Inpatient signs and symptoms and factors associated with death in children aged 5 years and younger admitted to two Ebola management centres in Sierra Leone, 2014: a retrospective cohort study

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Summary

Background Médecins Sans Frontières (MSF) opened Ebola management centres (EMCs) in Sierra Leone in Kailahun in June, 2014, and Bo in September, 2014. Case fatality in the west African Ebola virus disease epidemic has been highest in children younger than 5 years. Clinical data on outcomes can provide important evidence to guide future management. However, such data on children are scarce and disaggregated clinical data across all ages in this epidemic have focussed on symptoms reported on arrival at treatment facilities, rather than symptoms and signs observed during admission. We aimed to describe the clinical characteristics of children aged 5 years and younger admitted to the MSF EMCs in Bo and Kailahun, and any associations between these characteristics and mortality.

Methods In a retrospective cohort study, we included data from children aged 5 years and younger with laboratory-confirmed Ebola virus disease admitted to EMCs between June and December, 2014. We described epidemiological, demographic, and clinical characteristics and viral load (measured using Ebola virus cycle thresholds [Ct]), and assessed their association with death using Cox regression modelling.

Findings We included 91 children in analysis; 52 died (57·1%). Case fatality was higher in children aged less than 2 years (76·5% [26/34]) than those aged 2–5 years (45·6% [26/57]; adjusted HR 3·5 [95% CI 1·5–8·5]) and in those with high (Ct<25) versus low (Ct≥25) viral load (81·8% [18/22] *vs* 45·9% [28/61], respectively; adjusted HR 9·2 [95% CI 3·8–22·5]). Symptoms observed during admission included: weakness 74·7% (68); fever 70·8% (63/89); distress 63·7% (58); loss of appetite 60·4% (55); diarrhoea 59·3% (54); and cough 52·7% (48). At admission, 25% (19/76) of children were afebrile. Signs significantly associated with death were fever, vomiting, and diarrhoea. Hiccups, bleeding, and confusion were observed only in children who died.

Interpretation This description of the clinical features of Ebola virus disease over the duration of illness in children aged 5 years and younger shows symptoms associated with death and a high prevalence of distress, with implications for clinical management. Collection and analysis of age-specific data on Ebola is very important to ensure that the specific vulnerabilities of children are addressed.

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Introduction

By Aug 16, 2015, 27 952 cases of Ebola virus disease had been reported in Guinea, Liberia, and Sierra Leone as part of the west Africa Ebola epidemic.[1] Of the 15 186 people with laboratory-confirmed infection, 20% were aged 14 years or younger.[1] Sierra Leone had the highest rate and absolute number of confirmed infections in this age group.[1]

Evidence from all age groups shows that case fatality is highest in children under 5 years, suggesting that young children have different risks than do older children, adolescents, and adults.[2] However, data on the epidemiological, clinical, and laboratory features of Ebola virus disease in children are scarce.[3–5] Furthermore,

clinical data across all age groups published from the 2013–16 outbreak have captured historic symptoms reported on arrival to Ebola management facilities, and omitted ongoing signs objectively observed by clinical staff during admission.[2,6–8] Data on signs collected during admission have the potential to inform clinical practice and to improve our understanding of Ebola virus disease.

The first ever case of Ebola virus disease in Sierra Leone was reported in May, 2014, in Kailahun, a rural district in the southeast of the country, adjacent to the Guéckédou region of Guinea where the outbreak originated. Médecins Sans Frontières (MSF) opened a purpose-built Ebola management centre (EMC) in Sierra Leone in Kailahun in June, 2014. The EMC initially

received patients from across the entire country and patients often endured long and debilitating journeys to reach the centre. In September, 2014, a second MSF EMC was opened in Bo, which is the second largest city in Sierra Leone and centrally located with good road access.

In this study, we report on children with Ebola virus disease admitted to the two EMCs in Kailahun and Bo. Given the paucity of clinical information on Ebola virus disease in young children and their vulnerability, we aimed to describe the clinical characteristics of children aged 5 years and under, report their signs and symptoms on arrival and during admission, and assess the factors associated with death.

