

## Assessment of the severity of Ebola virus disease in Sierra Leone in 2014–2015

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### SUMMARY

The current Ebola virus disease (EVD) epidemic in West Africa is unprecedented in scale, and Sierra Leone is the most severely affected country. The case fatality risk (CFR) and hospitalization fatality risk (HFR) were used to characterize the severity of infections in confirmed and probable EVD cases in Sierra Leone. Proportional hazards regression models were used to investigate factors associated with the risk of death in EVD cases. In total, there were 17 318 EVD cases reported in Sierra Leone from 23 May 2014 to 31 January 2015. Of the probable and confirmed EVD cases with a reported final outcome, a total of 2536 deaths and 886 recoveries were reported. CFR and HFR estimates were 74·2% [95% credibility interval (CrI) 72·6–75·5] and 68·9% (95% CrI 66·2–71·6), respectively. Risks of death were higher in the youngest (0–4 years) and oldest ( $\geq 60$  years) age groups, and in the calendar month of October 2014. Sex and occupational status did not significantly affect the mortality of EVD. The CFR and HFR estimates of EVD were very high in Sierra Leone.

**Key words:** Death, Ebola virus, severity.

### INTRODUCTION

In August 2014, the World Health Organization (WHO) declared a ‘public health emergency of

international concern’, marking the start of the public health response to the current unprecedented Ebola virus disease (EVD) epidemic in West Africa [1, 2]. The epidemic started in Guinea in December 2013 [3, 4]. In Sierra Leone, the first outbreak was reported in Kailahun district on 23 May 2014 [5, 6]. By 5 April 2015, more than 25 500 confirmed, probable and suspected cases of EVD, as well as an estimated 10 572 deaths from Ebola virus (EBOV, Zaire species) disease cases [7, 8] with definitive final outcome, have been reported from six countries in West Africa – Guinea,

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Liberia, Mali, Nigeria, Senegal, and Sierra Leone [9]. To control the epidemic, different interventions, including early case identification, case isolation and treatment, contact tracing, quarantine, social mobilization, cross-border surveillance, exit screening at the airport, and safe burial, were implemented to minimize transmission and to provide clinical and psychosocial care for all individuals with EVD [10–14]. By the end of January 2015, more than 1 year after the first known case in Guinea, the numbers of reported cases and deaths were in decline.

Here, we provide a basis to characterize the severity profile of EVD, as well as to evaluate the effects of control intervention strategies. First, we assess the severity of infections during the epidemic in Sierra Leone from 23 May 2014 to 31 January 2015, and then investigate potential factors which may have affected severity. Finally, we examine the changes in time-delay distributions over time.

## METHODS

### Data sources

Daily data on individual confirmed, probable and suspected cases with EVD in Sierra Leone from 23 May 2014 to 31 January 2015 were obtained from the Ministry of Health and Sanitation of Sierra Leone (the viral haemorrhagic fever patient database designed by the U.S. CDC [15]). Cases were classified according to the EVD case definition of the World Health Organization (WHO) [9] and epidemiological information was collected using a standardized EBOV disease case investigation form (CIF), including age, sex, residence, occupation [e.g. farmer, religious leader, traditional/spiritual healer or healthcare worker (HCW) including but not limited to physicians, nurses, nursing assistants, laboratory technicians, cleaners and laundry staff, decontaminators, vaccinators and security], date of onset, hospital admission, case report, sample collected, sample tested, death or hospital discharge.

