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Ebola Patient Virus Cycle Threshold and Risk of Household Transmission of Ebola Virus

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Abstract

Background.—Identifying risk factors for household transmission of Ebola virus (EBOV) is important to guide preventive measures during Ebola outbreaks.

Methods.—We enrolled all confirmed persons with EBOV disease who were the first case patient in a household from December 2014 to April 2015 in Freetown, Sierra Leone, and their household contacts. Index patients and contacts were interviewed, and contacts were followed up for 21 days to identify secondary cases. Epidemiologic data were linked to EBOV real-time reverse-transcription polymerase chain reaction cycle threshold (Ct) data from initial diagnostic specimens obtained from enrolled index case patients.

Results.—Ct data were available for 106 (71%) of 150 enrolled index patients. Of the Ct results, 85 (80%) were from blood specimens from live patients and 21 (20%) from oral swab specimens from deceased patients. The median Ct values for blood and swab specimens were 21.0 and 24.0, respectively ($P = .007$). In multivariable analysis, a Ct value from blood specimens in the lowest quintile was an independent predictor of both increased risk of household transmission (P

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Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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= .009) and higher secondary attack rate among household contacts (P = .03), after adjustment for epidemiologic factors.

Conclusions.—Our findings suggest the potential to use Ct values from acute EBOV diagnostic specimens for index patients as an early predictor of high-risk households and high-risk groups of contacts to help prioritize EBOV disease investigation and control efforts.

Keywords

Ebola; Ebola virus; transmission; household contact; cycle threshold; epidemiology; risk factors; preventive factors; Sierra Leone

The 2014–2016 Ebola virus (EBOV) outbreak in Sierra Leone, Guinea, and Liberia had 28 646 reported cases and was associated with a mortality rate of 60% [1]. The first reported cases were detected in rural areas of Guinea and Sierra Leone, but transmission spread rapidly to involve major urban areas, including Freetown, Sierra Leone, and Monrovia, Liberia.

EBOV is known to be spread by person-to-person transmission through contact with infected body fluids, with household contacts and healthcare workers among the highest-risk groups [2–10]. Rapid diagnosis, isolation, investigation, and reporting of new cases of EBOV disease (EVD) are key components of EVD prevention and control [2]. Public health investigations to rapidly identify, evaluate, and place under observation all persons who have come into close contact with persons with EVD in the household or other settings in which physical contact or contact with body fluids has occurred are an important part of strategies to interrupt transmission [11]. Knowledge of risk factors for transmission is also important to guide preventive measures [3–11].

We conducted a prospective household transmission study in Freetown, Sierra Leone, during the 2014–2016 EVD epidemic, which demonstrated that EVD developed in approximately 10% of individual exposed contacts , and 27% of households had ≥1 secondary EVD cases [3]. Several index case, household, and contact epidemiologic risk and preventive factors were identified as independent predictors of household transmission [3].

Real-time quantitative reverse-transcription polymerase chain reaction (qRT-PCR) is the current standard for confirming acute EVD. qRT-PCR inversely measures the quantity of viral nucleic acid by determining the number of cycles of RNA replication that have occurred when EBOV-specific RNA signal is detected, the cycle threshold (Ct) value, which can thus be considered a surrogate measure of viral load [12–14]. It is plausible that higher presumed viral load in a patient’s acute specimen (lower Ct value) would be associated with increased rates of transmission, but this association has never been evaluated or reported.

We postulated that if such an association exists and could be established, it could have important implications for the ability of public health officials to predict households and contacts likely to have a higher risk of EBOV exposure. We recognized the opportunity to link the Ct value for specimens from index case patients—provided by most laboratories as part of the diagnostic evaluation of clinical specimens for EBOV—with epidemiologic data collected prospectively for index patients, households, and contacts enrolled in our

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household transmission study, and we included among our study objectives the examination of Ct values from index patients as a potential risk factor for transmission. This report describes the relationship between these Ct values and EVD secondary attack rates (SARs) in households and individual exposed contacts, in the context of previously reported epidemiologic risk factors for EVD in the same index patient and household contact cohort in Freetown, Sierra Leone.

