
Fever‡	1002/1151 (87.1)	746/846 (88.2)	256/305 (83.9)	1.34 (0.92–1.95)
Fatigue	866/1133 (76.4)	633/829 (76.4)	233/304 (76.6)	0.94 (0.68–1.28)
Loss of appetite	681/1055 (64.5)	498/778 (64.0)	183/277 (66.1)	0.92 (0.69–1.23)
Vomiting	753/1114 (67.6)	566/816 (69.4)	187/298 (62.8)	1.19 (0.89–1.59)
Diarrhea	721/1099 (65.6)	555/813 (68.3)	166/286 (58.0)	1.42 (1.06–1.89)
Headache	553/1035 (53.4)	407/757 (53.8)	146/278 (52.5)	1.03 (0.78–1.36)
Abdominal pain	439/992 (44.3)	311/715 (43.5)	128/277 (46.2)	0.85 (0.64–1.13)
Muscle pain	385/990 (38.9)	293/728 (40.2)	92/262 (35.1)	1.24 (0.92–1.67)
Joint pain	374/950 (39.4)	283/695 (40.7)	91/255 (35.7)	1.32 (0.98–1.80)
Chest pain	254/686 (37.0)	196/488 (40.2)	58/198 (29.3)	1.53 (1.07–2.20)
Cough	194/655 (29.6)	150/462 (32.5)	44/193 (22.8)	1.74 (1.18–2.61)
Difficulty breathing	155/665 (23.3)	123/472 (26.1)	32/193 (16.6)	1.68 (1.10–2.63)
Difficulty swallowing	169/514 (32.9)	138/375 (36.8)	31/139 (22.3)	2.22 (1.41–3.59)
Conjunctivitis	137/658 (20.8)	109/465 (23.4)	28/193 (14.5)	2.03 (1.29–3.29)
Sore throat	102/467 (21.8)	82/339 (24.2)	20/128 (15.6)	1.94 (1.13–3.46)
Confusion	84/631 (13.3)	68/446 (15.2)	16/185 (8.6)	2.00 (1.14–3.71)
Hiccups	108/947 (11.4)	91/699 (13.0)	17/248 (6.9)	2.15 (1.27–3.82)
Jaundice	65/627 (10.4)	52/443 (11.7)	13/184 (7.1)	1.83 (0.99–3.63)
Eye pain	48/622 (7.7)	39/438 (8.9)	9/184 (4.9)	1.95 (0.95–4.40)
Rash	37/642 (5.8)	30/453 (6.6)	7/189 (3.7)	1.90 (0.86–4.83)
Coma or unconsciousness	37/627 (5.9)	34/445 (7.6)	3/182 (1.6)	4.59 (1.61–19.34)

Table 1. (Continued.)

Variable	All Patients	Patients Who Died	Patients Who Recovered	Odds Ratio (95% CI)†
		no./total no. (%)		
Unexplained bleeding	168/932 (18.0)	140/693 (20.2)	28/239 (11.7)	1.83 (1.20–2.90)
Hematemesis	26/670 (3.9)	20/503 (4.0)	6/167 (3.6)	1.07 (0.44–3.01)
Blood in stool	48/843 (5.7)	35/614 (5.7)	13/229 (5.7)	0.98 (0.52–1.96)
Bleeding gums	19/837 (2.3)	18/608 (3.0)	1/229 (0.4)	6.69 (1.35–121.32)
Bloody nose	16/836 (1.9)	15/610 (2.5)	1/226 (0.4)	8.02 (1.54–148.62)
Bloody cough	20/831 (2.4)	16/605 (2.6)	4/226 (1.8)	1.63 (0.58–5.82)
Other bleeding	8/657 (1.2)	5/493 (1.0)	3/164 (1.8)	0.45 (0.11–2.23)
Bleeding at injection site	20/833 (2.4)	19/605 (3.1)	1/228 (0.4)	6.51 (1.32–118.04)
Blood from vagina§	14/431 (3.2)	13/290 (4.5)	1/126 (0.8)	6.0 (1.11–112.4)
Blood in urine	10/827 (1.2)	9/601 (1.5)	1/226 (0.4)	5.14 (0.90–98.73)
Bleeding under skin	5/827 (0.6)	5/604 (0.8)	0/223	NA

* Data are as of September 14, 2014. Patients with date of onset up to August 17, 2014, were included. Total numbers are the numbers of patients with data on the variable in question. NA denotes not applicable.
† Odds ratios are adjusted for country. CI denotes confidence interval.
‡ Fever was defined as a body temperature above 38°C; however, in practice, health care workers at the district level often do not have a medical thermometer and simply ask whether the person's body temperature is more elevated than usual.
§ Percentages reflect only female patients.

be interrupted, and case incidence reduced, within 2 to 3 weeks after the introduction of control measures.[1,5,7,14-17,24,27-31] This view is reinforced by the estimates of case reproduction number presented in this analysis. We estimate the R_0 to have varied between 1.71 (upper boundary of the 95% confidence interval, 2.01) in Guinea to 2.02 (upper boundary of the 95% confidence interval, 2.26) in Sierra Leone. This means that transmission has to be a little more than halved to achieve control of the epidemic and eventually to eliminate the virus from the human population. Considering the prospects for a novel Ebola vaccine, an immunization coverage exceeding 50% would have the same effect. Greater reductions in transmission would, of course, be desirable, but minimum requirements for the containment of EVD are far less severe than for the containment of more contagious diseases, such as measles. Between March and July 2014, the reproduction number in Guinea fluctuated around the threshold value of 1, suggesting that modest further intervention efforts at that point could have achieved control.

The analyses in this paper can be used to inform recommendations regarding control measures. The measured duration of the incubation period, and its variation, imply that the advice to follow case contacts for 21 days[1] is appropriate. To curtail transmission in the community, the period from symptom onset to hospitalization (a mean of 5 days but a maximum of >40 days) clearly needs to be reduced. Surprisingly, the mean was not shorter among health care workers, who are at risk both of acquiring and transmitting the infection to others. The average length of hospital stay of about 1 week (6.4 days) means that the number of beds required to treat EVD patients is roughly equal to the rising weekly case incidence. Even without allowing for underreporting, 995 patients with confirmed, probable, or suspected infection were known to need clinical care in the week of September 8 through 14 alone, which far exceeds the present bed capacity in Guinea, Liberia, and Sierra Leone (approximately 610 beds in total).

The data used in these analyses were collected in the field by various field teams across Guinea, Liberia, Nigeria, and Sierra Leone. Although they provide an excellent opportunity to better understand the current EVD epidemic in Africa, they understate the magnitude of the

Table 2. Estimates of Epidemiologic Variables for Confirmed and Probable Ebola Cases, According to Country, as of September 14, 2014.*

Variable	All Countries		Guinea		Liberia		Nigeria		Sierra Leone	
	no. of days	no. of patients with data	no. of days	no. of patients with data	no. of days	no. of patients with data	no. of days	no. of patients with data	no. of days	no. of patients with data
Incubation period										
Single-day exposures										
Observed†	9.4±7.4	500	10.7±8.7	35	9.5±6.6	259	NC	<10	9.0±8.1	201
Fitted‡	9.1±7.3	500	9.9±9.8	35	9.4±6.7	259	NC	<10	8.5±7.6	201
Multi-day exposures										
Observed†	11.4±NA	155	10.9±NA	20	11.7±NA	79	NC	<10	10.8±NA	48
Fitted‡	9.7±5.5	155	8.3±4.5	20	9.9±5.7	79	NC	<10	9.9±5.6	48
Serial interval§										
Observed	15.3±9.1	92	19.0±11.0	40	13.1±6.6	26	NC	<10	11.6±5.6	25
Fitted¶	15.3±9.3	92	19.0±11.2	40	13.1±7.8	26	NC	<10	11.6±6.3	25
R_0‖										
Mean (95% CI)	—		*1.71 (1.44–2.01)*		*1.83 (1.72–1.94)*		*1.2 (0.67–1.96)*		*2.02 (1.79–2.26)*	
Doubling time — days (95% CI)	—		*17.53 (13.18–26.64)*		*15.78 (14.4–17.37)*		*59.75 (13.27–∞)*		*12.84 (10.92–15.66)*	
R**										
Mean (95% CI)	—		*1.81 (1.60–2.03)*		*1.51 (1.41–1.60)*				*1.38 (1.27–1.51)*	
Doubling time — days (95% CI)	—		*15.7 (12.9–20.3)*		*23.6 (20.2–28.2)*		*NC*		*30.2 (23.6–42.3)*	
Interval from symptom onset										
To hospitalization	5.0±4.7	1135	5.3±4.3	484	4.9±5.1	245	4.1±1.4	11	4.6±5.1	395
To hospital discharge	16.4±6.5	267	16.3±6.1	152	15.4±8.2	41	NC	<10	17.2±6.2	70
To death	7.5±6.8	594	6.4±5.3	248	7.9±8.0	212	NC	<10	8.6±6.9	128
To WHO notification	6.1±8.5	2185	7.5±10.4	743	6.0±8.7	797	3.9±2.3	11	4.5±5.0	634
Interval from WHO notification										
To hospital discharge	11.8±7.2	312	11.1±5.8	164	11±8.0	41	NC	<10	12.7±8.4	102
To death	–3.0±13.8	584	–4.4±14.4	300	–1.8±13.6	221	NC	<10	–1.6±9.2	58
Interval from hospitalization										
To hospital discharge	11.8±6.1	290	11±5.4	159	12.8±8.1	40	NC	<10	12.4±5.8	86
To death	4.2±6.4	121	2.5±3.4	36	4.5±6.0	63	NC	<10	4.4±6.0	17
Duration of hospital stay — days††	6.42		4.99		6.72		NC		6.88	

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	rate (95% CI)	no. of patients with data	rate (95% CI)	no. of patients with data	rate (95% CI)	no. of patients with data	rate (95% CI)	no. of patients with data	rate (95% CI)	no. of patients with data
Case fatality rate										
All cases, based on current status	37.7 (36.1–39.2)	3747	57.5 (53.7–61.1)	677	34.7 (32.4–37.1)	1616	40.0 (19.8–64.3)	15	31.6 (29.3–34.1)	1439
All cases, based on definitive outcome	70.8 (68.6–72.8)	1737	70.7 (66.7–74.3)	542	72.3 (68.9–75.4)	739	45.5 (21.3–72.0)	11	69.0 (64.5–73.1)	445
Before August 18	71.3 (68.7–73.7)	1244	68.7 (64.3–72.8)	454	79.8 (75.7–83.4)	416	50.0 (23.7–76.3)	10	65.4 (60.4–70.1)	364
August 18–September 14	59.9 (54.7–64.9)	354	80.7 (71.2–87.6)	88	41.1 (34.3–48.2)	190	NC	<10	84.0 (74.1–90.6)	75
All hospitalized cases, based on definitive outcome	64.3 (61.5–67.0)	1153	64.7 (60.1–68.9)	450	67.0 (62.0–71.7)	361	40.0 (16.8–68.7)	10	61.4 (56.1–66.5)	332
According to sex										
Male	72.2 (69.1–75.1)	874	68.5 (62.6–73.9)	254	74.9 (70.4–79.0)	395	NC	<10	71.9 (65.7–77.5)	221
Female	69.9 (66.7–73.0)	818	72.7 (67.3–77.6)	286	71.6 (66.4–76.3)	317	NC	<10	64.4 (57.7–70.6)	208
According to age group										
<15 yr	73.4 (67.2–78.8)	218	78.1 (67.3–86.0)	73	70.7 (60.1–79.5)	82	NC	<10	71.4 (59.3–81.1)	63
15–44 yr	66.1 (63.1–69.0)	1012	64.9 (59.5–69.9)	319	70.6 (66.1–74.8)	422	NC	<10	61.4 (55.4–67.0)	264
≥45 yr	80.4 (76.2–84.0)	398	78.6 (71.1–84.6)	140	81.1 (74.4–86.4)	164	NC	<10	82.2 (73.1–88.8)	90
According to occupation										
Health care worker	69.4 (62.1–75.8)	170	56.1 (41.0–70.1)	41	80.0 (68.7–87.9)	65	NC	<10	68.4 (55.5–79.0)	57
Non–health care worker	70.9 (68.6–73.1)	1567	71.9 (67.8–75.6)	501	71.5 (68.0–74.8)	674	NC	<10	69.1 (64.3–73.5)	388

* Plus–minus values are means ±SD. NA denotes not available, NC not calculated, and WHO World Health Organization.
† Contacts on day 0 (i.e., on the day of symptom onset) were excluded.
‡ Contacts on day 0 (i.e., on the day of symptom onset) were excluded. Gamma probability distributions were fitted to confirmed and probable cases.
§ The serial interval is the interval between disease onset in an index case patient and disease onset in a person infected by that index case patient. In this category, the number of patients with data is the number of epidemiologically linked pairs in which the later case patient reported only one direct contact.
¶ Gamma probability distributions were fitted to confirmed and probable cases.
‖ The basic reproduction number (R_0) is the average number of secondary cases that arise when one primary case is introduced into an uninfected population. We estimated the R_0 and associated mean doubling time, using a serial interval of 15.3 days, for the period up to March 30, 2014, for Guinea; up to August 24, 2014, for Liberia and Nigeria; and up to July 6, 2014, for Sierra Leone. This number was estimated for individual countries only and not for the combined data.
** We estimated R, the mean value of R_t (the estimated net reproduction number), and associated mean doubling time, using a serial interval of 15.3 days, for the period of July 21 to August 31, 2014. This number was estimated for individual countries only and not for the combined data.
†† The mean duration of hospital stay was calculated as the weighted average of the observed means from the hospitalization-to-discharge and hospitalization-to-death distributions. This variable was not calculated in Nigeria because there were fewer than 10 case patients with data.

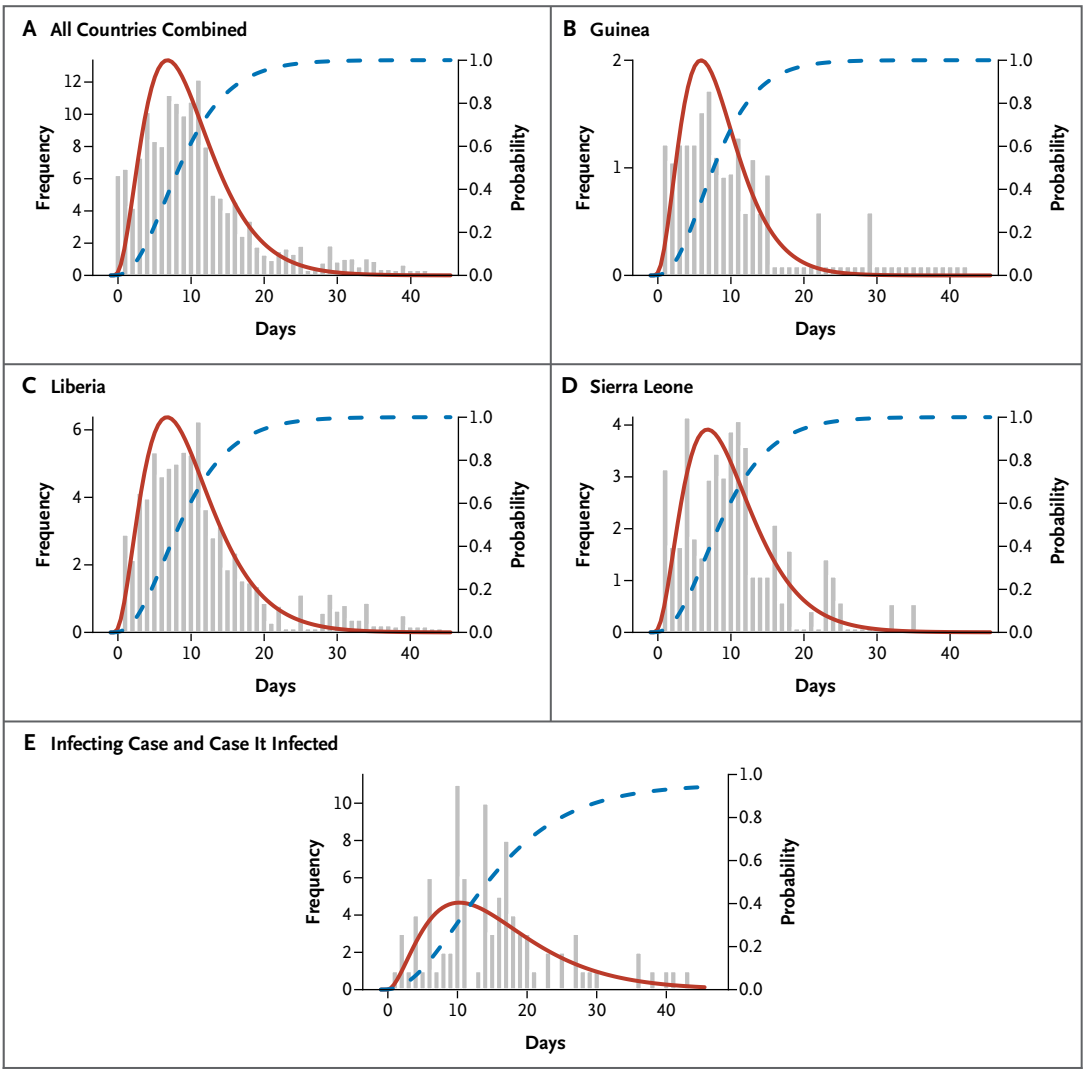

Figure 3. Time between Exposure and Disease Onset.

