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Maternal and perinatal outcomes in pregnant women with suspected Ebola virus disease in Sierra Leone, 2014

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Abstract

Objective: To describe maternal and perinatal outcomes among pregnant women with suspected Ebola virus disease (EVD) in Sierra Leone.

Methods: Observational investigation of maternal and perinatal outcomes among pregnant women with suspected EVD from five districts in Sierra Leone from June to December 2014.

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AUTHOR CONTRIBUTIONS

ML contributed to the conception of the study, data collection, data analysis, and writing and revising the manuscript. JJM contributed to the development of the first data collection tool, data collection, and revising the manuscript. FS contributed to planning and implementing the expansion of the project, data collection, and revising the manuscript. TO contributed to data collection and revising the manuscript. SE contributed to the conception and design of the study, data analysis, and revising the manuscript. GWS and APK contributed to the conception of the study and revising the manuscript. APK contributed to the conception of the study, revising the manuscript, and obtaining approval from the Sierra Leone Ministry of Health and Sanitation. JM contributed to the conception of the study, data collection, and revising the manuscript. DM contributed to the design of the study, data analysis, and revising the manuscript.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

Suspected cases were ill pregnant women with symptoms suggestive of EVD or relevant exposures who were tested for EVD. Case frequencies and odds ratios were calculated to compare patient characteristics and outcomes by EVD status.

Results: There were 192 suspected cases: 67 (34.9%) EVD-positive, 118 (61.5%) EVD-negative, and 7 (3.6%) EVD status unknown. Women with EVD had increased odds of death (OR 10.22; 95% CI, 4.87–21.46) and spontaneous abortion (OR 4.93; 95% CI, 1.79–13.55) compared with those without EVD. Women without EVD had a high frequency of death (30.2%) and stillbirths (65.9%). One of 14 neonates born following EVD-negative and five of six neonates born following EVD-positive pregnancies died.

Conclusion: EVD-positive and EVD-negative women with suspected EVD had poor outcomes, highlighting the need for increased attention and resources focused on maternal and perinatal health during an urgent public health response. Capturing pregnancy status in nationwide surveillance of EVD can help improve understanding of disease burden and design effective interventions.

Keywords

Ebola virus disease; Maternal health; Mortality; Perinatal outcomes; Sierra Leone; Spontaneous abortion; Stillbirth; West Africa

1 | INTRODUCTION

The 2014 Ebola virus disease (EVD) epidemic was the largest Ebola outbreak in history, severely affecting multiple countries in West Africa. Although there have been recent advances in treatment of EVD, management has usually consisted of supportive care, with mortality ranging from 25% to 90%.[1–6] For the 2014 EVD epidemic, the Centers for Disease Control and Prevention (CDC) and WHO estimated that 28% of all EVD cases (including suspected, probable, and laboratory-confirmed) and 45% of only laboratory-confirmed cases died as of April 2016.[7]

While data exist on EVD outcomes among the general population, information about outcomes among pregnant women is insufficient, with only a limited number of published reports. In the Democratic Republic of the Congo, 9 of 82 EVD-positive pregnant women survived a 1976 outbreak[8,9] and 1 of 15 EVD-positive pregnant women survived a 1995 outbreak.[8,10] In these reports, perinatal mortality was universal, with spontaneous abortions occurring in 23%–67% of pregnancies and no reports of neonates born to EVD-positive women surviving beyond 19 days.[9]

Prior to the 2014 EVD outbreak, Sierra Leone had one of the highest maternal mortality ratios in the world, estimated at 1100 maternal deaths per 100 000 live births.[11] Only one maternity hospital exists in Sierra Leone; this facility in Western Area serves as a tertiary referral center treating the most severely ill patients. EVD isolation units were established to evaluate and test people suspected of EVD in isolation from the community and other patients. Those testing positive for EVD were referred to Ebola Treatment Units (ETUs) for EVD management. Isolation units were intended to house patients temporarily and were not equipped to perform invasive procedures, such as cesarean deliveries. Given their limited

resources, many isolation units and ETUs did not admit pregnant women owing to their need for specialized care and expected poor outcomes. Often, one isolation unit in a district would accept pregnant women and become the unofficial referral center.