METHODS

Detailed methods for the household transmission study have been reported elsewhere [3]. Briefly, we enrolled laboratory-confirmed EVD case patients who were the first reported case patients in their household and their household contacts in greater Freetown from 15 December 2014 through 30 April 2015. EVD cases were identified through routine EVD surveillance, and suspected cases were investigated within 24 hours after notification. Households were visited for 21 days after index case isolation to determine whether contacts manifested EVD symptoms or died. We defined household contacts as persons who spent ≥1 night sharing the same residential unit of indoor living space as the index patient after symptom onset. Index patients or head of household proxies and contacts were interviewed to collect household, index case, and contact epidemiologic risk factor data. We developed multivariable models for case factors, case and household factors together, and case, household, and contact factors combined. The outcomes of interest were transmission to individual contacts, using individual SAR models, and transmission to households, using household transmission rate (HTR) models. The SAR was defined as the proportion of individual contacts in whom EVD developed and HTR as the proportion of households with ≥1 secondary EVD case during the 21-day follow-up period.

During the 2014–2016 EVD outbreak in Sierra Leone, laboratory testing for suspected cases of EVD in Freetown was conducted by 7 laboratories located throughout the city. Geographic proximity to the healthcare facility where the index patient was evaluated and laboratory capacity were factors determining which laboratory performed specimen testing. Laboratories used different methods of qRT-PCR testing similar to those previously reported for the laboratory in Bo District [14] to detect EBOV RNA from blood (live patients) and oral swab (deceased patients) specimens. In addition to a qualitative test result (eg, positive or negative), laboratories reported Ct values for positive specimens, an inverse measure of EBOV RNA and a surrogate for viral load [12, 13]. Although interlaboratory variations occurred between Ebola testing laboratories, the overall Ct values were comparable (see note to Supplementary Figure 1).

To obtain Ct data for enrolled index patients, we queried the national laboratory database, matching on name, case identification number, age, sex, address, and EVD onset date, and we linked results to the household transmission study epidemiologic database [3]. All matching was done in Sierra Leone, and identifiers were removed before departure.

We compared characteristics between index patients and households with a Ct value and those without a Ct value available, using likelihood ratio χ^2 and Kruskal-Wallis tests for categorical and continuous variables, respectively. We used logistic regression to examine

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the association between Ct values and the HTR and SAR as transmission outcome measures. For the SAR outcome, we adjusted for household clustering using generalized estimating equations. Using the percentiles of the distribution, we divided the Ct values for blood specimens into quintiles and those for oral swab specimens into 2 groups defined by the median for analysis. These divisions were for data display and not based on a biologic rationale.

For blood specimens, we added Ct data to the multivariable models of epidemiologic risk factors developed and reported for the parent household transmission study [3]. The number of oral swab specimens was too small to examine in multivariable analysis. We kept variables if they had a 2-sided statistical significance level ≤.05. We performed all analyses using SAS software (SAS). The investigation was determined to be a public health response activity by the Sierra Leone Ministry of Health and United States Centers for Disease Control and Prevention Ethical Review Boards, with a waiver of informed consent.

RESULTS

Ct data were available for 106 (71%) of 150 index patients enrolled in the parent household transmission study (Figure 1). Of the Ct results, 85 (80%) were from blood specimens obtained from live patients and 21 (20%) from oral swab specimens obtained from deceased patients. Index patient Ct data were available for 603 of 838 enrolled contacts (72%), including blood specimen data for 477 contacts and oral swab specimen data for 126. Ct results for 2 patients who lived alone were excluded from further analyses. The median Ct value for blood specimens was 21.0 (mean, 22.0, interquartile range, 18.5–24.6) compared with 24.0 for oral swab specimens (mean, 25.5; 22.6–29.1) ($P = .007$) (Figure 2). Ct values by laboratory are displayed in Supplementary Figure 1.

To assess the representativeness of the Ct data for the study population overall, we examined epidemiologic characteristics of index patients with blood specimen data, oral swab specimen data, and no Ct data available for analysis (Supplementary Table 1). There were no differences in age or sex between the 3 groups. Index patients with a Ct value available were more likely than those without Ct data to reside in an urban district ($P = .001$). We examined Ct values according to index patient characteristics to determine whether Ct values varied by epidemiologic or clinical characteristics of the study population (Supplementary Table 2). Ct values did not differ according to index patient age group, clinical symptoms, or symptom duration.