Panel A through D show the observed times (>0) between exposure and disease onset for all countries, Guinea, Liberia, and Sierra Leone, respectively, including only cases with multiple exposure days (histograms in gray), best-fit (gamma) probability density function (red curves) and cumulative distribution for the incubation period (blue curves). Panel E shows the observed times between disease onset in an index case patient and disease onset in the person infected by the index case patient (histograms in gray) and best-fit (gamma) probability density function (red curve) and cumulative distribution (blue curve) for the serial interval.

problem. It is likely that many cases have not been detected, and for those cases that have been reported, case records are often incomplete. Therefore, interpretation of the available case data requires care. We recognize, however, that data are being collected under extreme conditions, and the top priorities are patient care, contact tracing, and limiting transmission in the community, rather than epidemiologic investigations. In addition, in this initial assessment it was not possible to consider all the sources of heterogeneity (e.g., geographic and health care–related) affecting the development of this epidemic. Thus the future projections provided here should be regarded as indicative of likely future trends more than precise predictions. Despite these limitations and the resulting uncertainties, the results presented here help us to understand the spread of infection and the potential for control.

Some details of the current analysis remain

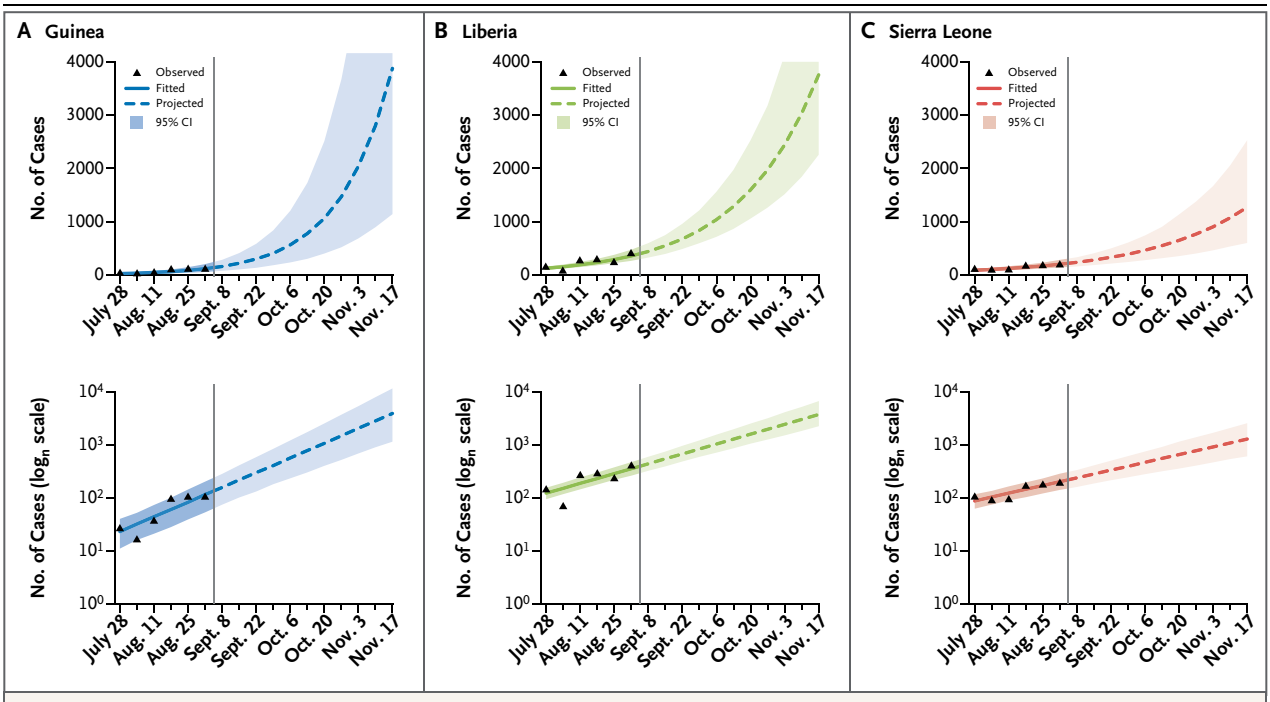

Figure 4. Observed and Projected Case Incidence.

Observed and projected weekly case incidence in Guinea (Panel A), Liberia (Panel B), and Sierra Leone (Panel C) are shown on linear (upper panels) and logarithmic (lower panels) scales

to be confirmed by further investigation. For example, our estimate of 15.3 days for the serial interval is slightly longer than past estimates.[32,33] This may reflect the difficulties of collecting temporally unbiased data on exposure through contact tracing, either in the current outbreak or during previous outbreaks. Alternatively, a longer serial interval may indicate that case isolation has been less effective in the current epidemic, resulting in a higher proportion of transmission events occurring late in the course of illness.

Case fatality is among the most important topics for further investigation. Our estimates of case fatality are consistent in Guinea (70.7%), Liberia (72.3%), and Sierra Leone (69.0%) when estimates are derived with data only for patients with recorded definitive clinical outcomes (1737 patients). Estimates for hospitalized patients with recorded definitive clinical outcomes are also consistent across countries but are lower than those for all patients with definitive clinical outcomes. In contrast, simply taking the ratio of reported deaths to reported cases gives estimates that differ among countries (Table 2). These discrepancies perhaps reflect the challenges of clinical follow-up and data capture. The lower case fatality rate among hospitalized patients than among all persons with EVD could indicate that hospitalization increased survival, that cases of EVD in nonhospitalized persons were more likely to be detected if they were fatal, or that some persons died before they could be admitted to the hospital. In each of the countries studied, the case fatality rate is lowest among persons 15 to 44 year of age, and highest among persons 45 years of age or older, and some limited variation in the case fatality rate among health care workers was observed among countries. The reasons for this variation are not yet known. Moreover, the case fatality rate among hospitalized patients may differ from that among patients who are never seen by a physician. Liberia has reported an unusually high proportion of deaths among patients with suspected (but not probable or confirmed) EVD cases (58% [440 of 754 patients]), as compared with Guinea (13% [4 of 30 patients]) and Sierra Leone (35% [74 of 213 patients]). The implication is that many true EVD case patients in Liberia may have died before receiving a definitive diagnosis.

Notwithstanding the geographic variation in case incidence within and among Guinea, Liberia, and Sierra Leone, the current epidemiologic outlook is bleak. Forward projections suggest that unless control measures — including improvements in contact tracing, adequate case isolation, increased capacity for clinical management, safe burials, greater community engagement, and support from international partners — improve quickly, these three countries will soon be reporting thousands of cases and deaths each week, projections that are similar to those of the Centers for Disease Control and Prevention. Experimental therapeutics and vaccines offer promise for the future but are unlikely to be available in the quantities needed to make a substantial difference in control efforts for many months, even if they are proved to be safe and effective. Furthermore, careful assessment of the most effective means of utilizing such interventions (e.g., vaccination or treatment of contacts versus health care workers) will be required while stocks remain limited. For the medium term, at least, we must therefore face the possibility that EVD will become endemic among the human population of West Africa, a prospect that has never previously been contemplated. The risk of continued epidemic expansion and the prospect of endemic EVD in West Africa call for the most forceful implementation of present control measures and for the rapid development and deployment of new drugs and vaccines.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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APPENDIX

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REFERENCES

1. World Health Organization. Ebola virus disease: Cuban medical team heading for Sierra Leone (http://www.who.int/csr/disease/ebola/en/).
2. Briand S, Bertherat E, Cox P, et al. The international Ebola emergency. N Engl J Med. DOI: 10.1056/NEJMp1409858.
3. World Health Organization. WHO statement on the meeting of the International Health Regulations Emergency Committee regarding the 2014 ebola outbreak in West Africa (http://www.who.int/mediacentre/news/statements/2014/ebola-20140808/en/).
4. Centers for Disease Control and Prevention. Ebola outbreaks 2000-2014. 2014 (http://www.cdc.gov/vhf/ebola/resources/outbreaks.html).
5. Okware SI, Omaswa FG, Zaramba S, et al. An outbreak of Ebola in Uganda. Trop Med Int Health 2002;7:1068-75.
6. Malaria risk for travellers to Africa. Wkly Epidemiol Rec 2001;76:25-7.
7. Borchert M, Mutyaba I, Van Kerkhove MD, et al. Ebola haemorrhagic fever outbreak in Masindi District, Uganda: outbreak description and lessons learned. BMC Infect Dis 2011;11:357.
8. Raabe VN, Mutyaba I, Roddy P, Lutwama JJ, Geissler W, Borchert M. Infection control during filoviral hemorrhagic fever outbreaks: preferences of community members and health workers in Masindi, Uganda. Trans R Soc Trop Med Hyg 2010;104:48-50.
9. World Health Organization. Case definition recommendations for ebola or Marburg virus diseases (http://www.who.int/csr/resources/publications/ebola/ebola-case-definition-contact-en.pdf?ua=1).
10. Garske T, Legrand J, Donnelly CA, et al. Assessing the severity of the novel influenza A/H1N1 pandemic. BMJ 2009;339:b2840.
11. Wallinga J, Teunis P. Different epidemic curves for severe acute respiratory syndrome reveal similar impacts of control measures. Am J Epidemiol 2004;160:509-16.
12. Cori A, Ferguson NM, Fraser C, Cauchemez S. A new framework and software to estimate time-varying reproduction numbers during epidemics. Am J Epidemiol 2013;178:1505-12.
13. Breman JG, Piot P, Johnson KM, et al.

The epidemiology of Ebola hemorrhagic fever in Zaire, 1976. In: Pattyn SR, ed. Ebola virus haemorrhagic fever. Amsterdam: Elsevier Science, 1978:85-97.
14. Roddy P, Howard N, Van Kerkhove MD, et al. Clinical manifestations and case management of Ebola haemorrhagic fever caused by a newly identified virus strain, Bundibugyo, Uganda, 2007-2008. PLoS One 2012;7(12):e52986.
15. Bwaka MA, Bonnet MJ, Calain P, et al. Ebola hemorrhagic fever in Kikwit, Democratic Republic of the Congo: clinical observations in 103 patients. J Infect Dis 1999;179:Suppl 1:S1-S7.
16. Dowell SF, Mukunu R, Ksiazek TG, Khan AS, Rollin PE, Peters CJ. Transmission of Ebola hemorrhagic fever: a study of risk factors in family members, Kikwit, Democratic Republic of the Congo, 1995. J Infect Dis 1999;179:Suppl 1:S87-S91.
17. Ndambi R, Akamituna P, Bonnet MJ, Tukadila AM, Muyembe-Tamfum JJ, Colebunders R. Epidemiologic and clinical aspects of the Ebola virus epidemic in Mosango, Democratic Republic of the Congo, 1995. J Infect Dis 1999;179:Suppl 1:S8-S10.
18. Team RoaWIS. Ebola haemorrhagic fever in Zaire, 1976. Bull World Health Organ 1978;56:271-93.
19. Althaus CL. Estimating the reproduction number of Ebola virus (EBOV) during the 2014 outbreak in West Africa. Plos Currents Outbreaks. 2014 (http://currents.plos.org/outbreaks/article/estimating-the-reproduction-number-of-zaire-ebolavirus-ebov-during-the-2014-outbreak-in-west-africa/).
20. Fisman D, Khoo E, Tuite A. Early epidemic dynamics of the West African 2014 Ebola outbreak: estimates derived with a simple two-parameter model. Plos Currents Outbreaks. 2014 (http://currents.plos.org/outbreaks/article/obk-14-0036-early-epidemic-dynamics-of-the-west-african-2014-ebola-outbreak-estimates-derived-with-a-simple-two-parameter-model/).
21. Gire SK, Goba A, Andersen KG, et al. Genomic surveillance elucidates Ebola virus origin and transmission during the 2014 outbreak. Science 2014;345:1369-72.
22. Gomes MFC, Pastore y Piontti A, Rossi L, et al. Assessing the international spreading risk associated with the 2014 West African Ebola outbreak. Plos Currents Outbreaks. 2014 (http://currents.plos.org/outbreaks/article/assessing-the-international-spreading-risk-associated-with-the-2014-west-african-ebola-outbreak/).
23. Nishiura H, Chowell G. Early transmission dynamics of Ebola virus disease (EVD), West Africa, March to August 2014. Euro Surveill 2014 Sep 11;19(36). pii: 20894.
24. Sureau PH. Firsthand clinical observations of hemorrhagic manifestations in Ebola hemorrhagic fever in Zaire. Rev Infect Dis 1989;11:Suppl 4:S790-S793.
25. Georges A-J, Leroy EM, Renaut AA, et al. Ebola hemorrhagic fever outbreaks in Gabon, 1994-1997: epidemiologic and health control issues. J Infect Dis 1999;179:Suppl 1:S65-S75.
26. Bray M, Mahanty S. Ebola hemorrhagic fever and septic shock. J Infect Dis 2003;188:1613-7.
27. Baron RC, McCormick JB, Zubeir OA. Ebola virus disease in southern Sudan: hospital dissemination and intrafamilial spread. Bull World Health Organ 1983;61:997-1003.
28. Branch SP, Division V, Control D, Eradication S. Ebola haemorrhagic fever in Zaire, 1976. Bull World Health Organ 1978;56:271-93.
29. Parkes-Ratanshi R, Elbireer A, Mbambu B, Mayanja F, Coutinho A, Merry C. Ebola outbreak response; experience and development of screening tools for viral haemorrhagic fever (VHF) in a HIV center of excellence near to VHF epicentres. PLoS One 2014;9(7):e100333.
30. Towner JS, Sealy TK, Khristova ML, et al. Newly discovered ebola virus associated with hemorrhagic fever outbreak in Uganda. PLoS Pathog 2008;4(11):e1000212.
31. Wamala JF, Lukwago L, Malimbo M, et al. Ebola hemorrhagic fever associated with novel virus strain, Uganda, 2007-2008. Emerg Infect Dis 2010;16:1087-92.
32. Khan AS, Tshioko FK, Heymann DL, et al. The reemergence of Ebola hemorrhagic fever, Democratic Republic of the Congo, 1995. J Infect Dis 1999;179:Suppl 1:S76-S86.
33. Muyembe T, Kipasa M; International Scientific and Technical Committee and WHO Collaborating Centre for Haemorrhagic Fevers. Ebola haemorrhagic fever in Kikwit, Zaire. Lancet 1995;345:1448.
34. Estimating the future number of cases in the Ebola epidemic — Liberia and Sierra Leone, 2014–2015. Morb Mortal Wkly Rep 2014 September 23 (Epub ahead of print).

