

Aetiology of Hospitalized Fever and Risk of Death at Two Rural Tertiary Care Hospitals in Uganda from August 2019 to August 2020

Paul W. Blair (✉ pblair6@jhmi.edu)

John Hopkins University School of Medicine

Kenneth Kobba

Infectious Diseases Institute

Francis Kakooza

Infectious Diseases Institute

Matthew L. Robinson

John Hopkins University School of Medicine

Emmanuel Candia

Infectious Diseases Institute

Jonathan Mayito

Infectious Diseases Institute

Edgar C. Ndawula

Infectious Diseases Institute

Abraham Kandathil

John Hopkins University School of Medicine

Alphonsus Matovu

Mubende Regional Referral Hospital

Gilbert Aniku

Arua Regional Referral Hospital

Yukari C Manabe

John Hopkins University School of Medicine

Mohammed Lamorde

Infectious Diseases Institute

Research Article

Keywords:

Posted Date: July 19th, 2022

DOI: <https://doi.org/10.21203/rs.3.rs-1808975/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Abstract

Background: Epidemiology of febrile illness in Uganda is shifting due to increased HIV treatment access, emerging viruses, and increased surveillance. We investigated the aetiology and outcomes of acute febrile illness in adults presenting to hospital using a standardized testing algorithm of available assays in two tertiary care hospitals in Uganda.

Methods: We recruited adults with a $\geq 38.0^{\circ}\text{C}$ temperature or history of fever within 48 hours of presentation. Medical history, demographics, and vital signs were recorded. Testing performed included a complete blood count, renal and liver function, malaria smears, blood culture, and human immunodeficiency virus (HIV). When HIV positive; cryptococcal antigen, CD4 count, and urine lateral flow lipoarabinomannan assay for tuberculosis. Participants were followed during hospitalization and at a 1-month visit. A Cox proportional hazard regression was performed to evaluate for baseline clinical features and risk of death.

Results: Of 132 participants, the median age was 33.5 years (IQR 24 to 46) and 58.3% (n=77) were female. Overall, 73 (55.3%) of 132 had a positive microbiologic result. Among those living with HIV, 31 (68.9%) of 45 had at least one positive assay; 16 (35.6%) had malaria, 14 (31.1%) tuberculosis, and 4 (8.9%) cryptococcal antigenemia. The majority (65.9%) were HIV-negative; 42 (48.3%) of 87 had at least one diagnostic assay positive; 24 (27.6%) had positive malaria smears and 1 was Xpert MTB/RIF Ultra positive. Overall, 16 (12.1%) of 132 died; 9 (56.3%) of 16 were HIV-negative, 6 died after discharge. High respiratory rate (≥ 22 breaths per minute) (hazard ratio [HR] 8.05; 95% CI: 1.81 to 35.69) and low (i.e., $<92\%$) oxygen saturation (HR 4.33; 95% CI: 1.38 to 13.61) were identified to be associated with increased risk of death.

Conclusion: In those with hospitalized fever, malaria and tuberculosis were common causes of febrile illness, but most deaths were non-malarial, and most HIV-negative participants did not have a positive diagnostic result. Those with respiratory failure had a high risk of death.

Introduction

Systemic causes of fever are notoriously challenging to differentiate clinically in sub-Saharan Africa (SSA), ranging from malaria to Ebola virus disease. Clinicians often rely on local epidemiology to guide empiric treatment decisions. However, during the past decade, the epidemiology of hospitalized, acute febrile illness (AFI) may have shifted in Uganda due to improved access to HIV treatment and increased detection of zoonotic infections. Additionally, disease recognition is largely limited to what well performing diagnostics are available.

A few decades ago during the early PEPFAR (U.S. President's Emergency Plan for AIDS Relief) era in SSA, HIV coinfections were responsible for the majority of hospitalizations with severe febrile illness and associated with high mortality.[1–3] The introduction of antiretroviral therapy (ART) and the World Health Organization (WHO) recommendation to 'treat all' regardless of CD4 T-cell count has reduced mortality.[4–6] However, late presentation remains a tenacious problem with significant opportunistic infection related early mortality after the initiation of ART.[7] Currently, national guidelines recommend universal HIV testing and ART ideally before the development of AIDS. Treating pre-emptively with ART[8], screening for cryptococcal antigen positivity, and urine lipoarabinomannan (LAM) testing in all hospitalized adults with HIV have been shown to decrease early mortality.[9] Since this shift to improved testing and treatment, the effect on the epidemiology of acute febrile illness among hospitalized adults in Uganda has yet to be fully characterized.

Due to high biodiversity and population density, many emerging and re-emerging zoonotic infections have been identified in Uganda particularly near the Rift Valley, further expanding the differential diagnosis of undifferentiated fever. With increasing surveillance, more cases of viral hemorrhagic fevers (VHF), including autochthonous and imported Ebola virus disease outbreaks, Crimean-Congo hemorrhagic fever (CCHF) and Rift Valley fever (RVF), have been detected in Uganda [10–14]. Therefore, our acute febrile illness cohort was developed to characterize most common causes of acute febrile illness in Uganda and to determine the frequency of febrile illness due to unknown etiologies. We describe herein the

characteristics of hospitalized patients with AFI at two tertiary care centers in Uganda and the diagnostic yield of available testing.

