Subsequent mortality in survivors of Ebola virus disease in Guinea: a nationwide retrospective cohort study

Mory Keita, Boubacar Diallo, Samuel Mesfin, Abdourahmane Marega, Koumpingnin Yacouba Nebie, N'Faly Magassouba, Ahmadou Barry, Seydou Coulibaly, Boubacar Barry, Mamadou Oury Baldé, Raymond Pallawo, Sadou Sow, Alpha Oumar Bah, Mamadou Saliou Balde, Steven Van Gucht, Mandy Kader Kondé, Amadou Bailo Diallo, Mamoudou Harouna Djingarey, Ibrahima Socé Fall, Pierre Formenty, Judith R Glynn, Lorenzo Subissi

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WHO Country Office, Conakry, Guinea (M Keita MD, B Diallo MD, S Mesfin BSc, K Y Nebie MD, A Barry MD, S Coulibaly MD, B Barry BSc, M O Baldé MD, R Pallawo MD); **Regional Directorate of Health, Conakry, Guinea** (A Marega PharmD); **Faculty of Medicine, Pharmacy and Odontostomatology** (N Magassouba PhD, S Sow MPH), **Department of Nephrology** (Prof A O Bah MD, M S Balde MD), **and Department of Public Health** (Prof M K Kondé PhD, **University of Conakry, Conakry, Guinea; Sciensano, Brussels, Belgium** (S Van Gucht PhD); **Health and Sustainable Development Foundation, Conakry, Guinea** (M K Kondé); **WHO Regional Office for Africa, Brazaville, Republic of the Congo** (A B Diallo MD, M H Djingarey MD, I S Fall PhD); **Health Emergencies Programme, WHO, Geneva, Switzerland** (P Formenty DVM); **London School of Hygiene & Tropical Medicine, London, UK** (Prof J R Glynn PhD); **and Global Outbreak Alert and Response Network, Conakry, Guinea** (L Subissi PhD)

Correspondence to: Dr Lorenzo Subissi, Sciensano, 1050 Brussels, Belgium **loresubissi@gmail.com**

Summary

Background A record number of people survived Ebola virus infection in the 2013–16 outbreak in west Africa, and the number of survivors has increased after subsequent outbreaks. A range of post-Ebola sequelae have been reported in survivors, but little is known about subsequent mortality. We aimed to investigate subsequent mortality among people discharged from Ebola treatment units.

Methods From Dec 8, 2015, Surveillance Active en ceinture, the Guinean national survivors' monitoring programme, attempted to contact and follow-up all survivors of Ebola virus disease who were discharged from Ebola treatment units. Survivors were followed up until Sept 30, 2016, and deaths up to this timepoint were recorded. Verbal autopsies were done to gain information about survivors of Ebola virus disease who subsequently died from their closest family members. We calculated the age-standardised mortality ratio compared with the general Guinean population, and assessed risk factors for mortality using survival analysis and a Cox proportional hazards regression model.

Findings Of the 1270 survivors of Ebola virus disease who were discharged from Ebola treatment units in Guinea, information was retrieved for 1130 (89%). Compared with the general Guinean population, survivors of Ebola virus disease had a more than five-times increased risk of mortality up to Dec 31, 2015 (age-standardised mortality ratio 5·2 [95% CI 4·0–6·8]), a mean of 1 year of follow-up after discharge. Thereafter (ie, from Jan 1–Sept 30, 2016), mortality did not differ between survivors of Ebola virus disease and the general population. (0·6 [95% CI 0·2–1·4]). Overall, 59 deaths were reported, and the cause of death was tentatively attributed to renal failure in 37 cases, mostly on the basis of reported anuria. Longer stays (ie, equal to or longer than the median stay) in Ebola treatment units were associated with an increased risk of late death compared with shorter stays (adjusted hazard ratio 2·62 [95% CI 1·43–4·79]).

Interpretation Mortality was high in people who recovered from Ebola virus disease and were discharged from Ebola treatment units in Guinea. The finding that survivors who were hospitalised for longer during primary infection had an increased risk of death, could help to guide current and future survivors' programmes and in the prioritisation of funds in resource-constrained settings. The role of renal failure in late deaths after recovery from Ebola virus disease should be investigated.