### Statistical analysis

#### *Case fatality risk (CFR) and hospitalization fatality risk (HFR)*

We characterized the severity of infections in confirmed and probable EVD cases in terms of the CFR and HFR, which were defined as the risk of death in all laboratory-confirmed/probable cases or

‘hospitalized only’ patients at Ebola treatment centres, holding centres, and community care centers (CCCs), respectively [16, 17]. Because of similar basic demographic characteristics between patients with missing and non-missing data on important variables (Supplementary Tables S1 and S2), we first estimated missing data based on existing data in a Bayesian framework to retain uncertainty. We fitted Weibull and lognormal distributions to the onset-to-reporting interval (Supplementary Fig. S1), and found that the mean onset-to-reporting interval was  $\sim 4$  days [3·91 days, 95% credibility interval (CrI) 3·84–3·98 and 4·20 days (95% CrI 4·09–4·31) for the Weibull and lognormal distributions, respectively]. Then we estimated the HFR and CFR using information available at different time points. We estimated the CFR in real-time based on available data on confirmed and probable cases during the epidemic. We divided the number of reported deaths that had occurred from 23 May 2014 to 31 January 2015 by day  $t$  by the number of cases that had been reported as having either died or recovered from 23 May 2014 to 31 January 2015 by day  $t$ . The estimators were obtained as follows:

$$\text{CFR}(t) = \frac{D(t)}{D(t) + R(t)},$$

where  $\text{CFR}(t)$  is the case fatality risk on day  $t$ ;  $D(t)$  is the cumulative number of deaths in cases with symptom onset on day  $t$ ;  $R(t)$  is the cumulative number of recoveries in cases with symptom onset on day  $t$ .

We estimated the HFR using the same approaches, limited to hospitalized cases.

#### *Time-delay distributions*

We examined the changes in three types of time-delay distributions over the course of the epidemic, including (1) the interval from symptom onset to case report, (2) the interval from symptom onset to sample tested, and (3) the interval from sample collected to sample tested. The onset-to-reporting interval was calculated by subtracting the date of case report from the date of initial symptom onset for each case. The onset-to-sample tested interval and the sample collected-to-sample tested interval were calculated similarly.

#### *Factors affecting CFR*

We investigated variables that might impact the risk of death in EVD cases: age group (0–4, 5–14, 15–44, 45–59,  $\geq 60$  years), sex, month of initial symptom onset, and HCW status. We performed the analysis using

Table 1. Characteristics of 17 318 Ebola virus disease cases in Sierra Leone by outcome and case definition, between 23 May 2014 and 31 January 2015

	Death			Recovery			Unknown outcome			P value*
	Confirmed	Probable	Suspected	Confirmed	Probable	Suspected	Confirmed	Probable	Suspected	
	(n = 2054)	(n = 482)	(n = 2256)	(n = 702)	(n = 184)	(n = 173)	(n = 5534)	(n = 1809)	(n = 4124)	
Age (years)										
0–4	150 (7)	66 (14)	426 (19)	35 (5)	9 (5)	9 (5)	331 (6)	265 (15)	422 (10)	<0.001
5–14	262 (13)	61 (13)	213 (9)	121 (17)	35 (19)	15 (9)	757 (14)	226 (12)	416 (10)	<0.001
15–44	1097 (53)	220 (46)	773 (34)	402 (57)	98 (53)	104 (60)	3160 (57)	768 (42)	2051 (50)	<0.001
45–59	282 (14)	56 (12)	246 (11)	88 (13)	20 (11)	23 (13)	736 (13)	206 (11)	579 (14)	0.02
≥ 60	205 (10)	69 (14)	510 (23)	52 (7)	20 (11)	15 (9)	398 (7)	269 (15)	531 (13)	<0.001
Unknown	58 (3)	10 (2)	88 (4)	4 (1)	2 (1)	7 (4)	152 (3)	75 (4)	125 (3)	0.01
Sex										
Men	1016 (49)	224 (46)	1136 (50)	343 (49)	90 (49)	95 (55)	2587 (47)	867 (48)	2124 (52)	<0.001
Unknown	30 (1)	12 (2)	52 (2)	11 (2)	3 (2)	3 (2)	134 (2)	87 (5)	121 (3)	<0.001

Values in parentheses are percentages.

\* The  $\chi^2$  or Fisher's exact test was used to compare between groups, as appropriate.

proportional hazards regression models, based on only EVD cases with a known final outcome.