The HTRs and SARs among contacts according to the Ct value of the index patient for the 85 index patients with blood specimens are presented in Figure 3A and 3B. The overall HTR was 24% (20 of 83 households), with a range from 12% in the third quintile to 53% in the lowest quintile. The overall SAR was 8.2% (39 of 477 contacts), with a range from 3% in the third quintile to 19% in the lowest quintile. Overall, there was a significant trend of declining SAR and HTR with increasing Ct values ($P = .03$ and .002, respectively). There was no association between Ct values and transmission among the 4 higher quintiles ($P = .89$ for HTR and $P = .82$ for SAR), with the significant trend accounted for by differences between those with a Ct value in the lowest quintile and those with a Ct value in any of the

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higher quintiles. For HTR, the rate was 52.9% among those with a Ct value in the lowest quintile compared with 16.7% for households with an index patient Ct value in a higher quintile ($P = .002$). The SARs were 18.9% and 5.1% among individuals in households with an index patient with Ct values in the lowest quintile or in a higher quintile, respectively ($P < .001$).

Transmission rates in households according to the Ct value of the index patient for the 21 index patients with oral swab specimens are presented in Table 1. The HTR was higher for index patients with Ct values less than the median (64% vs 40%), but this difference was not statistically significant ($P = .28$). The SAR was also higher for index patients with Ct values less than the median (27% vs 9%), and this difference was statistically significant ($P = .01$).

Table 2 presents results of multivariable analyses of Ct value as an additional risk factor for Ebola transmission in integrated models including epidemiologic factors previously identified in the published household transmission study. In an HTR model adjusted for the index patient and household factors identified as independent predictors of transmission in the original epidemiologic risk factor model (no reported fever in the index patient, index patient age <20 years, index patient death in the house, and no piped drinking water source for the household) [3], the Ct value was an independent predictor of household transmission using both a continuous and a categorical scale ($P = .048$ and $P = .007$, respectively). After an additional adjustment for the laboratory where EBOV testing was performed, Ct on the continuous scale was no longer statistically significant ($P = .06$), but a Ct value in the lowest quintile remained significant ($P = .009$).

In an SAR model adjusted for the factors previously identified as independent predictors of transmission in the original epidemiologic risk factor model (providing care for the index patient, avoiding the index patient, no reported fever in the index patient, index patient death in the house, and no piped drinking water source for the household) [3], Ct value was not associated with the SAR on a continuous scale ($P = .07$) but was an independent predictor of EBOV transmission using the categorical scale ($P = .04$). After an additional adjustment for EBOV testing laboratory, the P values were .06 and .03 for Ct on continuous and categorical scales, respectively. We performed sensitivity models to correct for possible overestimation of secondary cases infected by the index patients where we restricted to households with only a single or no secondary cases, and where we adjusted for time between symptom onset and specimen collection; the results were similar (Table 2). The laboratory category was not statistically significant in any of the models (Table 2).

DISCUSSION

We conducted a prospective study of risk factors for household transmission of EBOV in Freetown, Sierra Leone, during the 2014–2016 EVD outbreak [3]. After adjustment for case, household, and contact epidemiologic factors, we identified Ct results from the initial diagnostic specimen for the index patient as an independent predictor of increased household transmission. This finding suggests the potential for public health officials to use Ct results available at the time of index case diagnosis to help inform algorithms to identify and prioritize investigations and more intensive monitoring and follow-up toward

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the highest-risk households and contacts during EVD outbreaks. Thus, these findings could have important implications for EVD prevention and control policies.

In the epidemiologic component of our study of EBOV transmission from new EVD case patients to household contacts conducted in Sierra Leone in 2015, we identified several risk and preventive factors independently associated with the risk of household transmission [3]. EVD symptoms but no reported fever in the index patient, index patient death in the household, being a close relative of the index patient, and providing care to the index patient were identified as independent risk factors for household transmission, and behaviors to avoid the index patient and household access to a piped water source were associated with lower risk of household transmission [3]. In the current report, we build on these epidemiologic results by demonstrating that Ct values, an inverse surrogate measure of EBOV load, are independently associated with increased household transmission of EBOV in the same cohort.