Supplementary Appendix 1

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: WHO Ebola Response Team. Ebola virus disease in West Africa — the first 9 months of the epidemic and forward projections. N Engl J Med 2014;371:1481-95. DOI: 10.1056/NEJMoa1411100

Supplementary Appendix

Ebola Virus Disease in West Africa—the First 9 Months of the Epidemic and Forward Projections

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Data Sources

Using a standard Ebola virus disease (EVD) case investigation forms (see Supplementary Documents), clinical and demographic data were collected from confirmed, probable and suspected EVD cases identified in Guinea, Liberia, Nigeria, and Sierra Leone. To create the fullest possible picture of the unfolding epidemic, these data were supplemented by information collected in informal case reports, data from diagnostic laboratories, and from burials. The data recorded for each case include: district of residence, district of disease report, age, sex, signs and symptoms recorded between onset and clinical presentation, date of symptom onset, name of hospital and date of hospitalization, and date of death or discharge. A subset of cases provided information on potentially infectious contacts with other EVD cases, including possible exposure at funerals.

Data Cleaning

The datasets from individual countries were combined and cleaned to correct spelling errors in text fields. Date variables were cleaned by checking for consistency in date recording. The predominant format of date recording was day/month/year, but for some cases day and month were switched. Where this could be ascertained (e.g., any records with an entry after September 2014, or before March 2014 in Liberia or Sierra Leone, or before August 2014 in Nigeria), day and month were switched. Furthermore, dates prior to the beginning of the epidemic late November 2013 and dates after the date of the database (14 Sep 2014) were removed.

Delays between key events in disease progression were evaluated for each patient, and unrealistic delays flagged. These unrealistic delays included negative onset-to-notification delays, negative onset-to-hospitalization, negative onset-to-death, negative onset-to-discharge, negative hospitalization-to-discharge and negative hospitalization-to-death delays. Delays larger than 60 days for the following variables were also flagged: onset-to-hospitalization, onset-to-death, notification-to-hospitalization, notification-to-death, notification-to-discharge and hospitalization-to-death. For individuals with these unrealistic delays, the delay as well as the date variable with the date considered less reliably recorded were set to missing. The numbers of unrealistic delays which led to date exclusions are provided in Table S1.

We inferred dates of onset and notification for patients where these were missing based on information learned from cases with complete date records. For example, for a person with missing onset date but recorded notification date, we inferred the onset date to have been x days prior to the notification date, where x was the country-specific median observed delay between onset and notification dates for patients where both dates were recorded. For countries with less than 10 patients who had both required dates recorded, the overall median across all countries was used instead. We considered the date of notification to be most reliable, followed by date of hospitalization, date of death, date of discharge, date of isolation, date of symptom onset and date of outcome completion, in that order. Hence for inferring dates of symptom onset, we used the following set of rules:

- If the date of notification was available then we inferred the date of symptom onset as the date of notification minus the median onset-to-notification delay.
- Otherwise, if the date of hospitalization was available then we inferred the date of symptom onset as the date of hospitalization minus the median onset-to-hospitalization delay.

- Otherwise, if the date of death was available then we inferred the date of symptom onset as the date of death minus the median onset-to-death delay.
- Otherwise, if the date of hospital discharge was available then we inferred the date of symptom onset as the date of hospital discharge minus the median onset-to-hospital-discharge delay.
- Otherwise, if the date of isolation was available then we inferred the date of symptom onset as the date of isolation minus the median onset-to-isolation delay.
- Otherwise and finally, if the date of outcome completion was available then we inferred the date of symptom onset as the date of outcome completion minus the median onset-to-outcome-completion delay (unless sample size <10 and then the overall median is used).

For inferring dates of notification, we similarly used dates of hospitalization, death, hospital discharge, isolation, symptom onset, and outcome completion dates, in that order of preference.

District of onset was used whenever available, in 2455 cases out of 4020 confirmed/probable cases (61%). For the remaining 1565 cases, the district of residence was used as a proxy for the district of onset. Careful cross-checking allowed us to filter out erroneous district names. Overall, district information could be retrieved for a majority of confirmed/probable cases (3660 cases out of 4020, 91%).

Table S1. Frequency of unrealistic inter-event delays that were excluded from the dataset.

	negative delays*				long delays* (>60 days)			
	Guinea	Liberia	Nigeria	Sierra Leone	Guinea	Liberia	Nigeria	Sierra Leone
Onset-to-notification	6	53	2	30	NA	NA	NA	NA
Onset-to-hospitalization	3	24	2	21	0	2	0	3
Onset-to-death	0	8	0	6	1	2	0	3
Onset-to-discharge	0	0	0	0	NA	NA	NA	NA
Notification-to-hospitalization	NA	NA	NA	NA	0	0	0	0
Notification-to-death	NA	NA	NA	NA	0	0	0	0
Notification-to-discharge	NA	NA	NA	NA	0	2	0	0
Hospitalization-to-death	6	11	0	1	0	0	0	0
Hospitalization-to-discharge	0	0	0	0	NA	NA	NA	NA

*NA indicates contexts in which negative or long delays are not considered unreasonable.

District-level Synchrony

The countries of Guinea, Sierra Leone and Liberia can be divided into 67 administrative districts, with: 38 in Guinea, 15 in Liberia and 14 in Sierra Leone. Of the 3311 cases with reported or inferred onset times and known districts, 3106 were recorded in the 20 most affected districts. Of these 20 most affected districts, 6 were in Liberia, 7 were in Sierra Leone and 7 were in Guinea.

Patterns of correlation between the 20 districts with the highest reported case incidence suggest that district epidemics can be separated into four types at the current time.

1. **Little activity followed by clear recent accelerating growth of incidence.** Of the 20 districts with the largest outbreaks, 15 formed a coherent group in which there was little activity prior to week 20 (12 May 2014) but sustained high growth since then (Figure S1). The coherence of this sub-epidemic was strongest to the south with the 10 most southerly districts – either clustered around Montserrado or adjacent to Gueckedou -- showing very high degrees of correlation in their case incidence. 19% of all confirmed and probable cases have been reported from Montserrado. Kerouane is included in this group.
2. **Sustained transmission but no accelerating growth of incidence.** Two of the 20 most affected districts, Gueckedou and Ratoma, have been experiencing apparently independent outbreaks with sustained incidence since earlier in 2014 but without any reported period of sustained growth. Gueckedou is a province of Guinea adjacent to both Liberia and Sierra Leone in which the epidemic originated[1]. Ratoma, one of the five municipal communes of Conakry, was the first urban population to report cases.
3. **Sustained transmission and recent accelerating growth of incidence.** Case incidence for Macenta in southern Guinea, also one of the earliest affected districts, appears to be a combination of these first two epidemic types with a series of early outbreaks and then a recent sudden increase in cases.
4. **Decline in incidence.** Finally, Boffa and Telimele in Sierra Leone, appear to have experienced a linked but aborted take-off. These two districts (the most northerly of the 20 most affected districts) have incidence that is weakly negatively correlated with the southern outbreaks but positively correlated with each other. In these districts, incidence was decreasing around week 20, a period during which incidence was increasing elsewhere.

We also estimated how the correlation of incidence changed, on average, as a function of distance (Figure S2). Although there is some evidence of a continuous trend of decreasing correlation with distance, the average level of correlation across the entire affected region was high and local effects are only significantly different from the global average correlation for relatively short distances. The strength of association between correlation of incidence and distance was reduced when lags of 1 and 2 weeks were considered.

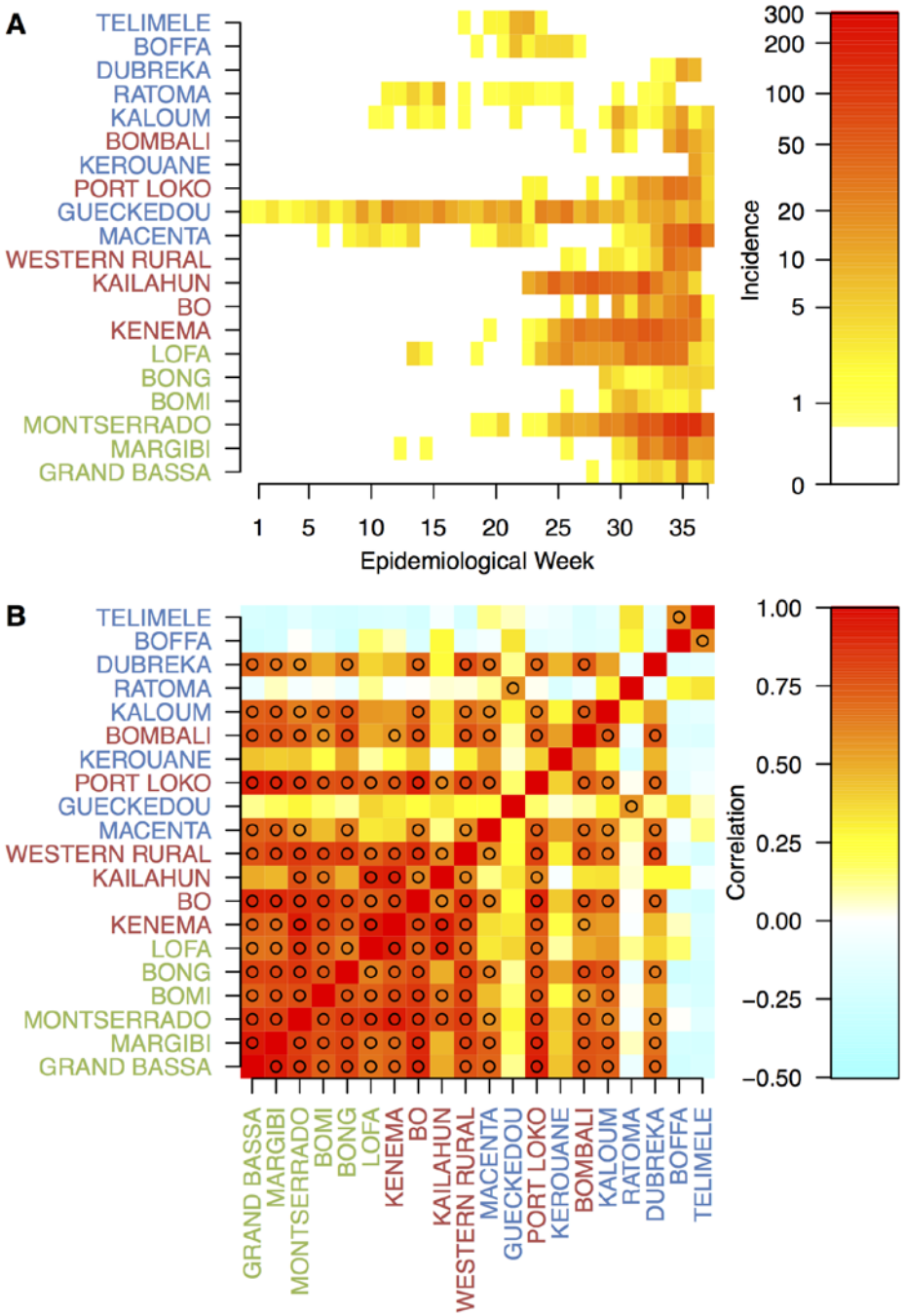

Figure S1. District-level weekly incidence of confirmed and probable cases (A) and correlation between log-transformed district-level weekly incidence of confirmed and probable cases for the 20 most affected districts. In B, coefficients are indicated by colour and were calculated using Pearson correlation coefficients[2] using the rcorr function of the R package Hmisc version 3.12-2. Significant correlations are indicated with an open circle adjusting for multiple comparisons using the Bonferroni correction. Districts are arranged by increasing latitude (South to North) from left to right and bottom to top, with colours indicating country (blue – Guinea, green – Liberia, and red – Sierra Leone).

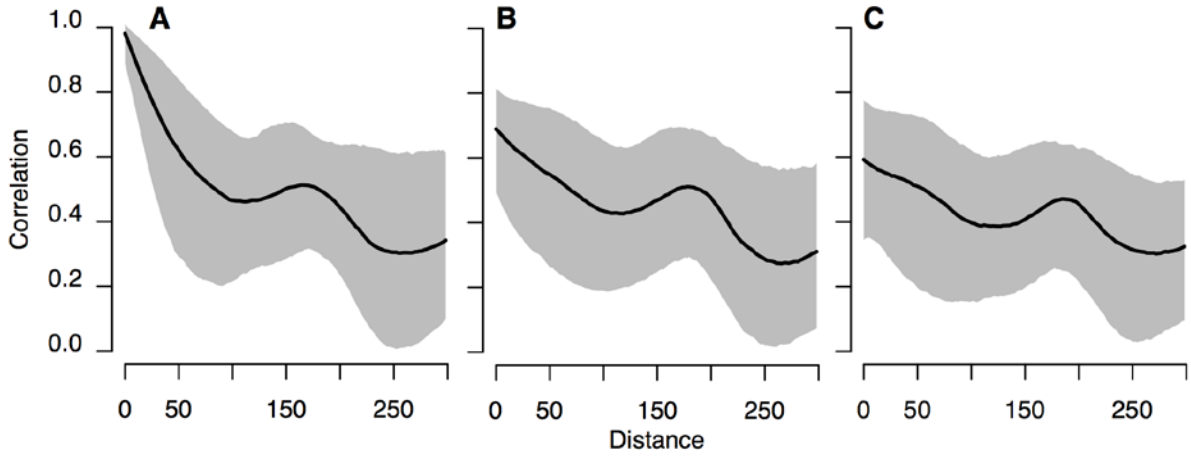

Figure S2. Spline correlogram showing multiple possible peaks in the distance correlation between affected districts with no lag (A), 1-week lag (B) and 2-week lag (C). All cases were assigned to the latitude and longitude of the centroid of the district in which they occurred. The spline correlogram (solid line) and confidence region (grey region) were estimated using the Sncf function of the R-package ncf (version 1.1-5) for all district pairs[2]. However, results are only shown for the first 300km of the maximum, ~600 km separation. A spline with 10 degrees of freedom was used to calculate the function shown here. No additional features were observed when the degrees of freedom of the spline were increased up to 20 (not shown).

Incubation Period

In order to obtain information on the incubation period, recorded dates of contact between confirmed or probable EVD cases and funeral attendance were analysed. There were 486 cases who had 1 or more live contacts but no reported funeral contacts, 67 cases with one or two funeral contacts but no live contacts, and 148 cases with both funeral and live contacts reported. To estimate the incubation period distribution, we considered three different inclusion criteria: (i) only including people who had a single reported day of potential exposure and (ii) only including people who had more than one reported potential exposure day. Cases without recorded onset date were excluded even if their approximate onset date could be inferred based on other recorded dates. We also explored the effect of excluding short delays between exposure and onset for reasons of biological implausibility and since the data are likely biased towards shorter exposures due to recall bias.

In the EVD databases, up to 3 different contacts and up to 2 different funerals were recorded per confirmed or probable case. For contacts with both living EVD cases and deceased EVD cases at funerals, the start and end date of the contact were recorded, with the start date generally much more frequently recorded than the end date. For contacts with living EVD cases, when only the start date was given, we assumed a 1-day contact window (that is, contact only occurred on the one date provided). If only the end date was given, the earliest exposure we considered was 42 days before the onset date (twice the assumed maximum incubation period). For funeral contacts, if only the start date or only the end date of contact were given, we assumed the duration of exposure was one

day. For each EVD case, we considered all dates of potential exposure recorded and calculated the delay between these and the onset date. Contacts on dates after the onset date were excluded.

For fitting gamma distributions to all non-negative recorded potential exposure days we calculated the log-likelihood

$$\ln L = \sum_i \ln \sum_j \gamma\left(d_{ij} + 0.5 \mid \alpha, \beta\right)$$

where i indexes individuals and j indexes the potential exposure days for each individuals, γ is the probability density function of the gamma distribution with shape and rate parameters α and β, respectively. d_{ij} is the recorded period between exposure and onset. We added a half day to each exposure delay (the mid-point of a day) to account for the fact that each such delay was rounded to an integer number of days.

We defined a censored log-likelihood, fitting only to the observed incubation periods longer than a specified cut-off for censoring, d_0, by re-normalising the distribution:

$$\ln L = \sum_i \ln \sum_{j:d_{ij}>d_0} \frac{\gamma\left((d_{ij} + 0.5 \mid \alpha, \beta)\right)}{1 - \Gamma(d_0 \mid \alpha, \beta)}$$

where delays less or equal to d_0 are censored.. Γ is the cumulative distribution function of the gamma distribution with parameters α and β.

The fits to data from confirmed and probable cases reporting single day or multiday exposure are shown in Figure S3 and detailed in Table S2.

