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Association of Lower Exposure Risk With Paucisymptomatic/Asymptomatic Infection, Less Severe Disease, and Unrecognized Ebola Virus Disease: A Seroepidemiological Study

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Background. It remains unclear if there is a dose-dependent relationship between exposure risk to Ebola virus (EBOV) and severity of illness.

Methods. From September 2016 to July 2017, we conducted a cross-sectional, community-based study of Ebola virus disease (EVD) cases and household contacts of several transmission chains in Kono District, Sierra Leone. We analyzed 154 quarantined households, comprising both reported EVD cases and their close contacts. We used epidemiological surveys and blood samples to define severity of illness as no infection, pauci-/asymptomatic infection, unrecognized EVD, reported EVD cases who survived, or reported EVD decedents. We determine seropositivity with the Filovirus Animal Nonclinical Group EBOV glycoprotein immunoglobulin G antibody test. We defined levels of exposure risk from 8 questions and considered contact with body fluid as maximum exposure risk.

Results. Our analysis included 76 reported EVD cases (both decedents and survivors) and 421 close contacts. Among these contacts, 40 were seropositive (22 paucisymptomatic and 18 unrecognized EVD), accounting for 34% of the total 116 EBOV infections. Higher exposure risks were associated with having had EBOV infection (maximum risk: adjusted odds ratio [AOR], 12.1 [95% confidence interval {CI}, 5.8–25.4; trend test: $P < .001$) and more severe illness (maximum risk: AOR, 25.2 [95% CI, 6.2–102.4]; trend test: $P < .001$).

Conclusions. This community-based study of EVD cases and contacts provides epidemiological evidence of a dose-dependent relationship between exposure risk and severity of illness, which may partially explain why pauci-/asymptomatic EBOV infection, less severe disease, and unrecognized EVD occurs.

Keywords. Ebola virus; exposure risk; epidemiology; public health; transmission.

The 2013–2016 Ebola virus disease (EVD) outbreak in West Africa was unprecedented in scale with >11 000 deaths and 6000 survivors reported [1]. After a single zoonotic spillover or human-reservoir relapsing event, Ebola virus (EBOV) can be transmitted from human to human as a result of high-risk

exposures such as direct contact with infected bodily fluids [2–4]. Once infected with EBOV, clinical manifestations ranged from asymptomatic EBOV infection to severe EVD and death [5]. Emerging evidence suggests that asymptomatic infection and mild illness occur as a substantial proportion of EBOV infections [6, 7], but the pathophysiology of a pauciasymptomatic/asymptomatic infection remains poorly understood and may result from a combination of nutritional, epidemiological, viral, and immunological host factors [6, 8, 9].

The quantity of viral inoculum and its contribution to different infection outcomes has been described in animal models for a number of viruses, including hepatitis B, adenovirus, African swine flu, and influenza [10–13]. Human challenge trials can measure the viable infectious dose of a virus in humans, but in the absence of these trials, epidemiological studies

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of viral exposures and disease outcomes can act as a surrogate type of investigation to understand how infectious dose impacts humans [14]. Guallar and colleagues reported 3 clusters of COVID-19 in Madrid, Spain, in which infected persons experienced different disease severity according to distinct magnitudes of reported exposure [15]. A dose-dependent effect of EBOV had been hypothesized after laboratory experiments of aerosolized EBOV showed that viable virus was recovered after 180 minutes and that nonhuman primates and rhesus monkeys could develop asymptomatic EBOV infection [16–18]. Similarly, in a small study with only 21 seropositive participants, exposure risk to EVD weakly correlated with seropositivity among asymptomatic and symptomatic household contacts [6]. In addition to the unknown role of host and viral determinants of disease severity, we have a limited understanding of how the full spectrum of disease severity, ranging from asymptomatic and pauci-/asymptomatic infection to severe EVD and death, relates to increasing levels and duration of exposure to EBOV.

In the 2 years following the EVD outbreak, we sought to explore the relationship between exposure risk and disease severity. We conducted a seroepidemiological investigation of multiple transmission chains in rural communities of Kono District, Sierra Leone. We hypothesized that a dose-dependent relationship occurs between exposure risk and severity of illness.