Methods

From August 2019 to August 2020, we recruited adults 18 years of age or older presenting to Mubende and Arua Regional Referral Hospitals (RRHs) emergency or outpatient departments designated to be hospitalized with a measured or reported temperature $\geq 38.0^{\circ}\text{C}$ occurring within the past 48 hours or a clinical history consistent with fever within 48 hours of presentation. There were 255 participants consecutively screened with 97 enrolled at Mubende RRH and 35 enrolled at Arua RRH. Participants with COVID-19 diagnoses were in separate designated areas, required scarce personal protective equipment, and were not enrolled. Exclusion criteria included being hospitalized for ≥ 72 hours, receipt of antibiotics, previous participation in the study, being a prisoner, and being a psychiatric patient.

The two tertiary care hospitals were chosen as study sites because both sites are located in regions with different ecology and serve different populations. Mubende RRH (bed capacity 173) is located in central Uganda and serves a district population of over 688,000 people.[15] Mubende is situated on a major road between Democratic Republic of the Congo and the capital of Uganda, Kampala. Arua RRH (bed capacity 323) is located in the more arid northwest Uganda (proximal to borders with Democratic Republic of the Congo and with South Sudan), serves over 785,000 people in the districts, and receives referrals from neighbouring countries. [16]

After informed consent, participants provided information about sociodemographic and comorbid medical conditions at enrolment. History suggestive of exposure to zoonotic infections was obtained including area of residence, occupation, environmental exposures, and healthcare exposure. [17] Also, recent antibiotic use was documented, relying on patient self-report or any clinical documents they possessed. Vital signs were recorded including temperature, heart rate, respiratory rate, blood pressure, and pulse oximetry; a Glasgow Coma Score (GCS) was calculated. Participants were prospectively followed until hospital discharge. Inpatient antibiotic usage, vital signs monitoring, intensive care unit admission, length of stay, timing of receipt of infectious disease test results, discharge diagnosis, and vital status at discharge were recorded. Upon discharge, participants returned after 3–8 weeks and were interviewed on duration of illness and antimicrobial use and serum, whole blood, and plasma stored for future assessment of seroconversion. If participants were unable to follow-up in-person, they were contacted via telephone to determine vital status.

Laboratory tests that were conducted included complete blood count, serum creatinine, serum alanine transferase (ALT), serum aspartate transferase (AST), blood cultures (one aerobic bottle, Bactec 9050, BD, NJ, United States), hepatitis A IgM (Vaxpert, Inc., Deira Dubai, UAE), hepatitis B sAg (SD Bioline, Abbott diagnostics, Gyeonggi-do, Republic of Korea), and HIV testing with consent (Determine HIV1/2: Abbott, OK, USA; Stat-Pak, Chembio Diagnostics Systems, Inc, NY, USA; SD Bioline: Gyeonggi-do, Republic of Korea), malaria rapid test (CareStart malaria Pf HRP2 antigen RDT), and thick malaria smears. A malaria smear result was stratified by any parasitaemia or ≥ 3000 parasites/microliter [18, 19]. If there was clinical suspicion, testing for tuberculosis was performed using PCR sputum testing (Xpert MTB/RIF Ultra, Cepheid, Sunnyvale, CA, USA). If HIV testing was positive, serum cryptococcal antigen, urine lipoarabinomannan (LAM; Alere Waltham, MA, United States), and plasma CD4 count (BD Facs Calibur, BD, NJ, United States) were measured. HIV testing and counselling were performed per Uganda's national guidelines.

We estimated that a target sample size of 365 patients would estimate the frequency of uncommon endemic viral infections with a 5% prevalence using a precision of 0.025 at 95% confidence. Here we report initial findings from an accrued sample size of 132 participants enrolled to date. Summary statistics were performed for baseline demographics and prevalence of difference diagnoses. Baseline demographics, symptom prevalence, physiologic parameters, clinical laboratory results, quick sequential organ failure assessment (qSOFA; range, 0 [best] to 3 [worst] points) scores [20], and subsequent diagnoses made by the research physicians on-site were summarized and stratified by HIV diagnosis and the presence of a laboratory-confirmed acute infectious disease diagnosis. We stratified these descriptive statistics between those living with HIV or were

newly diagnosed with HIV and those that were HIV-negative. Kaplan-Meier curve of survival stratified by HIV status. The logrank test was also performed to evaluate for a survival difference with HIV. Individuals lost to follow-up after discharge were censored at hospital discharge. After checking the proportional hazards assumption, univariate Cox regression was performed to evaluate for a survival difference associated with baseline demographics, HIV status (including both new and known), physiologic parameters, and laboratory parameters. The qSOFA (quick Sepsis Related Organ Failure Assessment) score dichotomized at a score of 2 and components of the qSOFA score were also independently fit. Dichotomized parameters were used at score cut offs (i.e., respiratory rate > 21 breaths per minute, Glasgow coma scale < 15, and systolic blood pressure 100 mmHg). P-values were not corrected for multiple comparisons due to a limited sample size.

Results

Participant characteristics

Among the participants (35 at Arua RRH and 97 at Mubende RRH), the median age was 33.5 years (interquartile range [IQR]: 24.0 to 46.0); 77 (58.3%) of 132 were female (Table 1). Participants presented from 10 districts in Uganda. Participants were enrolled at a median 4 days (IQR: 3 to 7 days) after onset of symptoms which did not differ significantly by HIV status (Table 2). The majority of those lost to follow-up (3 from Arua RRH and 11 from Mubende RRH), were male (71.4%; 11 of 14 participants) and the median age was 31.5 years (IQR: 27 to 50 years). 27 (20.5%) of 132 participants had a qSOFA severity score of 2 or greater. The most common symptoms included headache (76.0%), and anorexia (58.9%), and nausea or vomiting (58.9%) (Supplementary Table S1). The majority (68.2%) of patients had no known prior medical history. The median white blood count was 4.8×10^3 cells /uL with a median 129.0×10^3 platelets/uL (**Supplementary Table S2**).