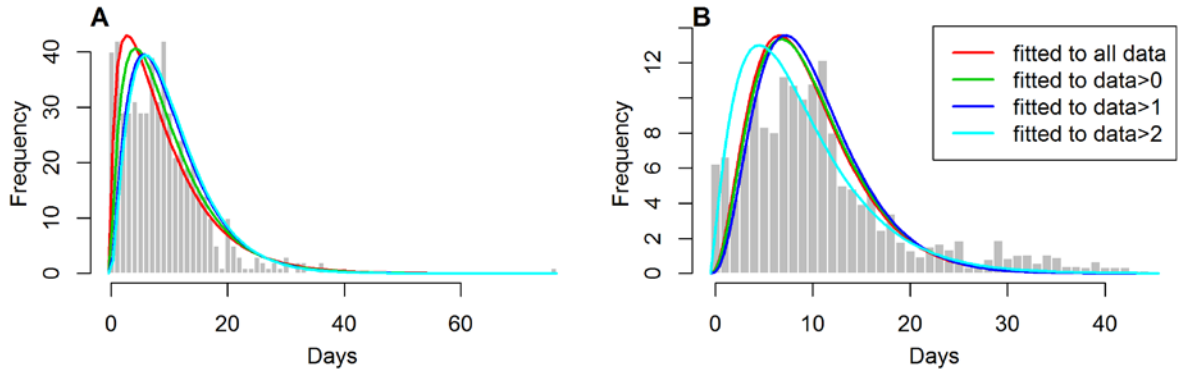

Figure S3: Gamma parametric fits to the distributions of incubation periods among confirmed and probable EVD cases reporting (A) single day and (B) multiday exposures.

Table S2. Sample sizes, observed medians, means and standard deviations (SDs) and means, SDs, shape and rate parameters of gamma distributions fitted to the data, including confirmed and probable cases reporting single day or multiday exposures.

		observed				fitted			
	Fitting to	Sample Size[#]	Median *	Mean *	SD	Mean	SD	Shape	Rate
single day exposure	all delays	540	8	8.7	7.5	8.7	7.7	1.41	0.154
	delays >0 days	500	8	9.4	7.4	9.1	7.3	1.75	0.182
	delays >1 days	458	9	10.2	7.2	9.7	6.9	2.21	0.216
	delays >2 days	429	9	10.7	7.2	9.9	6.8	2.34	0.225
multiday exposure	all delays	161	9	11	NA	9.5	5.5	3.39	0.338
	delays >0 days	155	9.5	11.4	NA	9.7	5.5	3.44	0.336
	delays >1 days	147	9.5	11.9	NA	9.9	5.4	3.8	0.364
	delays >2 days	71	9.5	12.8	NA	8.8	6.3	2.18	0.236

[#]Number of individuals, not exposure days. *For multiday exposures the observed means were calculated by calculating the mean of the individual means for each person to ensure equal weighting of all individuals. The median was similarly obtained by calculating the median of the individual medians for each person.

We explored the sensitivity of the results to the extreme assumption that infection happened on the first reported contact, that is, the one longest before the onset of symptoms. This had the expected effect of increasing both the mean and the standard deviation of the fitted gamma distribution from the 9.7 and 5.5 days to 15.5 and 9.4, respectively, among those cases reporting multiday exposures excluding data at zero days.

Table S3 describes the incubation period distribution estimated from confirmed, probable and suspected cases reporting multiday exposures (to be compared with Table 2 in the main text which presents the corresponding values for the observed data including confirmed and probable cases only).

Table S3. Mean and standard deviation (SD) incubation period in days among those confirmed, probable and suspected cases reporting multiday exposures excluding data at zero days, overall.

Exposures		Mean*	SD
Single day exposure	Observed	9.4	7.3
	Fitted	9.1	7.3
Multiday exposure	Observed	11.8	NA
	Fitted	10.2	6.0

*The observed mean for multiday exposure was obtained by calculating the mean across all cases of the individual mean delay from exposure to onset

Serial Interval and Generation Time

Observed serial intervals were extracted from the database by linking contacts specified by individual cases with case records for these contacts to calculate the delay from onset to onset. Contacts could either be made with cases while they were alive, or during funerals. We only included data on patients who had only named a single contact, cases and contacts without a recorded onset date were excluded, even if their approximate onset date could be inferred based on other recorded dates: this gave serial intervals from 162 cases with a live contact and 16 cases with a funeral contact. We fitted a gamma distribution to these observed serial intervals by maximum likelihood.

The generation time is the time from the infection of the index case (denoted t_1) until the infection of a case infected by that index (denoted t_2). However, the dates of these events are not typically known. It is often possible to determine the serial interval, defined as the time from the onset of symptoms in the index case (denoted o_1) until the onset of symptoms in the case infected by that index (denoted o_2). The time from infection to onset within case i is the incubation period, denoted $i_i = o_i - t_i$. Thus,

$$o_i = t_i + i_i$$

The serial interval for cases 1 and 2 is thus $o_2 - o_1$, whereas the generation time for cases 1 and 2 is $t_2 - t_1$. Thus,

$$o_2 - o_1 = (o_2 - i_2) + (i_2 - o_1)$$

and similarly,

$$i_2 - i_1 = (i_2 - o_1) + (o_1 - i_1).$$

If the timing of infectiousness in an EVD infected individual is correlated with the timing of disease onset in that case (i.e. if infectiousness begins on or around the time of symptom onset), it is reasonable to treat the time from the time of symptom onset in case 1 to the time of infection of case 2 (i_2-o_1) as independent of the incubation period (o_i-i_i). Then from the equations above, we see that both the serial interval and the generation time have the same distribution. For more general results on serial interval and generation time distributions, see Svensson[3].

Inter-event Delay Distributions

Gamma distributions were fitted to

- time from symptom onset to hospitalization,
- time from symptom onset to discharge,
- time from symptom onset to death,
- time from symptom onset to notification,
- time from notification to discharge,
- time from notification to death,
- time from hospitalization to discharge and
- time from hospitalization to death,

For all delay distributions cases without the relevant dates recorded were excluded from these analyses even if the approximate dates could be inferred based on other recorded dates. Overall and country-specific estimates were obtained (Figures S4 and S5).

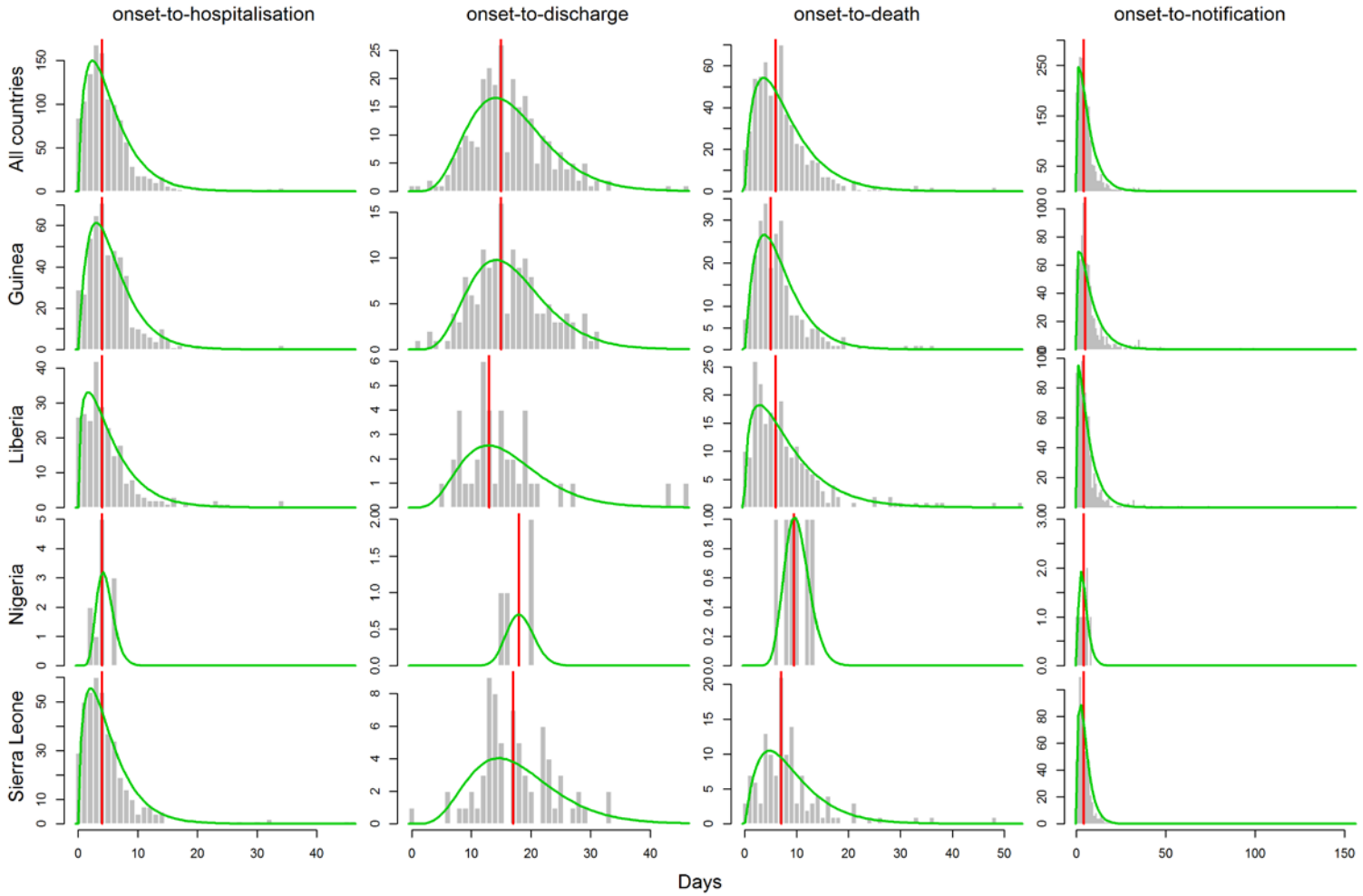

Figure S4. Gamma distribution parametric fits (green line) to the distributions of time from symptom onset to hospitalization, symptom onset to discharge, symptom onset to death and symptom onset to notification, overall and by country. The red line shows the median of the observed data, and the bars show the observed data.

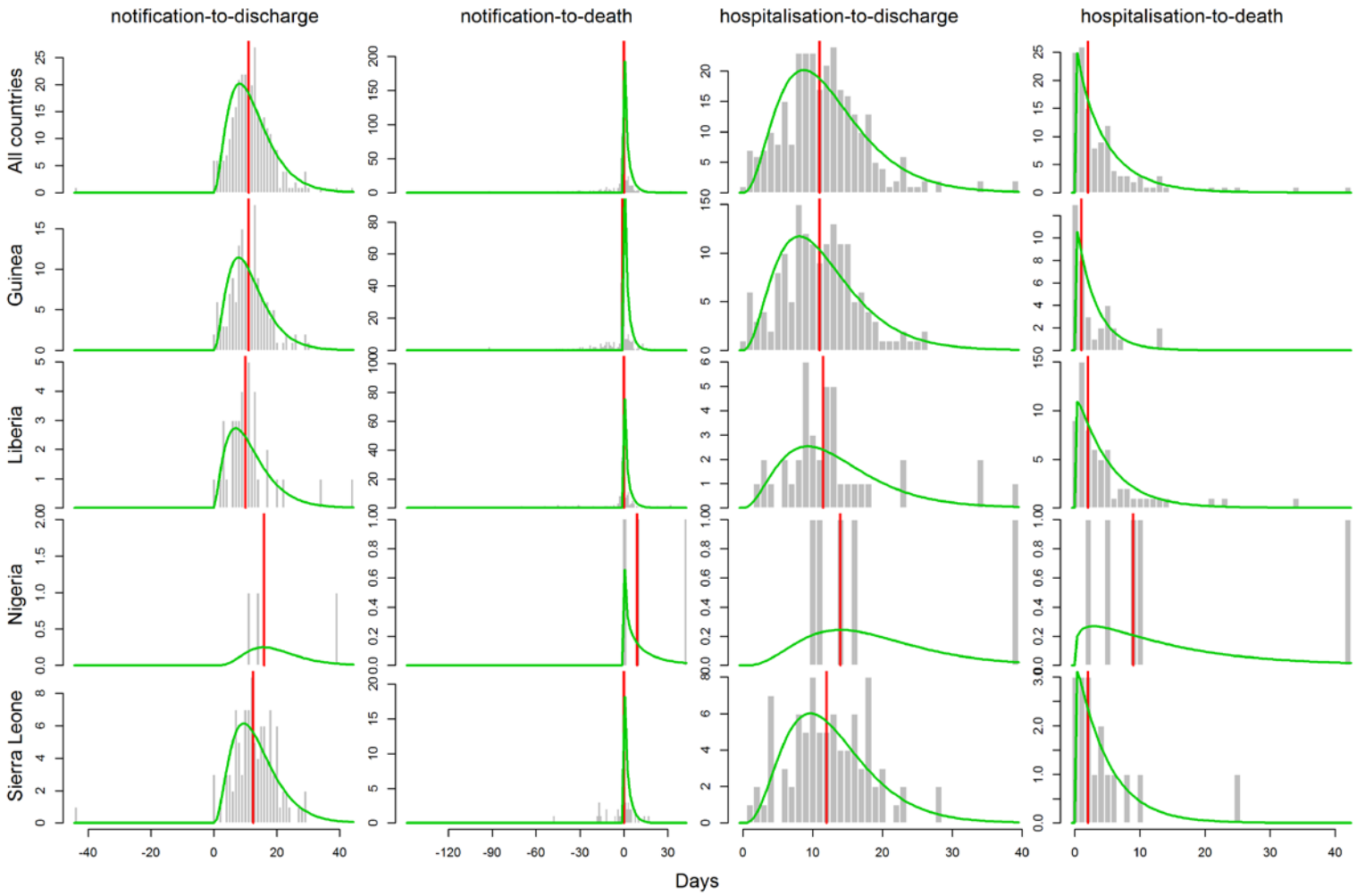

Figure S5. Gamma distribution parametric fits (green line) to the distributions of time from notification to discharge, notification to death, hospitalization to discharge and hospitalization to death, overall and by country. The red line shows the median of the observed data, and the bars show the observed data.

Case Fatality Rate

The case fatality rate (CFR) is defined as the percentage of cases which are fatal. When estimating this during an ongoing epidemic, the naïve method of dividing the number of deaths reported to date by the number of cases reported to date will be biased downwards due to the fact that among cases reported recently there may be a substantial number who are currently still sick some of who will die in the future. As these are counted in the cases, but not yet in the deaths, the estimate will be biased downwards. There are a number ways to prevent this bias from happening depending on the type of data available.

We estimated the CFR from data for the 46% of cases with recorded definitive clinical outcomes. Naïve estimates of the CFR derived from the ratio of recorded deaths to recorded cases significantly under-estimate the true CFR seen in this EVD epidemic, since the final clinical outcome of over half of the reported cases is not known. Such estimates can be corrected for the delay between case onset and date of death which can otherwise bias ratio-based estimates when incidence is non-stationary[1].

In addition to estimating the CFR based on all the information available to date, we estimated the CFR over time based on the cases which had onset by a particular date, demonstrating how information has accumulated over time, resulting in narrowing confidence intervals. Figure S6 shows the trends over time in the CFR calculated according to the different methods. When using final status and excluding those with missing information (panel A), the adjustment for the delay in outcome reporting is not necessary, and the CFR estimates appear fairly stable over time in recent weeks. When the estimates are based on the current status and missing information is interpreted as alive, without the delay adjustment (panel B), the estimates in recent weeks are clearly biased downwards, and the confidence intervals do not capture the delay biases. However, when adjusting for the reporting delays (panel C), the estimates appear stabilised, although at a different level compared to the final status. While the estimates based on final status are fairly consistent between countries, and at around 70% similar to what has previously been reported for Ebola Zaire, the adjusted estimates using the current status are considerably lower in Liberia and Sierra Leone. While often the reporting of deaths is more complete than the reporting of recoveries, typically biasing estimates of the case fatality rate upwards, in the current situation it may well be that deaths are missed as easily as recoveries as they are lost to follow up, for instance if case move back to their home villages where a substantial proportion might die.