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Introduction

During the 2013–16 Ebola virus epidemic in west Africa, 28 646 cases of Ebola virus disease and 11 323 deaths were recorded.[1] As a result, west Africa has the largest recorded cohort of survivors of Ebola virus disease, comprising more than 17 000 people.[1] Post-Ebola virus disease sequelae—including arthralgia, myalgia, abdominal pain, fatigue, anorexia, and late ocular complications—were reported in cohort studies[2–4] of survivors of the 1995 outbreak of Ebola virus in Kikwit, DR Congo. Studies[5–10] of subsequent outbreaks, including the 2013–16 outbreak in west Africa, have confirmed that many survivors of Ebola virus disease experience a broad range of sequelae, with hearing loss and neurological signs reported in addition to previously identified sequelae. In a large cohort study[11] done in Liberia, symptoms such as urinary frequency, headache, memory loss, fatigue, joint pain, and muscle pain were more frequent among survivors than controls (ie, antibody-negative close contacts of survivors). Long viral persistence in semen and other bodily fluids can occasionally result in recrudescence of Ebola virus disease in survivors, which can lead to disease transmission and subsequent re-emergence of Ebola virus in the community.[11–15]

Despite the extensive work published about the sequelae of Ebola virus disease, little information is available about deaths that have occurred in patients discharged from Ebola treatment units. In a study[16] in Sierra Leone that followed up 151 survivors for a mean of 10 months after discharge from Ebola treatment units, four deaths were recorded, all within 6 weeks of

Research in context

Evidence before this study

We searched PubMed with the search string ("Ebola" OR "Ebolavirus") AND ("survivor") AND ("death" OR "mortality") for articles published in any language up to April 4, 2019. Little evidence about mortality in people who survive Ebola virus disease is available. Of the 68 citations that our search identified, some investigated post-Ebola virus disease sequelae and viral persistence in bodily fluids, but only one assessed late deaths among survivors of Ebola virus disease. In that study, four deaths were reported among 151 survivors, who were followed-up for a mean of 10 months.

Added value of this study

To our knowledge, this is the largest study, and the first nationwide cohort study, of subsequent mortality among people who survived Ebola virus disease. We showed that mortality among survivors of Ebola virus disease was five times higher than that in the general population of Guinea in the year after discharge from Ebola treatment units. Mortality was higher in survivors who spent longer time in an Ebola treatment unit than in those who spent a shorter time in units, suggesting that those initially hospitalised for longer could be a high-risk group among survivors of Ebola virus disease. Renal failure was tentatively suggested as a contributing factor in 37 of the 59 reported deaths.

Implications of all the available evidence

This study confirms the high vulnerability of survivors of Ebola virus disease, particularly those with prolonged acute disease, and suggests that the overall case fatality rate for the disease has been previously underestimated. Increased mortality among survivors of Ebola virus disease compared with the general population is alarming and future studies should be done to investigate whether renal failure is a long-term sequela.

discharge. Initially, survivors of Ebola virus disease in Guinea were followed up mainly within research-focused cohort studies and no exhaustive national cohort was established.[9,17–20] WHO advised that an intensive programme (ideally integrated into existing routine health services and facilities) was necessary to address the medical and psychosocial needs of survivors and the risk of virus reintroduction.[21] Therefore, the National Coordination for the Fight against Ebola Virus, the WHO country office for Guinea, and other partners developed and implemented a community monitoring programme, Surveillance Active en ceinture (SA-Ceint), per guidelines from the WHO Ebola response phase 3 strategic document,[22] to closely follow-up survivors of Ebola virus disease, with the aim of avoiding reintroduction of Ebola virus into the community. In this study, we used these national level data to estimate mortality among survivors of Ebola virus disease after discharge from Ebola treatment units, assess the potential cause of mortality, and identify risk factors.

Methods

Study design and participants

We did a retrospective nationwide cohort study of mortality among survivors of the 2013–16 Ebola virus disease outbreak in Guinea. The study ran from Dec 8, 2015, to Sept 30, 2016. The names and contacts of all eligible survivors were identified from the Ebola virus disease database that is managed by the Guinean Ministry of Health and partners. This database was used for notification purposes during the Ebola outbreak. It contains complete epidemiological information available to the Ministry of Health and information about laboratory confirmation of disease for all suspected, probable, and confirmed cases of Ebola virus disease in Guinea, and was reviewed on a weekly basis.

All survivors were eligible to participate in the SA-Ceint programme if they could produce the certificate of medical clearance that they were given when discharged from the Ebola treatment unit. In this study, we analysed data collected by SA-Ceint, which was integrated into the workflow of other research projects—ie, Postebogui,[9] the JIKI trial,[17] EBOSEX,[20] and the Ebola ça suffit vaccination trial[18]—which were all approved by the Guinean National Committee for Ethics in Research and Health. Because the work of SA-Ceint was considered by the Guinean Ministry of Health to be public health practice in an emergency context, no ethics approval was sought for the programme. All participants in this study provided written informed consent at the outset.

