Investigation of Marburg Virus Disease Outbreak in Kween District, Eastern Uganda, 2017

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Abstract

Background: *Marburg virus disease (MVD), a severe hemorrhagic disease, is caused by the Marburg virus (MARV) and Ravn virus. Human in contact with infected Egyptian fruit bats or eating bush meat from an infected animal can cause MARV. On 17- Octo-2017, post-mortem samples from an eastern Uganda's Kween District resident tested positive for MARV. On 18-Oct, the National Rapid Response Team (NRRT) initiated an outbreak response.*

Methods: *We defined a suspected MVD case as sudden onset of fever with ≥3 of anorexia, headache, vomiting, abdominal pain, diarrhea, intense fatigue, and myalgia, and joint pain, history of contact with a patient with similar symptoms; or sudden-onset unexplained bleeding; or unexplained sudden death. Confirmed were suspects or close contacts with positive RT-PCR and ELISA tests for MARV. Probable cases were suspects epidemiologically linked to confirmed cases. We conducted active case-search and medical-record reviews for case finding. Contacts of case-patients identified were followed for 21 days. We developed a weighted risk score (WRS) to measure contacts' exposure risk and associated the WRS with the secondary attack rate (AR).*

Results: *We identified one probable and three confirmed cases all among 140 relatives of same family (AR=2.9%; 4/140). Case-patient A was a 30-year-old male who visited bat-inhabited caves, became symptomatic on 16-Sept and died on 24-Sept. Case-patient B, his 50-year-old sister, cared for him in hospital, developed symptoms on 4-Oct, and died on 13-Oct. Case-patient C, 42-year-old brother of both, cared for case-patient B, developed symptoms on 18-Oct, traversed many areas including crossing to Kenya and died on 26-Oct. Case-patient D had close contact with the other case-patients and subsequently sero-converted. We followed 299 contacts of case-patients A, B and C in multiple districts in Uganda and Kenya. Secondary cases only occurred among contacts with highest WRS (9-10, AR=8.6%).*

Conclusion: *Close, direct contact led to MARV transmission among family members during this outbreak. Enhanced surveillance, contact tracing, rapid confirmation of viral hemorrhagic fever cases and quick turnaround of laboratory results are key for early identification and effective control of future MVD outbreaks. Epidemic preparedness and cross-border surveillance should be further strengthened, especially in the area of social and behavioral interventions and law enforcement.*

Abbreviations
AR = Attack Rate
CDC = Centers for Disease Control and Prevention
DRRT=District Rapid Response Team
MARV = Marburg Virus
MVD = Marburg Virus Disease
NRRT=National Rapid Response Team
NTF = National Task Force
PHEOC = Public Health Emergency Operations Centre
SAR=Secondary Attack Rate
UMoH = Uganda Ministry of Health
UNICEF = United Nations Children's Fund
UVRI = Uganda Virus Research Institute
VHF = Viral Hemorrhagic Fever
WHO = World Health Organization
WRS = Weighted Risk Score.

Introduction
Marburg virus disease (MVD) is a severe viral hemorrhagic fever (VHF) caused by Marburg virus (MARV) and a closely related Ravn virus. Along with Ebola viruses, MARV belongs to the Filoviridae family [1]. Egyptian fruit bats (*Rousettus aegyptiacus*), which have been found in closed mines and caves in various locations in Uganda and other countries in Africa, are known natural reservoirs for MARV [2, 3]. Certain non-human primates, e.g., African green monkeys (*Chlorocebus sabaeus*), have also served as the source of infection during past outbreaks [4, 5]. Seasonal Marburg viremia was found in about 10% of juvenile *R. aegyptiacus* bats in Uganda's Kitaka mines, followed by outbreaks among humans a few weeks afterwards, probably due to human interaction with bats, bat excreta, or infected non-human primates [2]. MARV is usually transmitted from animals to humans when humans visit bat-inhabited caves, or are exposed to tissues of non-human primates. Secondary transmission between humans can occur among close and direct contacts [1-4, 6, 7]. MVD has an incubation period of 5-15 days and presents with sudden onset of severe headache, intense fatigue, high fever, progressing to liver damage, pancreatitis, delirium, shock, and massive hemorrhage [1]. The case-fatality rate in humans is high; death is usually due to multi-organ failure [1]. Currently, no proven MARV-specific therapies are available. MVD outbreaks were first documented in 1967 in Marburg and Frankfurt, Germany, and Belgrade, Yugoslavia [4]. Another 11 outbreaks have been documented from 1975 to 2014, four of which occurred or were linked to exposures in Uganda [8].