Because information about pregnant women with EVD is limited, the aim of the present study was to describe the maternal and perinatal outcomes among pregnant women with suspected EVD in Sierra Leone to help guide improvements in the clinical management of this population.

2 | MATERIALS AND METHODS

We conducted an observational investigation of maternal and perinatal outcomes among pregnant women with suspected EVD from isolation units treating pregnant women in Western Area, Bo, Bombali, Kenema, and Port Loko districts of Sierra Leone, including the large maternity hospital in Western Area, by collecting data retrospectively from June 29 to November 6, 2014, and prospectively from November 7 to December 20, 2014. Suspected EVD cases were defined as pregnant women with symptoms suggestive of EVD or relevant exposures (Fig. 1) who were tested for EVD in an isolation unit or elsewhere in the facility. Laboratory testing for EVD with polymerase chain reaction (PCR) was done on blood samples (or oral swab samples if the patient died prior to specimen collection) and used to classify pregnant women as EVD-positive or EVD-negative. The study received non-research determination by the CDC, requiring no patient consent; it was also approved by the Sierra Leone Ministry of Health and Sanitation.

CDC case investigation forms, medical charts, and laboratory testing results were used to retrospectively collect information about patient demographics, presenting symptoms, EVD testing, results, admission and testing dates, and maternal and perinatal outcomes. Starting on November 7, a revised tool was used for prospective data collection to capture more detailed information on EVD exposures, gestational age at presentation, and pregnancy complications prior to presentation. Pregnancy status and outcomes such as spontaneous abortion and stillbirth were based on patient and healthcare provider reports, not estimates of gestational age. The outcomes of all suspect cases were collected for the period they were cared for in isolation units, but not after discharge. For women who were transferred from the maternity hospital to ETUs for EVD management, we contacted the receiving ETUs to obtain information on maternal and perinatal outcomes. Based on the information provided about symptoms and complications, we attempted to classify the maternal cause of death.

SAS version 9.3 (SAS Institute, Cary, NC, USA) was used to compare demographics, patient characteristics, and outcomes of EVD-positive and EVD-negative women using Pearson χ^2 tests and logistic regression to calculate crude odds ratios by EVD status for maternal and perinatal outcomes. $P<0.05$ was considered statistically significant. In a subanalysis, we obtained numbers of live births in the Western Area maternity hospital and calculated maternal mortality ratios (per 100 000 live births) and stillbirth rates (per pregnancies) during the first 6 months of the epidemic (July–December 2014) and the 6 months preceding the outbreak in Western Area (January–June 2014).

3 | RESULTS

We collected data on 192 pregnant women with suspected EVD from June 29, 2014, through December 20, 2014, with 134 (69.8%) cases reported from the isolation unit in Western Area. Figure 2 presents these patients stratified by EVD status and outcome. Sixty-seven (34.9%) women with suspected EVD subsequently tested positive for Ebola virus (EVD-positive), while 118 (61.5%) women tested negative for Ebola virus (EVD-negative). Seven (3.6%) women had unknown test results due to lack of available testing, indeterminate results, or patient elopement. These women were not included in the EVD-status specific analyses.

Demographic characteristics are shown in Table 1. The median age of EVD-positive women was lower than for EVD-negative women (23 vs 26 years; $P<0.001$). A majority (81.3%) of women were married. Roughly half (n=57, 47.5%) of the women worked as farmers or traders, while 35 (29.2%) women reported no employment outside the home. Marital status and occupation did not differ significantly by EVD status. Labor status at presentation was available for 68 (36.8%) women. Among this group, 7 (21.2%) of the 33 EVD-positive women arrived in labor, compared with 18 (51.4%) of the 35 EVD-egative women ($P=0.010$). Gestational age at presentation was available for 104 (56.2%) women; 6 (14.0%) of EVD-positive women presented at term (>37 weeks) compared to 25 (41.0%) of EVD-negative women ($P=0.003$).