#### Prevalence of hospitalized cases

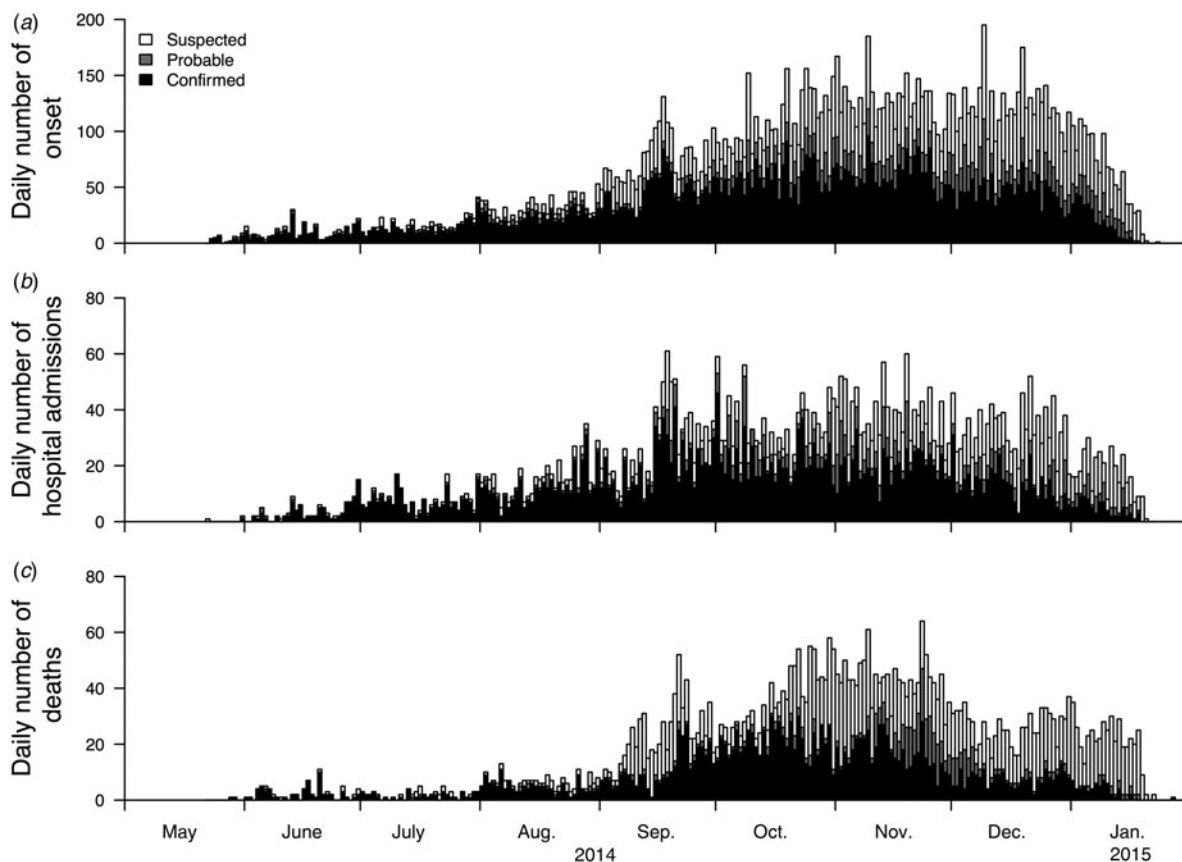
We evaluated access to hospital beds based on all cases [confirmed, probable, suspected EVD cases, and the excluded cases that were classified as non-EVD cases based on negative polymerase chain reaction (PCR) results, lacked a sample, or did not meet the case definition] in the database over the course of the epidemic. We also examined the prevalence of hospitalized cases over time. For cases with known final outcome status, the daily prevalence of hospitalized cases was calculated based on the reported time period to discharge or death since the date of hospital admission; whereas we assumed a 5-day hospital stay for cases with unknown final outcome. The CFRs, HFRs, time-delay distributions and proportional hazards regression models were estimated using Bayesian inference in order to account for their associated uncertainty and missing data [18]. We used uniform priors over the entire range of possible values for all parameter estimates. Convergence of Markov Chain Monte Carlo algorithms was judged using the R-hat criteria [19]. Posterior means and 95% credibility intervals were reported. All analyses were conducted with R v. 3.0.2 (R Foundation for Statistical Computing, Austria).