Table 1
Baseline demographic and physiologic vital sign characteristics

	Total (N = 132)	Arua RRH (N = 35)	Mubende RRH (N = 97)	HIV-negative (N = 87)	HIV-positive (N = 45)
Female sex – no. (%)	77 (58.3)	18 (51.4)	59 (60.8)	50 (57.5)	27 (60.0)
Age— years, median (IQR)	33.5 (24.0, 46.0)	31.0 (24.0, 47.5)	35.0 (24.0, 45.0)	30.0 (22.0, 44.5)	38.0 (30.0, 48.0)
COPD or asthma – no. (%)	1 (0.8)	0 (0.0)	1 (1.0)	1 (1.1)	0 (0.0)
Diabetes mellitus – no. (%)	5 (3.8)	2 (5.7)	3 (3.1)	3 (3.4)	2 (4.4)
Sickle cell disease/thalassemia— no. (%)	3 (2.3)	2 (5.7)	1 (1.0)	3 (3.4)	0 (0.0)
Duration of symptoms – days, median (IQR)	4.0 (3.0, 7.0)	4.0 (3.0, 7.0)	4.0 (3.0, 7.0)	4.0 (3.0, 7.0)	5.0 (3.0, 7.0)
Heart rate – beats per minute, median (IQR)	109.0 (92.8, 119.3)	103.0 (90.5, 113.5)	110.0 (94.0, 122.0)	107.0 (93.0, 119.5)	111.0 (93.0, 118.0)
Temperature – degrees Centigrade, median (IQR)	38.3 (38.0, 38.8)	38.300 (38.0, 38.8)	38.2 (38.0, 38.8)	38.3 (38.0, 38.8)	38.1 (38.0, 38.7)
Systolic blood pressure –mmHg, median (IQR)	110.5 (98.0, 122.0)	111.0 (95.0, 119.0)	111.0 (100.0, 122.0)	110.0 (100.0, 119.0)	114.0 (98.0, 127.0)
Diastolic blood pressure –mmHg, median (IQR)	68.0 (60.0, 78.0)	68.0 (60.5, 74.8)	68.0 (60.0, 78.0)	68.0 (59.0, 75.0)	69.0 (63.0, 80.0)
Respiratory rate – breaths per minute, median (IQR)	20.0 (18.0, 24.0)	20.0 (18.0, 26.0)	20.0 (18.0, 24.0)	22.0 (18.0, 25.5)	20.0 (18.0, 24.0)
Oxygen saturation – %, median (IQR)	98.0 (96.0, 99.0)	98.0 (96.0, 98.5)	98.0 (96.0, 99.0)	98.0 (96.0, 98.0)	98.0 (96.0, 99.0)
Glasgow coma scale – median (IQR)	15.0 (15.0, 15.0)	15.0 (15.0, 15.0)	15.0 (15.0, 15.0)	15.0 (15.0, 15.0)	15.0 (15.0, 15.0)
qSOFA score – median (IQR)	1.0 (0.0, 1.0)	1.0 (0.0, 1.0)	1.0 (0.0, 1.0)	1.0 (0.0, 1.0)	1.0 (0.0, 1.0)
qSOFA score ≥ 2 – no. (%)	27 (20.5)	8 (22.9)	19 (19.6)	19 (21.8)	8 (17.8)
RRH: Regional Referral Hospital; IQR: interquartile range; qSOFA: quick sequential organ failure assessment.					

Overall, 73 (55.3%) of 132 had a positive microbiologic result. The most common positive test results were a malaria thick smear (40/132; 30.3% participants > 0 parasite/high powered field) or malaria rapid diagnostic test (39/132; 29.6% participants). Thirty-five of 40 (87.5%) positive malaria smears were also positive on the malaria RDT (Fig. 1). The second most common diagnosis was tuberculosis from a positive urine LAM (14/45; 31.1% among those with HIV, 10.6% overall cohort) or sputum GeneXpert (2/14; 14.3% among tested, 1.5% overall cohort). Bacteraemia, excluding common contaminants, was identified in 9 (6.8%) of participants.

Characteristics of HIV-infected participants

Overall, 45 (34.1%) were HIV-infected; median CD4 count was 198.0 (IQR: 72.0, 347.0) in the setting of acute illness. There were 8 (17.8%) of 45 participants with a CD4 < 50. Sixteen (35.6%) of 45 were not known to have HIV; 10 were started on ART during hospitalization or within a month after hospitalization. The remaining 7 included 3 who died, 2 who had an unknown treatment history, 1 who was resistant to starting, and 1 who eloped from the hospital and was lost to follow-up. Seventeen (60.0%) of 29 known to have HIV were on ART prior to hospital presentation. Individuals with HIV were older (median 38.0

years; IQR: 30.0, 48.0) compared to those without HIV (median 30.0; IQR: 22, 44.5) $p = 0.005$, otherwise, they had similar baseline demographics (Table 1, **Supplementary Table S3**).

Microbiologic results among patients with HIV

Among those living with HIV, 31 (68.9%) of 45 had at least one positive microbiologic assay. Microbiologic and rapid diagnostic test results among those with newly diagnosed or known HIV included positive results for malaria (smear: $n = 16$, 35.6%; RDT: $n = 15$, 33.3%). There were 5 (11.1%) with cryptococcal antigenemia, 8 (9.2%) with evidence of hepatitis A and 2 (4.4%) with evidence of hepatitis B (**Table 2**). Bacteraemia occurred in 5 (11.1%) of 45 patients due to *Streptococcus pneumoniae* ($N = 2$), *Staphylococcus aureus*, *Salmonella* species, or *Proteus vulgaris* (Table 2). Fifteen (33.3%) of 45 participants with HIV also had TB; 1 out of 6 participants with sputum samples that tested positive for tuberculosis on Xpert and 14 (31.1%) had positive urine LAM results.

