Investigation of an isolated case of human Crimean–Congo hemorrhagic fever in Central Uganda, 2015[☆]

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Abstract

Background—Crimean–Congo hemorrhagic fever (CCHF) is the most geographically widespread tick-borne viral infection. Outbreaks of CCHF in sub-Saharan Africa are largely undetected and thus under-reported. On November 9, 2015, the National Viral Hemorrhagic Fever Laboratory at the Uganda Virus Research Institute received an alert for a suspect VHF case in a 33-year-old male who presented with VHF compatible signs and symptoms at Mengo Hospital in Kampala.

Methods—A blood sample from the suspect patient was tested by RT-PCR for CCHF and found positive. Serological testing on sequential blood specimens collected from this patient showed increasing anti-CCHFV IgM antibody titers, confirming recent infection. Repeat sampling of the confirmed case post recovery showed high titers for anti-CCHFV-specific IgG. An

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Conflicts of interest
All authors declare no conflicts of interest.

epidemiological outbreak investigation was initiated following the initial RT-PCR positive detection to identify any additional suspect cases.

Results—Only a single acute case of CCHF was detected from this outbreak. No additional acute CCHF cases were identified following field investigations. Environmental investigations collected 53 tick samples, with only 1, a *Boophilus decoloratus*, having detectable CCHFV RNA by RT-PCR. Full-length genomic sequencing on a viral isolate from the index human case showed the virus to be related to the DRC (Africa 2) lineage.

Conclusions—This is the fourth confirmed CCHF outbreak in Uganda within 2 years after more than 50 years of no reported human CCHF cases in this country. Our investigations reaffirm the endemicity of CCHFV in Uganda, and show that exposure to ticks poses a significant risk for human infection. These findings also reflect the importance of having an established national VHF surveillance system and diagnostic capacity in a developing country like Uganda, in order to identify the first cases of VHF outbreaks and rapidly respond to reduce secondary cases. Additional efforts should focus on implementing effective tick control methods and investigating the circulation of CCHFV throughout the country.

Introduction

Crimean–Congo hemorrhagic fever (CCHF) is an ancient viral disease, with human cases probably occurring as far back as the 12th century in present-day Tajikistan and other parts of central Asia. CCHF virus was formally recognized in 1944 during an outbreak in the Crimean Peninsula (Hoogstraal, 1979; Chumakov, 1945). Following the characterization of the causative agent of the outbreak, it was found to be related to a virus isolated from a febrile patient in the Kisangani area of the Democratic Republic of Congo (DRC) in 1956 (Woodall et al.,1967; Simpson et al.,1967), leading to the combined name Crimean–Congo hemorrhagic fever virus (CCHFV). Thereafter, CCHFV has been shown to be one of the most widespread tick-borne viruses, affecting both animal and human populations across most of Africa, Eastern Europe, and Asia. In animals, infection is mainly asymptomatic, while in humans, it can manifest as an acute and highly infectious viral hemorrhagic fever (VHF) that readily transmits to close contacts with a case-fatality rate as high as 50%, and higher (Ergonul, 2006; Schwarz et al.,1997) in hospitalized patients.

CCHFV is an enveloped, negative-sense RNA orthonairovirus of the Nairoviridae family. It is maintained in nature by tick vectors, principally of the *Hyalomma* species, through tick-to-tick enzootic and vertebrate-mediated epizootic cycles. Virus spillovers to humans usually occur through tick bites and direct contact with viremic animals and other infectious biological materials (Aslam et al., 2016; Sisman, 2013).

Over the last few years, public health interest in CCHFV as an important zoonosis has increased, partly due to its vast geographical range, including its emergence in new foci; its high degree of genetic diversity with the capability for new and potentially highly-

pathogenic variants to emerge (Elevli et al., 2010; Salehi-Vaziri et al., 2016); and recent discussion on its use as a potential bio-weapon (Christian, 2013). Consequently, CCHFV is classified as a bio-safety level 4 pathogen in countries where the disease is not endemic (Weidmann et al., 2016). Globally, all newly identified cases of CCHF in humans and animals are an internationally notifiable disease, and must be reported to WHO and OIE. Despite its high profile, CCHFV remains poorly characterized in much of sub-Saharan Africa, and very little is known about its epidemiology, population burden, and viral characteristics (Messina et al., 2015). Ironically, current evidence from phylogeographical studies indicates that CCHFV ancestry could have originated in Africa (Lukashev et al., 2016), and that outbreaks continue to occur, but remain undetected and uncharacterized. To this end, the potential public health impact from a disease whose endemicity in Uganda is poorly understood comes to the fore. We report on the detection, isolation, and confirmation of CCHFV in a single human case in a central Ugandan district in 2015, as well as CCHFV detection from a tick sample collected from the same locality.