Of the 181 women with known outcomes, 88 (48.6%) died, including 53 (81.5%) of the 65 EVD-positive women compared with 35 (30.2%) of the 116 EVD-negative women (OR 10.22; 95% CI, 4.87–21.46). Mortality data were not available for four women: two EVD-positive and two EVD-negative (Table 2).

Review of symptoms and complications data revealed that nearly all of the EVD-positive mothers who died (n=52; 98.1%) appeared to have an infection that could have contributed to maternal death, although 21 (39.6%) women also had an obstetric indication that may have contributed to maternal death (20 had obstetric hemorrhage and 1 had eclampsia). For the 35 EVD-negative maternal deaths, 19 (54.3%) women likely died from infection, 5 (14.3%) from obstetric hemorrhage, 3 (8.6%) from obstructed labor, and 2 (5.7%) died from uterine rupture. There was insufficient information to categorize the most likely cause of death for 1 EVD-positive and 6 EVD-negative women.

EVD-positive status was associated with increased odds of having a spontaneous abortion (OR 4.93, 1.79–13.55), neonatal death for live births (OR 65.00, 3.38–1251.28), and overall neonatal or fetal death prior to discharge (OR 12.30, 1.56–97.35); however, it was not associated with increased odds of having a stillbirth (OR 0.78, 0.23–2.63). During their time in an isolation unit, 1 (7.1%) of 14 neonates born to EVD-negative women died, while 5 (83.3%) of 6 neonates born to EVD-positive women died. The one surviving neonate born to an EVD-positive woman was lost to follow-up. Little information is known about this neonate and we were unable to confirm survival after 2 months of age. Excluding this neonate, all of the EVD-positive women had poor perinatal outcomes resulting in spontaneous abortion, stillbirth, neonatal death, or maternal death with an undelivered

pregnancy. Pregnancy outcomes for EVD-negative women were also poor with 81.2% (n=56) of pregnancies resulting in spontaneous abortion, stillbirth, or neonatal death (Table 2).

We conducted a mortality subanalysis for the Western Area maternity hospital. Mortality did not differ in the Western Area isolation unit compared with non-Western Area isolation units for EVD-positive women (P=0.590) and EVD-negative women (P=0.144) (Table 3). Among this hospital's general population, there was a 27% decrease in overall hospital admissions during the EVD outbreak compared with the 6 months prior to the facility's first suspected EVD patient in July 2014 (Table 4). The facility-based maternal mortality ratio increased by 66% and the rate of stillbirths increased by 18% during the EVD outbreak compared with the 6 months prior to the EVD outbreak (Table 4).

4 | DISCUSSION

These data represent the largest collection of information on pregnancy and perinatal outcomes for pregnant women with suspected EVD. We found that pregnant women are able to survive EVD infection, even after childbirth. Unfortunately, perinatal outcomes were extremely poor, and neonates born to EVD-positive women generally did not survive. This finding is consistent with publications about previous EVD outbreaks as well as reports from the 2014 EVD outbreak that describe poor neonatal survival.[8–10,12] During the 2014 EVD outbreak, Médecins Sans Frontières reported 31 pregnant women with EVD surviving among all eight Ebola Management Centers in Liberia, Sierra Leone, and Guinea between April 2014 and April 2015.[12] All of these women had spontaneous abortions or stillbirths except for one woman who had a live birth; however, this neonate died after 2 days. While treatment has typically been limited to supportive care, early access to treatment and recent advances in management may improve these poor survival rates. In January 2016, a study evaluating the efficacy of convalescent plasma for the treatment of EVD in Guinea found that mortality among pregnant women decreased after treatment.[13] Additionally, a neonate born to an EVD-positive woman (who died after delivery) was given the experimental drugs ZMapp (Mapp Biopharmaceutical, San Diego, CA, USA) and GS-5734 (Gilead Sciences, Foster City, CA, USA), survived, and was declared EVD-free.[14,15] This provides some hope that new and improved interventions may improve outcomes and reduce neonatal mortality.[14,15]