In our study, EBOV Ct values in the lowest quintile from blood specimens were associated with 3-fold higher HTRs as well as 3-fold higher SARs for household contacts of patients with EVD. Our findings point to the potential importance in future outbreaks of using blood specimen Ct values during outbreak investigation and contact tracing, along with other clinical and epidemiologic factors associated with EBOV transmission risk [3–5, 8–10] to help identify which households should be prioritized for investigation and close observation. Such risk stratification could be particularly important in large outbreaks, such as the one experienced in Sierra Leone and neighboring countries in 2014–2015, where resource and logistical limitations led to the need to prioritize public health prevention efforts, and in critical settings such as the current outbreak in the Democratic Republic of Congo, where there are challenges to contact follow-up in conflict zones [15] and prioritization could be helpful. However, it should be noted that even for index patients with high Ct values, there remained a risk of household transmission, and we could not discern a Ct value for which the risk was negligible and contact tracing unnecessary. Further studies are needed to confirm these findings in a larger number of patients and households with testing performed in a single laboratory or with methods standardized across laboratories.

Our study included a small number of oral swab specimens from deceased patients. We analyzed Ct values from swab specimens separately, because such specimens often result in higher Ct values and are thus not directly comparable to results from blood specimens [13]. In addition, Ct values from swab specimens can vary according to collection technique and are thus not as consistent as Ct results from blood specimens [13]. Nevertheless, our analysis of oral swab specimens showed an association between Ct values lower than the median and higher SARs among household contacts, with contacts exposed to index patients with Ct values below the median at a >3-fold increased risk of secondary EVD compared with contacts of index patients with Ct values above the median. These results strengthen the association between low Ct value and higher HTR, which we demonstrated in multivariable analysis using our larger sample of blood specimens. It is important to emphasize, however, that investigations for index patients who died in the house should be prioritized regardless of the oral swab specimen Ct value, given the strength of this epidemiologic factor as a predictor of EBOV transmission [3, 16].

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In our 2015 study, we visited households to collect epidemiologic risk factor data by interviewing index patients, heads of household, and contacts, which took a minimum of several days from the time of index case diagnosis to arrange and complete. A Ct value was routinely provided as part of EBOV diagnostic testing and available at the time of index case diagnosis—well before a public health visit to the household was made or interviews of household members conducted. Thus, there is a potential opportunity to identify households and groups of contacts at increased risk of EVD at an earlier time point by considering the index patient's Ct value, which could speed the implementation of important Ebola prevention and control measures. Our findings suggest that more rapid investigation of households may be warranted in situations where the index patient is demonstrated to have a very low Ct value, reflecting a very high viral load.

Statistically significant differences were demonstrated when Ct values were examined in concert with epidemiologic factors in a categorical fashion—that is, using percentage distribution cutoffs—but not when they were examined on a continuous scale. This is consistent with our finding that EBOV transmission risk is very high with the lowest Ct values but does not vary significantly over most of the spectrum of Ct values. Thus, adding very low Ct values (very high viral load) to algorithms used to predict high-risk households would be a practical way to use these findings. It is important to note that our study does not establish an absolute cutoff associated with increased risk, because techniques and consequently Ct values can vary to some degree between laboratories. Instead, we demonstrate that very low Ct values—those in the lowest quintile—are predictive of higher rates of household transmission.

High EBOV load has been linked to increased risk of index patient death in several studies [12, 17–20]. During the 2014–2016 Ebola outbreak in West Africa, Crowe et al [17] demonstrated that patients EVD who had low Ct values had a 4-fold increased risk of death compared with those with higher Ct values, and 3 other studies also showed an association between high viral load and increased mortality rate [18–20]. Considered together, the findings from our study and from studies in Sierra Leone and Guinea linking low Ct values and increased risk of death [17–20] point to the potential importance of using Ct values to predict high-risk households with a higher likelihood of secondary cases of Ebola among contacts as well as high-risk groups of patients with a higher likelihood of death.

In our review of the literature, death was the only reported outcome linked to Ct results, and there were no reports of epidemiologic studies evaluating the association of these test results with EBOV transmission. An association between EBOV load and transmission risk has not been previously established, nor has a minimal infectious dose of EBOV been determined in humans. However, a very small dose of EBOV has been shown to produce a lethal infection in macaques [21]. Furthermore, associations between high viral load and transmission have been demonstrated for a number of other viruses, including human immunodeficiency, hepatitis B, and hepatitis C virus [22–24]. Higher concentrations of the bacterial pathogen *Mycobacterium tuberculosis* in infectious aerosol have also been linked to increased rates of tuberculosis transmission [25]. Thus, our findings are biologically plausible, and they also have biologic precedence with other infectious pathogens.