On 17 October 2017, a patient from Kween District in eastern Uganda died at the neighboring Kapchorwa District Hospital. Her plasma sample tested positive for MARV at the Uganda Virus Research Institute (UVRI) by RT-PCR. On 18 October, the Uganda Ministry of Health (UMoH) activated the Public Health Emergency Operations Centre (PHEOC) and the National Task Force (NTF) for Epidemic Preparedness and Response to respond to this outbreak. On 19 October 2017, UMoH officially declared an MVD outbreak.

To effectively respond to this outbreak, PHEOC and NTF collaborated with several domestic and international partners and constituted a National Rapid Response Team (NRRT), which comprised field epidemiology fellows of the Uganda Public Health

Fellowship Program, UMoH epidemiologists, UVRI laboratorians, risk communication experts, and case management specialists. The NRRT was deployed to work with the District Rapid Response Team (DRRT) to investigate the outbreak, ascertain the extent of spread, conduct a risk assessment to inform response planning, and support the District Task Force on Epidemic Response to mount an effective response. This paper describes findings of the epidemiologic investigation.

Methods
Kween (1.4439° N, 34.5971° E) and Kapchorwa (1.3350° N, 34.3976° E) districts are in the mountainous Sebei Sub-region in eastern Uganda, on the slopes of Mount Elgon. Kween District (population: 102,000; bordering Kenya to its east) is a newly established rural district that was formerly part of Kapchorwa District. Most of its residents are peasants [9]. The bordering Kapchorwa District (population: 113,500) is more urban with 41% of its population living in urban areas [9]. The people of Kween and Kapchorwa districts are related and have close social, cultural, and economic ties. There are several caves within the two districts, which are inhabited by various species of animals, including non-human primates and bats. The Kapchorwa Hospital is the main referral general hospital for both districts.

The outbreak investigation team defined a suspected case as sudden onset of fever (≥37.5°C) with ≥3 of the following: anorexia, headache, vomiting, abdominal pain, diarrhea, intense fatigue, myalgia, joint pains, and history of contact with a patient with similar symptoms, or sudden-onset of unexplained bleeding, or unexplained sudden death. A probable case was a suspected case with close contact with a confirmed case. A confirmed case was a suspected case that tested positive for MARV by RT-PCR and/or IgM ELISA [8]. For the purpose of this investigation, a close contact of a probable case that subsequently tested positive by IgM, but refused to provide symptom information was categorized as a confirmed case. Suspected or probable cases that subsequently tested negative were classified as non-cases. A contact was any person exposed to a probable or confirmed MVD case-patient in ≥1 of the following ways: sleeping in the same household; touching blood or other body fluids, clothes or linens of case-patients; touching case-patient during the illness; touching the corpse during burial preparation or funeral; or having been breastfed by a case-patient.

The team reviewed medical records and conducted active case-finding and case investigation in the affected community. Trained contact tracers who are members of DRRT identified the contacts of confirmed and probable cases, and followed them daily for 21 days from the date of last contact with case-patients for any signs or symptoms suggestive of VHF. Data from case-patients and contacts were collected using standardized case investigation and contact listing forms, and entered into the Epi Info-based VHF database developed by the Centers for Disease Control and Prevention (CDC) (Beta version 0.9.6.0) [10]. Risk for secondary infection was assessed by place of residence, type of contact with each case-patient, and relationship to each case-patient. We developed a weighted risk score (WRS) to measure the exposure risk of contacts by assigning a risk score of: 1 for having slept in case-patients' homes; 2 for having touched or washed case-patients' soiled clothes or utensils; 3 for having touched case-patients' bodies; and 4 for having touched case-patients' bodily fluids such as blood, saliva, excreta, etc. We grouped WRS into four categories by total score: 0-2, 3-5, 6-8, and

9-10 points; and calculated the secondary attack rate (SAR) for each WRS score group.

Blood samples were collected from contacts that had any signs or symptoms suggestive of VHF, and from probable and suspected cases. Samples were sent to UVRI for MARV testing using RT-PCR or ELISA for MARV or both.

Ethical considerations
The Office of the Director General of Health Services, Ministry of Health of Uganda, gave the directive and approval to investigate this outbreak. The Office of the Associate Director for Science, Center for Global Health, CDC, Atlanta, determined that this activity was in response to a public health emergency and not human subject research. We obtained verbal informed consent from respondents ≥18 years of age and from their parents or guardians when respondents

were <18 years of age. We locked up the paper questionnaires in a secure location and stored the electronic data in a password-protected laptop to avoid disclosure of respondents' personal information. Data were not shared outside of the investigation team and, when being shared within the team, all identifying information was deleted in advance.