Methods

Patients
We included all children aged 5 years and younger admitted to the Kailahun and Bo EMCs between June and December, 2014, with confirmed Ebola virus disease. We used WHO case definitions to screen people before testing.[9] A suspected case was a person who had a sudden onset of fever and contact with a person with suspected, probable, or confirmed Ebola or a dead or sick animal. Or any person with sudden onset of high fever and at least three of the following symptoms: headache, lethargy, anorexia (loss of appetite), aching muscles or joints, stomach pain, difficulty swallowing, vomiting, difficulty breathing, diarrhoea, hiccups; or any person with inexplicable bleeding.

We used data that were collected for clinical purposes and anonymised before analysis. This study met the

criteria of the MSF Ethics Review Board for exemption from ethics review for retrospective analyses of routinely collected programmatic data.[10] The study protocol is available on the MSF open repository.

Procedures
Workers completed a case investigation form as soon as was feasible after the arrival of each patient and recorded demographic characteristics, exposure history, date of symptom onset, and past and present symptoms. Age was corroborated with family members whenever possible. After assessment of clinical status and epidemiological information, patients were admitted to "suspect/probable" tents and underwent a blood test, and people who tested positive for Ebola virus were transferred to a "confirmed" tent. Tests were done by laboratories run by the Public Health Agency of Canada (Kailahun) and the US Centers for Disease Control and Prevention (Bo).

Cases were confirmed by presence of Ebola virus RNA, detected with quantitative RT-PCR with two amplification targets in venous or capillary swab blood. The latter involved a capillary sample that was collected onto a cotton swab because venous sampling was not always feasible in young children. Results were accessible for 83 patients as cycle thresholds (Ct), a measure inversely related to viral load. The translation of Ct into viral load was not identical between the two laboratories. We tested whole blood samples before discharge for patients who were clinically convalescing (that is, no vomiting or

diarrhoea and temperature <37·5°C for 3 consecutive days).[11] During admission, empirical treatment followed standard protocols:[11] this included initial treatment with antibiotics and antimalarial drugs as well as supportive treatment including hydration, pain relief, and nutritional support.

A standardised chart was used to record specific symptoms and signs and axillary temperature was measured and recorded at least once daily. The same chart was used for children and adults. Clinical features assessed were: fever (temperature ≥38°C), hiccups, loss of appetite, vomiting, diarrhoea, breathlessness, cough, jaundice, skin rash, confusion, sore throat, conjunctival injection, haemorrhage, weakness, myalgia, arthralgia, abdominal pain, and headache. Clinical staff recorded data only if symptoms were observed; therefore, we assumed that missing data meant an absence of symptoms.

Data on temperature were summarised into one variable that captured whether a child had a temperature 38°C or greater at any time on the day of observation. An undocumented temperature was considered a missing value. There were records of localised pain according to the symptom checklist. Pain as a symptom and its localisation are difficult to determine accurately in children younger than 5 years, and there were no standardised objective tools to determine whether a child had pain. A single variable, "distress", was applied when one or more of sore throat; headache; or abdominal, joint, or muscle pain was recorded.

In a post-hoc analysis we summarised symptoms in a subgroup of children admitted within 3 days of reported symptom onset, to describe symptoms that occurred early in the course of illness but also with the advantage of limited recall bias as there was a shorter interval to recall symptoms because of their day of onset relative to admission.

We also analysed data with age grouped into <2 years or 2–5 years, since younger children are more vulnerable to infections. However, because the age–mortality relation is not linear, we selected an age cut-off with clinical meaning: breastfeeding, a risk factor for high-level exposure to the virus, generally ceases at age 2 years. Other variables included sex, EMC site, delay to admission to EMC from symptom onset (<1 week or ≥1 week, reflecting early and late presenters, respectively, in this context), viral load of first positive test (based on previously published data, a Ct cutoff of 25 was used to indicate high viral load when Ct <25),[12–14] and clinical features recorded during admission.

Two doctors reviewed the patient files containing the case investigation form, daily symptom checklists, observations, and additional clinical notes.