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A limitation of our study is that Ct testing was performed at 7 different laboratories. Although all laboratories used standard protocols, there is the possibility of some variability in methods and results between laboratories. Other limitations include the fact that not all index patients enrolled in our epidemiologic study had Ct values available. In addition, the sample of oral swab specimens was too small to include these results in multivariable analyses that considered epidemiologic factors as well as Ct results from index patients with blood specimens. Moreover, we were unable to completely control for death as a risk factor for transmission, because few persons who died had blood specimens, oral swab specimen measurements cannot be compared with blood specimen measurements, and there was no ascertainment of deaths that may have occurred after index patients were removed from the household. Nevertheless, we did adjust for death indirectly by examining the association of viral load and transmission for deceased patients with oral swab specimens. Strengths of our study included the prospective collection of a comprehensive set of epidemiologic data on index patients, households, and contacts, and the ability to evaluate Ct values from the initial diagnostic specimen obtained from index patients as potential predictors of transmission, using published multivariable models of epidemiologic risk factors developed for the same cohort.

Our study demonstrated an association between low Ct values (high EBOV load) and higher risk of household transmission of EBOV in multivariable analysis, independent of epidemiologic risk factors for transmission established in the same cohort. Risk was not evenly distributed but instead seemed to be associated with Ct values in the lowest quintile. Public health programs could consider using these findings in the context of other identified risk factors (including index patient death in the house [3, 16], absence of reported fever in the index patient [3], contact providing care for the index patient [3, 5, 8, 10], and physical contact or contact with body fluids of the index patient [4, 5, 8–10]) to identify a subset of households and contacts for closer, more intensive, and more frequent observation. Our findings also suggest the potential to use the Ct value from the acute EBOV diagnostic specimen for the index patient as an early predictor of high-risk settings where EBOV transmission is more likely. More research is needed to define practical Ct value cutoffs, to corroborate our findings in other outbreak settings, and to determine the applicability of these findings for nonhousehold settings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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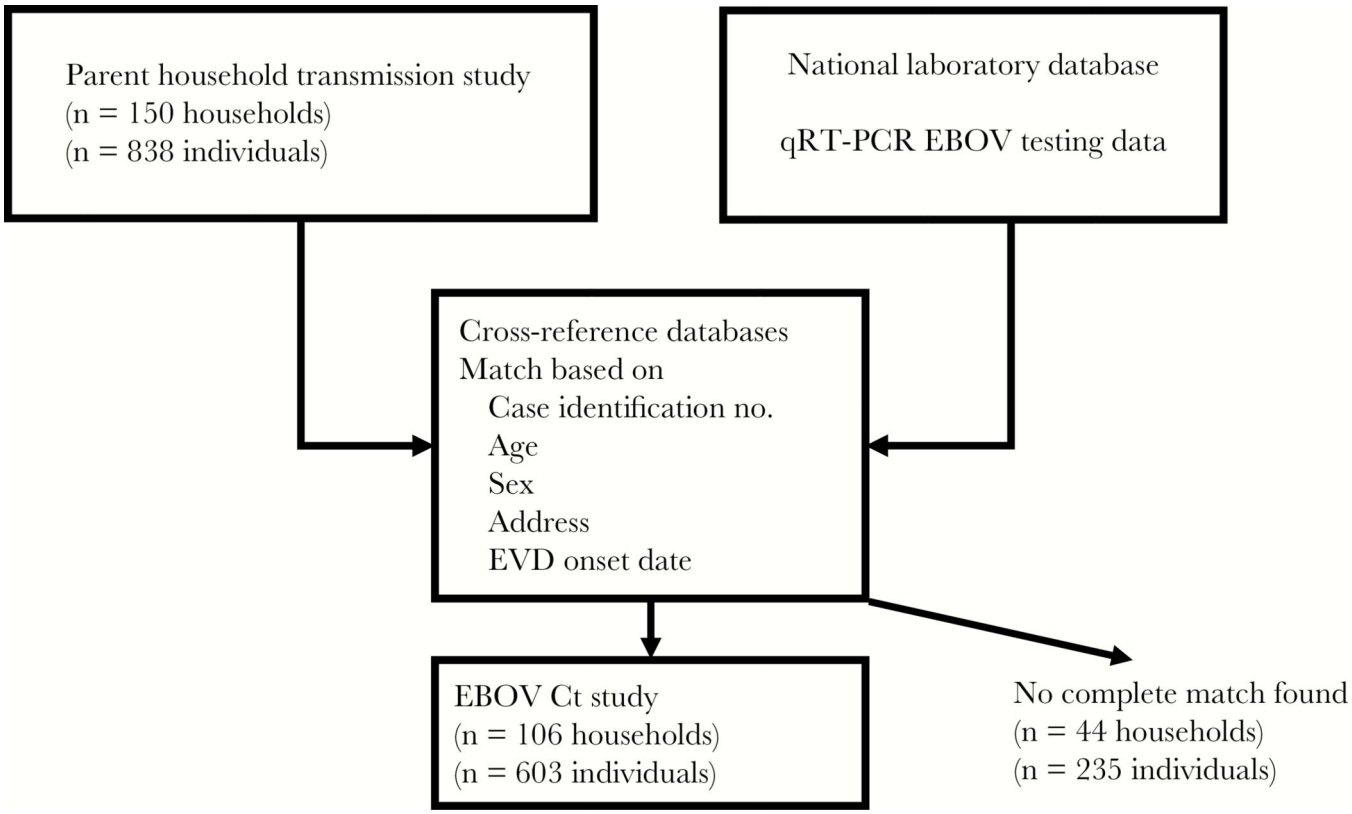