While poor maternal and perinatal outcomes among EVD-positive women were not surprising, the poor outcomes for EVD-negative women, including maternal deaths and stillbirths, were more common than expected. Pregnant women in isolation units during the height of the 2014 EVD outbreak were likely more severely ill than the average pregnant women seeking healthcare for labor or pregnancy complications and had fewer life-saving interventions available. Many of the EVD-negative women appeared to have infectious causes of death rather than the more common causes of maternal death, such as eclampsia and hemorrhage.[16] The high maternal mortality among EVD-negative pregnant women meeting the clinical criteria for suspected EVD may be more reflective of the illness or symptom severity of these women resulting from a non-EVD cause. One recent study in a nonpregnant population at an ETU in Sierra Leone found that nearly half of those presenting

to the ETU as suspected EVD cases had other infectious causes such as malaria, enteric illnesses, or lower respiratory tract infections.[17] Determining the specific infection responsible for death and the contribution of EVD was not possible for most maternal deaths because comprehensive testing was not performed to determine which proportion were infected or simultaneously co-infected with non-EVD pathogens. In addition to suffering from other severe non-EVD illnesses, a small number of EVD-negative pregnant women may have actually been EVD survivors who had subclinical or minimally symptomatic infections and cleared EVD prior to presentation,[18,19] yet were still susceptible to long-term sequelae of EVD. Little is known about EVD in pregnancy and pregnant women may still be at higher risk for pregnancy-related complications even after clearing the infection. However, no antibody testing was done at the isolation units, therefore it was not possible to identify EVD survivors. Additional laboratory diagnostics are important to determine the contribution of EVD to these poor outcomes, including testing for other infections and performing EVD antibody testing to differentiate survivors from EVD-negative women.

The 2014 EVD epidemic directly and indirectly impacted the health of all pregnant women in Sierra Leone by affecting access to and quality of routine healthcare. The fragile state of healthcare delivery during the outbreak likely exacerbated the poor outcomes of EVD-negative pregnant women, including worsening complications resulting from inadequate obstetric care in an under-resourced setting. There have been many reports that women did not get appropriate prenatal care because they avoided healthcare facilities owing to fear of contracting EVD.[15,20] For similar reasons, women may avoid healthcare facilities when they experience obstetric complications and present too late for successful treatment. The proportions of maternal and perinatal deaths were consistent both in the maternity hospital isolation unit and other isolation units.

Nationally representative data on pregnant women and their outcomes are needed to determine the true burden of EVD on pregnant women in Sierra Leone, including those infected with EVD and EVD-negative women who are indirectly impacted. During the 2014 EVD epidemic, EVD surveillance systems did not routinely capture information on pregnancy status. Strengthening the surveillance infrastructure of EVD (and other communicable diseases) by improving diagnostic testing of EVD and other diseases and routinely capturing pregnancy status would improve completeness of surveillance activities and estimates of EVD disease burden. It is also essential to improve measurement of maternal and perinatal mortality and capture information on causes of maternal death, which can be used to design effective interventions to eliminate preventable maternal and perinatal deaths.

During the 2014 EVD outbreak, there were continuous changes in the policies and practices for management of pregnant women with suspected EVD that may have affected the outcomes of these women, but the impact is difficult to quantify. Given the chaotic setting during which data were collected, some data were incomplete. However, data quality improved as collection became prospective, reducing recall bias and improving standardization by using one collection tool across districts. Pregnancy status was primarily self-reported, which may have excluded some pregnant women. Similarly, outcomes of spontaneous abortion or stillbirth were determined by administrative records based on

patient and healthcare provider reports, rather than documentation of gestational age. Our study population included pregnant women presenting to isolation units in only five districts and is not nationally representative. We attempted to follow up on the outcomes of pregnant women transferred to other facilities; however, we were unable to confirm the outcomes for 3 of 15 pregnant women.

Attempts to classify the cause of death were limited by the minimal clinical information available and lack of comprehensive testing for EVD and other infectious diseases. Having only one negative EVD result was considered sufficient for classification as EVD-negative and no antibody testing was performed to identify EVD survivors with prior infection. EVD testing was not conducted or results were unavailable for neonates born to EVD-positive women, and EVD testing was not performed on stillbirths, as it was not standard of care at the time.