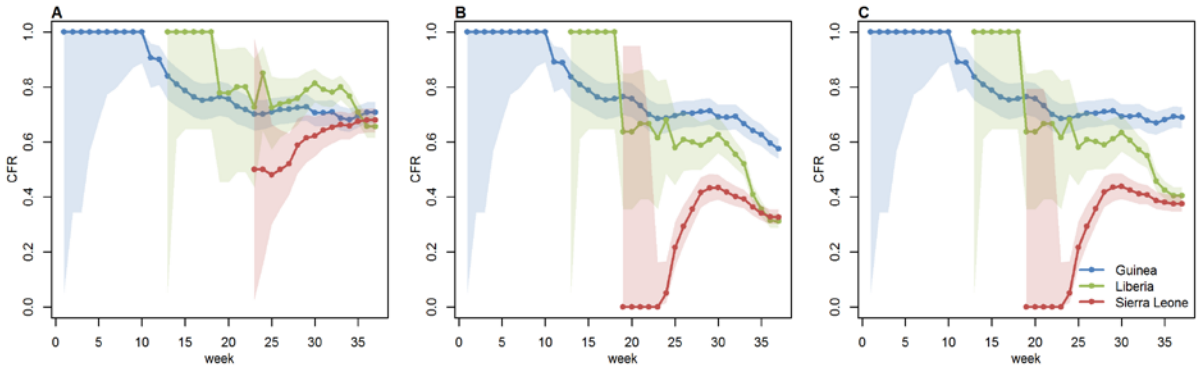

Figure S6. Cumulative CFR estimate (95% CIs) of confirmed and probable cases over time by country. (A) based on definitive clinical outcome, dividing total deaths by total cases with known final outcome (death or recovery), (B) naïve estimate, dividing total deaths by total cases (irrespective of outcome), and (C) the naïve estimate adjusted for the delay between case and death reporting[4].

For comparison with Table 2 of the main text (which presented CFR estimates for confirmed and probable cases), we estimated the CFR for confirmed, probable and suspected cases (Table S4).

Table S4. CFR (Point Estimate, 95% Confidence Interval and sample size n) estimates for Confirmed, Probable and Suspected EVD Cases by Country. All estimates based on recorded definitive outcome other than top row. --- = n<10 and CFR not calculated

	All countries	Guinea	Liberia	Nigeria	Sierra Leone
All cases (based on current status)	38.4 (37.1, 39.8; n = 4894)	55.3 (51.6, 59; n = 705)	39 (37.1, 40.9; n = 2487)	35.3 (17.3, 58.7; n = 17)	30.6 (28.4, 32.8; n = 1685)
All cases (based on definitive outcome)	73.6 (71.7, 75.4; n = 2250)	70.7 (66.8, 74.4; n = 543)	75.8 (73.3, 78.2; n = 1196)	45.5 (21.3, 72; n = 11)	72 (67.9, 75.8; n = 500)
All hospitalized cases (based on definitive outcome)	64.2 (61.6, 66.8; n = 1303)	64.7 (60.2, 69; n = 451)	65.6 (61.3, 69.6; n = 497)	40.0 (16.8, 68.7; n = 10)	62.3 (57.1, 67.3; n = 345)
By gender					
male	75.2 (72.6, 77.6; n = 1153)	68.6 (62.7, 74; n = 255)	78.1 (74.8, 81.1; n = 644)	---	74.8 (69.1, 79.8; n = 250)
female	71.9 (69.1, 74.5; n = 1028)	72.7 (67.3, 77.6; n = 286)	74.1 (70.1, 77.7; n = 510)	---	66.7 (60.3, 72.5; n = 225)
By age group					
<15 yrs	74.3 (68.7, 79.2; n = 261)	78.1 (67.3, 86; n = 73)	71.8 (63, 79.2; n = 117)	---	74.6 (63.4, 83.3; n = 71)
15-44 yrs	69.2 (66.7, 71.7; n = 1303)	65 (59.6, 70; n = 320)	73.6 (70.2, 76.8; n = 686)	---	64.5 (58.8, 69.8; n = 290)
>44 yrs	81.3 (77.7, 84.4; n = 518)	78.6 (71.1, 84.6; n = 140)	81.7 (76.7, 85.9; n = 268)	---	84 (75.8, 89.7; n = 106)
By occupation					
HCW	69 (62, 75.2; n = 187)	56.1 (41, 70.1; n = 41)	76.5 (66.2, 84.4; n = 81)	---	69 (56.2, 79.4; n = 58)
non-HCW	74 (72.1, 75.9; n = 2063)	71.9 (67.8, 75.7; n = 502)	75.8 (73.2, 78.2; n = 1115)	---	72.4 (68.1, 76.4; n = 442)

Risk Factors for Death

To identify risk factors for death, odd ratios were computed for all available symptom data, with or without accounting for differences between countries, using logistic regression. Only symptoms for which at least 5 observations were present in each category were considered. Each symptom is analysed independently. When accounting for differences between countries, the country of onset was included as a first covariate, before including the symptom effect. All models were fitted using the function 'glm' in the *R* software[3]. The significance of individual symptom effects was assessed using likelihood ratio tests. Results based on the analysis of all data combined are given in the main text, while Table S5 gives country-specific results for the 3 most affected countries.

Table S5: Demographic Characteristics, Signs and Symptoms among Confirmed and Probable Ebola Cases by Country, as of 14 September 2014

	Guinea				Liberia				Sierra Leone			
	OR	95%CI		p	OR	95%CI		p	OR	95%CI		p
Variable		Lower	Upper	value		Lower	Upper	value		Lower	Upper	value
Gender	1.28	0.88	1.87	0.2	0.81	0.5	1.29	0.37	0.71	0.46	1.09	0.11
Age Group												
<15 years old	1.45	0.8	2.77	0.23	0.76	0.4	1.49	0.41	1.36	0.75	2.57	0.32
15-44 years old	0.5	0.33	0.75	0	0.58	0.34	0.97	0.04	0.39	0.24	0.63	0
≥45 years old	1.91	1.22	3.07	0	2.82	1.46	6.01	0	3.18	1.71	6.29	0
General symptoms												
Fever	0.46	0.24	0.87	0.02	1.38	0.66	3.26	0.41	1.07	0.58	2.05	0.82
Fatigue	1.93	1.12	3.28	0.02	0.69	0.2	1.87	0.49	1.09	0.58	2.02	0.78
Loss of appetite	0.66	0.37	1.12	0.13	1.41	0.76	2.55	0.27	0.96	0.57	1.58	0.87
Vomiting	0.9	0.56	1.43	0.66	1.18	0.67	2.06	0.56	0.81	0.48	1.32	0.39
Diarrhea	1.93	1.22	3.04	0.01	1.18	0.63	2.12	0.6	0.74	0.46	1.18	0.21
Headache	1.71	1.06	2.74	0.03	1.58	0.9	2.74	0.11	1.09	0.68	1.74	0.73
Abdominal Pain	1.05	0.66	1.65	0.85	1.06	0.61	1.83	0.83	0.94	0.59	1.49	0.78
Muscle Pain	0.87	0.54	1.43	0.59	0.94	0.55	1.6	0.82	0.76	0.48	1.21	0.25
Joint Pain	1.07	0.64	1.8	0.81	1.47	0.85	2.59	0.17	1.19	0.73	1.95	0.49
Chest Pain	1.23	0.7	2.21	0.48	1.09	0.63	1.91	0.76	1.58	0.99	2.56	0.06
Cough	0.77	0.24	2.56	0.67	1.78	1.01	3.24	0.05	1.53	0.93	2.57	0.1
Difficulty Breathing	3.56	0.83	19	0.09	1.71	0.89	3.53	0.11	1.54	0.93	2.61	0.1
Difficulty Swallowing	2.06	0.51	10.5	0.32	2.21	1.11	4.83	0.02	1.32	0.74	2.45	0.35
Conjunctivitis	5	1.32	24.8	0.02	1.91	0.99	3.94	0.05	2.06	1.03	4.27	0.04
Sore Throat	1.39	0.42	4.92	0.6	0.89	0.44	1.87	0.74	3.8	1.92	8.25	0
Confused	---	---	---	---	1.69	0.79	4.05	0.19	1.59	0.74	3.59	0.24
Hiccups	---	---	---	---	5.25	1.54	32.9	0.01	1.07	0.55	2.19	0.84
Jaundice	2.05	0.89	5.57	0.09	2.97	0.84	18.9	0.1	2	0.95	4.62	0.07
Eye Pain	---	---	---	---	6.36	1.3	115	0.02	1.29	0.64	2.74	0.49
Rash	---	---	---	---	4.88	0.97	88.8	0.06	1.52	0.68	3.76	0.32
Coma/Unconscious	---	---	---	---	0.72	0.24	2.67	0.59	5.19	1.46	33.1	0.01
General symptoms	---	---	---	---	6.06	1.23	110	0.02	3.33	0.89	21.7	0.08
Hemorrhagic Symptoms												
Unexplained bleeding	2.24	1.17	4.69	0.01	1.78	0.76	4.87	0.19	1.26	0.6	2.79	0.55
Hematemesis	---	---	---	---	1.83	0.49	11.9	0.4	0.13	0.01	0.91	0.04
Blood in Stool	0.85	0.31	2.73	0.77	1.11	0.34	4.96	0.87	1.03	0.34	3.42	0.97
Bleeding Gums	---	---	---	---	2.62	0.49	48.5	0.3	---	---	---	---
Bloody Nose	---	---	---	---	---	---	---	---	4.7	0.84	87.9	0.08
Blood in Cough	---	---	---	---	0.89	0.21	6.07	0.88	2.31	0.57	15.6	0.26
Bleeding Other	---	---	---	---	1.27	0.2	24.5	0.83	---	---	---	---
Bleeding at injection site	---	---	---	---	3.68	0.72	67.4	0.14	---	---	---	---
Blood in Vomit	---	---	---	---	---	---	---	---	---	---	---	---
Bleeding from Vagina	---	---	---	---	1.84	0.32	34.7	0.55	---	---	---	---
Bleeding in urine	---	---	---	---	---	---	---	---	2.9	0.46	56	0.28
Bleeding Skin	---	---	---	---	---	---	---	---	---	---	---	---

--- = n<5 and OR not calculated

Estimation of *R* and Forward Projections

In this section, we detail the methods used to estimate the time varying instantaneous reproduction number (R_t), to estimate the basic reproduction number (R_0) and to make forward projections of incidence by country.

Basic underlying model and inference

We assumed the daily incidence could be approximated by a Poisson process using the renewal equation:

$$I(t) \sim \text{Pois}\left(R_t \sum_{s=1}^{T} \omega_s I(t-s) \right)$$

with $I(t), (t = 0,...,T)$ being the incidence of onset at time *t*, ω describing the serial interval distribution (assumed to be Gamma with mean 15.3 days and coefficient of variation 0.66 as estimated from the data), and R_t is the instantaneous reproduction number at time *t*.

It is then possible to calculate the likelihood of observing k cases with onset of symptoms on day *t*, conditional on the incidence up to day *t-1*, as:

$$P\left(I(t) = k \mid R_t, \{I_x\}_{x=0,\ldots,t-1}, \omega\right) = \frac{\lambda_t^{\,k}}{k!} e^{-\lambda_t}$$

with $\lambda_t = 1 \Big/ \left(R_t \sum_{s=1}^{T} \omega_s I(t-s) \right)$. Therefore the likelihood, L , of the observed time-series (from time 1 to T), conditional on the incidence observed on day 0, is:

$$L = \prod_{t=1..T} \left(P\left(I(t) = k \mid R_t, \{I_x\}_{x=0,\ldots,t-1}, \omega\right) \right).$$

Given this likelihood, a posterior distribution for R_t may be obtained either analytically[5] (using a Gamma distributed prior for R_t) or using Markov Chain Monte Carlo (MCMC) sampling.

Estimation of time varying instantaneous reproduction number (R_t)

For each country, we estimated the instantaneous reproduction over time R_t over sliding 4-week windows[5], chosen to maintain sample size and therefore precision in the estimate without hiding potential temporal trends (Figure S7). Estimates are shown for the 4-week time periods in which estimates could be obtained for confirmed and probable cases.

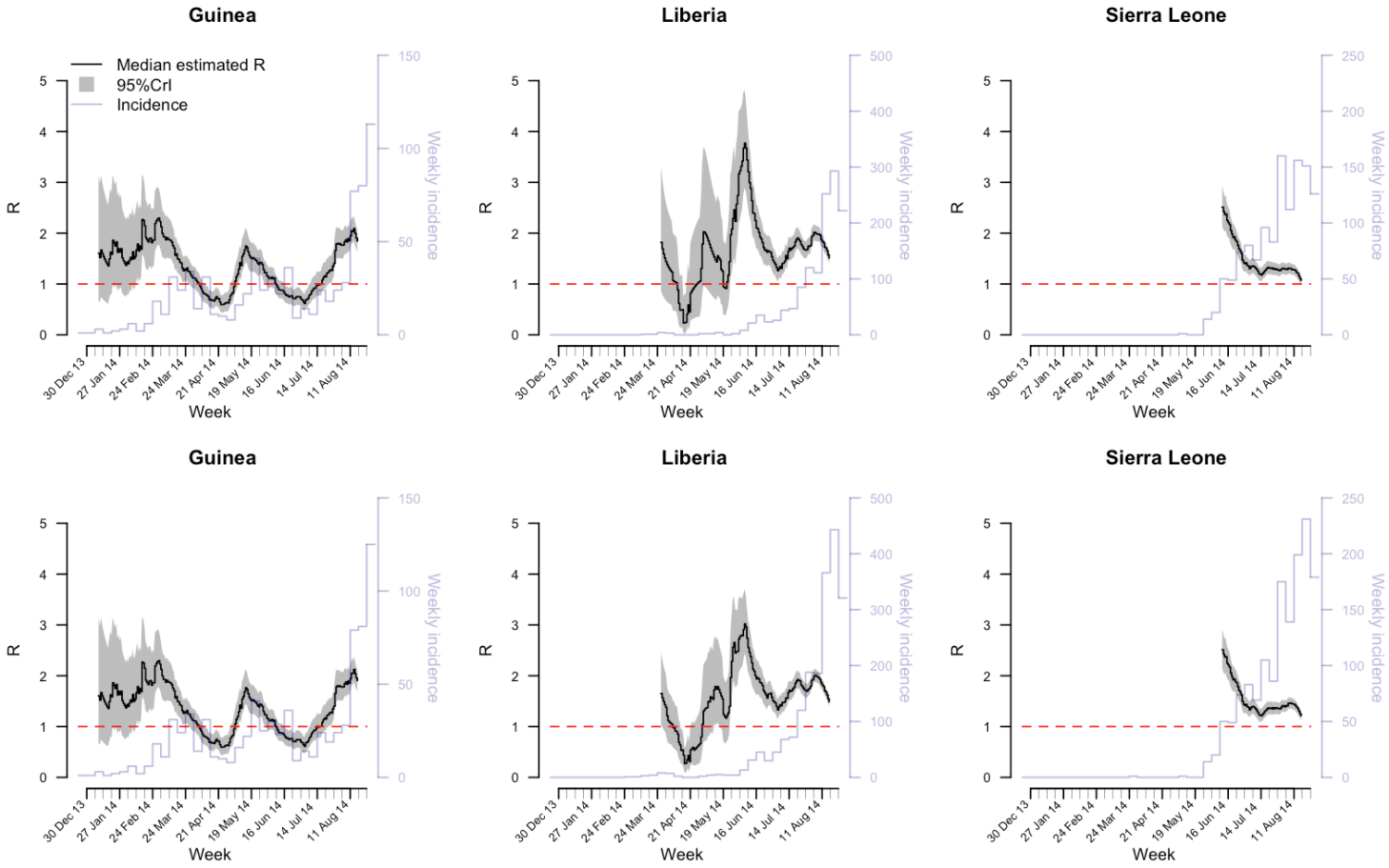

Figure S7: Estimates of the instantaneous reproduction number (R_t) over sliding 4-week windows, by country and by week of symptom onset based on the detailed case dataset. Estimates are shown at the windows mid-points. The top row is based on confirmed and probable cases, the bottom row is based on confirmed, probable and suspected cases. The serial interval is assumed to have a mean of 15.3 days. In each country, R_t is estimated from the day following the onset of symptoms of the first confirmed/probable case in that country. For Sierra Leone, estimates start the day following the onset of symptoms of the second confirmed/probable case. Indeed, the first and second cases have symptoms onset 23 days apart from each other, and are thus not likely to be epidemiologically linked.