Statistical analysis

We calculated the number and proportion of children experiencing the specified symptoms during admission and calculated exact CI for proportions using established

	<2 years (n=34)	2–5 years (n=57)
Death	26 (76·5%)	26 (45·6%)
Weakness	21 (61·8%)	47 (82·4%)
Fever†	27 (79·4%)	36 (63·2%)
Distress‡	11 (32·4%)	47 (82·5%)
Loss of appetite	15 (44·1%)	40 (70·2%)
Diarrhoea	24 (70·6%)	30 (52·6%)
Cough	17 (50·0%)	31 (54·4%)
Vomiting	13 (38·2%)	24 (42·1%)

Data are n (%). *Common symptom=symptom documented >35 times. †Two patients were excluded from this analysis because they did not have one or more temperature recordings during admission. ‡ Includes reports of headache, myalgia, arthralgia, abdominal pain, or sore throat.

Table 1: Case fatality and common symptoms and signs during admission by age group*

	Number of cases	Number of deaths (%)	Unadjusted analysis*		Adjusted analysis*	
			HR (95% CI)*	p	HR (95% CI)*	p
Age (years)						
<2	34	26 (76·5%)	1·9 (0·9–3·9)	0·09	3·5 (1·5–8·5)	0·0047
2–5	57	26 (45·6%)	1·0		1·0	
Sex						
Male	48	26 (54·2%)	0·9 (0·4–1·8)	0·72	1·0 (0·5–2·1)	0·95
Female	43	26 (60·5%)	1·0		1·0	
EMC location						
Kailahun	57	32 (56·1%)	0·7 (0·3–1·4)	0·35	1·2 (0·5–2·7)	0·74
Bo	34	20 (58·8%)	1·0		1·0	
Ebola viral load†						
Ct<25	22	18 (81·8%)	5·5 (2·7–11·3)	<0·0001	9·2 (3·8–22·5)	<0·0001
Ct≥25	61	28 (45·9%)	1·0		1·0	

EMC=Ebola management centre. Ct=cycle threshold. *HR includes only those patients with a known date of disease onset. †Includes only those 61 patients with a known date of disease onset and with a Ct result recorded at admission.

Table 2: Final regression model of variables associated with death

methods.[15] CIs were then presented, according to age and survival status, along with the overall case fatality by age.

We used χ² tests to assess unadjusted associations between demographic characteristics, laboratory results, occurrence of symptoms, and the probability of death while admitted to an EMC. We then assessed the association between death and potential risk factors using a left-truncated Cox regression model in which patients with a known date of disease onset contributed to the population at risk from the time they were admitted to an EMC. The adjusted model included all available variables considered, a priori, as potentially associated with death: age, sex, EMC site, and viral load. We used unadjusted Kaplan-Meier curves and the log rank test to compare survival patterns by age group and viral load. Data cleaning and analysis were done with Stata versions 11.2 and 14.1 (StataCorp, College Station, TX, USA).
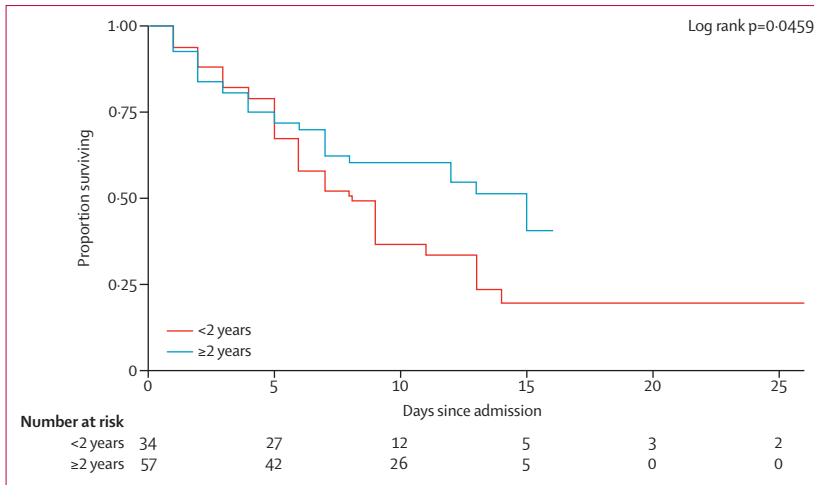
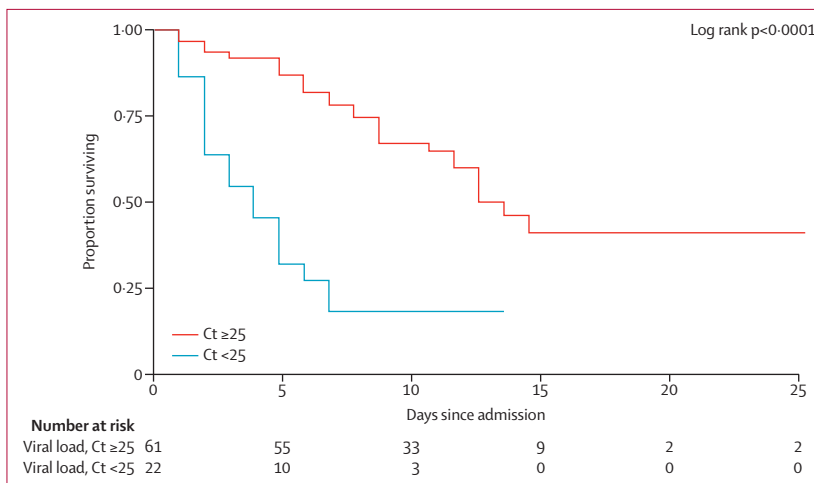**Figure 1:** Unadjusted Kaplan-Meier survival estimates by age