Table 2

Diagnostic test results stratified by HIV status and outcome

Diagnostic test	HIV status			p-value	Outcome		
	Total (N=132)	HIV-negative (N=87)	HIV-positive (N=45)		Survived (N=102)	Died (N=16)	p-value
Malaria antigen RDT – no. (%)	39 (29.5)	24 (27.6)	15 (33.3)	0.493	33 (32.4)	1 (6.7)	0.037
Malaria smear qualitative result – no. (%)							
> 0 parasites/HPF	40 (30.3)	24 (27.6)	16 (35.6)	0.43	10 (9.8)	0 (0.0)	0.35
≥3,000 parasites/HPF	12 (9.1)	10 (11.5)	2 (4.4)	0.22	6	1	
Missing values	10	6	4				
Serum cryptococcal antigen – no. (%)	–	–	5 (11.1)	–	4/31 (12.9)	1/7 (14.3)	0.922
Urine lipoarabinomannan – no. (%)	–	–	14 (31.1)	–	9/31 (29.0)	4/9 (44.4)	0.157
Sputum GeneXpert – no./total samples (% of cohort)	2/14 (14.3)	1/8 (12.5)	1/6 (16.7)	0.825	2/9 (22.2)	0/3 (0.0)	0.371
Serum hepatitis A IgM – no. (%)	9 (6.9)	1 (3.3)	8 (9.2)	0.139	9 (8.8)	0 (0.0)	0.216
Missing values	1	0	1				
Serum hepatitis B sAg – no. (%)	7 (5.3)	5 (5.7)	2 (4.4)	0.752	5 (4.9)	1 (6.2)	0.819
Blood culture positivity	9 (6.8)**	4 (4.6)**	5 (11.1)	0.273	5 (4.9)***	2 (12.5)	0.241

RDT: rapid diagnostic test; HPF: high powered fever; sAg: surface antigen.

Microbiologic results among patients without HIV

Among those without HIV, 42 (48.3%) of 87 had a positive assay. Malaria was common 24 (27.6%) of 87 were smear positive. Rapid diagnostic test results included malaria (RDT: 27.6%), hepatitis A (3.3%), and hepatitis B (5.7%) (**Table 2**). Clinically relevant blood culture growth occurred in 4 (4.6%) of patients with *Streptococcus pneumoniae* being most common isolate ($N = 2$), and an additional isolate each ($N = 1$) of *Citrobacter freundii*, and *Streptococcus spp.* One culture

grew common contaminant coagulase negative staphylococcus, and another grew *Micrococcus luteus*. There were 1 out of 8 sputum samples that tested positive for tuberculosis on PCR testing.

Fatal cases

At one-month follow-up, 16 (13.6%) of 118 died; 10 in hospital and 6 after discharge or hospital transfer. Death occurred a median of 3.0 days (IQR: 1 to 7 days) from enrolment. The median age among those that died was 38.0 years (IQR: 29 to 42.5, range: 18 to 80), and 7 (37.5%) had HIV (**Supplementary Table S4**). Among those who died, the most common presenting symptom was cough (n = 9, 56.2%).

At initial presentation, those that died were more tachypnoeic (median 24.5 breaths per minute, IQR: 22 to 31 breaths per minute) compared to survivors (median 20 breaths per minute; IQR: 18 to 24 breaths per minute). Fatal cases also had lower initial oxygen saturation (median 95.5%; IQR: 92.3 to 98% compared to median 98.0%; IQR: 96.0 to 99.0%) (**Supplementary Table S4**). The initial qSOFA score was higher among fatal cases (median 1.5; IQR: 1.0 to 2.0) compared to non-fatal cases (median 1.0; IQR: 0.0 to 1.0). Half of fatal cases had an initial qSOFA score ≥ 2 compared to 16.7% of non-fatal cases. Among fatal cases, the initial mean white blood count was 4.4×10^3 per microliter (IQR: 3.0 to 7.7×10^3 per microliter) and platelet count was 107.0×10^3 per microliter (IQR: 71.8 to 155.0×10^3 per microliter). The median ALT and AST were 26.0 U/L (IQR: 22.25 to 48.50) and 80.0 U/L (IQR: 34.75 to 215.75), respectively, which were higher (ALT p = 0.031; AST p = 0.001) among fatal cases than non-fatal cases (**Supplementary Table S5**). The majority (N = 14; 87.5%) of fatal cases had blood cultures without growth. All fatal cases had a negative malaria RDT (and one positive smear) compared to 32.4% of non-fatal cases had a positive malaria smear and 34.3% of non-fatal cases that had a positive malaria RDT (**Table 2**). There were 4 fatal cases (3 post-discharge) that had HIV and a positive urine LAM, highly suggestive of a diagnosis of tuberculosis. All LAM-positive cases received anti-tuberculosis treatment and one was treated for concomitant cryptococcal meningitis.