Examination of these trends allowed us to evaluate the initial periods over which R_t appeared approximately constant, from which the basic reproduction number (R_0) was estimated. It also allowed us to define a time period later in the epidemic which was used to estimate a value of R_t to be used for projecting future incidence.

Estimation of the basic reproduction (R_0)

Estimating R_0 is equivalent to estimating a constant instantaneous reproduction number over the initial period where the epidemic is growing exponentially. This period $[0, T_{\exp}]$ was informed by both the analysis above and visual inspection of plots of the log transformed incidence over time. We then assumed that over this period, $R_0 = R_t$ and thus obtained the posterior distribution for the basic reproduction number.

$T_{\exp}$ was thereby set to 30 March 2014 for Guinea, to 24 August 2014 for Liberia and Nigeria, and to 6 July for Sierra-Leone, to obtain country-specific estimates of R_0 .

Additionally, given our estimates of the mean serial interval are somewhat larger than previously published values[6,7], we repeated this analysis for mean serial intervals of 11 and 13 days. Finally, all analyses were repeated considering either incidence of confirmed and probable cases or confirmed, probable and suspected cases. Estimates are shown in Table S6.

Table S6: Basic reproduction number (R_0) by country, based on the date of symptom onset of confirmed and probable cases or of confirmed, probable and suspected cases, from the line list database. Estimates are shown for 3 values of the mean serial interval (in days).

			Guinea	Liberia	Nigeria	Sierra-Leone
			Median R_0 (95% CrI)			
Confirmed and probable	Mean Serial interval	15.3	1.71 (1.44 ; 2.01)	1.83 (1.72 ; 1.94)	1.20 (0.67 ; `.96)	2.02 (1.79 ; 2.26)
		13	1.6 (1.32 ; 1.87)	1.68 (1.6 ; 1.77)	1.11 (0.67 ; 1.8)	1.84 (1.65 ; 2.06)
		11	1.5 (1.25 ; 1.74)	1.58 (1.5 ; 1.65)	1.07 (0.64 ; 1.66)	1.68 (1.5 ; 1.89)
Confirmed, probable, suspected	Mean Serial interval	15.3	1.71 (1.46 ; 2.00)	1.8 (1.72 ; 1.89)	1.18 (0.66 ; 1.86)	2.04 (1.81 ; 2.29)
		13	1.61 (1.35 ; 1.89)	1.69 (1.6 ; 1.77)	1.12 (0.63 ; 1.76)	1.84 (1.64 ; 2.05)
		11	1.49 (1.27 ; 1.74)	1.57 (1.49 ; 1.65)	1.07 (0.64 ; 1.68)	1.68 (1.49 ; 1.9)

Estimation of the recent instantaneous reproduction number (*R*) for projection

We then estimated country-specific instantaneous reproduction numbers, *R*, for the most recent 6-week period for use in generating forward projections. The end date was chosen as the latest date for which available data were likely to be complete (accounting for delays in reporting and inclusion in the database). The start date was chosen as the earliest date for which the 4-weekly instantaneous reproduction number estimated above could be assumed constant, following the period of initial exponential growth. The method was applied to both the daily case count data (on reporting dates) and the line list database (on onset dates). When using the reporting dates, we estimated *R* between 28 July 2014 and 7 September 2014. Given the delay between onset and report, when using the onset dates, we estimated *R* between 21 July 2014 and 31 August 2014. In the main text, we report results based on the daily case count data (on reporting dates) as they reflect the most current account of the situation, and are more comparable to other publicly available data.

Given uncertainty surrounding the epidemiological situation before the period when the instantaneous reproduction number was estimated, we jointly estimated *R* for that period as well as back-calculated the incidence before that period, using the known relationship between serial interval, growth rate and reproduction number[8]. The joint posterior distribution of *R* and the early epidemic curve (from which forward projections were generated) was inferred using MCMC sampling.

Again, sensitivity analyses were performed by estimating *R* assuming different mean serial intervals, and including suspected as well as confirmed and probable cases in the analysis. Estimates are presented in Table S7.

Table S7: Estimates of the instantaneous reproduction number (R) for the most recent 6 weeks by countries. Estimates are based on the daily case count data (on reporting dates from 28 July 2014 to 7 September 2014) and on the line list database (on date of symptom onset from 21 July 2014 and 1 September 2014) of confirmed and probable cases or of confirmed, probable and suspected cases. Estimates are shown for three values of the mean serial interval in days.

				Guinea	Liberia	Sierra Leone
				Median R (95% CrI)		
Daily case count	Confirmed and probable	Mean serial interval	15.3	1.81 (1.6 ; 2.03)	1.51 (1.41 ; 1.60)	1.38 (1.27 ; 1.51)
			13	1.67 (1.49 ; 1.85)	1.43 (1.34 ; 1.52)	1.32 (1.21 ; 1.42)
			11	1.54 (1.38 ; 1.72)	1.34 (1.26 ; 1.42)	1.27 (1.16 ; 1.38)
	Confirmed, probable, suspected	Mean serial interval	15.3	1.92 (1.73 ; 2.16)	1.57 (1.48 ; 1.66)	1.35 (1.24 ; 1.46)
			13	1.78 (1.57 ; 1.96)	1.48 (1.41 ; 1.56)	1.3 (1.2 ; 1.4)
			11	1.62 (1.45 ; 1.78)	1.39 (1.32 ; 1.46)	1.25 (1.15 ; 1.35)
Line list database	Confirmed and probable	Mean serial interval	15.3	1.87 (1.65 ; 2.1)	1.49 (1.38 ; 1.61)	1.08 (0.99 ; 1.18)
			13	1.72 (1.52 ; 1.93)	1.41 (1.32 ; 1.51)	1.07 (0.98 ; 1.17)
			11	1.59 (1.42 ; 1.77)	1.33 (1.24 ; 1.42)	1.06 (0.97 ; 1.15)
	Confirmed, probable, suspected	Mean serial interval	15.3	1.93 (1.73 ; 2.14)	1.47 (1.39 ; 1.57)	1.24 (1.14 ; 1.33)
			13	1.76 (1.57 ; 2)	1.4 (1.32 ; 1.48)	1.2 (1.11 ; 1.28)
			11	1.63 (1.45 ; 1.8)	1.32 (1.24 ; 1.39)	1.16 (1.08 ; 1.25)

Forward projections

We used two methods to project country-specific national case numbers by week of symptom onset up to 16 November 2014.

Method A (regression): The number of incident cases per week (over the time periods defined in the previous paragraph) were log transformed (with an addition of 0.5 to avoid taking the logarithm of zero) and regressed against week number (from 1 to 6 where week 1 = 21-27 July for onset dates, and 28 July-3 August for report dates, and week 6 = 25-31 August for onset dates and 1-7 September for report dates). Projections were obtained from the fitted values. The bounds presented in Figures S8 and S10 are 95% prediction intervals (PIs) and 95% confidence intervals (CIs).

For method A, we only considered confirmed and probable cases, from both the line list and the daily case count databases.

Method B (renewal equation): We simulated future incidence in each country using a stochastic branching process model based on the renewal equation[9], assuming a Poisson offspring distribution:

$$I(t) \sim \text{Pois}\left(R\sum_{s=1}^{T} \omega_s I(t-s) \right)$$

with $I(t)$ being the incidence of onset at time t, ω describing the serial interval distribution (assumed to be Gamma with mean 15.3 days and coefficient of variation 0.66 as estimated from the data), and *R* is the instantaneous reproduction number. For each simulation, the initial conditions and *R* were jointly sampled from their joint posterior distributions (see previous paragraph). Confidence intervals were generated from 1,000 simulations.

For method B, projections were obtained for confirmed and probable cases, and for confirmed, probable and suspected cases, from both the line list and the daily case count databases (Figures S9, S11-S13).

While method B gives narrower confidence intervals, the central estimates generated by each method are close to identical.

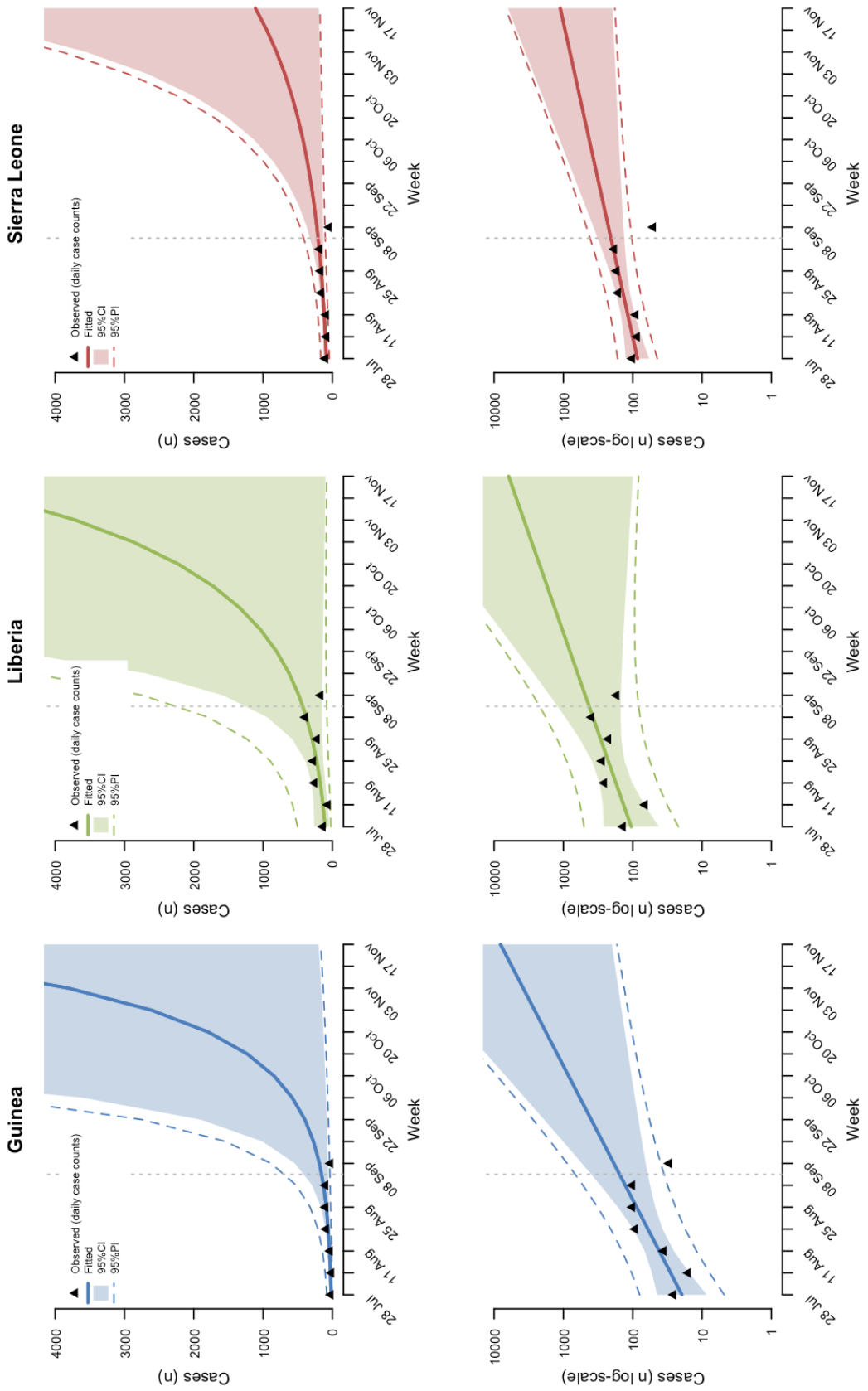

Figure S8: National Projections using Confirmed and Probable Cases from the daily case count database (by date of report) using Method A. The vertical dotted lines indicate the date up to which data were used for R estimation.

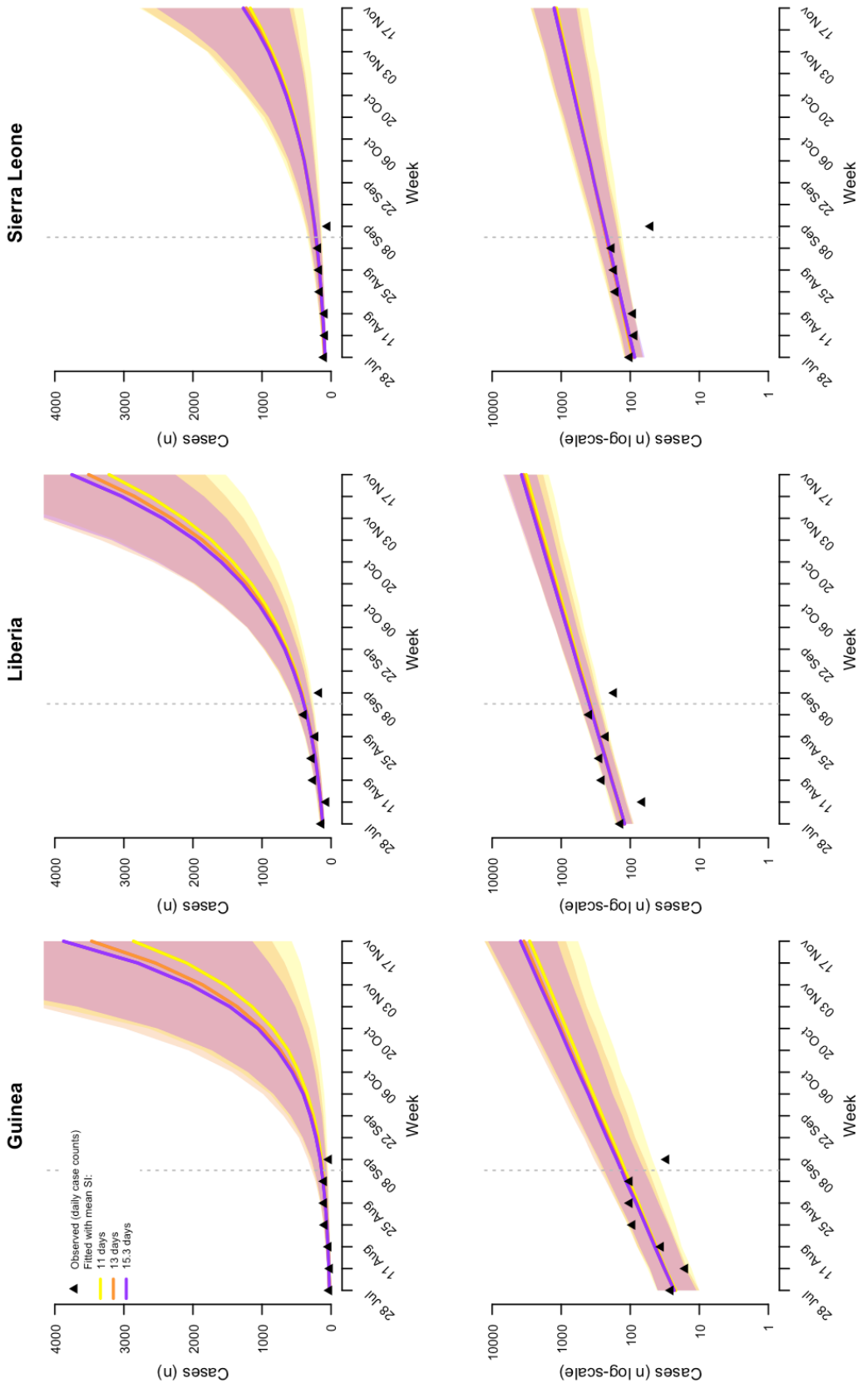

Figure S9: National Projections using Confirmed and Probable Cases from the daily case count database (by date of report) using Method B. The vertical dotted lines indicate the date up to which data were used for R estimation.