METHODS

Patient Consent Statement

The study protocol was approved by the Sierra Leone Ethics and Scientific Review Committee and the University of California, San Francisco Institutional Review Board. Written consent was obtained for all participants, and permission to access the Viral Hemorrhagic Fever (VHF) database was given by the Kono District Ebola Response Center (DERC), which acted as a coordinating body for Ebola response operations during the outbreak.

Study Setting, Population, and Procedures

We conducted a cross-sectional, community-based study in Kono District, Sierra Leone, from September 2016 to July 2017. This seroepidemiological investigation of transmission chains occurred in the communities of Ngo Town, Ndogboya, Bumpe, and Joe Town within Kono District. The first transmission chain started in late August 2014 during the burial ceremony in Port Loko District of an individual who had died of EVD. A participant in that burial then returned to her home village of Joe Town, Kono District, developing and unwittingly transmitting EVD, resulting in 7 EVD cases (4 survivors, 3 deaths) within the community (Supplementary Figure 1A). The other communities are thought to be linked through 1 large transmission chain, starting in mid-October 2014, and causing outbreaks

in Ngo Town (1 survivor, 4 deaths; Supplementary Figure 1B), Ndogboya (8 survivors, 18 deaths; Supplementary Figure 1C), and Bumpe (12 survivors, 26 deaths; Supplementary Figure 1D).

Our study included any reported EVD case and their contacts who lived in these communities at the time of the local EVD outbreak. Reported EVD cases were identified through the district VHF database and were confirmed in interviews with community leaders and healthcare workers, EVD survivors from the communities, the Ebola Survivor Association, and household members. EVD contacts were defined as exposed individuals who lived in a quarantined household (during the Ebola epidemic, all known EVD contacts were placed under mandatory 21-day quarantine within their homes) or someone who lived outside of a quarantine household but who was identified as a close contact in our interviews with EVD survivors, household surrogates of those who died of EVD, or the VHF database.

We obtained a list of households that had been quarantined during the Ebola epidemic from the Kono DERC. In collaboration with community leaders and EVD survivors, our team of local staff corroborated and confirmed all of the quarantined households in each community. These households included all of the reported EVD cases. In 14 households with EVD deaths, we obtained data via a proxy, who was an adult with either the closest relationship or the head of the household. During interviews with EVD survivors, we obtained an additional list of close contacts. We then identified these close contacts, confirmed their exposure history, and enrolled these individuals.

Each study visit included an epidemiological survey, blood draw, and open-ended interview. We collected the exposure risk and other covariate data in the epidemiology survey. At the end of the survey, we conducted an open-ended interview. We asked participants to describe the story of how EVD affected their household, with a focus on particular exposure and transmission events. We held focus groups to corroborate the transmission chain from other informational sources.

The blood samples were transported to a local laboratory for biospecimen processing into plasma aliquots and maintained in a cold chain. These samples were transported to the National Institute of Allergy and Infectious Diseases, National Institutes of Health, in Fort Detrick, Maryland, where serological testing occurred. After receiving the serology results, we disseminated all of the results to participants. We then reinterviewed participants who were found to be seropositive to further reconstruct possible transmission chains and sources of exposure.

Laboratory Measurements

Seropositivity to anti-glycoprotein EBOV-specific immunoglobulin G (IgG) antibodies was used to classify the outcome variables and determined through testing of the blood plasma samples. We used the Filovirus Animal Nonclinical Group

(FANG) immunoassay, which has 94.4% sensitivity and 96.7% specificity when a cutoff of 548 enzyme-linked immunosorbent assay units (EU) per milliliter was applied to the West African EVD survivor population [19].

Epidemiological Measurements

Primary outcomes were EBOV infection (presence or absence) and severity of EVD illness (5 levels). We assumed that participants who were seropositive had an EBOV infection following exposure. Therefore, EBOV infection was defined as those who were seropositive in addition to the reported EVD cases (survivors, decedents). Severity of EVD illness was defined as an ordinal variable with the following progression of disease: no infection, pauci-/asymptomatic infection, unrecognized EVD, reported EVD cases who survived, and reported EVD cases who died. The classification of unrecognized EVD vs reported EVD cases who survived was based on whether an individual had been identified as a case by the Kono DERC during the outbreak and recorded in the VHF database. The unrecognized EVD cases identified in this study did not receive testing nor medical care during their illness, remained at home through the duration of their infection, and reported on average less symptoms during their post-EVD exposure period [19]. All reported EVD cases who survived and died had at least 1 laboratory-confirmed polymerase chain reaction–positive test result record in the VHF database, except for 2 decedents who were probable cases.