Procedures

From Dec 8 to Dec 31, 2015, the SA-Ceint team attempted to contact all survivors of Ebola virus disease. They classified survivors as either willing to participate, lost to follow-up, or reportedly dead. A field team investigated the deaths of people who were reported to have died, completed verbal autopsies (ie, interviews in which a description of illness and events is recorded, and a checklist of symptoms is gone through) with the closest family members of the deceased, and reviewed medical files shared by family members (when available). WHO medical epidemiologists, who were in charge of the field investigation of reported deaths, then suggested the main contributor to death. Each cause of death was reviewed and validated by a panel of experts from WHO and the Guinean Ministry of Health.

Survivors who agreed to participate were actively followed up from Jan 1 to Sept 30, 2016. Active follow up consisted of body fluid testing, visits from mental health experts on a voluntary basis, and, from April 1, weekly communications with the SA-Ceint team. By Sept 30, 2016, 99% of survivors had been discharged

from the Ebola treatment unit for more than a year. All participants received a monthly allowance, including a free mobile phone with monthly credit and other forms of support (eg, rice, flour) as part of the survivor package. In exchange, they were asked to call the SA-Ceint team on a weekly basis to provide updates on their health status and the health status of their close contacts. During follow-up, deaths were reported via the same phone by family members of the survivors. The main outcome of the study was post-discharge all-cause mortality.

Statistical analysis

The outcome of this analysis, late death, was defined as death from any cause after discharge from an Ebola treatment unit. Independent variables (age, sex, days in the Ebola treatment unit, date of discharge from the Ebola treatment unit, and area of residence) were recorded at discharge. Categorical variables were reported as numbers and percentages and compared with the Pearson's χ^2 test. Date of discharge from the Ebola treatment unit was divided into quartiles on the basis of the median date and IQRs. Duration of hospitalisation in days was divided into two groups: less than the median or equal to or more than the median. Missing observations for this variable were included in the Cox regression models as unknown. Survival of the participants by each independent variable was compared with the log-rank test.

For the survival analysis, the observation period ran from the date of discharge from an Ebola treatment unit (which was available for all survivors), to the date of death or the date of the end of the SA-Ceint programme (Sept 30, 2016). All survivors of Ebola virus disease who subsequently died on an unknown date died before Dec 31, 2015. Therefore, we used the midpoint between their discharge from the Ebola treatment unit and December 31, 2015, as an estimate of their date of death.

We calculated overall mortality risk (ie, reported deaths among survivors with known mortality status at the end of follow-up) and standardised mortality ratios by using indirect standardisation. Because the risk of death associated with Ebola virus disease is likely to decrease with time, we calculated standarised mortality ratios for two different periods: from discharge from the Ebola treatment unit until Dec 31, 2015 (corresponding to a median of 13·0 months [IQR 10·4–14·9] of follow-up), and from Jan 1 to Sept 30, 2016 (median 9·0 months [IQR 9·0–9·0]). We used age-specific mortality in the Guinean population from the third General Population and Housing Census[23] and the number of survivors by age group in the study population to calculate age-specific expected deaths. These values were then compared with age-specific recorded deaths to derive standardised mortality ratios.

We constructed a multivariable Cox proportional hazards regression model to identify factors associated with late death. Variables with p values less than 0·2 in a log-rank test were included in the first model, and variables with p values less than 0·1 in a likelihood ratio test were kept in the final model. The proportionality assumption was checked with the Schoenfeld and scaled Schoenfeld residuals' test, and no violation of the final model's proportionality was found. The goodness of fit of the final model was assessed by the Cox-Snell residuals. All tests were two sided with 95% CIs.

Analyses were repeated by calculating the person-years at risk for people whose date of death was unknown in two ways: as if they all died the day after discharge from the Ebola treatment unit (shortest possible delay of a late death) and as if they all died on Dec 31, 2015 (the earliest date by which all deaths on unknown dates were confirmed). A complete case analysis was also done including only people with known dates of death, and known duration of hospitalisation. All analyses were done in STATA/SE (version 14.0).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Of the 1270 known survivors of the 2013–16 Ebola virus disease outbreak in Guinea whom we attempted to contact, 140 were lost to follow-up (figure). A further 55 were