Figure 2: Unadjusted Kaplan-Meier survival estimates by viral cycle threshold

See **Online** for appendix

Role of the funding source

There was no funding source for this study. TS had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between June 26 and Dec 31, 2014, 1686 patients were cared for at the EMCs in Bo and Kailahun. Of the 1269 patients with confirmed Ebola virus disease, 97 (7·6%) were aged 5 years or younger (62/857 [7·2%] in Kailahun and 35/412 [8·5%] in Bo); data were missing for six children and, thus, 91 children were included in our cohort. Median age was 3 years (IQR 1–4) and 43 (47%) were girls; 52 (57·1%) children died.

The identity of the source case was not recorded for 37 (41%) children. The source case was a non-parent relative for 22 children (24%) and a parent in 35% (32) of children; the proportion of parent source-cases was

47% (16/34) in children younger than 2 years and 28% (16/57) in the 2–5 years age group.

For the 67 (74%) children for whom the date of symptom onset was recorded, the median delay to admission was 4 days (IQR 2–7 days). Median length of stay for all admitted children was 8 days (IQR 5–13 days).

Ct and date-of-onset data were available for 61 children, and we did adjusted analysis on data from this subset of children. In an adjusted model including all variables considered, a priori, of interest, age and Ct result were significantly associated with case fatality, but sex and EMC site were not. Case fatality was higher in children younger than 2 years (76·5% [26/34]) than in those aged 2–5 years (45·6% [26/57]) (table 1; data by 1-year age groups shown in the appendix p 1), adjusted HR 3·5 (95% CI 1·5–8·5; table 2, figure 1. Those with Ct <25 were nine times as likely to die as those who had a Ct ≥25 (81·8% [18/22] vs 45·9% [28/61], respectively; adjusted HR 9·2 [95% CI 3·8–22·5]; figure 2, table 2). The proportional hazards assumption was marginally violated for the age variable. However, in a secondary adjusted analysis stratified by age there was little change in adjusted HRs.

Of symptoms reported during admission, hiccups, bleeding, and confusion were present only in children who died (7·7%, 26·9%, 11·5%, respectively; table 3, figure 3). Three symptoms, on unadjusted analysis, were significantly more common in those who died than those who survived: fever (80·0 vs 59·0%; p=0·030), vomiting (51·9 vs 25·6%; p=0·012), and diarrhoea (75·0 vs 38·5%; p<0·001; table 3). Conversely, distress was more commonly reported for children who survived compared with those who died (82·1 vs 50·0%; p=0·002), where the proportion of all children with distress documented during admission was 63·7% (95% CI 53·0–73·6; table 3).

Weakness, fever, distress, loss of appetite, diarrhoea, and cough were present in more than half the children at some point during admission (table 3). Data on fever were recorded for 76 children (84%); of these, 19 (25%) had no fever either reported in their history before admission or a measured temperature <38°C on the day of admission. Therefore, they did not meet the WHO definition for a suspected case. In a subgroup of 27 children who presented within 3 days of illness onset, weakness (76·2%), fever (70·8%), loss of appetite (52·6%), and diarrhoea (50·0%) were commonly reported at admission (ie, these symptoms occurred on days 1–3 of illness), but only fever (56·5%) and weakness (40·7%) were frequent in the 3 days after admission (appendix p 2).