Figure 1.

Flow chart of index patient and contact inclusion in the Ebola virus (EBOV) cycle threshold (Ct) study. Of 150 index patients enrolled in the parent household transmission study, Ct data were available for 106 (71%). Of 838 enrolled contacts, index patient Ct data were available for 603 (72%). Abbreviations: EVD, EBOV disease; qRT-PCR, quantitative reverse-transcription polymerase chain reaction.

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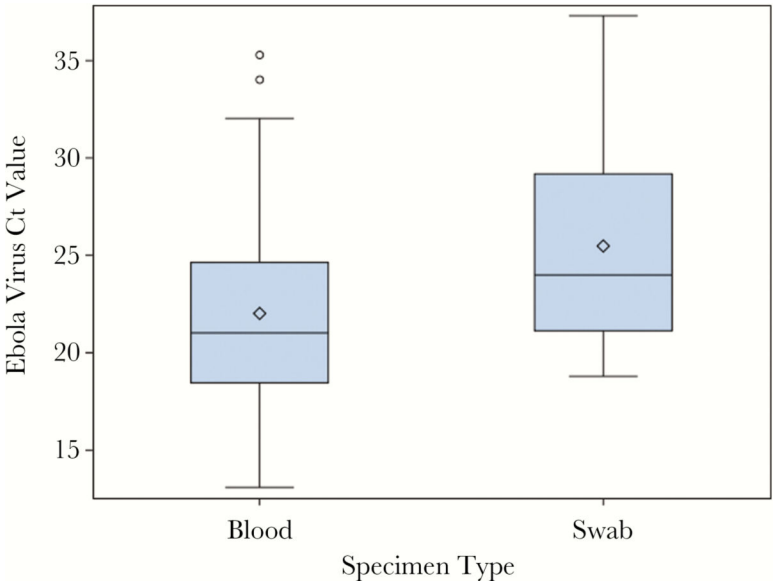

Figure 2.

Box plot of Ebola virus cycle threshold (Ct) values for 85 blood specimens from live patients versus 21 oral swab specimens from deceased patients.

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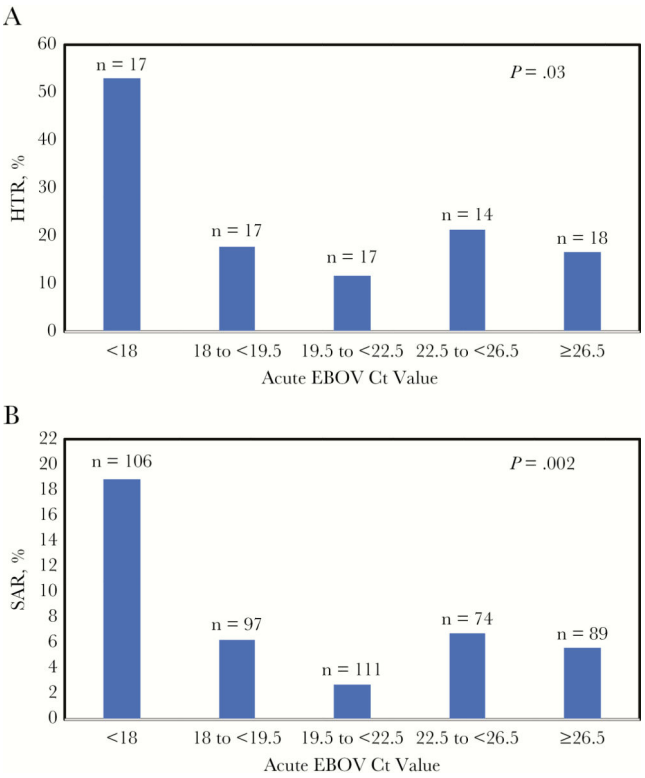

