

ORIGINAL MANUSCRIPT

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

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Word count (abstract): 177

Word count (main text): 2,278

Running head: Ebola in Sierra Leone

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 among EVD cases. In total, there were 17,318 EVD cases reported in Sierra Leone from 23rd May 2014 through 31st January 2015. Among the probable and confirmed EVD cases with a reported final outcome, a total of 2,536 deaths and 886 recoveries were reported. The estimates of CFR and HFR were 74.2% (95% credibility interval, CI: 72.6%-75.5%) and 68.9% (95% CI: 66.2%-71.6%) respectively. Risks of death were higher among youngest (0-4 y) and oldest (≥ 60 y) age groups, and in the calendar months of October 2014. Sex and occupation status did not significantly affect the mortality of EVD. The estimates of CFR and HFR of EVD were very high in Sierra Leone.

Key words: Ebola virus; death; 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 the 23rd May 2014 [5, 6]. By 5th 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, 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 one 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 23rd May 2014 through 31st January 2015, and then investigate potential factors which may have affected severity. Finally, we examine the changes in time delay distributions over time.

METHODS

Sources of data

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

Statistical analysis

The case fatality risk and hospitalization fatality risk

We characterized the severity of infections in confirmed and probable EVD cases in terms of the case fatality risk (CFR) and hospitalization fatality risk (HFR), which were defined as the risk of death among all laboratory confirmed/probable cases or 'hospitalized only' patients at Ebola treatment centers, holding centers, 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 (Tables S1-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 (Figure S1), and found that the mean onset-to-reporting interval was approximately four days (3.91 days (95% CI: 3.84-3.98) and 4.20 days (95% CI: 4.09-4.31) for the Weibull and lognormal distributions, respectively). Then we estimated the HFR and CFR using information available on 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 23rd May 2014 to 31st January 2015 by day t by the number of cases that had been reported as having either died or recovered from 23rd May 2014 through 31st January 2015 by day t. The estimators were obtained as follows:

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

where

CFR(t) is the case fatality risk on day t

D(t) is the cumulative number of deaths among cases with symptom onset on day t

R(t) is the cumulative number of recoveries among cases with symptom onset on day t

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

The 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.

The factors affecting CFR

We investigated variables that might impact the risk of death among EVD cases: age group (0-4 years, 5-14y, 15-44y, 45-59y and $\geq 60y$), sex, month of initial symptom onset, and HCW status. We performed the analysis using proportional hazards regression models, based on only EVD cases with a known final outcome.

The prevalence of hospitalized cases

We evaluated the access to hospital beds based on all cases (confirmed, probable and 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 days hospital stay when 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 version 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

In total, there were 17,318 EVD cases reported in Sierra Leone between 23rd May 2014 and 31st January 2015, of whom 8,290 and 2,475 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. Among the probable and confirmed EVD cases only 32% (3,422/10,765) had a reported final outcome (Table 1). A total of 2,536 deaths and 886 recoveries were reported. The majority of the EVD cases occurred among people 15-44 years of age. There was no significant difference between the proportion of male and female cases (Table 1).

The CFR and HFR

We found that the estimates of CFR and HFR, after an initial decline in July-August 2014, increased and stabilized at somewhat higher levels through the remaining period (Figure 2). The estimate of CFR at the end of January 2015 was 74.2% (95% credibility interval, CI: 72.6%-75.5%). Similarly, the estimate of HFR was 68.9% (95% CI: 66.2%-71.6%).

The factors affecting CFR

Proportional hazards regression models indicated that the youngest (0-4 y) and oldest (≥ 60 y) age classes 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 health care workers) status.

The time delay distributions

The timing of key events for patient identification and treatment evolved during the epidemic (Figures 3A symptoms onset to reporting; 3B symptom onset to sample testing and 3C sample collection to testing). 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 (Figure 3A, Table S3). There was a relatively large proportion of the cases (for example, 45% in July and October 2014) with more than 8 days of delay from onset to sample testing.