To create the disease classifications of paucisymptomatic infection and unrecognized EVD, we used contact participants' serostatus and self-reported, postexposure symptoms of each contact participant. We created a 16-item symptom checklist from the World Health Organization (WHO) EVD case definition and asked contact participants to report the presence or absence of each symptom. Other household members were asked to verify signs and symptoms. We then compiled these responses and classified each contact participant as either asymptomatic or symptomatic. Participants who were seropositive and asymptomatic (answered no to all 16 questions) were classified as having had a pauci-/asymptomatic infection. We settled on "pauci-/asymptomatic" as the description of individuals who reported being asymptomatic because of the potential for mild symptoms and recall error. Contact participants who were seropositive and symptomatic were defined as having had unrecognized EVD.

The explanatory variable was exposure risk, which was adapted from classifications used elsewhere in the EVD literature [3, 6]. We asked contact participants to recall their interactions with EVD case(s) according to 8 types of exposures (see below). Each response to the exposure question was binary (yes/no). We assigned each participant to a single maximal exposure type. We ordered exposure risk to create a 5-level categorical variable according to the questionnaire (from highest

to minimal/no exposure) as follows: highest—contact with body fluids through caregiver, tactile burial, or other practices (Q8, Q7); high—direct contact with body fluids (Q6); intermediate—washing an EVD case's clothes (Q5) or sleeping in the same room (Q4); low—eating from the same dish, or sharing a pot (Q3) or being within 2 meters of an EVD case or body fluids (Q2); and minimal or no contact (staying >2 meters from any EVD case or body fluids) (Q1).

Reconstructing the Chain of EBOV Transmission

We reconstructed temporal and geospatial arrays of EBOV transmission chains inclusive of pauci-symptomatic infection and unrecognized EVD, using methods described elsewhere [20]. In brief, we were able to draft, assess, and confirm the transmission chain, and created a classification scheme to describe probabilistic epidemiological links (types 1, 2, 3) between an EVD case and a participant who was EBOV infected. Type 1 links were considered more likely to be true epidemiological links than type 2, and type 2 more likely than type 3. We used the most probable links to construct the transmission chain.

Data Analyses

We described the 5-level exposure risk in the cohort but also presented these data grouped into 3 levels for its potential simplified public health communication benefit: minimal or no contact (Q1), indirect contact (Q2–Q3), and direct contact (Q4–Q8). We assessed the associations of 5-level exposure variable to subsequent EBOV infection and severity of illness. We analyzed this relationship with a mixed-effect logistic regression model for the outcome of EBOV infection and with a mixed-effect multinomial logistic regression model for the outcome of severity of EVD illness. Based on evidence from the literature [3, 20], we adjusted for age, sex, educational level, and type of work, and included household as a random effect. We were unable to adjust for viral load (or cycle threshold value) or comorbidities because these data were not collected and/or available. To further evaluate the epidemiologic evidence for a dose-response relationship, we performed Cochran-Armitage test for trend. We repeated these analyses with the 3-level exposure variable and included them in the [Supplementary Materials](#) as a sensitivity analysis. In analyses of the transmission chain, we estimated the effective reproduction number, $R(t)$, by dividing the total number of new EVD cases in each generation by the number of EVD cases in the previous generation [20]. These analyses were performed in R version 3.2.4 software (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

The analysis cohort included 497 participants; 76 reported EVD cases and 421 contact participants were identified from the initial outbreak ([Figure 1](#)). Sociodemographic characteristics are presented in [Table 1](#). Forty of 421 (9.5%) contact

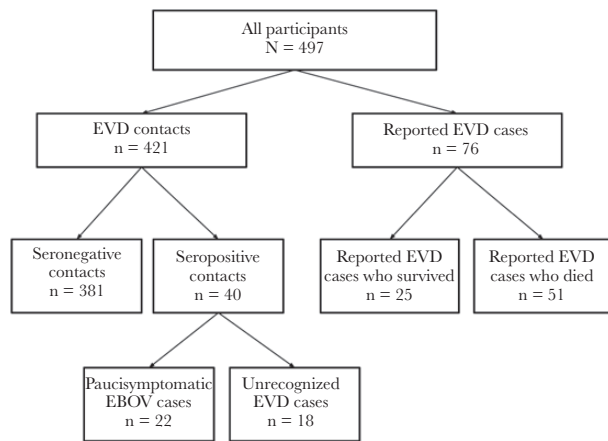


Figure 1. Flow diagram of study participants and classification in disease groups. Abbreviations: EBOV, Ebola virus; EVD, Ebola virus disease.