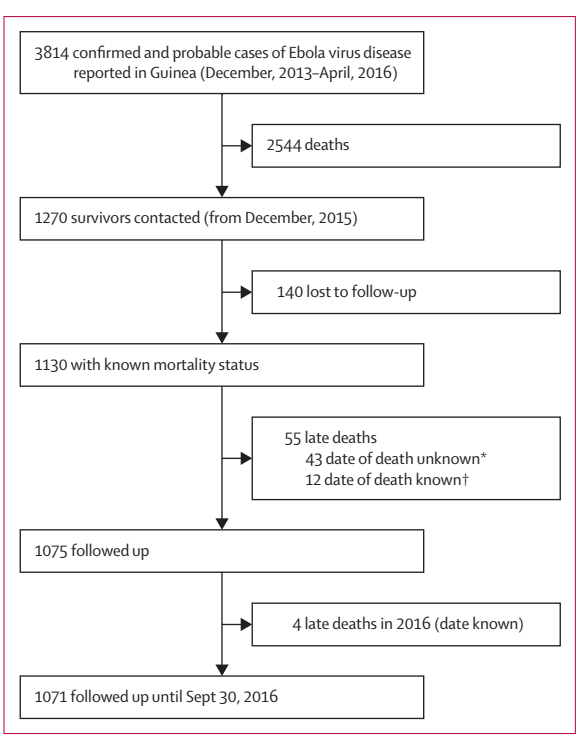

Figure: **Study profile**
*Died before Jan 1, 2016. †Three died in 2014, and nine in 2015.

reported to have died between discharge from Ebola treatment units and being sought out to participate in this study, and four more died during follow-up. Overall mortality was 5·2% (ie, 59 deaths among 1130 patients) during median follow-up of 21·9 months (IQR 19·2–23·8). Table 1 details the characteristics of survivors of Ebola virus disease. Baseline characteristics of those who were followed up and those who were lost to follow-up were broadly similar, but area of residence and month of discharge from the Ebola treatment unit differed significantly between groups (table 1). Of the 1130 survivors for whom follow-up information was available, 610 (53%) were female; median age at discharge from the Ebola treatment unit was 28 years (IQR 18–40). The median duration of hospitalisation (ie, the time from admission to an Ebola treatment unit to discharge) was 12 days (IQR 9–15). Date of admission (and therefore duration of hospitalisation) was missing for 73 (6%) survivors.

The exact date of death was unknown for 43 of the 59 deaths recorded. Of the 16 initial survivors for whom an exact date of death was available, five died within a month of discharge from Ebola treatment units (2, 6, 10, 14, and 30 days after discharge), an additional three died within 3 months of discharge (53, 57, and 87 days after discharge), four died 3–12 months after discharge (5, 6, 6, and 10 months after discharge), and four died more than a year after discharge (16, 17, 19, and 21 months after discharge).

Among people who did not die, the shortest duration of follow-up was 5·4 months, and the longest was 32·7 months. Total follow-up time was 1987·4 person-years. Mortality varied by age, and was highest in people older than 55 years (table 2). Compared with the number of deaths expected according to the 2014 Guinean census,[23] more deaths were recorded than would be expected at all ages among our cohort up to Dec 31, 2015 (table 3), but not during the rest of the follow-up period. The ratio of recorded deaths to expected deaths varied by age, but we noted no consistent pattern (table 3). Up to Dec 31, 2015, it was highest among people aged 5–14 years, and lowest among those younger than 5 years (table 3). During the same period, survivors of Ebola virus disease had a more than five times greater risk of death than the general Guinean population (standardised mortality ratio 5·2 [95% CI 4·0–6·8]; table 3). For Jan 1–Sept 30, 2016, the standardised mortality ratio was 0·6 (95% CI 0·2–1·4). People with unknown dates of death contributed 23·0 person-years at risk to the main analysis. In an analysis in which extreme values were used for unknown dates of death (ie, in which it was assumed that all deaths occurred the day after discharge from the Ebola treatment unit or that all deaths occurred on Dec 31, 2015), the standardised mortality ratio for the period to Dec 31, 2015 hardly changed (5·4 [95% CI 4·1–7·0] for early deaths and 5·1 [3·9–6·6] for late deaths).

Mortality after discharge from Ebola treatment units did not differ significantly between male and female

	Died before end of follow-up* (n=1130)	Lost to follow-up (n=1270)	p value for proportion lost to follow-up†
Age (years)			
<5	3/43 (7%)	10/53 (19%)	0·41
5–14	6/135 (4%)	14/149 (9%)	..
15–24	8/255 (3%)	33/288 (11%)	..
25–34	6/274 (2%)	36/310 (12%)	..
35–44	17/217 (8%)	24/241 (10%)	..
45–54	4/103 (4%)	13/116 (11%)	..
55–64	8/74 (11%)	9/83 (11%)	..
65–74	5/26 (19%)	0/26 (0%)	..
≥75	2/3 (67%)	1/4 (25%)	..
Date of discharge from Ebola treatment unit‡	..	..	<0·0001
January, 2014–September, 2014	16/284 (6%)	32/316 (10%)	..
October, 2014–November, 2014	12/292 (4%)	63/355 (18%)	..
December, 2014–January, 2015	16/272 (6%)	28/300 (9%)	..
February, 2015–April, 2016	15/282 (5%)	17/299 (6%)	..
Sex			
Female	31/610 (5%)	77/687 (11%)	0·82
Male	28/520 (5%)	63/583 (11%)	..
Area of residence			
Conakry	5/240 (2%)	46/286 (16%)	0·002
Elsewhere	54/890 (6%)	94/984 (10%)	..
Days in hospital§			
<12 days	14/486 (3%)	59/545 (11%)	0·52¶
≥12 days	42/571 (7%)	78/649 (12%)	..
Unknown	3/73 (4%)	3/76 (4%)	..