In conclusion, we found that among a population of pregnant women with suspected EVD in Sierra Leone, EVD-positive women had a significantly higher number of adverse pregnancy outcomes and maternal deaths than EVD-negative women. Although worse outcomes were not surprising for EVD-positive pregnant women, the outcomes of EVD-negative pregnant women were also poor. Although pregnant women with suspected EVD may be more ill than the general population of pregnant women, the high mortality highlights the widespread need to invest in maternal health services. Nationwide surveillance of EVD and other infectious diseases among pregnant women can improve understanding of the burden of these diseases to inform effective interventions to improve maternal and perinatal outcomes.

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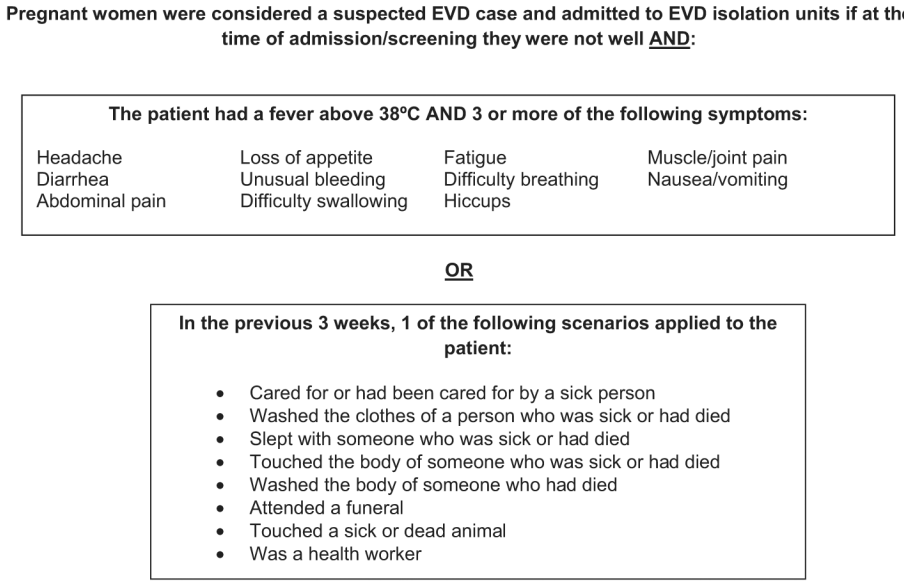

FIGURE 1.

Criteria for determination of EVD status among pregnant women, Sierra Leone, 2014.

Abbreviation: EVD, Ebola virus disease.

