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Epidemiological and laboratory characterization of a yellow fever outbreak in northern Uganda, October 2010–January 2011

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SUMMARY

Background: In November 2010, following reports of an outbreak of a fatal, febrile, hemorrhagic illness in northern Uganda, the Uganda Ministry of Health established multisector teams to respond to the outbreak.
Methods: This was a case-series investigation in which the response teams conducted epidemiological and laboratory investigations on suspect cases. The cases identified were line-listed and a data analysis was undertaken regularly to guide the outbreak response.
Results: Overall, 181 cases met the yellow fever (YF) suspected case definition; there were 45 deaths (case fatality rate 24.9%). Only 13 (7.5%) of the suspected YF cases were laboratory confirmed, and molecular sequencing revealed 92% homology to the YF virus strain Couma (Ethiopia), East African genotype. Suspected YF cases had fever (100%) and unexplained bleeding (97.8%), but jaundice was rare (11.6%). The overall attack rate was 13 cases/100 000 population, and the attack rate was higher for males than females and increased with age. The index clusters were linked to economic activities undertaken by males around forests.
Conclusions: This was the largest YF outbreak ever reported in Uganda. The wide geographical case dispersion as well as the male and older age preponderance suggests transmission during the outbreak was largely sylvatic and related to occupational activities around forests.

1. Introduction

Yellow fever (YF) is an acute viral hemorrhagic disease caused by the yellow fever virus. The YF virus is an enveloped positive sense single-stranded RNA virus that belongs to the genus *Flavivirus*.[1] The natural host of the virus is non-human primates and the vectors in Africa are usually mosquitoes of species *Aedes africanus* in forest areas and *Aedes aegypti* in urban areas.[2]

In humans, the acute phase occurs 3–6 days after infection and is characterized by non-specific symptoms that last up to 4 days. Fifteen percent of the patients enter a toxic phase characterized by high fever, unexplained bleeding, jaundice, and multiple organ failure, and 50% of these patients die within 2 weeks.[3]

To confirm the disease, serological testing by way of ELISA for YF virus-specific IgM or isolation of the virus from blood samples is usually undertaken, since these are the recommended standard diagnostic tests for YF.[4] Blood samples may be subjected to PCR testing or exceptionally to next generation sequencing (NGS)[5] for the detection of YF virus genetic material. Immunohistochemical techniques are valuable for detecting the viral antigen in liver autopsy tissues.[4] Treatment is supportive since there is no known cure,[6] and vaccination is the mainstay of YF control.[7]

YF is a moving epizootic in endemic regions of tropical Africa and South America lying within a band from 15°N to 10°S of the equator and accounts for an estimated 200 000 cases of YF (with 30 000 deaths) per year globally.[8]

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The largest YF outbreak in East Africa occurred in Ethiopia from 1960 to 1962 and accounted for about 30 000 deaths.[9] YF outbreaks have also been reported from Sudan (1940,[10] 2003,[11] and 2005[12]) and Kenya (1992–93[13]). The first YF outbreak in Uganda was reported in 1941 from Bwamba County, western Uganda.[14] Subsequent YF outbreaks in Uganda were reported in Kabarole District in 1952,[15] Entebbe in 1959 and 1971,[16] and Luwero in 1964.[17]

After 1972, political instability in the country led to a decline in YF surveillance activities in Uganda and hence many suspected YF cases notified by the health facilities were not investigated. Following the introduction of the Integrated Disease Surveillance and Response (IDSR) strategy in Uganda in 2000,[18] a clinical health facility-based surveillance system for YF was instituted, though most of these reports were not accompanied by specimens to facilitate laboratory investigations. It is therefore possible that undetected human cases were occurring despite the absence of confirmed outbreaks in the country over the past four decades.

In November 2010, the Uganda Ministry of Health received reports of an outbreak of a fatal, febrile, hemorrhagic illness in northern Uganda. Multisector teams were established to support the outbreak response. This report highlights the activities and findings of the epidemiology and laboratory team during the outbreak. Entomological and reactive vaccination outcomes will be reported separately.

2. Methods

2.1. Epidemic site

A total of 15 districts in northern Uganda, including Abim, Agago, Apac, Kitgum, Kaabong, Kotido, Lamwo, Arua, Lira, Pader, Gulu, Nebbi, Napak, Dokolo, and Yumbe reported suspected cases of YF (Figure 1). The districts share borders with southern Sudan and Kenya where outbreaks have been reported in the past.[10–13] The northern region is home to a number of game reserves and parks including Kidepo Valley National Park and Murchison Falls National Park. Northern Uganda has just recovered from a nearly two-decade civil war that confined more than 90% of the population to internally displaced people's (IDP) camps. The YF outbreak occurred within 2 years after these people had returned to their original homes.