Results
Description of cases
We identified four case-patients (one probable and three confirmed), of who three died (case-fatality rate: 75%) (Figure). Two case-patients were men and two were women. All four case-patients came from the same family. Symptoms of three case-patients whose data were available included fever (100%), bleeding (100%), diarrhea (75%), intense fatigue (50%), severe headache (50%), and joint or muscle pain (50%).
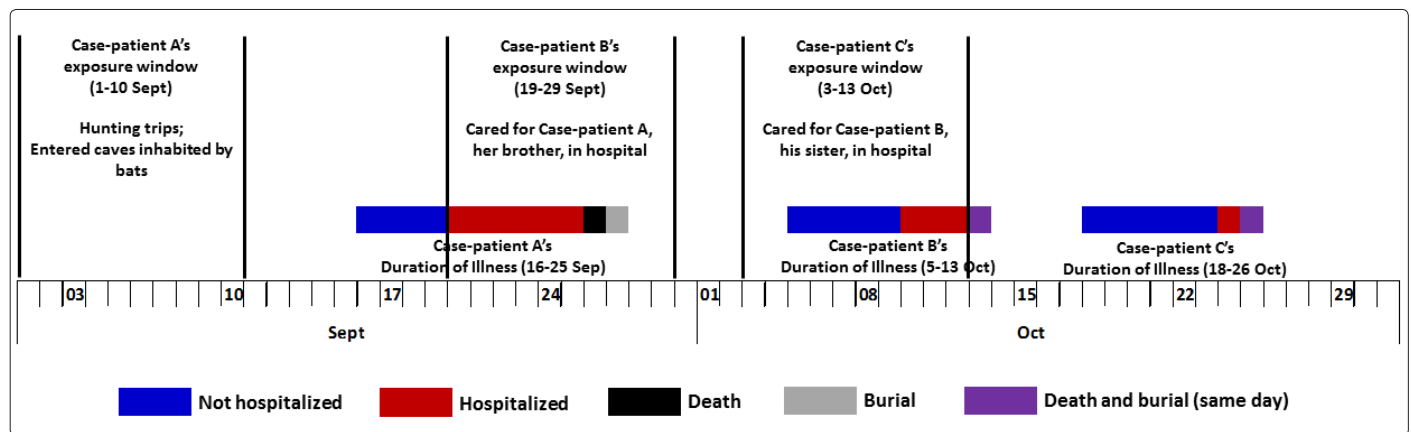

Figure: Illness duration of three symptomatic cases of Marburg Virus Disease and associated events: Uganda, August-October, 2017

Case-patient a (probable) was a 35-year old herdsman who resided in Kween District. He reportedly made frequent hunting trips in Kaptum sub-county, Kween District, during which he visited several heavily bat-infested caves near his home. On 16 September, he developed a fever, joint pain and muscle pain, and sought medical care from a private clinic in Kaproron. On 20 September, he was referred to a Health Centre IV in Kween District for more treatment as his fever persisted and had developed bleeding at injection sites. At the Health Centre IV, his condition deteriorated, developing more hemorrhagic symptoms, progressing to convulsions and unconsciousness. On 23 September, he was referred to Kapchorwa Hospital for further management, where he died on 25 September. No blood samples were collected because the attending clinicians did not suspect VHF. On 27 September, the deceased case-patient was accorded a traditional burial, which involved high-risk procedures such as washing and touching the dead body by the family members not aware of a possibility of VHF. The case-patient's linen and personal effects were not disinfected.

Case-patient B (confirmed), a 50-year old sister of Case-patient A, cared for him at home and hospital while he was ill and participated in the subsequent traditional burial rituals, which involved washing and touching the dead body. On 5 October, she became febrile, followed by bleeding from the nose. On 10 October, she was admitted to Kaproron Health Centre IV in Kween District with high fever and bleeding from multiple body orifices. On 11 October, she was

referred to Kapchorwa General Hospital for further management. The Kween District Surveillance Officer, who had been previously trained on Integrated Disease Surveillance and Response (IDSR), noticed the rarity of having two persons with VHF-like symptoms from the same family within three weeks, and reported the situation to UMoH, which prompted the response. The patient died on 13 October and was accorded a safe burial on the same day, supervised by a trained burial team. A laboratorian went to the community and collected post-mortem blood specimens and sent them to UVRI for VHF testing. On 17 October, UVRI reported that her blood samples tested positive for MARV by RT-PCR. Based on the incubation period of MVD (5-15 days) and her symptom onset date (5 October), she likely was infected during 19-29 October while she cared for Case-patient A while he was hospitalized or during the subsequent traditional burial ritual (Figure).