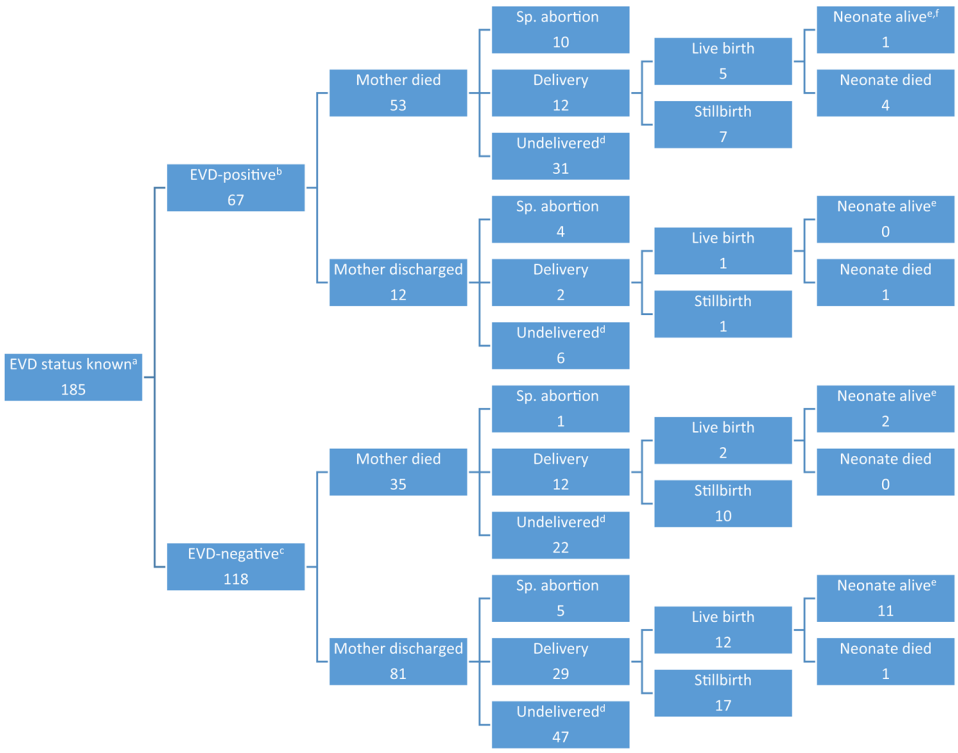

FIGURE 2.

Maternal and perinatal outcomes by Ebola status, Sierra Leone, 2014. Abbreviations: EVD, Ebola virus disease; Sp. abortion, spontaneous abortion. [a]Of 192 pregnant women, 7 women had an unknown EVD status. [b]Of 67 EVD-positive women, 2 had an unknown outcome (1 of whom had a stillbirth). [c]Of 118 EVD-negative women, 2 had an unknown outcome. [d]These women did not deliver during their time in the isolation unit (prior to death or discharge), and the outcome of the mother and fetus after discharge is not known. Four women were admitted to the isolation unit during the second trimester and 1 woman was admitted at the beginning of the third trimester. The gestational age of the other 2 women was not known. [e]Alive at time of discharge from isolation unit. [f]One neonate was reported to be alive 2 mo after birth but survival has not been confirmed.

TABLE 1

Demographic data reported by pregnant women at presentation to isolation unit, Sierra Leone, 2014.

Characteristics	Ebola test result[a] Positive (n=67)[c]	Negative (n=118)[c]	*P* value[b]
Age, y[d]			
Median age [range]	23 [13−37]	26 [15−50]	< 0.001
13−18	14 (21.5)	18 (15.7)	0.060
19−24	21 (32.3)	27 (23.5)	
25−34	28 (43.1)	51 (44.3)	
≥35	2 (3.1)	19 (16.5)	
Married[e]			0.758
Yes (n=91, 81.3%)	38 (82.6)	53 (80.3)	
No (n=21, 18.8%)	8 (17.4)	13 (19.7)	
Occupation[f]			0.077
Farmer/trader (n=57, 47.5%)	18 (38.3)	39 (53.4)	
Unemployed/housewife (n=35, 29.2%)	15 (31.9)	20 (27.4)	
Student (n=13, 10.8%)	8 (17.0)	5 (6.8)	
Nurse (n=7, 5.8%)	5 (10.6)	2 (2.7)	
Police (n=2, 1.7%)	0	2 (2.7)	
Other (n=6, 5.0%)	1 (2.1)	5 (6.8)	
Healthcare worker (HCW)[g]			0.128
HCW (n=8, 6.3%)	5 (10.6)	3 (3.8)	
Not HCW (n=118, 93.7%)	42 (89.4)	76 (96.2)	
Isolation unit district			< 0.001
Bo(n=ll, 5.9%)	10 (14.9)	1 (0.8)	
Kenema (n=16, 8.6%)	12 (17.9)	4 (3.4)	
Bombali (n=24, 12.9%)	11 (16.4)	13 (11.0)	
Port Loko (n=4, 2.2%)	1 (1.5)	3 (2.5)	
Western Area (n=130, 70.3%)	33 (49.3)	97 (82.2)	
Details at presentation to healthcare facility			
Labor status at presentation (n=68)[h]			0.010
In labor (n=25, 36.8%)	7 (21.2)	18 (51.4)	
Not in labor (n=43, 63.2%)	26 (78.8)	17 (48.6)	
Gestational age at presentation, wk (n=104)[i]			0.003
<28 (n=29, 27.9%)	18 (41.9)	11 (18.0)	
28−37 (n=44, 42.3%)	19 (44.2)	25 (41.0)	
>37(n=31, 29.8%)	6 (14.0)	25 (41.0)	

[a] Seven women had an unknown Ebola test result.