Using Cox proportional hazards regression, risk of death was not found to be increased by age, sex, or HIV diagnosis (Fig. 2). HIV was not associated with risk of death (HR: 1.70; 95% CI: 0.62 to 4.69; logrank p = 0.32). High respiratory rate (≥ 22 breaths per minute) (hazard ratio [HR] 8.05; 95% CI: 1.81 to 35.69) and low (i.e., $< 92\%$) oxygen saturation (HR 4.33; 95% CI: 1.38 to 13.61) were identified to be associated with increased risk of death, but not heart rate (Fig. 3). Low (< 15) Glasgow Coma Score was associated with an increased risk of death (HR 3.05) but lacked statistical significance (95% CI: 0.86 to 10.80). A high qSOFA (≥ 2 points) was associated with the largest increased risk of parameters evaluated (HR: 5.23; 95%CI: 1.89 to 14.45). Clinical laboratory parameters were not associated with increased risk of death except for AST (HR: 1.03 per 100 U/L; 95% CI: 1.00 to 1.06) and a trend towards significance was observed with ALT (HR: 1.15 per 100 U/L; 95% CI: 0.98 to 1.35).

Discussion

In this prospective multi-site AFI cohort in rural Uganda, death occurred mostly among young adults with a low prevalence of baseline comorbid illness. Malaria and tuberculosis were common causes of febrile illness, but malaria was not a common cause of death. Among participants that died, clinical and laboratory features suggestive of systemic infections were observed including respiratory distress, elevated liver transaminases; a microbiologic diagnosis was not attained for most cases. Among deaths, over 40% occurred after hospital discharge and tuberculosis was the most common laboratory diagnosis. Our findings emphasize the need for more in-depth assessment of causes and prevention of death due to non-malarial causes of fever among hospitalized adults in Uganda.

While HIV infection remains common, the majority of febrile hospitalized adult participants did not have HIV. Our findings are consistent with recent studies suggesting that a lower proportion of febrile patients is due to HIV during the universal antiretroviral therapy era. The prevalence of HIV in this cohort was similar to that of hospitalized patients with febrile illness in the East African region in Tanzania ranging from 32% [21] to 39% in 2007 to 2008 [22]. However, HIV prevalence was 85%

among septic patients in Uganda in a 2008 to 2009 cohort [23]. A more recent sepsis cohort from 2017 to 2019 had less but still a majority (55%) of participants had HIV[24]. Similarly, the majority (67%) of participants had HIV in a sepsis cohort in Malawi from 2018 to 2019 [25]. HIV prevalence in our cohort may be lower than previous cohorts in Uganda due to different level of severity in rural settings but could also represent decreased trends after the initiation of a 'treat all' approach. While larger studies and weighting with population-level demographics would be needed for incidence conclusions, this suggests that opportunistic infections may no longer represent the most common causes of febrile illness requiring hospitalization in Uganda. Importantly, however, tuberculosis was identified as a common cause of illness in this cohort and remains a major cause of severe infectious illness regardless of HIV status.

Overall, 16 new diagnoses of HIV were identified in this prospective cohort with universal HIV testing, emphasizing the importance of continuing to test all hospitalized febrile patients for HIV. These findings emphasize that HIV testing is high yield for hospitalized adult patients with febrile illness and unknown HIV serostatus in Uganda. Additionally, this provides an opportunity to leverage existing resources for linkage to HIV care per national standards. The deaths that occurred among people with HIV after discharge additionally highlights the need for continuity of care resources particularly among severely ill patients with HIV.

Respiratory dysfunction noted by respiratory rate and oxygen saturation was identified as a major risk factor for death in this cohort. While respiratory rate is a known prognosticators as part of the qSOFA score [26], lack of access to respiratory support at these clinical sites may have been a factor leading to fatal outcomes. Similar to other referral hospitals in SSA, access to invasive and non-invasive respiratory support, including highly skilled nursing, high flow oxygen, and ventilatory equipment was not readily available at these hospitals. Improved access to respiratory support may decrease hospitalized deaths due to infection.

Our study has notable limitations. First, participants were lost to follow-up and causes of death after discharge were unknown. Participant attrition was in part due to hesitation to return to medical centres during the COVID-19 pandemic. Causes of death were not ascertainable with telephone follow-up. Second, the sample size is limited and associations with mortality that exist may not have been observed in our data. For example, there was no survival difference observed with HIV, but we present here our interim analysis observations and smaller effect sizes may be observed in a larger cohort. Third, diagnostic test results reported here did not have extensive diagnostic testing with serology or multiplex PCR. However, testing was protocolized and in line with recommendations for rapid diagnostic testing and diagnostic assays currently available in Uganda. More expansive diagnostic testing is ongoing to understand the aetiologies of the unknown causes of febrile illness and death including emerging or neglected causes of illness including viral and rickettsial infections.

Taken together, these findings highlight the need to strengthen clinical and microbiology laboratory testing capacity to identify the aetiologies of acute febrile illness, particularly in settings where the epidemiology of febrile illness is shifting. These results are mostly from the pre-COVID era and aetiologies of fever may have directly or indirectly changed. Evaluation of optimization of follow-up, treatments, or diagnoses are urgent areas of study to improve outcomes among hospitalized adults in SSA.

Conclusions

The majority of deaths occurred among those less than 50 years of age and due to non-malarial febrile illness. Rickettsial and viral aetiologies of severe febrile illness may represent an undetected and pervasive burden of disease[27, 28]. Urgent surveillance efforts and field-ready clinical diagnostics are needed to identify treatable causes of mortality.

Declarations

Ethics approval and consent to participate

This study was conducted in compliance with the Declaration of Helsinki and Good Clinical Practice Guidelines. The study and informed consent process were reviewed and approved by the Joint Clinical Research Centre (JCRC) Research Ethics Committee (JC1518) and the Uganda National Council for Science and Technology (UNCST), HS 371ES, and Johns Hopkins University School of Medicine Internal Review Board (IRB00176961). All participants signed written informed consents prior to study procedures.

Consent for publication

Not applicable.

Availability of data and materials

The data that support the study findings may be available upon reasonable request to the corresponding author.