participants who were seropositive had not previously been identified as EVD cases by either the DERC or community queries. Among the 40 seropositive contact participants, 18 (45%) reported the presence of symptoms while 22 (65%) reported the absence of symptoms (χ^2 test: $P = .39$). The seropositive contact participants, who probably had pauci-/asymptomatic infection or unrecognized EVD, accounted for 34% of 116 EBOV infections (76 reported EVD cases + 40 seropositive contacts) (Figure 2).

We identified that 37 of 40 seropositive participants were in quarantined households and 3 were outside of the quarantine; all 3 were symptomatic contact participants and probably had

unrecognized EVD. When we reinterviewed participants who were found to be seropositive, one of the unrecognized EVD cases outside the quarantine traveled to another community while feeling mildly ill and stayed with family who subsequently developed EVD.

Transmission Chains

Each community sustained a transmission chain, and we used temporal data of the 76 EVD cases to estimate the average effective reproduction number among communities (Table 2). In the first generation of transmission, 4 individuals transmitted EBOV to 49 individuals ($R(1)$, 12.25 [95% confidence interval {CI}, 11.27–13.23]). In the second generation of transmission, 49 individuals transmitted EBOV to 37 individuals ($R(2)$, 1.62 [95% CI, 1.21–2.03]). In the third generation of transmission, 37 individuals transmitted EBOV to 13 individuals ($R(3)$, 0.42 [95% CI, .05–.79]). In the fourth generation of transmission 13 individuals transmitted EBOV to 6 individuals ($R(4)$, 0.51 [95% CI, .0–1.07]).

Associations of Exposure Risk With Infection and Severity of Illness

Direct contact was reported in 30.3% of uninfected and 71.2% of infected participants. The majority of pauci-/asymptomatic infection, however, involved minimal or no contact while the majority of those with unrecognized EVD, EVD survivors, and EVD decedents reported direct contact. When we further examined exposure risk patterns, participants with direct contact reported mostly high- and highest-risk exposures (direct contact, or contact with

Table 1. Sociodemographic Characteristics of the Community-Based Cohort in Kono District, Sierra Leone

| Characteristic | All Infected | Uninfected | Pauci-symptomatic | Unrecognized EVD | Survivor | Decedent |
|--------------------------|--------------|------------|-------------------|------------------|-----------|-----------|
| Sex | | | | | | |
| Female | 47 (42.3) | 156 (41.2) | 11 (50.0) | 9 (44.4) | 9 (39.1) | 19 (39.6) |
| Male | 64 (57.7) | 223 (58.8) | 11 (50.0) | 10 (55.6) | 14 (60.8) | 29 (60.4) |
| Age, y | | | | | | |
| ≤19 | 27 (22.9) | 155 (40.9) | 6 (27.3) | 6 (33.3) | 4 (17.4) | 11 (22.9) |
| 20–29 | 23 (19.5) | 64 (16.9) | 5 (36.6) | 3 (16.7) | 4 (13.0) | 2 (4.2) |
| 30–39 | 20 (16.9) | 57 (15.0) | 1 (4.6) | 1 (5.6) | 4 (17.4) | 14 (29.2) |
| 40–49 | 24 (20.3) | 51 (13.5) | 4 (18.2) | 5 (27.8) | 5 (21.7) | 10 (20.8) |
| ≥50 | 24 (20.3) | 52 (13.7) | 3 (13.6) | 3 (16.7) | 7 (30.4) | 11 (22.9) |
| Education | | | | | | |
| None | 57 (52.3) | 133 (35.1) | 9 (40.9) | 7 (38.9) | 11 (47.8) | 30 (62.5) |
| Primary | 20 (18.3) | 118 (31.1) | 4 (18.2) | 3 (16.7) | 5 (21.7) | 8 (16.7) |
| Secondary and above | 32 (29.4) | 124 (32.7) | 9 (40.9) | 8 (44.4) | 7 (30.4) | 8 (16.7) |
| Employment | | | | | | |
| Healthcare | 14 (13.1) | 67 (17.7) | 3 (13.6) | 4 (22.2) | 1 (4.4) | 6 (12.5) |
| Indoor | 17 (15.9) | 98 (25.9) | 3 (13.6) | 5 (27.8) | 4 (17.4) | 5 (10.4) |
| Outdoor | 76 (71.0) | 212 (55.9) | 15 (68.1) | 9 (50.0) | 17 (73.9) | 35 (72.9) |
| Head of household | | | | | | |
| No | 46 (42.2) | 256 (67.6) | 11 (50.0) | 10 (55.6) | 8 (34.8) | 17 (35.4) |
| Yes | 63 (57.8) | 122 (32.2) | 11 (50.0) | 8 (44.4) | 15 (65.2) | 29 (60.4) |