Data are n/N (%) or n (%). *Patients who were lost to follow-up were not included. †Pearson's $\chi 2$ test was used to compare the proportion of people followed up (ie, N) with the proportion lost-to-follow-up. Quartiles (based on the median and IQR dates). §Calculated by subtracting the date of admission to an Ebola treatment unit from the date of discharge. ¶Patients for whom these data were unknown were excluded from the p value calculation.

Table 1: **Characteristics of survivors of Ebola virus disease in Guinea (n=1270)**

	Post-discharge deaths	Person-years	Deaths per 100 person-years (95% CI)
<5 years	3	69·2	4·3 (1·4–13·4)
5–14 years	6	233·8	2·3 (1·2–5·7)
15–24 years	8	452·7	1·8 (0·9–3·5)
25–34 years	6	493·9	1·2 (0·5–2·7)
35–44 years	17	379·8	4·5 (2·8–7·2)
45–54 years	4	182·9	2·2 (0·8–5·8)
55–64 years	8	130·9	6·1 (3·1–12·2)
65–74 years	5	41·6	12·0 (5·0–28·9)
≥75 years	2	2·6	75·7 (18·9–300·0)
Overall	59	1987·4	3·0 (2·3–3·8)

When the date of deaths was unknown, we used the midpoint between the date of discharge from the Ebola virus unit and earliest date by which we knew that all deaths had occurred (Dec 31, 2015). People for whom the date of deaths was unknown contributed 23·0 person-years.

Table 2: **Number of late deaths, person-years, and mortality by age at discharge from Ebola treatment units (N=1130)**

	Deaths (per 100 persons-years)*	Person-years of survivors of Ebola virus disease		Recorded deaths		Expected deaths		Ratio of recorded deaths to expected deaths (95% CI)	
		Until Dec 31, 2015	January–September, 2016	Until Dec 31, 2015	January–September, 2016	Until Dec 31, 2015	January–September, 2016	Until Dec 31, 2015	January–September, 2016
<5	3·3	39·3	29·9	3	0	1·3	1·0	2·3 (0·6–6·4)	0
5–14 years	0·3	137·6	96·2	6	0	0·4	0·3	14·5 (5·9–30·1)	0
15–24 years	0·4	268·1	184·6	8	0	1·0	0·7	8·1 (3·8–15·5)	0
25–34 years	0·6	293·5	200·4	5	1	1·8	1·2	2·7 (1·0–6·1)	0·8 (0·04–4·0)
35–44 years	0·9	229·8	150·0	15	2	2·0	1·3	7·6 (4·4–12·2)	1·6 (0·3–5·1)
45–54 years	1·3	108·9	74·0	4	0	1·4	1·0	2·8 (0·9–6·9)	0
55–64 years	1·8	81·6	49·3	8	0	1·5	0·9	5·3 (2·5–10·1)	0
65–74 years	3·6	26·1	15·5	4	1	0·9	0·6	4·3 (1·4–10·3)	1·8 (0·8–8·9)
≥75	9·2	1·9	0·8	2	0	0·2	0·1	11·4 (1·9–37·8)	0
Overall	..	1186·8	800·6	55	4	10·5	7·0	5·2 (4·0–6·8)	0·6 (0·2–1·4)

For the period from discharge from Ebola treatment units until Dec 31, 2015 (median follow-up 13·0 months [IQR 10·4–14·9]), the standardised mortality ratio was 5·2 (95% CI 4·0–6·8). For Jan 1 to Sept 30, 2016—ie, the active follow-up period (median follow-up 9·0 months [IQR 9·0–9·0])—the standardised mortality ratio was 0·6 (95% CI 0·2–1·4). *Data are from the third General Population and Housing Census (RGPH3), National Institute for Statistics (2014).[21]

Table 3: **Age-specific mortality in the Guinean population and weights used to calculate standardised mortality ratios, by age at discharge from Ebola treatment units**