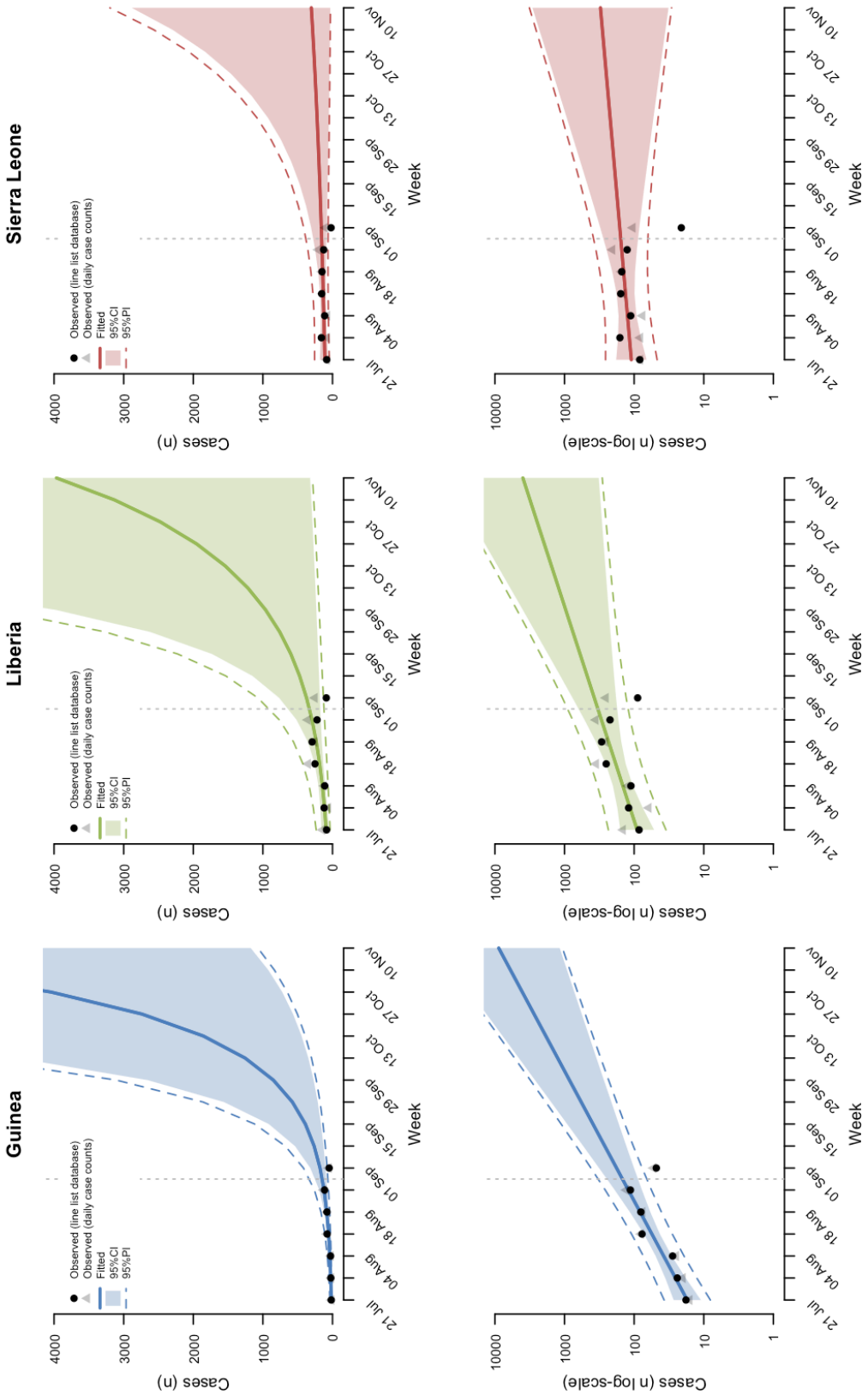

Figure S10: National Projections using Confirmed and Probable Cases from the line list database (by date of onset) using Method A. Weekly incidence of onset from the daily case count database is also presented (grey triangles) for comparison. The vertical dotted lines indicate the date up to which data were used for R estimation.

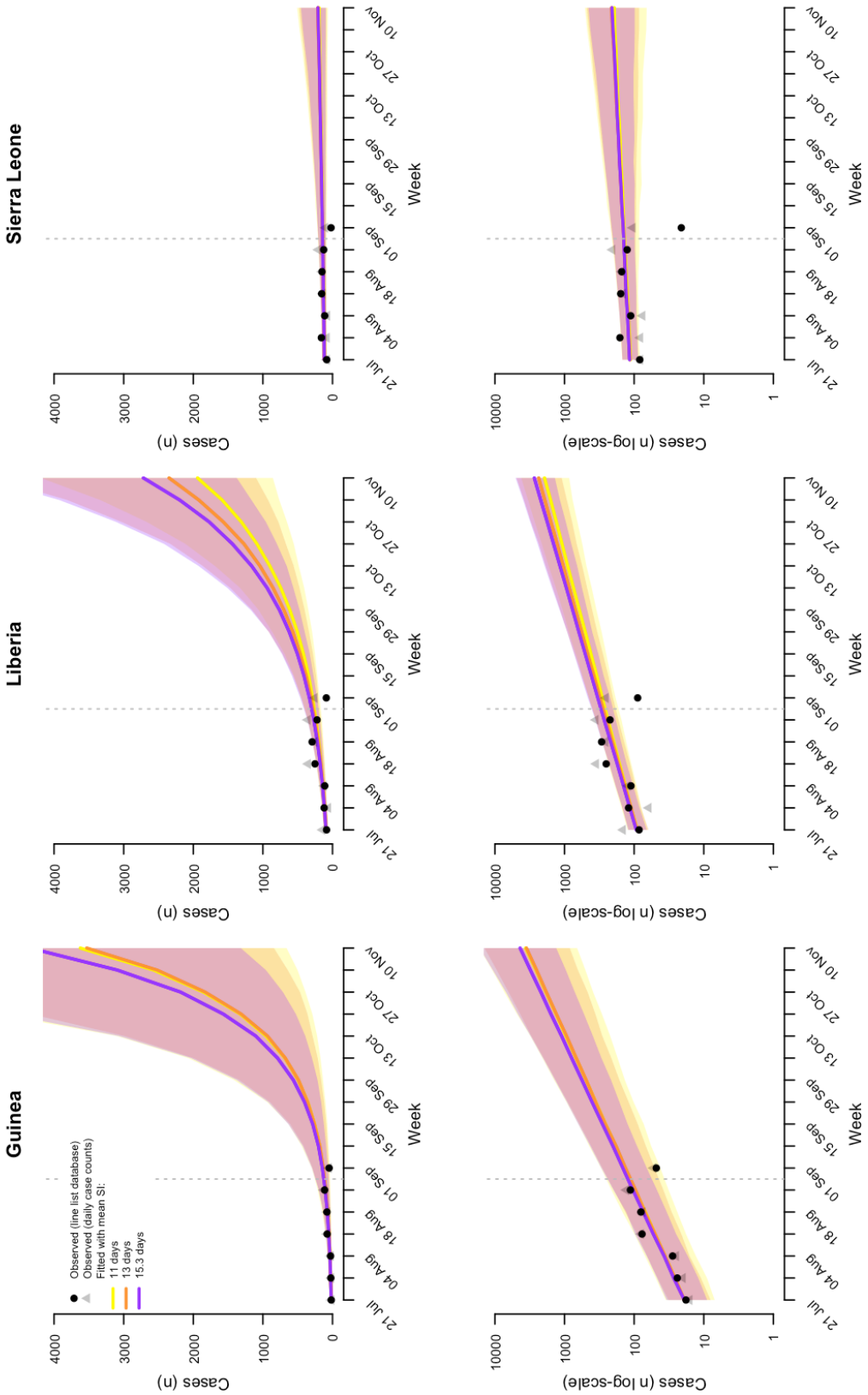

Figure S11. National Projections using Confirmed and Probable Cases from the line list database (by date of onset) using Method B. Weekly incidence of onset from the daily case count database is also presented (grey triangles) for comparison. The vertical dotted lines indicate the date up to which data were used for R estimation.

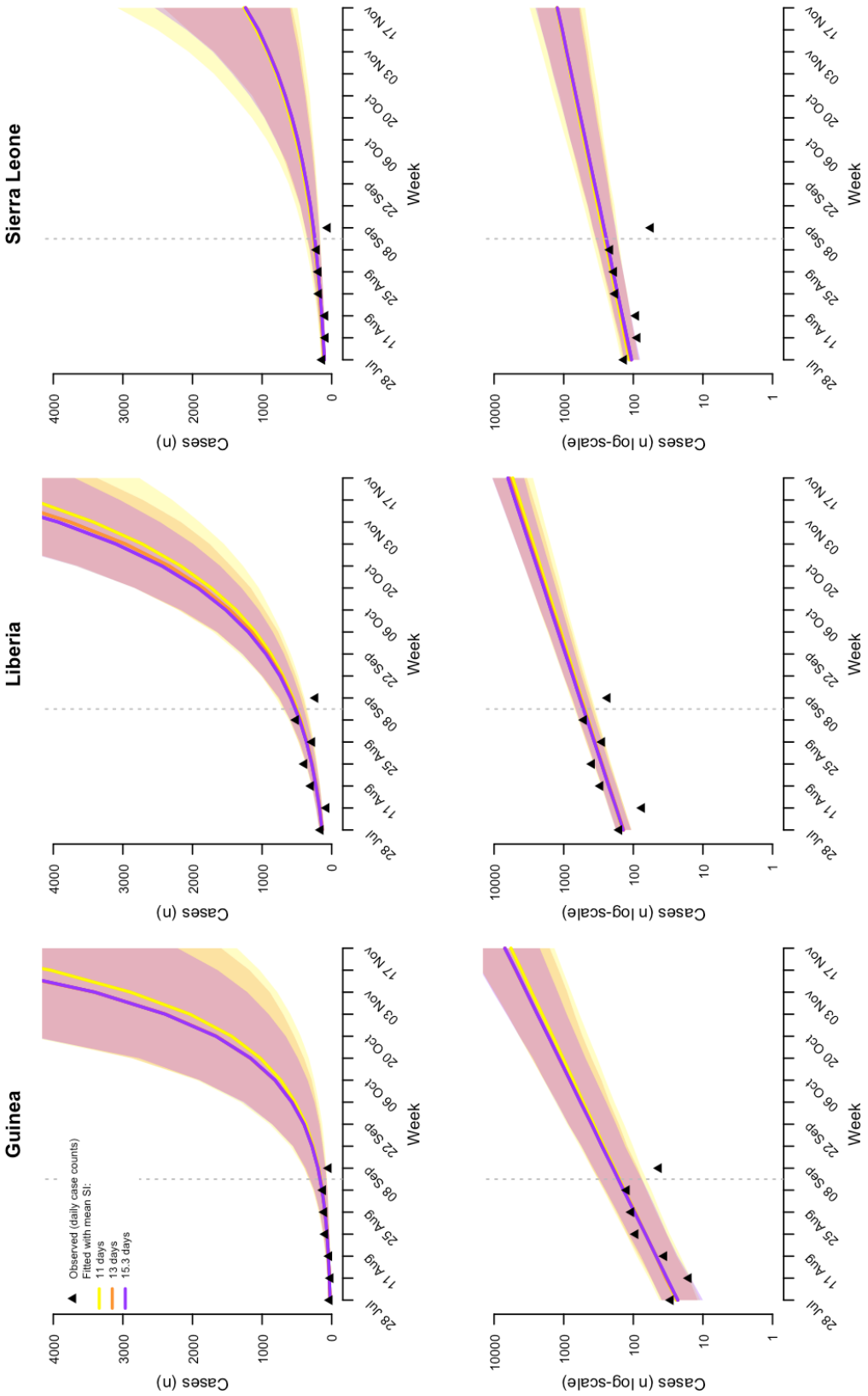

Figure S12. National Projections using Confirmed, Probable and Suspected Cases from the daily case count database (by date of report) using Method B. The vertical dotted lines indicate the date up to which data were used for R estimation.

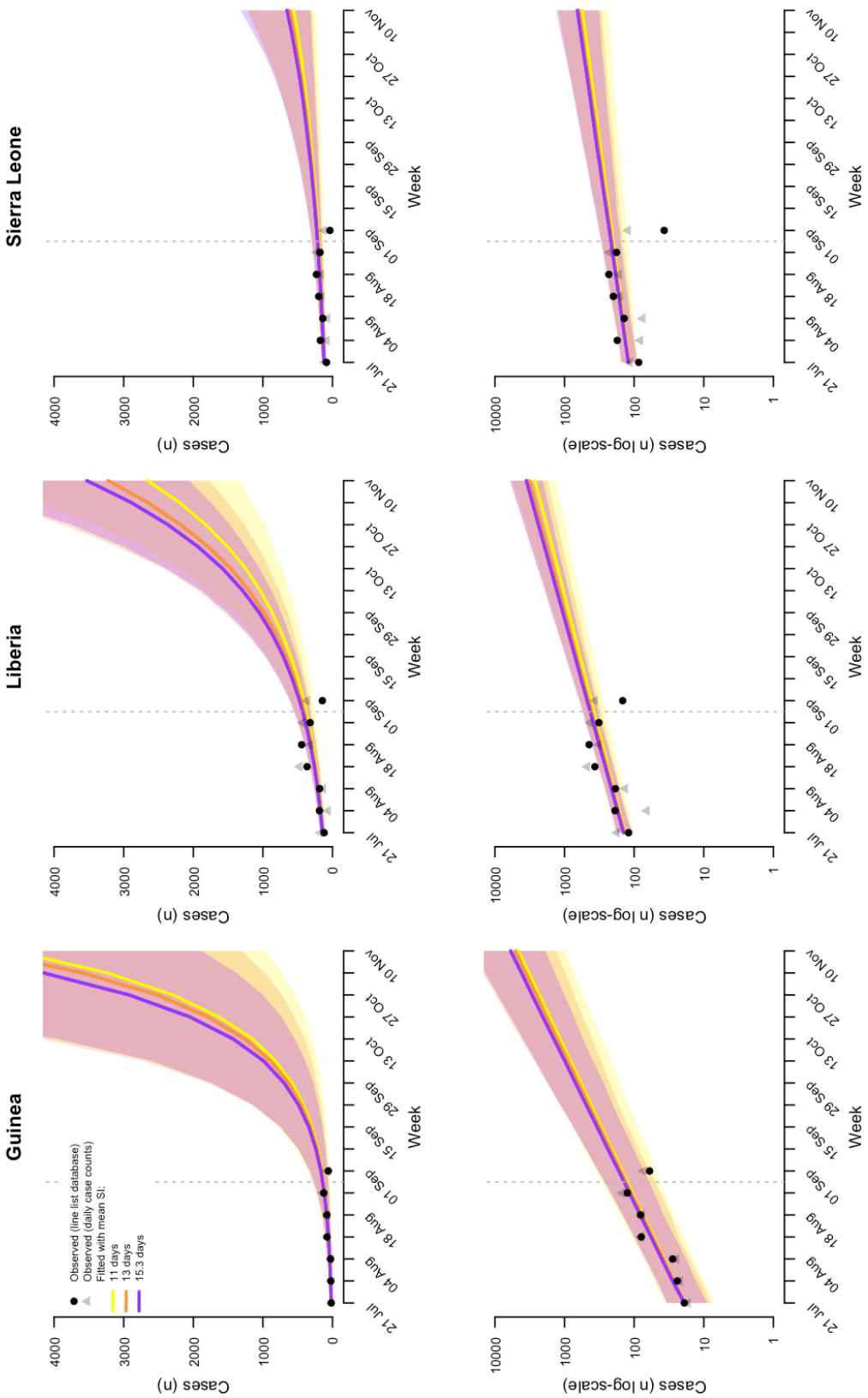

Figure S13. National Projections using Confirmed, Probable and Suspected Cases from the line list database (by date of onset) using Method B. Weekly incidence of onset from the daily case count database is also presented (grey triangles) for comparison. The vertical dotted lines indicate the date up to which data were used for R estimation.