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: EVD, Ebola virus disease.

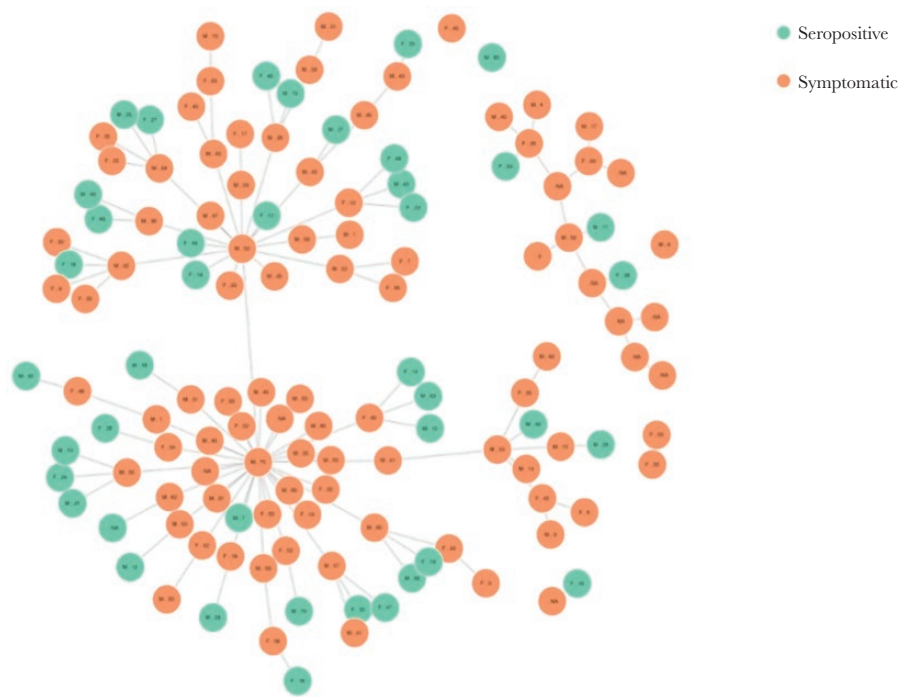


Figure 2. Geospatial depiction of the transmission chains inclusive of pauci-/asymptomatic infection and unrecognized Ebola virus disease (EVD). Contact participants identified through the serosurvey are indicated by green circles while EVD cases are indicated by orange circles.

bodily fluids) in contrast to intermediate-risk exposures (eating the same meals, sleeping in the same room) (Table 3).

In adjusted analyses, we observed a dose-dependent relationship based on increasing exposure risk against the outcomes (Table 4). An increasing level of exposure risk was associated with higher odds of infection and severe illness (trend test: $P < .001$ for both). Highest exposure risk had the strongest magnitude, which was 12.1 (95% CI, 5.7–25.4) times the odds of infection and 25.2 (95% CI, 6.2–102.4) times the odds of severe illness than minimal exposure. High exposure risk was also statistically significant. These associations and its dose-response relationship were replicated with the 3-level exposure risk variable (Supplementary Table 1).