See Online for appendix

	Crude hazard ratio (95% CI)	Adjusted hazard ratio* (95% CI)	p value†
Age group (years)			
<55	Ref	Ref	0·0004
≥55	3·61 (2·01–6·49)	3·28 (1·82–5·92)	
Area of residence			
Conakry	Ref	Ref	0·013
Elsewhere	2·92 (1·17–7·31)	2·76 (1·10–6·92)	
Days in hospital			
<12 days	Ref	Ref	0·003
≥12 days	2·66 (1·45–4·86)	2·62 (1·43–4·79)	
Unknown	1·41 (0·41–4·92)	1·16 (0·33–4·05)	

Hazards ratios were calculated with a Cox proportional hazards regression model (1987·4 person-years; N=1130). Variables with a p value less than 0·2 in the log-rank test were included in the first model, and variables with a p value less than 0·1 according to a likelihood ratio test were kept in the final model. Age was divided into two groups to avoid overfitting the model. Ref=reference. *Adjusted for age, area of residence, and days in hospital. †Calculated with a likelihood ratio test.

Table 4: **Hazard ratios for late death (n=59) among survivors of Ebola virus disease**

survivors, or between those treated at different stages of the Ebola epidemic (table 1). Mortality was lower in Conakry (ie, an urban area) than elsewhere, and was higher in those with longer stays in Ebola treatment units than in those with shorter stays in Ebola treatment units (table 1). Age, area of residence (ie Conakry *vs* non-urban area), and duration of stay in Ebola treatment units were independently associated with mortality (table 4). Survivors who were hospitalised for at least 12 days during their episode of Ebola virus infection had more than double the risk of death that those hospitalised for less than 12 days had (adjusted hazard ratio 2·62 [95% CI 1·43–4·79]). An analysis in which we used extreme values for unknown dates of death produced similar results (appendix p 1).

We gathered limited information about the possible cause of death for 52 of the 59 reported deaths. Unfortunately, because of data management challenges encountered in Guinea, we could not link this information to each study participant, and the medical files reviewed for each death are no longer available. In 37 deaths, renal failure had a role in the view of a team of medical epidemiologists who reviewed available medical files and verbal autopsies completed by family members. Three of these patients who died were inpatients in the haemodialysis centre at Donka National Hospital (the main hospital in Conakry) at the time of death. Most of the other postulated diagnoses of renal failure were based on anuria (as reported by family members), and some were based on creatinine concentrations. Other conditions that were judged to have had a main role in deaths were malaria (five people), pulmonary tuberculosis (three), high blood pressure (three), septic shock (one), brain tumour (one), and suicide (one). One person died as the result of an accident.

Discussion

Although much is known about the sequelae of Ebola virus disease, little is known about the risk of death among survivors of Ebola virus disease. Here, for the first time, we report high mortality among survivors of Ebola virus disease in Guinea compared with the general population. Increased age, living in a non-urban area, and longer stays in Ebola treatment units were associated with increased risk of post-discharge mortality.

In a previous study,[16] Bower and colleagues reported four (3%) late deaths among 151 survivors of Ebola virus disease in Sierra Leone with a mean follow-up of

10 months. This finding is consistent with overall mortality in our study (5·2% with a median follow-up of 21·9 months). However, mortality was not constant over time. All four deaths in the Sierra Leone study[16] occurred within the first 6 weeks of discharge from Ebola treatment units. In our study, date of death was known for only 16 people, eight of whom died within 3 months of discharge, and 12 within 10 months of discharge. 55 of the 59 deaths in our study had occurred by Dec 31, 2015, a median of 13 months after discharge. It is possible that the true mortality rate was higher, because mortality was probably higher among those lost to follow-up than among those included.

During the first year of follow-up (ie, up to Dec 31, 2015), age-specific mortality in survivors of Ebola virus disease was more than five times that expected in the Guinean population. Between Jan 1, and Sept 30, 2016, mortality among survivors was not significantly higher than that in the general population. This finding is in line with observations from a cohort study[11] of Liberian survivors of Ebola virus disease enrolled roughly a year after discharge from Ebola treatment units, in which survivors did not have an increased risk of death compared with controls (ie, antibody-negative close contacts of survivors).[11] The data that we used for the comparison of mortality came from the mortality report based on the latest available national census (2014), which was administered by the Guinean National Institute for Statistics under the technical assistance of experts from the UN Population Fund, and published in 2017.[23] Thus, these data were representative of the Guinean population. However, a limitation of the census is that the number of deaths was based not on death records but rather extrapolated from the questionnaire given to the census participants.

Although poorer people, who would be expected to have higher background risk of mortality than richer people, might have been more affected by Ebola virus disease and thus over-represented in our sample, this is unlikely to explain such a large increase in early mortality, and is not supported by the 2016 mortality data in our study. The lower risk of death among survivors in Conakry compared with those in non-urban areas might be because health care is easier to access in the city.