Case-patient C (confirmed) was a 39-year-old brother of Case-patients A and B. He cared for Case-patient B while she was hospitalized. On 18 October, he started to develop symptoms, including fever, fatigue, abdominal pain, anorexia, joint pain, and bloody vomit. However, he believed his disease was due to witchcraft; therefore, he evaded healthcare at the established Marburg treatment unit and made trips to his own Sabiny tribe in Kween and Kapchorwa, as well as to Alale and Kitale, West Pokot, Kenya to seek traditional healing. On 24 October, the patient returned to his Kween District home gravely ill. His family members contacted the local healthcare

center for medical treatment. On 25 October, he was admitted and isolated with fever, intense fatigue, abdominal pain, anorexia, joint pain, and bloody vomit. He died on 26 October. A blood sample from the patient tested positive for MARV at UVRI. A safe and dignified burial was carried out by a trained burial team on 26 October. His window of exposure was from 3-13 October, most likely while caring for Case-patient B while she was symptomatic but not hospitalized (Figure).

The ensuing initial investigations identified 42 close family contacts of Case-patient A while he was symptomatic. Blood specimens collected on 13 October from case-patient A's wife tested weakly positive for MARV-specific IgM. A follow-up specimen collected on 24 November, tested positive for MARV-specific IgG, indicating a sero-conversion. She declined to provide information on her symptoms and refused to cooperate with the investigation team. For the purpose of this investigation, this serologically confirmed person was classified as Case-patient D. In total, four cases (probable or confirmed) were identified during this MVD outbreak. Intense, active case finding in the affected community identified 34 additional persons that met the suspected case definition. However, their blood samples all tested negative for MVD by RT-PCR. Hence, they were ruled non-cases.

Contact-tracing findings

The outbreak response team identified and followed 299 contacts of Case-patients A, B, and C for 21 days (Table). Of these contacts, most were from Kween District where the three case-patients resided; 19 from Kenya where Case-patient C travelled to visit family members and sought traditional healing. Nearly half of the contacts (47%; 140/299) were family members of relatives of the case-patients, whereas more than 1/5 of the contacts were healthcare-related, i.e., healthcare workers (15%; 46/299) or patients housed in the same wards with a probable or confirmed case-patient (6.0%; 18/299).

Of the 299 contacts of Case-patients A, B and C, three developed secondary infection with MARV (SAR=1.0%; 3/299). All three occurred among Kween District residents (SAR=1.3%; 3/225). Two infections (Case-patients B and D) occurred among contacts of the Case-patient A (SAR=2.6%; 2/78); one (Case-patient C) among contacts of Case-patient B (SAR=0.83%; 1/120); whereas none occurred among contacts of Case-patient C. All three infections were among family members of the case-patients (SAR=2.1%; 3/140). SARs did not differ significantly by place of residence, case-patient, or relationship to case-patients. We calculated WRS of 263 contacts. Secondary cases occurred only among contacts with the highest WRS (9-10, SAR=8.6%; p=0.0022) (Table).

Table. Risk of secondary infection by exposure among contacts identified and traced during an outbreak of Marburg Virus Disease: Kenya & Uganda, September – October, 2017

	Num. of contacts	Num. of secondary infections	Attack rate (%)	Fisher exact p-value
Total	299	3	1.0	-
Residence				1.0
Kween District, Uganda	225	3	1.3	
Kapchorwa District, Uganda	41	0	0	
Other Districts in Uganda	13	0	0	
West Pokot and Kitale Districts, Kenya	19	0	0	
Unspecified	1	0	0	
Contact by case-patient				0.27
Case-patient A	78	2	2.6	
Case-patient B	120	1	0.83	
Case-patient C	101	0	0	
Relationship to case-patients				0.87
Family member or relative	140	3	2.1	
Healthcare worker	46	0	0	
Patient sharing the same ward	18	0	0	
Friend and neighbor	33	0	0	
Traditional healer (for Case-patient C)	1	0	0	
Other or unspecified	61	0	0	
Weighted risk score*†				
0-2	69	0	0	0.0022
3-5	93	0	0	
6-8	66	0	0	
9-10	35	3	8.6	

*The weighted risk score was calculated as follows:
1 point = Slept in confirmed case-patient's home;
2 points = Touched case-patient's clothes or utensils;
3 points = Touched case-patient's body;
4 points = Touched case-patient's bodily fluids (such as blood, saliva, excreta).
† The weighed risk scores could not be calculated for 36 REV due to insufficient data.