DISCUSSION

This seroepidemiological investigation of EBOV transmission chains in Kono District, Sierra Leone, found a dose-dependent

relationship between exposure risk and severity of EVD illness. This finding extends a growing body of EBOV literature [16–18], suggesting that the size of the initial dose of EBOV that a person is exposed to plays a role in severity of illness. Furthermore, identification of missed cases in the process of reconstructing the transmission chains, including pauci-/asymptomatic infection and unrecognized EVD cases, substantiates the true burden of EBOV infection from the West African outbreak and helps to identify potential patterns of transmission dynamics. Most missed cases were identified within quarantined households, but there were 3 close contacts with unrecognized EVD who were confirmed to be outside of quarantined households. These nonquarantined and unrecognized EVD cases may have unwittingly propagated the disease to other communities in Kono and elsewhere. Similar observations were made in Guinea and underscore the ongoing surveillance challenges faced by underresourced and underdeveloped health systems [21].

Table 2. Estimation of the Average Effective Reproduction Number Among the Communities

| Community | Generation 1 | Generation 2 | Generation 3 | Generation 4 |
|-----------|------------------------------|------------------------------|------------------------------|------------------------------|
| | Reproduction No. (Incidence) | Reproduction No. (Incidence) | Reproduction No. (Incidence) | Reproduction No. (Incidence) |
| Joe Town | 2.0 (2) | 3.5 (7) | 0.43 (3) | 0.67 (2) |
| Ngo Town | 2.0 (2) | 1.5 (3) | 0.33 (1) | 0.00 (0) |
| Ndogboya | 16.0 (16) | 1.3 (20) | 0.20 (4) | 0.25 (1) |
| Bumpe | 29.0 (29) | 0.24 (7) | 0.71 (5) | 0.60 (3) |
| Overall | 12.3 (49) | 1.62 (37) | 0.42 (13) | 0.51 (6) |

Table 3. Description of Exposure Risk by Ebola Virus Infection and Severity of Ebola Virus Disease Illness

| Characteristic | All Infected | Uninfected | Pauci-symptomatic | Unrecognized EVD | Survivor | Dead |
|----------------------------------|--------------|------------|-------------------|------------------|------------|-----------|
| 3-level exposure variable | | | | | | |
| Minimal or no contact | 19 (17.1) | 170 (44.9) | 14 (63.6) | 1 (5.6) | 0 (0) | 4 (8.3) |
| Indirect | 13 (11.7) | 94 (24.8) | 4 (18.2) | 5 (27.8) | 0 (0) | 4 (8.3) |
| Direct | 79 (71.2) | 115 (30.3) | 4 (18.2) | 12 (66.7) | 23 (100.0) | 40 (83.3) |
| 5-level exposure variable | | | | | | |
| Minimal or no contact | 19 (17.1) | 170 (44.9) | 14 (63.6) | 1 (5.6) | 0 (0) | 4 (8.3) |
| Low risk | 13 (11.7) | 94 (24.8) | 4 (18.2) | 5 (27.8) | 0 (0) | 4 (8.3) |
| Intermediate risk | 3 (2.7) | 8 (2.11) | 1 (4.6) | 0 (0.0) | 1 (4.4) | 1 (2.1) |
| High risk | 34 (30.6) | 68 (17.9) | 1 (4.6) | 7 (38.9) | 9 (39.1) | 17 (35.4) |
| Maximum risk | 42 (37.8) | 39 (10.3) | 2 (9.1) | 5 (27.8) | 13 (56.5) | 22 (45.8) |

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: EVD, Ebola virus disease.

We found that 34% of EBOV infections were seropositive and probably had either pauci-/asymptomatic infection or unrecognized EVD. This proportion is consistent with our prior seroepidemiological study in Sukudu, Kono District, and other community-based studies [6, 20], confirming that the public health significance of missed cases is substantial and worthy of consideration as Ebola control and care strategies are revised. Given that some of the missed cases in our study were found outside of the quarantine, containment efforts should not only make every effort to identify and isolate people who have been infected with EVD, but also provide those who are infected with aggressive treatment in line with the 2016 revised WHO clinical care guidelines [22–25]. In our study, individuals with pauci-/asymptomatic infection or unrecognized EVD did not require hospitalization, which highlights the spectrum of EVD severity and the ongoing need to provide clinical care in communities, either through specialized community care centers or appropriately designed clinics.