## RESULTS

In total, there were 17 318 EVD cases reported in Sierra Leone between 23 May 2014 and 31 January 2015, of whom 8290 and 2475 were confirmed and probable cases, respectively (Table 1). The daily numbers of confirmed, probable, and suspected EVD cases over time are shown in Figure 1. There were increased daily numbers of hospitalizations and deaths for EVD cases since September 2014. Of the probable and confirmed EVD cases only 32% (3422/10 765) had a reported final outcome (Table 1). A total of 2536 deaths and 886 recoveries were reported. The majority of the EVD cases occurred in people aged 15–44 years. There was no significant difference between the proportion of male and female cases (Table 1).

#### CFR and HFR

We found that the estimates of CFR and HFR, after an initial decline in July–August 2014, increased and



**Fig. 1.** Daily incidence of cases of Ebola onset, hospitalization and deaths for all ages in Sierra Leone, between 23 May 2014 and 31 January 2015. (a) Daily numbers of onset. (b) Daily numbers of hospital admissions. (c) Daily numbers of deaths.

stabilized at somewhat higher levels through the remaining period (Fig. 2). The CFR estimate at the end of January 2015 was 74.2% (95% CrI 72.6–75.5). Similarly, the HFR estimate was 68.9% (95% CrI 66.2–71.6).

#### Factors affecting CFR

Proportional hazards regression models indicated that the youngest (0–4 years) and oldest ( $\geq 60$  years) age groups and October (and marginally November) 2014 had increased hazard rates (Table 2). We did not find evidence of differences in risk of mortality by sex or occupation (including HCW) status.

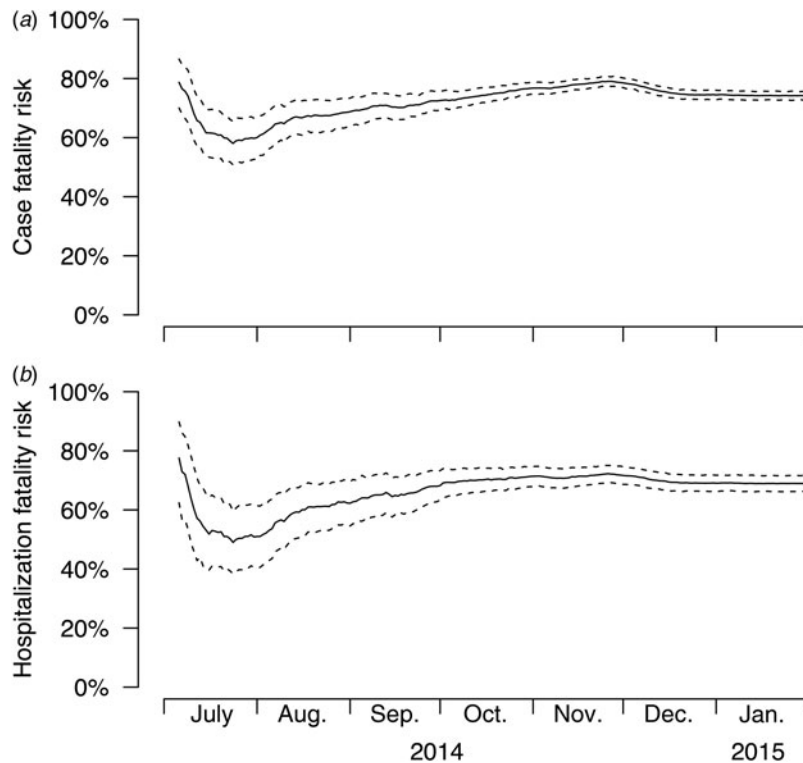
#### Time delay distributions

The timing of key events for patient identification and treatment evolved during the epidemic, i.e. symptom onset to reporting, symptom onset to sample testing, and sample collection to testing (Fig. 3*a–c*,