The prevalence of hospitalized cases

A consequence of the delayed test results was a substantial proportion of hospital resources dedicated to treat potential cases for whom confirmation or even probable infection was not established (Figure 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 (Figure 4). After this time the vast majority of these patients were either suspected or considered non-cases.

DISCUSSION

By 31st January 2015, a total of 8,290 confirmed cases and 2,475 probable cases have been reported in Sierra Leone, with almost 2,600 deaths among 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 (Figures 1, 3 and 4). The severity of infections, as measured by the CFR, was high (74.2%) and generally stable during the current epidemic (Figure 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 among hospitalized cases than among 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 (HR=0.99 (95% CI: 0.90, 1.09)), and between HCWs and non-HCWs (HR=0.99 (95% CI: 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 (HR=1.57 (95% CI: 1.34, 1.84) in 0-4y and HR=1.21 (95% CI: 1.05, 1.39) in ≥60y) compared to middle age groups, a finding that is similar to the previous outbreaks and current epidemic [5, 21-25]. Cases with initial symptom onset as the epidemic expanded (in October-November 2014) had a significantly higher risk of death (HR=1.26 (95% CI: 1.08, 1.54) in October 2014 and HR=1.15 (95% CI: 0.99, 1.36) in November 2014), as compared to cases earlier in the epidemic (symptom onset in May-July 2014 and other months). Possible reasons include hospitals (Ebola treatment centers, holding centers and 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 health care facilities in Sierra Leone which provide beds to cases in need of care, including Ebola treatment centers, holding centers, and community care centers. 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 differed among these facilities. The prevalence of hospitalized cases started to rise since June 2014. In late September 2014, approximately 400 cases were hospitalized (Figure 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 (Figure 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 centers [9, 27]. However, delays in testing samples remained challenging with a high proportion of cases having delays of 8 days or more before receiving laboratory testing results [28]. Earlier case identification, isolation, and supportive care and treatment in health care 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 Hemorrhagic 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, such as 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 (Tables S1-S2). The HFR and CFR estimates were derived based on only cases with reported final outcome (3,422 cases and 1,156 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 treatments received during hospitalization, could affect the risk of death. Nevertheless, our study provides an initial framework for retrospective assessment of severity of Ebola virus infections in Sierra Leone, and further work could examine the application of this approach to the analysis of severity by districts.

FINANCIAL SUPPORT

JYW, PW and BJC were supported by the Harvard Center for Communicable Disease Dynamics from the National Institute of General Medical Sciences (grant no. U54 GM088558), the Health and Medical Research Fund, Food and Health Bureau, Government of the Hong Kong Special Administrative Region (grant no. 14131432), and a commissioned grant from the Health and Medical Research Fund from the Government of the Hong Kong Special Administrative Region. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute Of General Medical Sciences or the National Institutes of Health.

POTENTIAL CONFLICTS OF INTEREST

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

ACKNOWLEDGMENTS

We thank Kei Owada and Tim Eckmanns for helpful discussions. The Ebola control contributions of all of the Sierra Leone field laboratories are highly appreciated.

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FIGURE LEGENDS

Figure 1: Daily incidence of cases of Ebola onset, hospitalization and deaths for all ages in Sierra Leone, between 23rd May 2014 and 31st January 2015. (A) Daily number of onset. (B) Daily number of hospital admissions. (C) Daily number of deaths.

Figure 2: Real-time estimates of (A) the case fatality risk and (B) the hospitalization risk among all probable and confirmed cases (black lines) and the risk of fatality among hospitalized probable and confirmed cases only (red lines) in Sierra Leone, between 23rd May 2014 and 31st January 2015. Blank solid lines represent the posterior mean, dotted lines show 95% credibility interval.

Figure 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, among confirmed and probable EVD cases in Sierra Leone, between 23rd May 2014 and 31st January 2015.

Figure 4: Prevalence of Ebola hospitalized cases in Sierra Leone, between 23rd May 2014 and 31st January 2015.