Although we found that severity of EVD illness was associated with exposure risk, some individuals reporting minimal- or low-risk exposures in our cohort still exhibited a range of symptoms, from unrecognized EVD to death. EVD has been described as a caregivers' disease given that the virus is most frequently propagated via tactile acts of care for the sick, dying, and deceased [26]. Some of these tactile acts of care resulted as minimal- or low-risk exposures, and these exposed individuals may be at

risk for severe disease and are difficult to identify in the context of health systems that are underresourced and underdeveloped due to historical, structural, and political-economic causes, and which may quickly be overwhelmed during an Ebola epidemic [27]. Although community resistance, lack of trust, and poor contact identification rate and follow-up have the potential to create additional barriers [28–30], public health providers should consider more intensive surveillance of contacts as the health system strengthens. If minimal-risk or low-risk exposures were to be tracked, then symptomatic individuals could be expeditiously referred to care. Even if they do not develop severe EVD, this population may still be at risk for prolonged clinical sequelae such as memory loss and joint pain.

In the 4 communities described in our study, we found that the epidemic curve declined by the third reproductive generation. The timing of epidemic decline was similar to what was found in the few other studies that have described effective reproduction number within single communities [20]. The short timeline within communities emphasizes the need for a rapid response and strong health system to implement control and care interventions. In such a system, we would also be more likely to identify individuals who would otherwise go on to become unrecognized EVD cases, and this could contribute to rapid epidemic decline [31, 32].

Our study has several limitations. First, we may have missed cases beyond the identified contact participants

Table 4. Associations of Exposure Risk by Ebola Virus Infection and Severity of Ebola Virus Disease Illness

| Exposure Level | EBOV Infection | | Disease Severity | |
|-------------------|--------------------------|--------|--------------------------|--------|
| | Adjusted OR ^a | PValue | Adjusted OR ^a | PValue |
| Minimal exposure | Ref | NA | Ref | |
| Low risk | 1.2 | .06 | 1.3 | .53 |
| Intermediate risk | 3.4 | .01 | 3.5 | .08 |
| High risk | 4.5 | <.001 | 5.1 | <.001 |
| Maximal risk | 9.6 | <.001 | 11.24 | <.001 |

Abbreviations: EBOV, Ebola virus; NA, not applicable; OR, odds ratio.

^aConfounding variables included age, sex, educational level, and type of work.

who were identified as exposed, but lack of resources did not permit us to conduct a serosurvey of entire communities. Second, contact participants and surrogates for the deceased were asked to recall exposures with the EVD case(s) and symptoms during the post-EVD exposure period; some exposures and mild symptoms may have been forgotten, were underreported due to lack of trust and misconception, or were unobserved in the case of the surrogates. To mitigate, we disclosed serostatus after the exposure measurements were obtained. Furthermore, we considered participants who reported the absence of symptoms to be pauci-symptomatic, acknowledging that the group was probably comprised of asymptomatic and mildly symptomatic individuals. These individuals, however, did not know their serological status when the interview occurred, so this measurement error was biased to the null. Third, our cutoff for IgG antibody titers was established through previous studies. Little is known about pauci-/asymptomatic infection; the initial antibody response may be lower or antibody titers may have waned, creating the possibility that we missed additional pauci-/asymptomatic individuals who were part of our study population. Fourth, we were unable to measure potential confounders such as viral load (or cycle threshold value) and comorbidities; given that these covariates were unlikely to change the exposure behaviors, any bias would have been toward the null. Fifth, the generalizability of these communities may be more specific to those that experienced local EVD outbreaks late in the epidemic, when control measures were stronger and missed cases were less likely. Nonetheless, our study was sufficiently powered to demonstrate a dose-dependent relationship with regression models, adjusting for confounders and clustering, in contrast to previous work using more limited statistical approaches.

In conclusion, this study found an association of lower exposure risk with pauci-/asymptomatic infection, unrecognized EVD, and less severe disease, which provides impetus for further investigation into the relationship between exposure risk and severity of illness for EBOV, severe acute respiratory syndrome coronavirus 2, and other viral pathogens. Given that our study and others have reported transmission to individuals without direct contact of EVD cases, we believe the EVD outbreak response community should consider eye protection and masking in the provision of personal protective gear to communities facing EVD outbreaks. Reducing exposure risk among household members unable to quarantine in separate locations or forced into caregiving roles while awaiting ambulances and safe transport to Ebola treatment centers has the potential to prevent severe and deadly EVD.

Supplementary Data

Supplementary materials are available at *Open Forum 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.

Notes

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