respectively). The onset-to-reporting and sample collection-to-testing intervals tended to be quite rapid early in the epidemic (May–August 2014) when relatively few cases were identified but as the epidemic grew lags became longer and more evident. These delays began to be resolved after November 2014 (Fig. 3*a*, Supplementary Table S3). There was a relatively large proportion of cases (e.g. 45% in July and October 2014) with  $>8$  days delay from onset to sample testing.

#### Prevalence of hospitalized cases

A consequence of the delayed test results was a substantial proportion of hospital resources were dedicated to treat potential cases for whom confirmation or even probable infection was not established (Fig. 4). The number of hospitalized cases began to increase in June 2014 and peaked in September 2014 at 462 inpatients and most of these were confirmed or probable cases (Fig. 4). After this time most of these



**Fig. 2.** Real-time estimates of (a) the case fatality risk and (b) the hospitalization fatality risk in all probable and confirmed cases in Sierra Leone, between 23 May 2014 and 31 January 2015. Solid lines represent the posterior mean, dotted line show 95% credibility intervals.

patients were either suspected or considered non-cases.

## DISCUSSION

By 31 January 2015, a total of 8290 confirmed cases and 2475 probable cases had been reported in Sierra Leone, with almost 2600 deaths in confirmed and probable cases with definitive final outcome. Case incidence has declined since the end of December 2014, although reporting delays may be partly responsible (Figs 1, 3, 4). The severity of infections, as measured by the CFR, was high (74.2%) and generally stable during the current epidemic (Fig. 2), despite improvements in clinical management protocols. A similar pattern was observed in HFR. Fatality risks were somewhat lower for HFR (68.9%) than CFR, which were similar to those in the previous EVD outbreaks [3, 5, 20]. The lower risk of death observed in hospitalized cases than in all cases with EVD may reflect improved survival associated with hospitalization but also might reflect a bias from very severe cases dying before admission to the hospitals [5].

We evaluated a number of demographic factors potentially affecting the risk of death (Table 2). Unlike some previous studies, fatality risks were similar between males and females [hazard rate (HR) 0.99, 95% CrI 0.90–1.09], and between HCWs and non-HCWs (HR 0.99, 95% CrI 0.75–1.26), which indicated that sex and occupation had no substantial effect on severity. This might suggest that although HCWs had better training and personal protective equipment, which could reduce the risk of infection, and possibly had good access to care compared to non-HCWs, the risk of death was similar between HCWs and non-HCWs.

The youngest and oldest age groups were associated with statistically significant greater risks of mortality (0–4 years: HR 1.57, 95% CrI 1.34–1.84) and ( $\geq 60$  years: HR 1.21, 95% CrI 1.05–1.39) compared to middle-aged groups, a finding that is similar to the previous outbreaks and the current epidemic [5, 21–25]. Cases with initial symptom onset as the epidemic expanded (October–November 2014) had a significantly higher risk of death (HR 1.26, 95% CrI 1.08–1.54 in October 2014; HR 1.15, 95% CrI 0.99–

Table 2. Factors affecting risk of deaths in confirmed and probable cases with definitive final outcome, between 23 May 2014 and 31 January 2015 ( $n = 2936$ )

Factor	$n^*$	HR	(95% CrI)
Age (years)			
0–4	226	1.57	(1.34–1.84)
5–14	423	0.89	(0.77–1.01)
15–44	1572	Ref.	
45–59	401	1.06	(0.92–1.20)
≥60	314	1.21	(1.05–1.39)
Sex			
Female	1512	Ref.	
Male	1424	0.99	(0.90–1.09)
Onset month in 2014			
May–July	211	Ref.	
August	187	1.08	(0.86–1.37)
September	529	1.11	(0.95–1.34)
October	690	1.26	(1.08–1.54)
November	751	1.15	(0.99–1.36)
December	408	0.89	(0.74–1.10)
HCW† status			
Non-HCW	2835	Ref.	
HCW	101	0.99	(0.75–1.26)

HR, Hazard rate; CrI, credibility interval; HCW, healthcare worker.