Discussion

We have presented an overview of Ebola virus disease in young children that includes data on symptoms during admission. All children with hiccups, bleeding, or confusion died. Furthermore, unadjusted analysis

showed a significant association between a fatal outcome and symptoms of vomiting, diarrhoea, and fever during admission. Weakness, fever, and distress were present in more than 63% of the children, and more than half had loss of appetite, diarrhoea, and cough. At admission, 25% of children did not have fever. Case fatality was 57·1% overall and was higher in children younger than 2 years than in those aged 2–5 years and in those with a high viral load.

The paucity of published age-disaggregated symptom data in young children during admission for Ebola virus disease hinders comparison of our results. In Uganda, in 2000–01, Mupere and colleagues[3] reported data for 168 inpatients younger than 18 years affected by Sudan Ebola virus. However, they included only 20 patients with laboratory-confirmed disease and did not disaggregate clinical observations by age. In 2015, the WHO Ebola Response Team in west Africa reported age-specific outcomes for Guinea, Liberia, and Sierra Leone.[2] However, as with other published descriptions of the epidemic, the authors reported only symptom history on arrival at health facilities.[2,6,8] In our experience it was often difficult to elicit a reliable symptom history on arrival at the EMC. The symptom profile of children once admitted differed from the history of symptoms reported at admission, with some indication of this effect even in children who presented in the first 3 days of their illness. This difference might reflect disease evolution, but could also be a discrepancy between reported and actual symptoms.

The presence of weakness, fever, and distress in most of the children in our cohort is similar to the findings of Qin and colleagues[16] who reported these signs and symptoms in more than half of their all-age cohort during admission. Some symptoms (gastrointestinal symptoms, fever, disorientation, hiccups, and bleeding) were more prevalent in patients who died. Qin also noted an association between vomiting, diarrhoea, loss of appetite, weakness, and "mental symptoms" and death.[16] All children with confusion, bleeding, and hiccups in our cohort died, suggesting that these symptoms could be strongly associated with a fatal outcome.

Pain has consistently been reported less often in children with Ebola virus disease than in adults,[2] possibly because of the difficulty in identifying pain in children. We acknowledge that pain is a subjective and difficult symptom to define, and that a caregiver report is not entirely reliable indicator of pain. Since objective tools to classify pain in young children were not used in our cohort, we classified any symptom suggestive of pain (sore throat, myalgia, arthralgia, abdominal pain, or headache) as distress. Distress was reported less frequently in children who died. This finding might be a pathophysiological reality, represent good palliative care, or perhaps reflect poorer recognition of distress in children who were too sick to visibly show discomfort. Distress was also reported less commonly in children

	Patients who survived (n=39)	Patients who died (n=52)	p (survived vs died)	All patients (n=91)
Fever (reported or ≥38°C)	23 (59·0%)	40* (80·0%)	0·0304	63* (70·8%)
Hiccups	0	4 (7·7%)	0·07	4 (4·4%)
Loss of appetite	25 (64·1%)	30 (57·7%)	0·5	55 (60·4%)
Vomiting	10 (25·6%)	27 (51·9%)	0·0115	37 (40·7%)
Diarrhoea	15 (38·5%)	39 (75·0%)	0·0004	54 (59·3%)
Breathlessness	3 (7·7%)	12 (23·1%)	0·0503	15 (16·5%)
Cough	22 (56·4%)	26 (50·0%)	0·54	48 (52·7%);
Jaundice	0	0·0%		0
Skin rash	3 (7·7%)	3 (5·8%)	0·71	6 (6·6%)
Confused/ disoriented	0	6 (11·5%)	0·0282	6 (6·6%)
Conjunctival injection	7 (17·9%)	5 (9·6%)	0·24	12 (13·2%)
Bleeding	0	14 (26·9%)	0·0004	14 (15·4%)
Weakness	29 (74·4%)	39 (75·0%)	0·94	68 (74·7%)
Distress†	32 (82·1%)	26 (50·0%)	0·0016	58 (63·7%)

Data are n (%), unless otherwise stated. *Two patients did not have at least one recorded temperature during admission so were not included: N=50 for patients who died; N=89 for all patients for fever.†Any of headache, myalgia, arthralgia, abdominal pain, or sore throat reported.