[b] Calculated using χ^2 or independent *t* test.

[c] Values are given as number (percentage). Percentages calculated using column totals for all patients with data available for that variable. The number of patients with data available can vary for each variable.

[d] Age was not available for 5 women (2 EVD-positive; 3 EVD-negative).

[e] Marital status was not documented for 73 women (21 EVD-positive; 52 EVD-negative).

[f] Occupation was not documented for 65 women (20 EVD-positive; 45 EVD-negative).

[g] HCW status was not documented for 59 women (20 EVD-positive; 39 EVD-negative).

[h] Labor status at presentation was unknown for 117 women (34 EVD-positive; 83 EVD-negative).

[i] Gestational age at presentation was unknown for 81 women (24 EVD-positive; 57 EVD-negative).

TABLE 2

Maternal and perinatal outcomes by Ebola status, Sierra Leone, 2014.[a]

Outcome	Ebola test result		
	Positive (n=67)	**Negative (n=118)**	**Odds ratio (95% confidence interval)**
Mother's final status (n=181)[b]			10.22 (4.87−21.46)
Discharged from isolation (ref)	12 (18.5)	81 (69.8)	
Died	53 (81.5)	35 (30.2)	
Spontaneous abortion (n=185)			4.93 (1.79−13.55)
No (ref)	53 (79.1)	112 (94.9)	
Yes	14 (20.9)	6 (5.1)	
Neonate's delivery status (n=56)			0.78 (0.23−2.63)
Alive (ref)	6 (40.0)	14 (34.1)	
Stillborn	9 (60.0)[f]	27 (65.9)	
Final neonatal survival status for live births (n=19)			65.00 (3.38−1251.28)
Alive (ref)	1 (16.7)[d]	13 (92.9)	
Died	5 (83.3)	1 (7.1)	
Neonatal/fetal status prior to discharge (n=128)[b,c]			12.30 (1.56−97.35)
Alive (ref)	1 (1.7)[d]	13 (18.8)	
Dead[e]	58 (98.3)	56 (81.2)	

[a] Values are given as number (percentage) unless indicated otherwise. Percentages calculated using column totals.

[b] Mother's final status unknown for 4 women (2 EVD-positive; 2 EVD-negative).

[c] Neonatal status unknown because mother's final status unknown or mother discharged while still pregnant (57 patients [8 EVD-positive; 49 EVD-negative]).

[d] One neonate was reported alive 2 mo after birth, but survival has not been confirmed. Little information is known about this neonate except that it was born at 38 wk of gestation on the day the mother presented to the hospital complaining of fever, headache, fatigue, weakness, vomiting, and abdominal pain. The mother died following delivery as a result of postpartum hemorrhage.

[e] Includes 22 undelivered neonates from the 35 mothers who died, and totals for spontaneous abortion, stillbirth, and neonatal death.

[f] Includes one stillbirth to an EVD-positive women who had an unknown outcome.

TABLE 3

Maternal deaths according to location of isolation unit, Sierra Leone, 2014.

	Non-Western area		Western area		
Ebola test result	**No. alive**	**No. dead**	**No. alive**	**No. dead**	***P* value**[a]
Positive	8	26	6	27	0.590
Negative	12	9	71	26	0.144

[a] χ^2 test.

TABLE 4

Comparison of patient load and outcomes at the maternity hospital in the Western Area urban district before and during the Ebola outbreak, Sierra Leone, 2014.

Variable	Prior to Ebola outbreak: January-June 2014	During Ebola outbreak: July-December 2014
Total hospital admissions	5138	3774
No. of maternal deaths	32	53
No. of live deliveries	2300	2290
Maternal mortality ratio[a]	1391/100 000 live deliveries	2314/100 000 live deliveries
Stillbirth rate[b]	137/1000 total deliveries	161/1000 total deliveries

[a] Maternal deaths per 100 000 live deliveries.

[b] Stillbirths per 1000 total deliveries.