Outbreak investigations

Ethical considerations

All field and laboratory investigations were performed as part of the Ugandan Ministry of Health (MoH) and WHO protocol requirements for responding to and managing VHF outbreaks in Uganda. These activities do not require Ethics committee approval or written consent of case participants.

Case description

The case patient was a 33-year-old male paraveterinarian, mainly selling veterinary drugs in the areas surrounding the Ngoma trading center in Nakaseke District (Figure 1). He had a second home in the neighboring Luweero town in Luweero District, also shown in Figure 1. These 2 semirural townships are approximately 30 km apart and lie within a large livestock grazing area popularly known as the Ugandan cattle corridor. The patient had no history of travel outside his routine area of operation in the weeks prior to his illness.

As illustrated in Figure 2(A), onset of disease symptoms started in the afternoon of November 6, 2015, when the patient developed a mild fever and general body weakness that progressed to high body temperature and chills within a few hours. He presented himself to a private medical facility within Ngoma township and was treated for presumed malaria. The following morning, he developed additional symptoms of severe headache, constitutive pains (chest, muscles, joint, and abdominal), dizziness, and loss of appetite. Onset of hemorrhagic signs, including bloody diarrhea, hematemesis, epistaxis, and subconjunctival hematoma, was observed on the 3rd day post symptom onset, when the patient was transferred to another private health clinic in Luweero town and later the same day to Mengo Hospital, Kampala (Figure 1). Within a few hours of admission, he developed petechiae hemorrhage and a confused and violent behavior. Blood chemistry and hematological examinations showed significantly elevated liver enzymes (ALT, 1289 IU/L; ALP, 317 IU/L; and AST, 4426 IU/L), hypoalbuminemia (24.0 g/L), normal renal function, and slight abnormalities in

hematological values (WBC, 11.0/mm^3; RBC, 6.4/mm^3; HGB, 17.0 g/dL; and PLT, 21.0/mm^3). A chest x-ray examination showed a normal profile.

While at Mengo Hospital, the patient's illness was primarily managed with supportive therapy: antibiotics, rehydration, and body temperature control. He remained admitted for 11 days, during which time he was also given a transfusion of 11 units of blood. The patient began to clinically improve after admission to Mengo Hospital, with diarrhea subsiding on the 3rd day post admission, followed by reduced vomiting, epistaxis, gum bleeding, hematuria, and melena by the 4th day. During the few weeks following discharge, he experienced skin exfoliation around most parts of his body, starting with the feet. The last symptom to subside was dizziness.

Laboratory investigations for VHF

On November 10, 2015, a blood sample from the patient was received at the VHF diagnostics laboratory based at the Uganda Virus Research Institute (UVRI) in Entebbe. Upon receipt of the sample, nucleic acids were extracted using the Magmax RNA isolation procedure (Ambion, Austin, TX, USA), following the kit manufacturer's instructions. The eluted RNA was then analyzed using established RT-PCR assays for Ebola, Marburg, CCHF, and Rift Valley fever viruses, as previously described (Shoemaker et al., 2012; Albarino et al., 2013). Repeat tests on the same blood specimen and on subsequent specimens received from the patient were positive for CCHFV RNA. Further laboratory investigations were performed to examine the onset of immune response to CCHF. Using established serological techniques (Bryan et al., 1996), testing of sequential blood specimens showed increasing anti-CCHFV IgM antibody titers, confirming a recent infection. A 5th sample, collected 3 months post recovery, showed high titers for anti-CCHFV-specific IgG, as shown in Figure 2(B).

Outbreak response and environmental sample investigations

As part of the routine protocol for responding to a suspected VHF outbreak in Uganda, the MoH organized a multidisciplinary team of public health investigators that deployed to the area where the patient resided, primarily to identify new suspect cases and to determine the magnitude of the outbreak. The team visited various health centers in Nakaseke and its neighboring district of Luweero because of the epidemiological linkage to the confirmed case patient. The team reviewed medical records in various health centers and performed an active case search in the community. Healthcare workers in both districts were also re-educated on the standard case definition for VHF surveillance in Uganda. Patient information and blood samples were collected from any newly suspected patients.