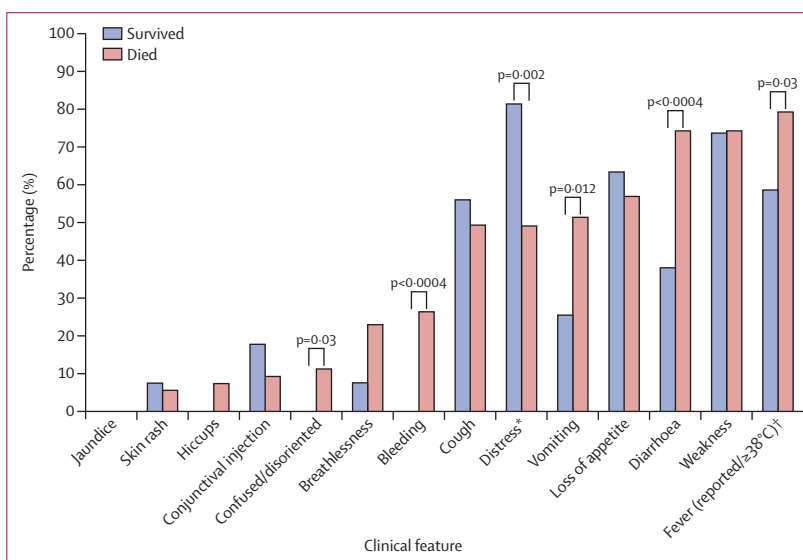*Table 3:* Symptom prevalence during admission by outcome

Figure 3: Outcome according to symptom and sign prevalence during overall admission period
*Any of headache, myalgia, arthralgia, abdominal pain, or sore throat reported. †Two patients did not have at least one recorded temperature during admission so were not included.

younger than 1 year, probably the result of poorer identification of pain in this youngest age group. In summary, a substantial proportion of children with Ebola virus disease experience distress, to which pain could be an important contributor. Efforts to objectively quantify pain, especially in the pre-verbal child, would be an important addition to clinical care protocols.

The WHO case definition for suspected Ebola virus disease, requiring fever, has been shown to be insensitive across all ages and our data support this finding for

children aged 5 years and younger.[17] In our cohort, the requirement of fever would miss 25% of cases at initial presentation, which is an unacceptably high proportion of patients.

The 76·5% case fatality we observed in children younger than 2 years was higher than that in older children in the cohort, and higher than older patients admitted to the same EMCs (case fatality rate 42% in confirmed cases aged older than 5 years; unpublished programme data, JG personal communication). This finding concurs with data published elsewhere,[2] and suggests a heightened physiological and sociological vulnerability of infants, especially where a related caregiver was not always present or able to provide care. Unfortunately, there was insufficient information available from our cohort to explore the role of a reduced level of care or complete absence of a known caregiver on mortality. Our finding that children with a high viral load at admission were nine times more likely to die than those with a low viral load is consistent with the association of viral load and case fatality noted across all ages in the west Africa outbreak.[12,18] The longer delay to arrival in those who survived compared with those who died most likely reflects survivor bias; children who had a milder illness were more likely to survive to reach the EMC.

A strength of our analysis is that it includes ongoing inpatient signs and symptoms, allowing for their evolution over time. These signs and symptoms were verified by clinical staff, and we did not rely on self-report or caregiver report. However, an inherent limitation of our retrospective analysis is that data were collected for programmatic purposes under difficult field conditions, with few trained staff. This constraint is reflected through missing records and variables, including epidemiological, symptom, and treatment information. Missing data on the clinical checklist were assumed to mean the symptom was absent; however, it might also be the result of staff not comprehensively documenting the symptom profile. The reliability of some variables such as the date of symptom onset and age may have been affected by problems of recall, as well as by children arriving unaccompanied or with unfamiliar caregivers. The absolute numbers of children with discrete symptoms and signs were small; however, we did identify significant associations between individual symptoms and mortality.