\* Sample size ( $n$ ) for onset month did not add up to the total sample size because of missing dates of symptom onset and of the exclusion of onset month in January 2015 (reporting delay). We estimated the missing dates when estimating the parameters of the proportional hazard regression model.

† Staff working in a healthcare setting (including healthcare providers, cleaners, decontaminators, vaccinators, etc.).

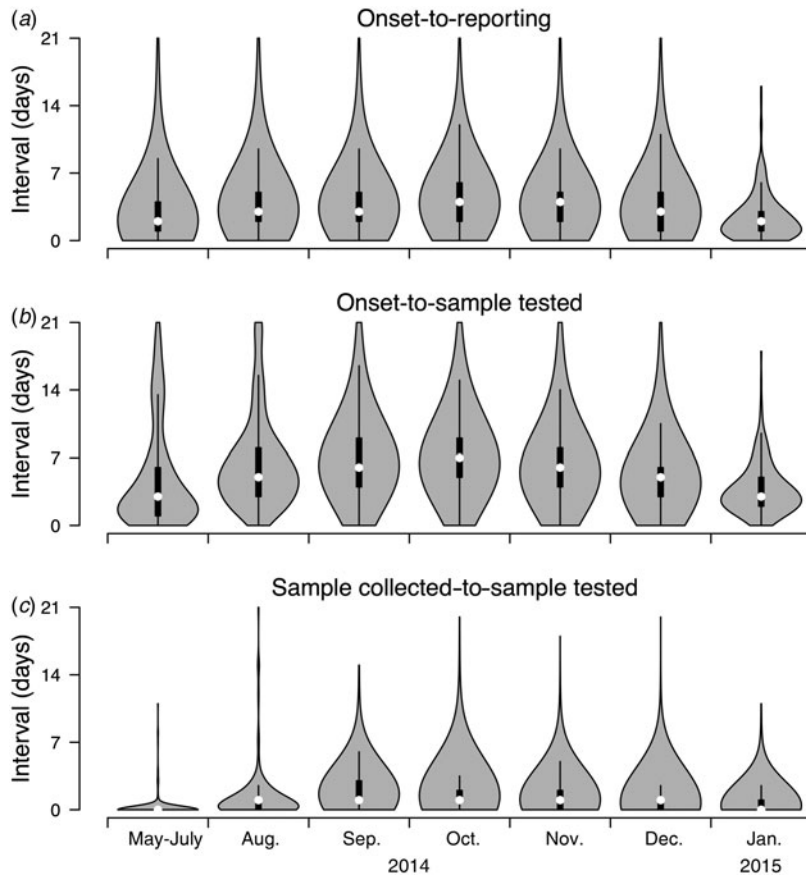
1.36 in November 2014), compared to cases earlier in the epidemic (symptom onset in May–July 2014 and other months). Possible reasons include hospitals (Ebola treatment centres, holding centres, CCCs) had reached their full capacity, resulting in a surge of suspected and probable patients staying home while they waited to be transported and admitted for triage or for supportive care.

There are different levels of Ebola healthcare facilities in Sierra Leone which provide beds to cases in need of care, including Ebola treatment centres, holding centres, and CCCs. Cases admitted to any of these facilities were classified as being ‘hospital admitted’, so our estimate of HFR was an average of HFR from different facilities given that patient care was likely to be different in these facilities. The prevalence of hospitalized cases started to rise from June 2014. In late September 2014, about 400 cases were