At the end of 3 weeks of active case-finding, 7 suspect cases, including 1 probable case (in a 2-year-old child of the patient), had been identified. We defined a suspect case as any individual residing in Nakaseke District who presented with acute onset of illness, fever (38 °C), and other constitutional signs and symptoms with unexplained diagnosis. However, none of these suspect patients were found to be acutely infected with CCHFV upon laboratory investigation. Similarly, no deaths attributable to CCHF were identified in the area. When the patient was interviewed, the most significant risk of exposure was

attributed to "a small brown" tick that he had removed from the body of a colleague a few weeks prior to disease onset. We were unable to locate this individual to interview or collect samples for testing during our investigations. The index patient reported to our team that this colleague never became ill, had moved away from the village where the infection occurred, and was unable to be located for follow-up.

In order to investigate the presence of CCHFV in the environment, the field investigation team randomly collected 53 ticks from cattle located on 2 farms within 25 km of the index village, shown in Figure 1. These 2 farms were among those farms where the confirmed patient had previously participated in animal treatments. The collected ticks were identified by experienced laboratory personnel using morphological keys (Walker et al., 2003) and consisted of *Hyalomma truncatum* (52.8%), *Boophilus decoloratus* (34.0%), *Haemaphysalis punctata* (9.4%), and *Rhipicephalus appendiculatus* (3.8%). All ticks, individually stabilized in RNALater (Sigma-Aldrich, St. Louis, MO, USA), were transported to the UVRI VHF laboratory. They were then processed in order to test for CCHFV RNA. Briefly, ticks were removed from RNALater, ground, and homogenized in Magmax lysis buffer by Genogrinding (Genogrinder 2000, OPS Diagnostics, Lebanon, NJ, USA). Thereafter, RNA from the tick homogenate was extracted using the Magmax protocol before testing for CCHFV RNA by real time RT-PCR (Deyde et al., 2006). One of the 53 ticks, a *Boophillus decoloratus* tick, was found positive by RT-PCR for presence of CCHFV RNA.

Virus isolation, RNA sequencing, and phylogenetic analysis

All initial and subsequent human samples obtained from the patient were shipped to CDC's Viral Special Pathogens Branch laboratories in Atlanta, USA, for viral isolation attempts and genomic sequencing. Using Vero-E6 cell cultures, a viral isolate was obtained from the clinical sample of the confirmed case. The tick sample was not cultured as it was shipped as a total nucleic acid eluate, and it could not be genetically sequenced due to the low RNA copy number in the sample. Full-length S segment genomic sequencing on the human viral isolate revealed that the implicated virus was related to the DRC (Africa 2) lineage (Figure 3).

Discussion and conclusions

We report a single human case of CCHF in a remote area in central Uganda. This is the fourth confirmed CCHF outbreak in Uganda within 2 years after more than 50 years of no reported human CCHF cases in this country (Hoogstraal, 1979; Chamberlain et al., 2005). The 3 other outbreaks occurred in 2013 in the districts of Agago (3 cases) and Kiboga (2 cases), and in Kampala City (1 case). These findings reflect the importance of having established a national surveillance system and diagnostic capacity for VHFs in a developing country like Uganda. The VHF surveillance system established by UVRI and MoH since 2010 has previously assisted in the rapid identification and confirmation of multiple VHF outbreaks, including significant outbreaks of Ebola and Marburg virus (Shoemaker et al., 2012; Albarino et al., 2013).

The increased detection of CCHF cases over the past 2 years could be due to environmental changes that affect the biology of the vectors and/or the frequency of human contact with the

viral host/vector, as previously proposed for filovirus outbreaks in Uganda (Polonsky et al., 2014). However, we believe it is primarily due to increased vigilance and awareness of these severe infections and potential VHF outbreaks within the Ugandan population. Our reasons for thinking so are twofold. First, within 3 days of initial presentation in a rural health setting, the confirmed case was transferred to a tertiary health facility in Kampala that had adequate capacity and was better equipped to manage suspected VHF cases. In most of rural sub-Saharan Africa, community attention to "mysterious" diseases is only formally acted upon when clusters of severe illness or death appear, and rarely from the presentation of a single individual with severe clinical signs and symptoms (MacNeil et al., 2011; Hewlett and Amola, 2003). Secondly, no further cases occurred amongst the community or healthcare staff. In previous CCHF outbreaks, large nosocomial outbreaks in rural areas have been observed after significant direct exposure to a patient before adequate infection control measures have been put in place (Aradaib et al., 2010; Naderi et al., 2011). We believe this is due to increased health education and infection control messages being widely disseminated and adopted into daily practice in most of the Ugandan health care facilities and village communities over the past several years (Mbonye et al., 2014; Lukwago et al., 2013).