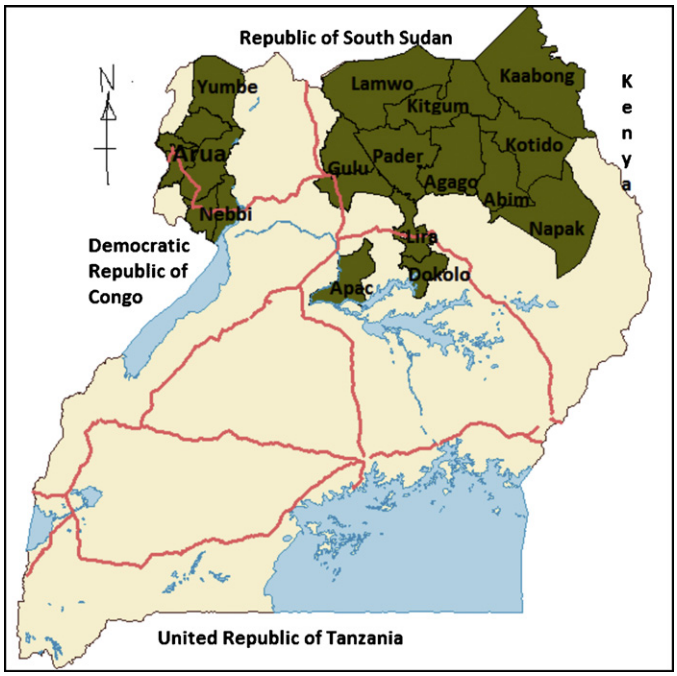

Figure 1. Map showing districts reporting suspect cases, northern Uganda, 2010–2011.

2.2. Investigation teams

The epidemiology and laboratory team was one of the subcommittees of the national task force established to respond to the outbreak. The experts on the team included medical epidemiologists, physicians, laboratory experts, and social workers drawn from the Ministry of Health, other sectors in government, and partner organizations like the World Health Organization (WHO), Centers for Disease Control and Prevention (CDC), Médecins Sans Frontières (MSF), and the African Field Epidemiology Network (AFENET).

2.3. Epidemiology and laboratory activities

2.3.1. Epidemiology

This was a case-series investigation in which the field teams conducted detailed clinical descriptions of all suspected cases. A working case definition was developed for the initially unknown disease, and following the identification of YF using the NGS approach,[19] this was modified (Table 1) to facilitate the identification of additional YF cases at the health facility and community level. All new suspected YF cases were given supportive treatment[4] at designated treatment centers that maintained case line-lists with key variables including: identifiers, age, sex, occupation, residence, date of onset of illness, date of admission to health facility, clinical signs and symptoms, YF vaccination status, types of specimens collected, date of specimen collection, laboratory results, case classification, and case outcome.

2.3.2. Laboratory

Prior to the confirmation of YF, the types of specimens taken reflected the proposed differential diagnoses (Table 2). Hence from each suspected case, one to five blood specimens of 1–3 ml each were obtained for blood culture, viral serology and genetic testing by PCR and/or NGS, blood chemistry, full blood counts, and blood smears. Stool was also obtained in a plain container for microscopy or placed in Cary–Blair transport medium for stool culture. Liver autopsy specimens were obtained and preserved in10% formalin to facilitate YF antigen detection through immunohistochemical testing. After the confirmation of YF by NGS,[19] samples from new suspected cases were collected for blood chemistry, full blood counts, and YF testing by PCR and IgM, with confirmation by plaque reduction neutralization test (PRNT). Because of an ongoing hepatitis E epidemic in northern Uganda, specimens testing negative for YF were subsequently tested for hepatitis E virus and other infections, as elaborated in Table 2.

2.4. Data analysis

A Microsoft Excel data-entry screen incorporating all the variables on the YF line-list was developed and used to capture all the information on the cases reported during the outbreak. The population projections for the affected districts[20] were obtained and used to compute disease attack rates by age, sex, and geographic location. Attack rate maps were drawn using Epi Map software.[21] Epidemic curves were drawn using the dates of onset to determine outbreak trends.

All epidemiological and laboratory data were collected as part of the routine outbreak investigation by national multisector teams, hence ethical clearance was not obtained.