Table 1: Characteristics of 17,318 EVD cases in Sierra Leone by outcome and case definition, between 23rd May 2014 and 31st January 2015.

	Death				Recovery				Unknown outcome			
	Confirmed (n=2054)	Probable (n=482)	Suspected (n=2256)	p-value [#]	Confirmed (n=702)	Probable (n=184)	Suspected (n=173)	p-value [#]	Confirmed (n=5534)	Probable (n=1809)	Suspected (n=4124)	p-value [#]
Age (years)												
0-4	150 (7%)	66 (14%)	426 (19%)	<0.001	35 (5%)	9 (5%)	9 (5%)	0.99	331 (6%)	265 (15%)	422 (10%)	<0.001
5-14	262 (13%)	61 (13%)	213 (9%)	<0.001	121 (17%)	35 (19%)	15 (9%)	0.01	757 (14%)	226 (12%)	416 (10%)	<0.001
15-44	1097 (53%)	220 (46%)	773 (34%)	<0.001	402 (57%)	98 (53%)	104 (60%)	0.42	3160 (57%)	768 (42%)	2051 (50%)	<0.001
45-59	282 (14%)	56 (12%)	246 (11%)	0.02	88 (13%)	20 (11%)	23 (13%)	0.76	736 (13%)	206 (11%)	579 (14%)	0.02
60+	205 (10%)	69 (14%)	510 (23%)	<0.001	52 (7%)	20 (11%)	15 (9%)	0.31	398 (7%)	269 (15%)	531 (13%)	<0.001
Unknown	58 (3%)	10 (2%)	88 (4%)	0.04	4 (1%)	2 (1%)	7 (4%)	<0.001	152 (3%)	75 (4%)	125 (3%)	0.01
Sex												
Men	1016 (49%)	224 (46%)	1136 (50%)	0.30	343 (49%)	90 (49%)	95 (55%)	0.35	2587 (47%)	867 (48%)	2124 (52%)	<0.001
Unknown	30 (1%)	12 (2%)	52 (2%)	0.09	11 (2%)	3 (2%)	3 (2%)	0.94	134 (2%)	87 (5%)	121 (3%)	<0.001