Competing interests

All authors declare no conflict of interest

Funding

The study was funded by the CAPA-CT II project which is part of the EDCTP2 programme supported by the European Union. Protocol development was supported by the National Institutes of Health T32 AI007291-27 to PWB.

Authors' contributions

JM participated in study implementation and drafting the first draft of the manuscript, KK & CE were involved in study implementation and review of manuscript. FK, PWB, RM, KA, MA, AG, MCY and LM participated in study design, sourcing for funding, study implementation and review of the manuscript.

Acknowledgements

Not applicable.

Authors' information (optional)

Not applicable.

References

1. Gupta A, Nadkarni G, Yang WT, Chandrasekhar A, Gupte N, Bisson GP, Hosseinipour M, Gummadi N: **Early mortality in adults initiating antiretroviral therapy (ART) in low- and middle-income countries (LMIC): a systematic review and meta-analysis.** *PloS one* 2011, **6**(12):e28691.
2. Gupta RK, Lucas SB, Fielding KL, Lawn SD: **Prevalence of tuberculosis in post-mortem studies of HIV-infected adults and children in resource-limited settings: a systematic review and meta-analysis.** *AIDS (London, England)* 2015, **29**(15):1987-2002.
3. Cox JA, Lukande RL, Nelson AM, Mayanja-Kizza H, Colebunders R, Van Marck E, Manabe YC: **An autopsy study describing causes of death and comparing clinico-pathological findings among hospitalized patients in Kampala, Uganda.** *PloS one* 2012, **7**(3):e33685.
4. Group TAS, Danel C, Moh R, Gabillard D, Badje A, Le Carrou J, Ouassa T, Ouattara E, Anzian A, Ntakpe JB *et al*: **A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa.** *The New England journal of medicine* 2015, **373**(9):808-822.

5. Otieno G, Whiteside YO, Achia T, Kwaro D, Zielinski-Gutierrez E, Ojoo S, Sewe M, Musingila P, Akelo V, Obor D *et al*: **Decreased HIV-associated mortality rates during scale-up of antiretroviral therapy, 2011-2016.** *Aids* 2019, **33**(15):2423-2430.
6. Price AJ, Glynn J, Chihana M, Kayuni N, Floyd S, Slaymaker E, Reniers G, Zaba B, McLean E, Kalobekamo F *et al*: **Sustained 10-year gain in adult life expectancy following antiretroviral therapy roll-out in rural Malawi: July 2005 to June 2014.** *Int J Epidemiol* 2017, **46**(2):479-491.
7. Tenforde MW, Walker AS, Gibb DM, Manabe YC: **Rapid antiretroviral therapy initiation in low- and middle-income countries: A resource-based approach.** *PLoS medicine* 2019, **16**(1):e1002723.
8. Mfinanga S, Chanda D, Kivuyo SL, Guinness L, Bottomley C, Simms V, Chijoka C, Masasi A, Kimaro G, Ngowi B *et al*: **Cryptococcal meningitis screening and community-based early adherence support in people with advanced HIV infection starting antiretroviral therapy in Tanzania and Zambia: an open-label, randomised controlled trial.** *Lancet* 2015.
9. Gupta-Wright A, Corbett EL, van Oosterhout JJ, Wilson D, Grint D, Alufandika-Moyo M, Peters JA, Chiume L, Flach C, Lawn SD *et al*: **Rapid urine-based screening for tuberculosis in HIV-positive patients admitted to hospital in Africa (STAMP): a pragmatic, multicentre, parallel-group, double-blind, randomised controlled trial.** *Lancet* 2018, **392**(10144):292-301.
10. **CRIMEAN-CONGO HEMORRHAGIC FEVER - EAST AFRICA: UGANDA (LUWERO)**
[<http://www.promedmail.org/post/5541551>]
11. **Outbreaks Chronology: Ebola Virus Disease**
[https://www.cdc.gov/vhf/ebola/outbreaks/history/chronology.html#modalIdString_outbreaks]
12. **Chronology of Marburg Hemorrhagic Fever Outbreaks** [<https://www.cdc.gov/vhf/marburg/resources/outbreak-table.html>]
13. MacNeil A, Farnon EC, Wamala J: **Proportion of Deaths and Clinical Features in Bundibugyo Ebola Virus Infection, Uganda.** *Emerg Infect Dis* 2010 Dec, **16**(12):1969-1972.
14. Shoemaker TR, Balinandi S, Tumusiime A, al e: **Impact of enhanced viral haemorrhagic fever surveillance on outbreak detection and response in Uganda.** *Lancet Infect Dis* 2018, **18**(4):373-375.
15. **Mubende Regional Referral Hospital Profile**
[<http://sustainuganda.org/sites/sustainuganda.org/files/Mubende%20Regional%20Referral%20Hospital%20Profile.pdf>]
16. **Arua Regional Referral Hospital Profile**
[<http://sustainuganda.org/sites/sustainuganda.org/files/Arua%20Regional%20Referral%20Hospital%20Profile.pdf>]
17. de St Maurice A, Nyakarahuka L, Purpura L, Ervin E, Tumusiime A, Balinandi S, Kyondo J, Mulei S, Tusiime P, Manning C *et al*: **Rift Valley Fever: A survey of knowledge, attitudes, and practice of slaughterhouse workers and community members in Kabale District, Uganda.** *PLoS Negl Trop Dis* 2018, **12**(3):e0006175.
18. Mwangi TW, Ross A, Snow RW, Marsh K: **Case definitions of clinical malaria under different transmission conditions in Kilifi District, Kenya.** *J Infect Dis* 2005, **191**(11):1932-1939.
19. Afrane YA, Zhou G, Githeko AK, Yan G: **Clinical malaria case definition and malaria attributable fraction in the highlands of western Kenya.** *Malar J* 2014, **13**:405.
20. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche J-D, Coopersmith CM *et al*: **The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3).** *JAMA* 2016, **315**(8):801-810.
21. Nadjm B, Mtove G, Amos B, Walker NF, Diefendal H, Reyburn H, Whitty CJ: **Severe febrile illness in adult hospital admissions in Tanzania: a prospective study in an area of high malaria transmission.** *Trans R Soc Trop Med Hyg* 2012, **106**(11):688-695.