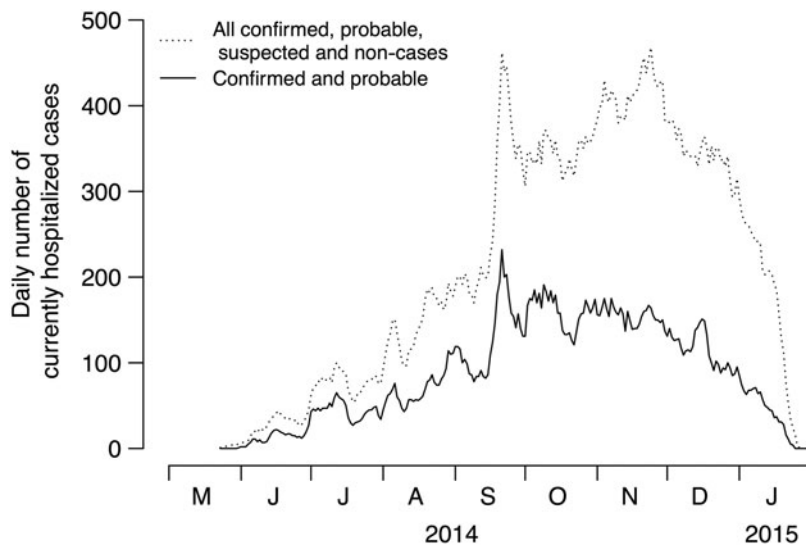
hospitalized (Fig. 4), which was the bed capacity in Sierra Leone at that time [26]. The implication is that many cases with EVD in some areas in Sierra Leone may not have received medical care because hospitals were full.

Our results show that onset-to-reporting, onset-to-sample testing and sample collecting-to-sample testing intervals shortened after the September–October 2014 peak (Fig. 3) as the capacity for case management increased, community engagement improved, there was improvement in sample collection, and improvement in laboratory testing, as well as better transportations of patients to the Ebola treatment centres [9, 27]. However, delays in testing samples remained challenging with a high proportion of cases having delays of ≥8 days before receiving laboratory testing results [28]. Earlier case identification, isolation, and supportive care and treatment in healthcare facilities remain important tasks to control the epidemic more effectively [28, 29].

There are some limitations in this study. The greatest limitation of our analysis was the issue of data quality in the viral haemorrhagic fever database [15], where some important variables were missing or infrequently updated. These data quality issues may limit accurate interpretation of the data. Incomplete information on final outcomes because of under-detection and underreporting has been discussed before [5, 22, 30–32]. We relied on information such as dates of recovery inferred from the best available data, and dates of hospital discharge or death, for our analyses. Before applying the Bayesian approach, we compared sex and age distributions between cases with missing and non-missing dates of discharge and dates of death. We did not identify substantial differences in the two distributions (Supplementary Tables S1 and S2). The HFR and CFR estimates were derived based on only cases with reported final outcome (3422 cases and 1156 hospitalized cases either recovered/died). We only considered variables including age, sex, occupation and onset month in the proportional hazards model to minimize the extent of missing information. However, other factors such as past travel experience, funeral attendance, or isolation ward admission and treatment received during hospitalization, could affect the risk of death. Nevertheless, our study provides an initial framework for retrospective assessment of severity of EBOV infections in Sierra Leone, and further work could examine the application of this approach to the analysis of severity by district.



**Fig. 3.** Distribution of (a) the interval from symptom onset to reporting, (b) the interval from symptom onset to sample testing, and (c) the interval from sample collected to sample testing, in confirmed and probable Ebola virus disease cases in Sierra Leone, between 23 May 2014 and 31 January 2015.



**Fig. 4.** Prevalence of Ebola hospitalized cases in Sierra Leone, between 23 May 2014 and 31 January 2015.

## SUPPLEMENTARY MATERIAL

For supplementary material accompanying this paper visit <http://dx.doi.org/10.1017/S0950268815003003>

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## DECLARATION OF INTEREST

B.J.C. has received research funding from MedImmune Inc. and Sanofi Pasteur for studies of influenza vaccine effectiveness, and consults for Crucell NV.

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