We were unable to sequence the viral RNA from the single RT-PCR-positive tick due to low viral load in the sample. This prevented us from genetically matching the CCHFV in the tick with the virus from the case patient. Detecting CCHFV by RT-PCR in any tick collected from an epidemiologically linked location where the confirmed case had been prior to illness onset, however, shows that CCHFV is actively circulating in the environment; our investigations strongly suggest that a tick was the likely source of infection. In addition, the phylogenetic relatedness of the human isolate to previously identified CCHFV isolates in the region –UG3010-1956 (DRC), Semunya-1958 (Uganda), and Beruwe-2008 (DRC) – that form the African type 2 grouping also indicates endemicity (Deyde et al., 2006; Grard et al., 2011).

In conclusion, we report a confirmed human case of CCHF in the central region of Uganda. No secondary transmissions were associated with the case. Importantly, similarly to other previously reported CCHF cases in Uganda, the index patient was acutely ill and additional subclinical cases may not have been detected by the surveillance system. Further efforts should focus on implementing effective tick control methods and investigating the endemic characteristics of CCHFV throughout Uganda.

Acknowledgments

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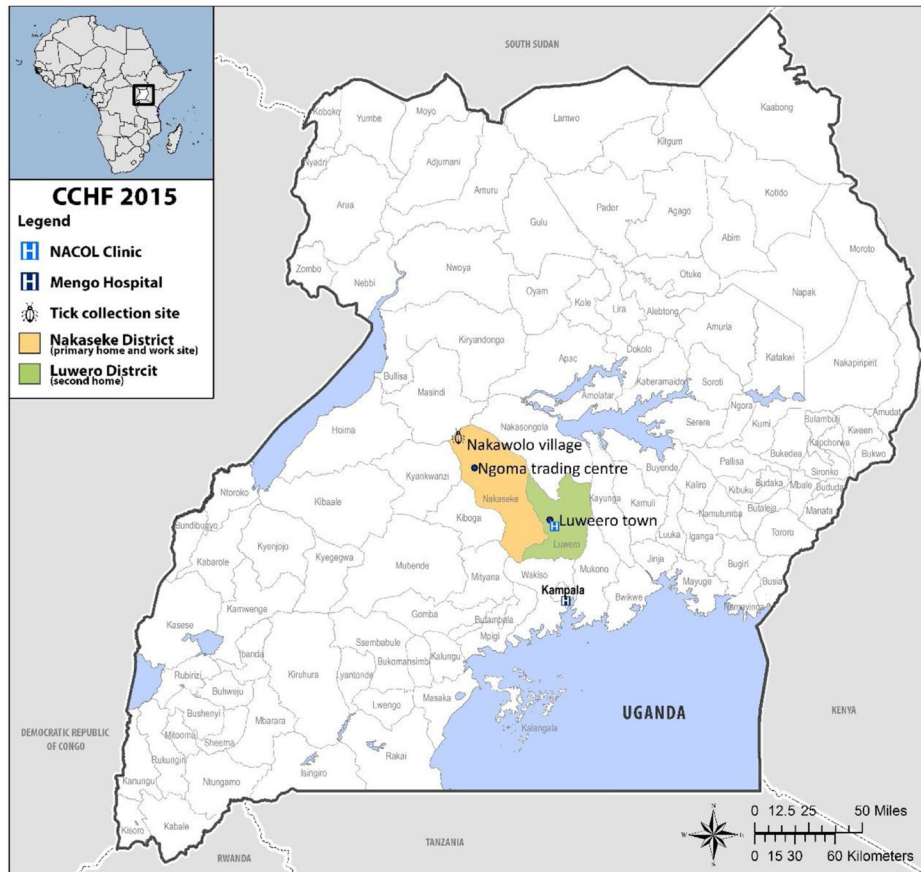
Figure 1.
Locations where patient with confirmed CCHF lived, worked, was hospitalized, and tick collections were performed. Inset map shows location of Uganda in Africa.
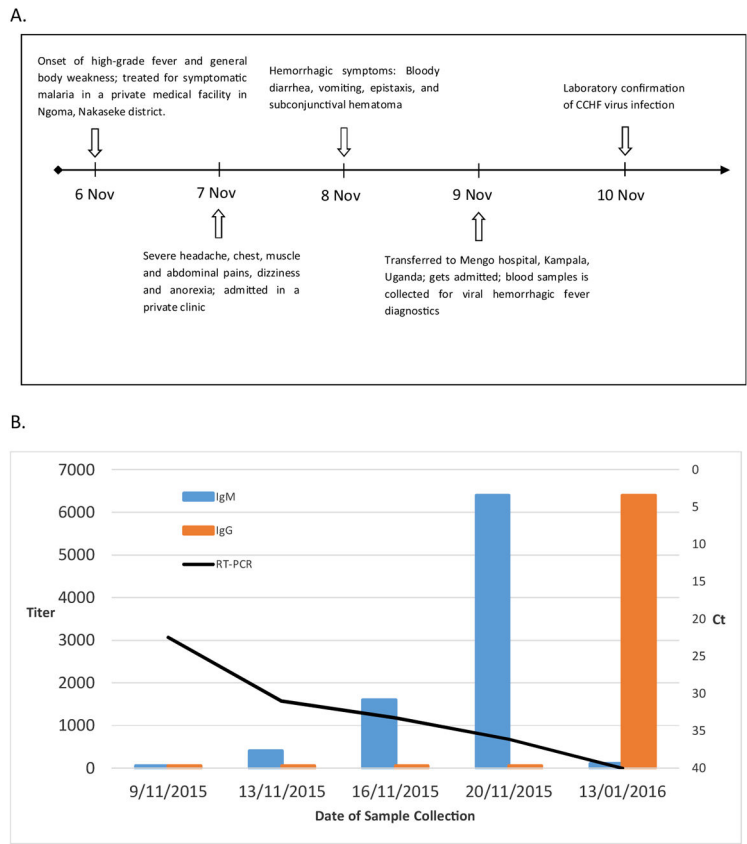
A.