22. Crump JA, Morrissey AB, Nicholson WL, Massung RF, Stoddard RA, Galloway RL, Ooi EE, Maro VP, Saganda W, Kinabo GD *et al*: **Etiology of severe non-malaria febrile illness in Northern Tanzania: a prospective cohort study**. *PLoS neglected tropical diseases* 2013, **7**(7):e2324.
23. Jacob ST, Moore CC, Banura P, Pinkerton R, Meya D, Opendi P, Reynolds SJ, Kenya-Mugisha N, Mayanja-Kizza H, Scheld WM: **Severe sepsis in two Ugandan hospitals: a prospective observational study of management and outcomes in a predominantly HIV-1 infected population**. *PloS one* 2009, **4**(11):e7782.
24. Cummings MJ, Bakamutumaho B, Owor N, Kayiwa J, Namulondo J, Byaruhanga T, Muwanga M, Nsereko C, Baldwin MR, Lutwama JJ *et al*: **Stratifying Sepsis in Uganda Using Rapid Pathogen Diagnostics and Clinical Data: A Prospective Cohort Study**. *Am J Trop Med Hyg* 2021, **105**(2):517-524.
25. Lewis JM, Mphasa M, Keyala L, Banda R, Smith EL, Duggan J, Brooks T, Catton M, Mallewa J, Katha G *et al*: **A longitudinal observational study of aetiology and long-term outcomes of sepsis in Malawi revealing the key role of disseminated tuberculosis**. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2021.
26. Sabir L, Ramlakhan S, Goodacre S: **Comparison of qSOFA and Hospital Early Warning Scores for prognosis in suspected sepsis in emergency department patients: a systematic review**. *Emerg Med J* 2021.
27. Blair PW, Lamorde M, Dumler JS: **Rickettsioses and Q Fever in Tanzania: Estimating the Burden of Pervasive and Neglected Causes of Severe Febrile Illness in Sub-Saharan Africa**. *Am J Trop Med Hyg* 2021.
28. Pisharody SR, Matthew; Carugati, Manuela; Nicholson, William; Perniciaro, Jamie; Biggs, Holly; Maze, Michael; Hertz, Julian; Allan, Kathryn; Halliday, Jo; Mmbaga, Blandina; Saganda, Wilbrod; Lwezaula, Bingileki; Kazwala, Rudovick; Cleaveland, Sarah; Maro, Venance; Crump, John: **Incidence of acute Q fever and spotted fever group rickettsioses, Kilimanjaro, Tanzania, 2007-2008 and 2012-2014**. *American Journal of Tropical Medicine & Hygiene* 2021.