Limitations of our study include that most dates of death were missing, and that the verbal autopsy and clinical data used to judge possible causes of death are no longer available. However, the distribution of deaths over time, and the possibility that renal failure contributed to more than 60% of the deaths might suggest that most deaths were linked to Ebola sequelae. Although evidence was weak for most patients, renal failure is a biologically plausible cause of death in survivors of Ebola virus disease. The virus is often detected in urine samples during the acute phase of the disease because it can infect the kidney,[24] and some patients with Ebola virus develop acute kidney injury,[25,26] which can lead to longer-term renal failure and increased mortality even after initial apparent recovery.[27,28]

In this analysis, we used data collected by SA-Ceint, so we could only investigate variables collected as part of the programme. No information about sequelae or exposure to drugs was available, so we could not further assess whether treatment was associated with adverse outcomes, as tentatively noted by Etard and colleagues.[9] SA-Ceint followed up 89% of people discharged from Ebola treatment units—a remarkable achievement. However, Guinea has far fewer survivors of Ebola virus disease than does Sierra Leone (which has more than 10 000) and Liberia (which has almost 6000), which could explained why successful implementation of a nationwide follow-up programme was possible. Nevertheless, Guinean health authorities encountered challenges in coordinating such a rapidly implemented programme within a health system that was ravaged by the epidemic. For example, although the main contributor to subsequent death among survivors of Ebola virus disease was investigated and available for most deaths, we do not know the data on which these judgments were based, and the information to link these data to the Guinean Ministry of Health database could not be retrieved.

Our finding of an increased risk of mortality after recovery from Ebola virus disease emphasises that survivors' monitoring programmes should be strengthened and should not focus exclusively on testing of bodily fluids. Furthermore, our study provides preliminary evidence that survivors hospitalised for longer than 12 days with Ebola virus disease could be at particularly high risk of mortality and should be specifically targeted, and perhaps also evidence that renal function should be monitored. Guidelines for how to implement such programmes, to be followed by the ministries of health of affected countries, are being constantly updated by a pool of Ebola experts, who are coordinated by WHO.[21]

Future research should focus on the long-term effect of Ebola virus infection, including possible effects of kidney function. Duration of Ebola virus disease and viral persistence in bodily fluids should also be investigated as potential risk factors in future epidemiological studies. Finally, our work should be replicated in DR Congo, Liberia, Sierra Leone, and elsewhere, to enable steps to be taken to understand—and, if possible, prevent—these late deaths after recovery from Ebola virus disease.

Contributors

MK, BD, AM, KYN, NM, AB, MOB, RP, MKK, ABD, MHD, ISF, JRG, and LS designed the study. SM, SC, and BB managed the data. AOB and MSB provided data for cases admitted to their hospital's nephrology department. MK and SS appraised the Ebola virus disease follow-up programme. JRG and LS did the statistical analyses. MK, SVG, PF, JRG, and LS wrote the Article, which all authors reviewed and approved.

Declaration of interests

We declare no competing interests.

Data sharing

The data might be made available upon request, with agreement from the Guinean Ministry of Health. For further information, contact the corresponding author.

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References

1 Coltart CEM, Lindsey B, Ghinai I, Johnson AM, Heymann DL. The Ebola outbreak, 2013–2016: old lessons for new epidemics. *Philos Trans R Soc Lond B Biol Sci* 2017; published online May 26. DOI:10.1098/rstb.2016.0297.

2 Kibadi K, Mupapa K, Kuvula K, et al. Late ophthalmologic manifestations in survivors of the 1995 Ebola virus epidemic in Kikwit, Democratic Republic of the Congo. *J Infect Dis* 1999; **179** (suppl 1)**:** S13–14.

3 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)**:** S1–7.

4 Rowe AK, Bertolli J, Khan AS, et al. Clinical, virologic, and immunologic follow-up of convalescent Ebola hemorrhagic fever patients and their household contacts, Kikwit, Democratic Republic of the Congo. Commission de Lutte contre les Epidémies à Kikwit. *J Infect Dis* 1999; **179** (suppl 1)**:** S28–35.

5 Wendo C. Caring for the survivors of Uganda's Ebola epidemic one year on. *Lancet* 2001; **358:** 1350.

6 Clark DV, Kibuuka H, Millard M, et al. Long-term sequelae after Ebola virus disease in Bundibugyo, Uganda: a retrospective cohort study. *Lancet Infect Dis* 2015; **15:** 905–12.