We noticed that, after their symptom onset, all three case-patients with known symptom information had substantial delays in seeking care (4 days for Case-patient A, 5 days for Case-patient B, and 6 days for Case-patient C; average: 5 days).

Outbreak response
In response to this outbreak, UMoH, in collaboration with several domestic and international partners, including UVRI, World Health Organization (WHO), US CDC, United Nations Children's Fund (UNICEF), and the Uganda Red Cross, mounted a major response to contain the outbreak (details will be described in a separate report). On 8 December 42 days after the death of Case-patient C (26 October 2017), UMoH declared the MVD outbreak over [11].

Discussion
We documented an outbreak of MARV, initially linked with bat exposure, which was family-clustered despite healthcare-associated exposures; and developed a scoring system quantifying exposure to assist risk-stratification of contacts. The family clustering swayed the community to believe that the case-patients were bewitched, and prompted ill case-patients to seek help of traditional healers across district and country borders. Case-patient A likely contracted MARV from the bats in the caves he frequented during hunting expeditions before illness onset. Case-patient B likely contracted MARV from Case-patient A and Case-patient C from Case-patient B considering their dates of illness onset, likely exposure to bodily fluids during care or burial practices or both. Because of a lack of information on symptoms, Case-patient D could have contracted MARV from case-patient A, B, or C by conjecture.

The natural reservoirs for MARV, *R. aegyptiacus*, are distributed throughout Africa, and have been associated with several previous MVD outbreaks in Uganda [2, 6, 8, 12]. In an ecologic investigation conducted in the Python Cave, southwestern Uganda, from August 2008 to November 2009, where a previous MVD outbreak had occurred among gold miners, 2.5% of the estimated 40,000 bats had evidence of active infection, and seven bat tissue samples yielded MARV [12, 13]. Infections of MARV in these bats, especially in older juvenile bats (about six months of age), peaked twice annually: once from mid-December to mid-March, and again from mid-June to mid-September. Most of the previous MVD outbreaks coincided with these two annual peaks [12]. In this outbreak, Case-patient A had onset on 16 September, which coincided with the end of the second annual peak.

Case-patient A exposed 78 persons after symptom onset, including clinicians and patients sharing the hospital ward with him. Lacking the clinical suspicion of VHF, these healthcare associated-contacts used no protective measures beyond standard precautions; yet none other than the family members who cared for him were infected. Similarly, before Case-patient C's admission and isolation, while symptomatic, he travelled widely in Kween District and in the neighboring West Pokot District in Kenya to visit his family members and seek traditional healing. During his travels, he had contact with at least 19 persons, none of whom suspected his MVD status. These data indicate that the development of MVD might require intimate contact such as that among household members. This observation is also supported by the finding that secondary cases only occurred among contacts with the highest WRS.

Experiences during the response to the Ebola epidemic in West Africa indicated that early diagnosis and treatment of VHF patients might improve their chance of survival [14]. In this outbreak, three of the four case-patients died. This high case-fatality rate (75%) might have been due to delays (average: 5 days) in seeking medical care. Also, Case-patients A and B were not immediately recognized as VHF patients, which likely delayed VHF-specific medical interventions.

Early identification, laboratory confirmation, and isolation of initial case-patients are the key for successful and effective control of communicable disease outbreaks. During this outbreak, the first case-patient was never diagnosed during his course of illness, suggesting that a gap still exists in the surveillance and early identification of VHF in Uganda. The second case-patient was noticed by the IDSR-trained District Surveillance Officer, indicating that IDSR training might have had a positive impact for the identification of this MVD outbreak.

Instead of seeking medical care in his home district, Case-patient C travelled extensively in Uganda and in western Kenya to seek traditional healing while symptomatic, potentially exposing many in the community with this deadly virus. This incident exposed a number of persistent gaps in global health security, including the role of anthropology, behavioral science and sociology, risk communication, cross-border surveillance and coordination, and public health law enforcement during outbreak response. The international community should continue to improve multi-sectoral, and multi-disciplinary collaboration (involving public health, animal husbandry, agriculture, wildlife, law enforcement, anthropology, social and behavioral science), as well as community engagement of stakeholders including traditional healers, so that outbreaks of international concern may be identified and contained at their sources.

Conclusion
This MVD outbreak occurred due to close contact in a single family, with fatal consequences. Effective coordination and collaboration amongst the multidisciplinary partners was key to a successful response and containment of this deadly disease. Epidemic preparedness and cross-border surveillance should be further strengthened, especially in the areas of social and behavioral interventions and law enforcement. Training of health workers on IDSR should be reemphasized and implemented.

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