Figures

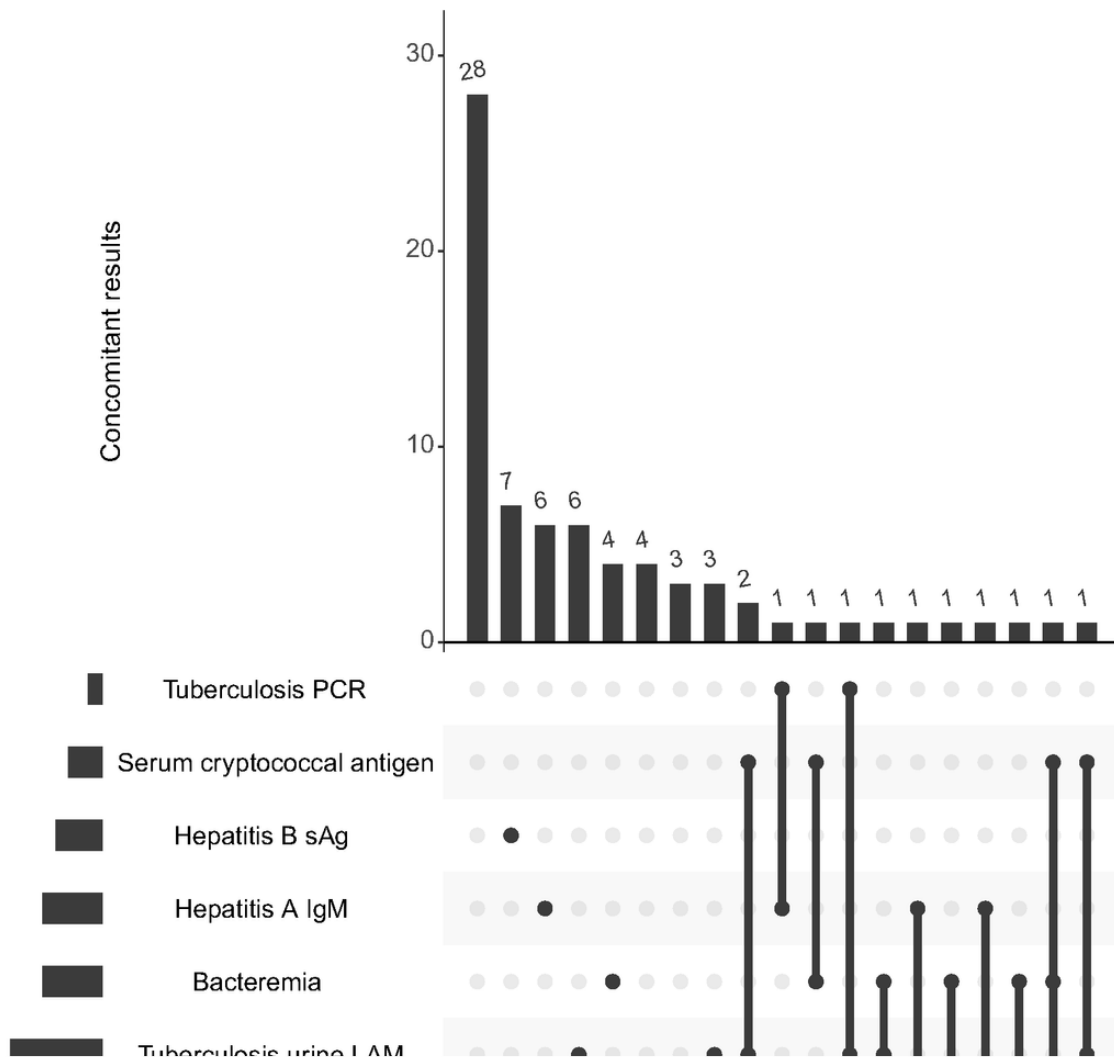
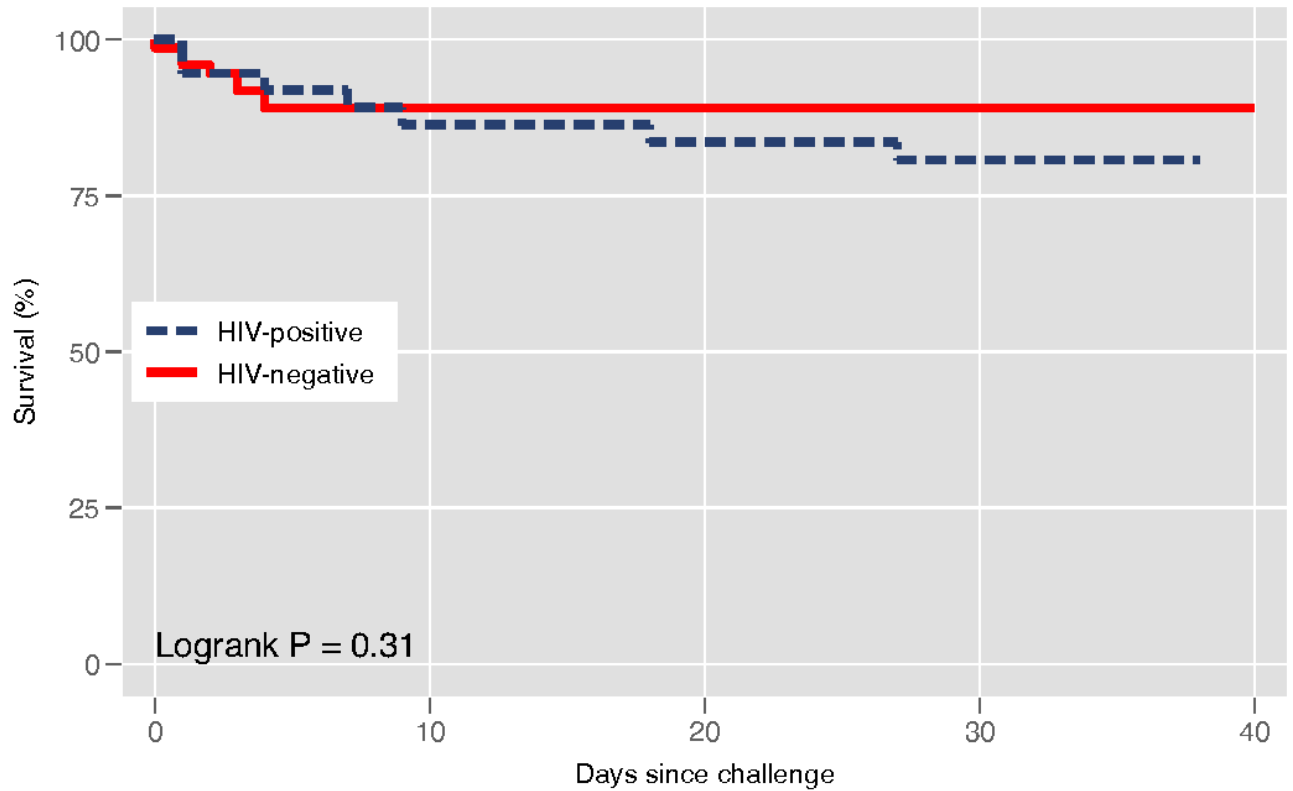


Figure 1

Diagnostic UpSet plot demonstrating the frequency of participants with one or more overlapping positive microbiologic results within the cohort. HRP2: *Plasmodium falciparum* antigen histidine rich protein 2; sAg: surface antigen; LAM: lipoarabinomannan.



No. at Risk:									
HIV-positive	37	(5)	31	(1)	30	(1)	20	(0)	0
HIV-negative	73	(8)	61	(0)	61	(0)	46	(0)	1

Figure 2

Kaplan-Meier plot of survival over time stratified by HIV status.

Figure 3

Forest plot of univariate unadjusted hazard ratio estimates of demographic characteristics, physiologic parameters, and clinical laboratory results for risk of death.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [SupplementaryTables.docx](#)