An important limitation of the study relates to the Ct measurement, as there was probably variation between the two laboratories in the translation of Ct into an objective measure of viral load. We used a cut-off of Ct 25 for high and low viral load. The interpretation across different laboratory providers of Ct in relation to replication competent viral load urgently requires harmonisation given the importance of this parameter. However, inclusion of site of testing in the model did not affect the outcome, lending support to our approach to combine data from the two laboratories for analysis. Finally, our study included only children admitted to EMCs, and thus is not necessarily applicable to overall Ebola-related morbidity and mortality in paediatric cases in the community.

Our findings support existing data that show that young children with Ebola virus disease have a very high case fatality rate. Children with a high viral load at presentation are especially vulnerable. Programme managers and researchers should aim to collect and analyse age-specific data so that the specific vulnerabilities of children are not overlooked.

References
1 WHO. Ebola Situation Report, 19 August 2015. Geneva: World Health Organization, 2015. http://apps.who.int/iris/bitstream/10665/183035/1/ebolasitrep_19Aug2015_eng.pdf?ua=1&ua=1 (accessed March 24, 2016).
2 WHO Ebola Response team. Ebola Virus Disease among Children in West Africa. *N Engl J Med* 2015; **372:** 1274–77.
3 Mupere E, Kaducu OF, Yoti Z. Ebola haemorrhagic fever among hospitalised children and adolescents in northern Uganda: epidemiologic and clinical observations. *Afr Health Sci* 2001; **1:** 60–65.
4 Olupot-Olupot P. Ebola in children: Epidemiology, clinical features, diagnosis and outcomes. *Pediatr Infect Dis J* 2015; **34 (3):** 314–16.
5 McElroy AK, Erickson BR, Flietstra TD, et al. Biomarker correlates of survival in pediatric patients with Ebola virus disease. *Emerg Infect Dis* 2014; **20:** 1683–90.
6 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.
7 Dallatomasina S, Crestani R, Sylvester Squire J, et al. Ebola outbreak in rural West Africa: epidemiology, clinical features and outcomes. *Trop Med Int Health* 2015; **20:** 448–54.
8 Schieffelin JS, Shaffer JG, Goba A, et al. Clinical illness and outcomes in patients with Ebola in Sierra Leone. *N Engl J Med* 2014; **371:** 2092–100.
9 WHO. Case definition recommendations for Ebola or Marburg virus diseases. Geneva: World Health Organization, 2014. http://www.who.int/csr/resources/publications/ebola/case-definition/en/ (accessed June 20, 2014).
10 MSF. MSF Ethics Review Board standard operating procedures. Geneva, Médecins Sans Frontières, 2013. http://fieldresearch.msf.org/msf/handle/10144/294968 (accessed June 20, 2015).
11 Sterk E. Filovirus haemorrhagic fever guideline. Barcelona, Médecins Sans Frontières, 2008. www.medbox.org/filovirus-haemorrhagic-fever-guideline/download.pdf (accessed Aug 19, 2015).
12 Fitzpatrick G, Vogt F, Gbabai OBM, et al. The contribution of Ebola viral load at admission and other patient characteristics to mortality in a Médecins Sans Frontières (MSF) Ebola Case Management Centre (CMC), Kailahun, Sierra Leone, June–October, 2014. *J Infect Dis* 2015; **212:** 1752–58.
13 Centers for Disease Control and Prevention. Ebola Virus NP Real-Time RT-PCR Assay 2014. http://www.fda.gov/downloads/MedicalDevices/Safety/EmergencySituations/UCM418810.pdf (accessed July 18, 2015).

14   Centers for Disease Control and Prevention. Ebola Virus VP40 Real-Time RT-PCR Assay. 2014. http://www.fda.gov/downloads/MedicalDevices/Safety/EmergencySituations/UCM418815.pdf (accessed July 18, 2014).

15   Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. *Biometrika* 1934; **26:** 404–13.

16   Qin E, Bi J, Zhao M, et al. Clinical features of patients with Ebola virus disease in Sierra Leone. *Clin Infect Dis* 2015; published online May 20. doi:10.1093/cid/civ319.

17   Lado M, Walker NF, Baker P, et al. Clinical features of patients isolated for suspected Ebola virus disease at Connaught Hospital, Freetown, Sierra Leone: a retrospective cohort study. *Lancet Infect Dis* 2015; **15:** 1024–33.

18   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.