B.

Figure 2.
CCHF outbreak investigation in Uganda, 2015. (**A**) Timeline for disease onset, clinical
manifestations, and management. (**B**) Anti-CCHFV antibody and CCHFV trends, Nakaseke
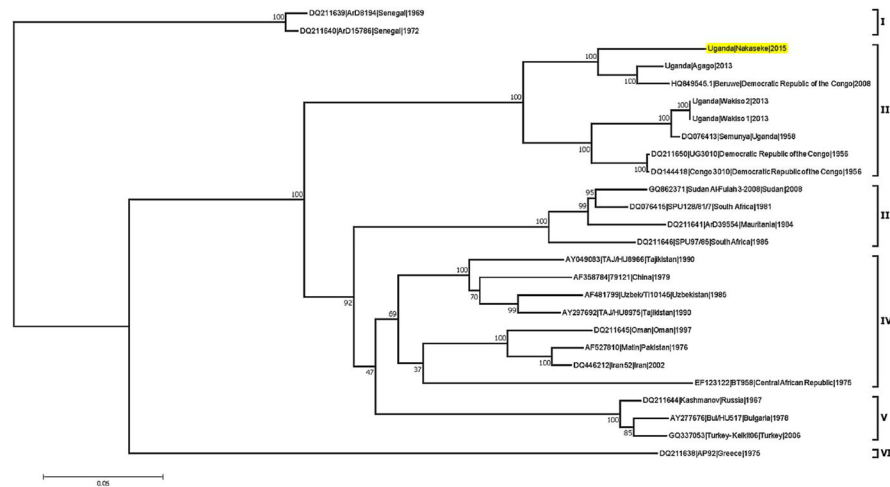District, Uganda, 2015.

Figure 3.
Molecular Phylogenetic analysis of CCHF S segments by Maximum Likelihood method. The evolutionary history was inferred by using the Maximum Likelihood method based on the Tamura 3-parameter model (Tamura, 1992). The tree with the highest log likelihood (−10038.19) is shown. The percentage of trees in which the associated taxa clustered together is shown next to the branches. Initial tree(s) for the heuristic search were obtained automatically by applying Neighbor–Join and BioNJ algorithms to a matrix of pairwise distances estimated using the Maximum Composite Likelihood (MCL) approach, and then selecting the topology with superior log likelihood value. A discrete Gamma distribution was used to model evolutionary rate differences among sites (5 categories (+G, parameter = 0.4820)). The rate variation model allowed for some sites to be evolutionarily invariable ([+I], 29.66% sites). The tree is drawn to scale, with branch lengths measured in the number of substitutions per site. The analysis involved 26 nucleotide sequences. All positions with less than 95% site coverage were eliminated. That is, fewer than 5% alignment gaps, missing data, and ambiguous bases were allowed at any position. There were a total of 1568 positions in the final dataset. Evolutionary analyses were conducted in MEGA7 (Kumar et al., 2016). Values at nodes represent bootstrap values following 1000 replicates. Genbank accession numbers used in tree are DQ211639, DQ211640, HQ849545.1, DQ076413, DQ211650, DQ144418, GQ862371, DQ076415, DQ211641, DQ211646, AY049083, AF358784, AF481799, AY297692, DQ211645, AF527810, DQ446212, EF123122, DQ211644, AY277676, GQ337053, DQ211638, (Uganda CCHF sequence accession #'s pending).