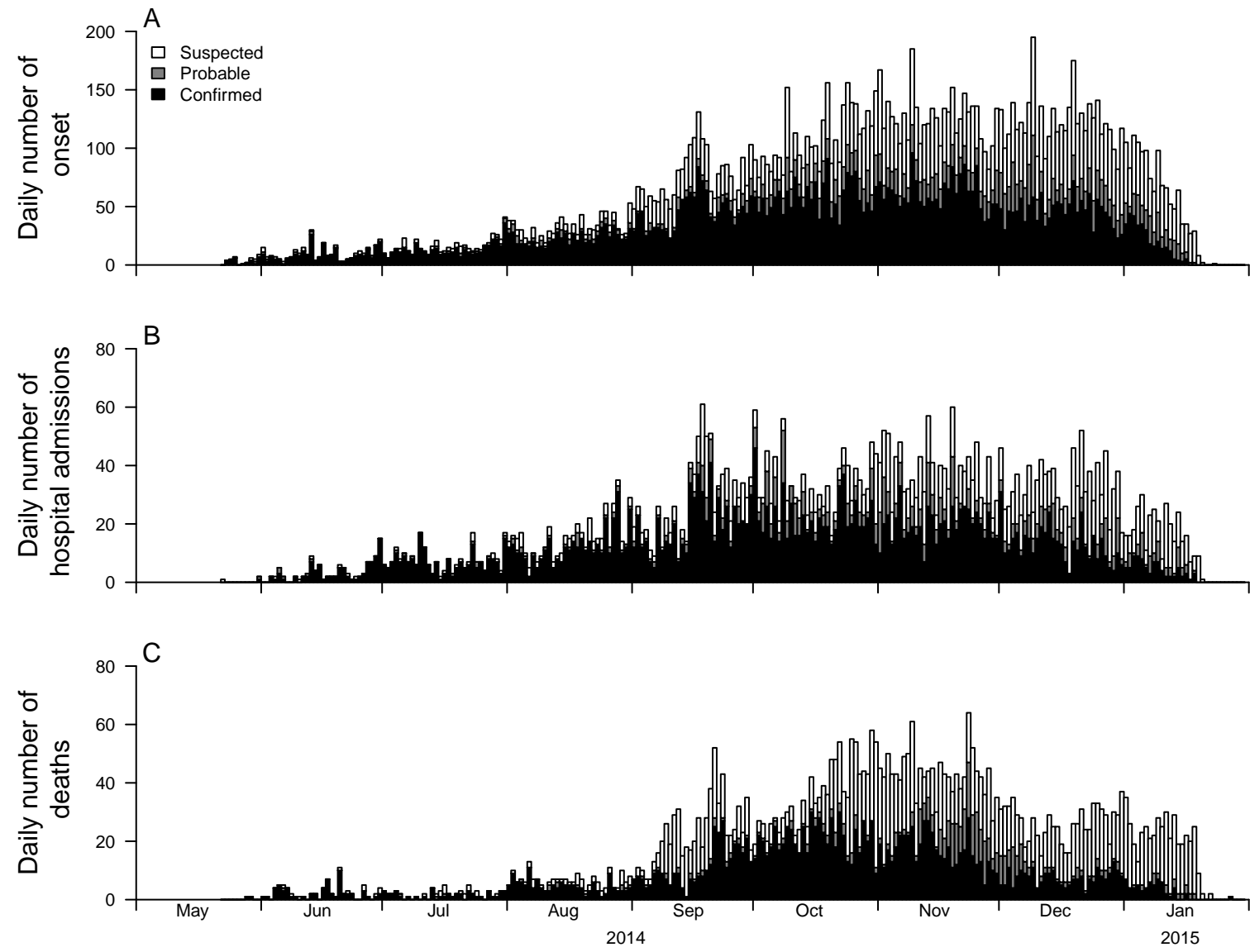
[#] The χ^2 or fisher's exact test was used to compare among groups, as appropriate

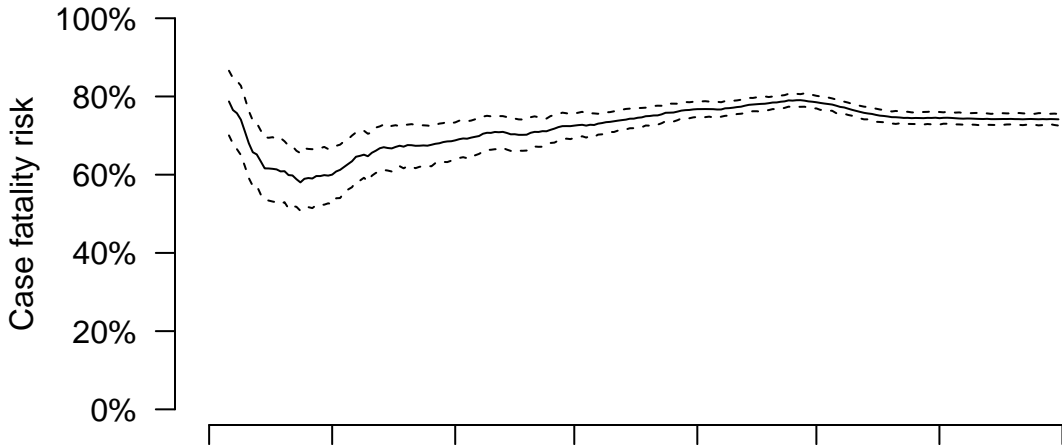
Table 2: Factors affecting risk of deaths among confirmed and probable cases with definitive final outcome, between 23rd May 2014 and 31st January 2015 (n=2,936).

Factor	n#	HR	95% CI
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)

HCW = staffs working in health care setting (including health care providers, cleaners, decontaminators, vaccinators, etc).

#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.



A**B**