7 Qureshi AI, Chughtai M, Loua TO, et al. Study of Ebola virus disease survivors in Guinea. *Clin Infect Dis* 2015; **61:** 1035–42.

8 Mattia JG, Vandy MJ, Chang JC, et al. Early clinical sequelae of Ebola virus disease in Sierra Leone: a cross-sectional study. *Lancet Infect Dis* 2016; **16:** 331–38.

9 Etard J-F, Sow MS, Leroy S, et al. Multidisciplinary assessment of post-Ebola sequelae in Guinea (Postebogui): an observational cohort study. *Lancet Infect Dis* 2017; **17:** 545–52.

10 Kupferschmidt K. Infectious diseases. Surviving Ebola survival. *Science* 2015; **348:** 1406–07.

11 PREVAIL III Study Group, Sneller MC, Reilly C, et al. A longitudinal study of Ebola sequelae in Liberia. *N Engl J Med* 2019; **380:** 924–34.

12 Deen GF, Broutet N, Xu W, et al. Ebola RNA persistence in semen of Ebola virus disease survivors—final report. *N Engl J Med* 2017; **377:** 1428–37.

13 Subissi L, Keita M, Mesfin S, et al. Ebola virus transmission caused by persistently infected survivors of the 2014–2016 outbreak in west Africa. *J Infect Dis* 2018; **218** (suppl 5)**:** S287–91.

14 Dokubo EK, Wendland A, Mate SE, et al. Persistence of Ebola virus after the end of widespread transmission in Liberia: a case report. *Lancet Infect Dis* 2018; **18:** 1015–24.

15 Subissi L. Can Ebola virus re-emerge from survivors' body fluids other than semen? *Lancet Infect Dis* 2018; **18:** 933–34.

16 Bower H, Smout E, Bangura MS, et al. Deaths, late deaths, and role of infecting dose in Ebola virus disease in Sierra Leone: retrospective cohort study. *BMJ* 2016; **353:** i2403.

17 Sissoko D, Laouenan C, Folkesson E, et al. Experimental treatment with favipiravir for Ebola virus disease (the JIKI trial): a historically controlled, single-arm proof-of-concept trial in Guinea. *PLoS Med* 2016; **13:** e1001967.

18 Henao-Restrepo AM, Camacho A, Longini IM, et al. Efficacy and effectiveness of an rVSV-vectored vaccine in preventing Ebola virus disease: final results from the Guinea ring vaccination, open-label, cluster-randomised trial (Ebola Ça Suffit!). *Lancet* 2016; **389:** 505–18.

19 Sissoko D, Duraffour S, Kerber R, et al. Persistence and clearance of Ebola virus RNA from seminal fluid of Ebola virus disease survivors: a longitudinal analysis and modelling study. *Lancet Glob Health* 2017; **5:** e80–88.

20 Kondé MK, Diop MK, Curtis MY, et al. Sex practices and awareness of Ebola virus disease among male survivors and their partners in Guinea. *BMJ Glob Health* 2017; **2:** e000412.

21 WHO. Interim guidance: clinical care for survivors of Ebola virus disease. 2016. http://apps.who.int/iris/bitstream/10665/204235/1/WHO_EVD_OHE_PED_16.1_eng.pdf (accessed Dec 21, 2017).

22 WHO. Surveillance strategy during phase 3 of the Ebola response. 2015. https://www.who.int/csr/resources/publications/ebola/surveillance-strategy-phase3/en/ (Aug 23, 2019).

23 National Statistics Insitute. Third general population and housing census (RGPH3): mortality, 2014. 2017. http://www.stat-guinee.org/images/Publications/INS/RGPH3/RGPH3_mortalite.pdf (accessed Sept 8, 2018).

24 Zeng X, Blancett CD, Koistinen KA, et al. Identification and pathological characterization of persistent asymptomatic Ebola virus infection in rhesus monkeys. *Nat Microbiol* 2017; **2:** 17113.

25 Hunt L, Gupta-Wright A, Simms V, et al. Clinical presentation, biochemical, and haematological parameters and their association with outcome in patients with Ebola virus disease: an observational cohort study. *Lancet Infect Dis* 2015; **15:** 1292–99.

26 Leligdowicz A, Fischer WA, Uyeki TM, et al. Ebola virus disease and critical illness. *Crit Care* 2016; **20:** 217.

27 Loef BG, Epema AH, Smilde TD, et al. Immediate postoperative renal function deterioration in cardiac surgical patients predicts in-hospital mortality and long-term survival. *J Am Soc Nephrol* 2005; **16:** 195–200.

28 Chawla LS, Kimmel PL. Acute kidney injury and chronic kidney disease: an integrated clinical syndrome. *Kidney Int* 2012; **82:** 516–24.