Figure 3.

Transmission rates in households and among individual contacts according to the Ebola virus (EBOV) cycle threshold (Ct) value of the index patient. *A,* Household transmission rate (HTR); the HTRs for the 5 Ct quintiles, from lowest to highest, were 52.9, 17.7, 11.8, 21.4, and 16.7. *B,* Secondary attack rate (SAR) among individual contacts; the SARs for the 5 Ct quintiles, from lowest to highest, were 18.9, 6.2, 2.7, 6.8, and 5.6. Data are displayed for the 85 index patients with blood specimen Ct data available.

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Table 1.

Household Transmission Rate and Contact Secondary Attack Rate for 21 Deceased Index Patients with an Oral Swab Specimen

Ct Value[a]	HTR, % of Households (No./Total)	SAR, % of Contacts (No./Total)
<24	64 (7/11)	27 (14/52)
≥24	40 (4/10)	9 (7/74)
P value (univariate)	.28	.01[b]

Abbreviations: Ct, cycle threshold; HTR, household transmission rate; SAR, secondary attack rate (among individual contacts).

[a] Ct values are dichotomized at the median value among the 21 case patients.

[b] Adjusted for household clustering.

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Table 2.

Multivariable Models for Risk Factors Associated With Ebola Virus Transmission to Households and Individual Household Contacts, Including Cycle Threshold Values and Epidemiologic Factors

Model No.	Model Type	Variables Adjusted for	Scale for Ct Values	*P* Value	OR (CI)	Additionally Adjusted for Laboratory[a]	
						P Value	OR (CI)
1	HTR	Index patient fever, index patient age, piped water[b]	Continuous	.048[d,e]	0.85 (.72–.99)[e]	.06[f]	0.84 (.70–1.01)
2	HTR	Index patient fever, index patient age, piped water[b]	Categorical (lowest quintile vs higher quintiles)	.007[d,e]	7.11 (1.73–29.27)[e]	.009[f]	7.43 (1.62–34.07)
3	SAR	Providing care for index patient, fever, avoiding index patient, piped water[c]	Continuous	.07[d,e]	0.91 (.81– 1.01)[e]	.06[f]	0.89 (.78–1.00)
4	SAR	Providing care for index patient, fever, avoiding index patient, piped water[c]	Categorical (lowest quintile vs higher quintiles)	.04[d,e]	3.02 (1.07–8.53)[e]	.03[f]	3.44 (1.18–9.99)

Abbreviations: CI, confidence interval; Ct, cycle threshold; HTR, household transmission rate (with household transmission as the outcome); OR, odds ratio; SAR, secondary attack rate among individual contacts (with transmission to individual contacts as the outcome).

[a] Adjustment is made for 2 laboratories with highest overall Ct values versus all other laboratories.

[b] Wet symptom (bleeding, vomiting, diarrhea) length: this factor was included in the parent household transmission model but was removed from the current model because it was no longer statistically significant.

[c] First-degree relative of index patient: this factor was included in the parent household transmission model but was removed from the current model because it was no longer statistically significant.

[d] *P* values restricted to households with ≤1 secondary case (n = 75 households): model 1, *P* = .07; model 2, *P* = .03; model 3, *P* = .08; and model 4, *P* = .01.

[e] *P* values adjusted for time between symptom onset and date of serum specimen collection: model 1, *P* =.08; model 2, *P* = .01; model 3, *P* = .06; and model 4, *P* = .03.

[f] Laboratory category was not statistically significant in any of the models: model 1, *P* = .82; model 2, *P* = .88; model 3, *P* = .45; and model 4, *P* = .51.