References

1. MMWR. Ebola viral disease outbreak--West Africa, 2014. MMWR 2014;63:548–51.
2. Bjørnstad ON, R.A. I, Lambin X. Spatial population dynamics: analyzing patterns and processes of population synchrony. Trends Ecol Evol 1999;14:427-32.
3. Svensson A. A note on generation times in epidemic models. Mathematical Biosciences 2007;208:300–11.
4. Garske T, Legrand J, Donnelly CA, et al. Assessing the severity of the novel influenza A/H1N1 pandemic. BMJ 2009;339.
5. WHO. Ebola virus disease. Fact sheet N°103; Updated April 2014. Available at: http://www.who.int/mediacentre/factsheets/fs103/en/. 2014.
6. Ajelli M, Merler S. Transmission potential and design of adequate control measures for Marburg hemorrhagic fever. PloS one 2012;7:e50948.
7. Muyembe T, Kipasa M. Ebola haemorrhagic fever in Kikwit, Zaire. International Scientific and Technical Committee and WHO Collaborating Centre for Haemorrhagic Fevers. Lancet 1995;345:1448.
8. Wallinga J, Lipsitch M. How generation intervals shape the relationship between growth rates and reproductive numbers. Proc Biol Sci 2007;274:599-604.
9. Fraser C. Estimating Individual and Household Reproduction Numbers in an Emerging Epidemic. PLoS One 2007;2:e758.

VIRAL HEMORRHAGIC FEVER CASE INVESTIGATION FORM

Outbreak Case ID: _____

Health Facility Case ID: _____

Date of Case Report: ____/____/_____ (D, M, Yr)

Section 1. Patient Information

Patient's Surname: _____ Other Names:_____ Age: _____ ☐ Years ☐ Months

Gender: ☐ Male ☐ Female Phone Number of Patient/Family Member:_____ Owner of Phone: _____

Status of Patient at Time of This Case Report: ☐ Alive ☐ Dead *If dead,* Date of Death: ___/___/____ (D, M, Yr)

Permanent Residence:

Head of Household: _____ Village/Town: _____ Parish: _____

Country of Residence: _____ District: _____ Sub-County: _____

Occupation:

☐ Farmer ☐ Butcher ☐ Hunter/trader of game meat ☐ Miner ☐ Religious leader ☐ Housewife ☐ Pupil/student ☐ Child

☐ Businessman/woman; type of business: _____ ☐ Transporter; type of transport: _____

☐ Healthcare worker; position: _____ healthcare facility: _____ ☐ Traditional/spiritual healer

☐ Other; please specify occupation: _____

Location Where Patient Became Ill:

Village/Town: _____ District: _____ Sub-County: _____

GPS Coordinates at House: latitude: _____ longitude: _____

If different from permanent residence, Dates residing at this location: ___/___/____ - ___/___/____ (D, M, Yr)

Section 2. Clinical Signs and Symptoms

Date of Initial Symptom Onset: ____/____/_____ **(D, M, Yr)**

Please tick an answer for <u>ALL</u> symptoms indicating if they occurred during <u>this illness</u> between symptom onset and case detection:

Fever	☐ Yes ☐ No ☐ Unk
If yes, Temp: ____° C Source: ☐ Axillary ☐ Oral ☐ Rectal	
Vomiting/nausea	☐ Yes ☐ No ☐ Unk
Diarrhea	☐ Yes ☐ No ☐ Unk
Intense fatigue/general weakness	☐ Yes ☐ No ☐ Unk
Anorexia/loss of appetite	☐ Yes ☐ No ☐ Unk
Abdominal pain	☐ Yes ☐ No ☐ Unk
Chest pain	☐ Yes ☐ No ☐ Unk
Muscle pain	☐ Yes ☐ No ☐ Unk
Joint pain	☐ Yes ☐ No ☐ Unk
Headache	☐ Yes ☐ No ☐ Unk
Cough	☐ Yes ☐ No ☐ Unk
Difficulty breathing	☐ Yes ☐ No ☐ Unk
Difficulty swallowing	☐ Yes ☐ No ☐ Unk
Sore throat	☐ Yes ☐ No ☐ Unk
Jaundice (yellow eyes/gums/skin)	☐ Yes ☐ No ☐ Unk
Conjunctivitis (red eyes)	☐ Yes ☐ No ☐ Unk
Skin rash	☐ Yes ☐ No ☐ Unk
Hiccups	☐ Yes ☐ No ☐ Unk
Pain behind eyes/sensitive to light	☐ Yes ☐ No ☐ Unk
Coma/unconscious	☐ Yes ☐ No ☐ Unk
Confused or disoriented	☐ Yes ☐ No ☐ Unk

Unexplained bleeding from any site	☐ Yes ☐ No ☐ Unk
If Yes:	
Bleeding of the gums	☐ Yes ☐ No ☐ Unk
Bleeding from injection site	☐ Yes ☐ No ☐ Unk
Nose bleed (epistaxis)	☐ Yes ☐ No ☐ Unk
Bloody or black stools (melena)	☐ Yes ☐ No ☐ Unk
Fresh/red blood in vomit (hematemesis)	☐ Yes ☐ No ☐ Unk
Digested blood/"coffee grounds" in vomit	☐ Yes ☐ No ☐ Unk
Coughing up blood (hemoptysis)	☐ Yes ☐ No ☐ Unk
Bleeding from vagina, other than menstruation	☐ Yes ☐ No ☐ Unk
Bruising of the skin (petechiae/ecchymosis)	☐ Yes ☐ No ☐ Unk
Blood in urine (hematuria)	☐ Yes ☐ No ☐ Unk
Other hemorrhagic symptoms	☐ Yes ☐ No ☐ Unk
If yes, please specify: _____	

Other non-hemorrhagic clinical symptoms: ☐ Yes ☐ No ☐ Unk

If yes, please specifiy: _____

Section 3. Hospitalization Information

At the time of this case report, is the patient hospitalized or currently being admitted to the hospital? ☐ Yes ☐ No

If yes, Date of Hospital Admission: ____/____/_____ (D, M, Yr) Health Facility Name: _____

Village/Town: _____ District: _____ Sub-County: _____

Is the patient in isolation or currently being placed there? ☐ Yes ☐ No *If yes,* date of isolation: ____/____/_____ (D, M, Yr)

Was the patient hospitalized or did he/she visit a health clinic previously <u>for this illness</u>? ☐ Yes ☐ No ☐ Unk

If yes, please complete a line of information for each previous hospitalization:

Dates of Hospitalization	Health Facility Name	Village	District	Was the patient isolated?
___/___/____ - ___/___/____ (D, M, Yr)				☐ Yes ☐ No
___/___/____ - ___/___/____ (D, M, Yr)				☐ Yes ☐ No

Outbreak Case ID: _____

Section 4. Epidemiological Risk Factors and Exposures

IN THE PAST ONE(1) MONTH PRIOR TO SYMPTOM ONSET:

1. Did the patient have contact with a known or suspect case, or with any sick person before becoming ill? ☐ Yes ☐ No ☐ Unk

If yes, please complete one line of information for each sick source case:

Name of Source Case	Relation to Patient	Dates of Exposure (D, M, Yr)	Village	District	Was the person dead or alive ?	Contact Types**
		__/__/__ - __/__/__			☐ Alive ☐ Dead, date of death: __/__/____ (D, M, Y)	
		__/__/__ - __/__/__			☐ Alive ☐ Dead, date of death: __/__/____ (D, M, Y)	
		__/__/__ - __/__/__			☐ Alive ☐ Dead, date of death: __/__/____ (D, M, Y)	

****Contact Types: (list all that apply)**

1 – Touched the body fluids of the case (blood, vomit, saliva, urine, feces)
2 – Had direct physical contact with the body of the case (alive or dead)
3 – Touched or shared the linens, clothes, or dishes/eating utensils of the case
4 – Slept, ate, or spent time in the same household or room as the case

2. Did the patient attend a funeral before becoming ill? ☐ Yes ☐ No ☐ Unk

If yes, please complete one line of information for each funeral attended:

Name of Deceased Person	Relation to Patient	Dates of Funeral Attendance (D, M, Yr)	Village	District	Did the patient participate (carry or touch the body)?
		__/__/____ - __/__/____			☐ Yes ☐ No
		__/__/____ - __/__/____			☐ Yes ☐ No

3. Did the patient travel outside their home or village/town before becoming ill? ☐ Yes ☐ No ☐ Unk

If yes, Village: _____ District: _____ Date(s): __/__/____ - __/__/____ (D, M, Yr)

4. Was the patient hospitalized or did he/she go to a clinic or visit anyone in the hospital before this illness? ☐ Yes ☐ No ☐ Unk

If yes, Patient Visited: _____ Date(s): __/__/____ - __/__/____ (D, M, Yr)

Health Facility Name: _____ Village: _____ District: _____

5. Did the patient consult a traditional/spiritual healer before becoming ill? ☐ Yes ☐ No ☐ Unk

If yes, Name of Healer: _____Village: _____ District: _____ Date: __/__/____ (D, M, Yr)

6. Did the patient have direct contact (hunt, touch, eat) with animals or uncooked meat before becoming ill? ☐ Yes ☐ No ☐ Unk

If yes, please tick all that apply:

Animal:	Status (check one only):
☐ Bats or bat feces/urine	☐ Healthy ☐ Sick/Dead
☐ Primates (monkeys)	☐ Healthy ☐ Sick/Dead
☐ Rodents or rodent feces/urine	☐ Healthy ☐ Sick/Dead
☐ Pigs	☐ Healthy ☐ Sick/Dead
☐ Chickens or wild birds	☐ Healthy ☐ Sick/Dead
☐ Cows, goats, or sheep	☐ Healthy ☐ Sick/Dead
☐ Other; *specify*_____	☐ Healthy ☐ Sick/Dead

7. Did the patient get bitten by a tick in the past 2 weeks? ☐ Yes ☐ No ☐ Unk

Section 5. Clinical Specimens and Laboratory Testing

Specimen/shipping instructions:

- Label sample with **patient name, date of collection,** and **case ID**
- Send sample **cold** with a **cold/ice pack,** and **packaged appropriately**.
- Collect whole blood in a purple top (EDTA) tube – green or red top tubes acceptable if purple not available
- **Preferred sample volume = 4ml** (minimum sample volume = 2ml)

Has this patient had a sample submitted previously? ☐ Yes ☐ No

Sample 1: *Do not complete UVRI Only*

Sample Collection Date: ____/____/_____ (D, M, Yr)

Sample Type:

☐ Whole Blood
☐ Post-mortem heart blood
☐ Skin biopsy
☐ Other specimen type, specify: _____

Sample 2: *Do not complete UVRI Only*

Sample Collection Date: ____/____/_____ (D, M, Yr)

Sample Type:

☐ Whole Blood
☐ Post-mortem heart blood
☐ Skin biopsy
☐ Other specimen type, specify: _____

Section 6. Case Report Form Completed by:

Name: _____ Phone: _____ E-mail: _____

Position: _____ District: _____ Health Facility: _____

Information provided by: ☐ Patient ☐ Proxy; *If proxy*, Name:_____ Relation to Patient: _____

Case Name: _____ **Outbreak Case ID:** _____

If the patient is deceased or has already recovered from illness, please fill out the next section.
If the patient is currently admitted to the hospital, leave the next section blank (it will be completed upon discharge)

Section 7. Patient Outcome Information

Please fill out this section at the time of patient recovery and discharge from the hospital OR at the time of patient death.

Date Outcome Information Completed: ____/____/_____ (D, M, Yr)

Final Status of the Patient: ☐ Alive ☐ Dead

Did the patient have signs of unexplained bleeding at any time during their illness? ☐ Yes ☐ No ☐ Unk
If yes, please specify: _____

If the patient has recovered and been discharged from the hospital:

Name of hospital discharged from: _____ District: _____
If the patient was isolated, Date of discharge from the isolation ward: ____/____/_____ (D, M, Yr)
Date of discharge from the hospital: ____/____/_____ (D, M, Yr)

If the patient is dead:

Date of Death: ____/____/_____ (D, M, Yr)
Place of Death: ☐ Community ☐ Hospital: _____ ☐ Other: _____
Village: _____ District: _____ Sub-County: _____

Date of Funeral/Burial: ____/____/_____ (D, M, Yr) Funeral conducted by: ☐ Family/community ☐ Outbreak burial team
Place of Funeral/Burial:
Village: _____ District: _____ Sub-County: _____

Please tick an answer for ALL symptoms indicating if they occurred at any time during this illness including during hospitalization:

Fever	☐ Yes ☐ No ☐ Unk
If yes, Temp: ____° C Source: ☐ Axillary ☐ Oral ☐ Rectal	
Vomiting/nausea	☐ Yes ☐ No ☐ Unk
Diarrhea	☐ Yes ☐ No ☐ Unk
Intense fatigue/general weakness	☐ Yes ☐ No ☐ Unk
Anorexia/loss of appetite	☐ Yes ☐ No ☐ Unk
Abdominal pain	☐ Yes ☐ No ☐ Unk
Chest pain	☐ Yes ☐ No ☐ Unk
Muscle pain	☐ Yes ☐ No ☐ Unk
Joint pain	☐ Yes ☐ No ☐ Unk
Headache	☐ Yes ☐ No ☐ Unk
Cough	☐ Yes ☐ No ☐ Unk
Difficulty breathing	☐ Yes ☐ No ☐ Unk
Difficulty swallowing	☐ Yes ☐ No ☐ Unk
Sore throat	☐ Yes ☐ No ☐ Unk
Jaundice (yellow eyes/gums/skin)	☐ Yes ☐ No ☐ Unk
Conjunctivitis (red eyes)	☐ Yes ☐ No ☐ Unk
Skin rash	☐ Yes ☐ No ☐ Unk
Hiccups	☐ Yes ☐ No ☐ Unk
Pain behind eyes/sensitive to light	☐ Yes ☐ No ☐ Unk
Coma/unconscious	☐ Yes ☐ No ☐ Unk
Confused or disoriented	☐ Yes ☐ No ☐ Unk

Other non-hemorrhagic clinical symptoms: ☐ Yes ☐ No ☐ Unk
If yes, please specifiy: _____

Case Name: _____ MoH/UVRI Case ID: _____

If the patient is deceased or has already recovered from illness, please fill out the next section.
If the patient is currently admitted to the hospital, leave the next section blank (it will be completed upon discharge)

Section 7. Patient Outcome Information

Please fill out this section at the time of patient recovery and discharge from the hospital OR at the time of patient death.

Date Outcome Information Completed: ____/____/_____ (D, M, Yr)

Final Status of the Patient: ☐ Alive ☐ Dead

Did the patient have signs of unexplained bleeding at any time during their illness? ☐ Yes ☐ No ☐ Unk
If yes, please specify: _____

If the patient has recovered and been discharged from the hospital:

Name of hospital discharged from: _____ District: _____
If the patient was isolated, Date of discharge from the isolation ward: ____/____/_____ (D, M, Yr)
Date of discharge from the hospital: ____/____/_____ (D, M, Yr)

If the patient is dead:

Date of Death: ____/____/_____ (D, M, Yr)
Place of Death: ☐ Community ☐ Hospital: _____ ☐ Other: _____
Village: _____ District: _____ Sub-County: _____

Date of Funeral/Burial: ____/____/_____ (D, M, Yr) Funeral conducted by: ☐ Family/community ☐ Outbreak burial team
Place of Funeral/Burial:
Village: _____ District: _____ Sub-County: _____

Please tick an answer for ALL symptoms indicating if they occurred at any time during this illness including during hospitalization:

Fever	☐ Yes ☐ No ☐ Unk
If yes, Temp: ____° C Source: ☐ Axillary ☐ Oral ☐ Rectal	
Vomiting/nausea	☐ Yes ☐ No ☐ Unk
Diarrhea	☐ Yes ☐ No ☐ Unk
Intense fatigue/general weakness	☐ Yes ☐ No ☐ Unk
Anorexia/loss of appetite	☐ Yes ☐ No ☐ Unk
Abdominal pain	☐ Yes ☐ No ☐ Unk
Chest pain	☐ Yes ☐ No ☐ Unk
Muscle pain	☐ Yes ☐ No ☐ Unk
Joint pain	☐ Yes ☐ No ☐ Unk
Headache	☐ Yes ☐ No ☐ Unk
Cough	☐ Yes ☐ No ☐ Unk
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Hiccups	☐ Yes ☐ No ☐ Unk
Pain behind eyes/sensitive to light	☐ Yes ☐ No ☐ Unk
Coma/unconscious	☐ Yes ☐ No ☐ Unk
Confused or disoriented	☐ Yes ☐ No ☐ Unk

Other non-hemorrhagic clinical symptoms: ☐ Yes ☐ No ☐ Unk
If yes, please specifiy: _____