A longitudinal observational study of aetiology and long-term outcomes of sepsis in Malawi revealing the key role of disseminated tuberculosis

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Summary: We describe aetiology and long-term outcomes of sepsis in Malawi, to inform urgently-needed locally-adapted sepsis protocols. Disseminated tuberculosis dominates and receipt of antituberculous chemotherapy is associated with survival. Significant post-discharge mortality is driven by late deaths in HIV-infected people.

ABSTRACT

Background

Sepsis protocols in sub-Saharan Africa (sSA) are typically extrapolated from high-income settings, yet sepsis in sSA is likely caused by distinct pathogens and may require novel treatment strategies. Data to guide such strategies are lacking. We aimed to define causes and modifiable factors associated with sepsis outcome in Blantyre, Malawi to inform design of treatment strategies tailored to sSA.

Methods

We recruited 225 adults meeting a sepsis case-definition defined by fever and organ dysfunction, in an observational cohort study at a single tertiary centre. Aetiology was defined using culture, antigen detection, serology and PCR. Effect of treatments on 28-day outcomes were assessed by Bayesian logistic regression.

Results

143/213 (67%) of participants were HIV-infected. We identified a diagnosis in 145/225 (64%) participants: most commonly tuberculosis (34%) followed by invasive bacterial (17%) and arboviral infections (13%) and malaria (9%) Tuberculosis was associated with HIV infection whereas malaria and arboviruses with the absence of HIV infection. Antituberculous chemotherapy was associated with survival (aOR 28-day death 0.17 [95% CrI 0.05-0.49] for receipt of antituberculous therapy). Of those with confirmed aetiology, 83% received the broad-spectrum antibacterial ceftriaxone but it would be expected to be active in only 24%.

Conclusions

Sepsis in Blantyre, Malawi, is caused by a range of pathogens; the majority are not susceptible to the broad-spectrum antibacterials that most patients receive. HIV status is a key determinant of aetiology. Novel antimicrobial strategies for sepsis tailored to sSA – including consideration of empiric antitubercular therapy in the HIV-infected - should be developed and trialed.

Key words: Africa South of the Sahara; Critical Illness; Tuberculosis, HIV; Antimicrobial resistance

INTRODUCTION

Sepsis, a life-threatening organ dysfunction triggered by a dysregulated host response to infection[1], is estimated to cause 11 million deaths worldwide per year, with a disproportionate burden on Low and Middle Income Countries (LMIC) including sub-Saharan Africa (sSA)[2]. Progress in improving sepsis outcomes in high-income settings has been made through early recognition and timely delivery of basic care including rapid administration of appropriate antimicrobial therapy and fluid resuscitation[3]. In sSA, however, mortality remains high[4].

Many aspects of optimal sepsis management are, in principle, deliverable in resource-limited hospitals, but applying sepsis protocols derived from high-resource settings to hospitals in sSA has resulted in unexpected results, the most well-known being the harmful effect of liberal intravenous fluid therapy[5,6]. To develop LMIC-targeted sepsis protocols, data from LMIC are urgently needed. This was highlighted in the recent WHO global report on the epidemiology and burden of sepsis[7] in which sepsis aetiology and long-term sequelae were identified as particular gaps.

Standard antimicrobial treatment for sepsis in both high- and low-resource settings typically consists of broad spectrum antibacterial therapy, but limited available data from sepsis[4,8] and fever aetiology[9] studies in sSA suggest that mycobacterial, viral, bacterial zoonotic or parasitic causes of illness are common and not covered by standard antibacterial therapy[10]. Data on sepsis aetiology beyond bloodstream infection in sSA are lacking[4], but aligning the causes of infection with their effective treatments is central to not only preventing death and disability, but also reducing unnecessary antimicrobial use, a key driver of antimicrobial resistance (AMR).

To address these data gaps, we here provide a description of sepsis aetiology in Blantyre, Malawi, describe long-term sepsis outcomes and identify elements of current sepsis management in sSA that are associated with outcome.

METHODS

Study setting and design

We undertook an observational cohort study recruiting at Queen Elizabeth Central Hospital (QECH), Blantyre, Malawi, a 1300-bed government teaching hospital providing free healthcare to the city (2018 population 800,064[11]). Malawi is a low-income country in South-East Africa, with an estimated adult HIV prevalence of 9%[12], and a tuberculosis incidence of 133/100,000 person-years[13]. Blantyre has a subtropical climate with a rainy season from November to April. Malaria is endemic, peaking in the rainy season[14]. In this study, adults (≥16 years) with sepsis were recruited from the emergency department 0700-1700 Monday-Friday. As study design predated Sepsis-3 guidelines, inclusion criteria were evidence of infection (fever [axillary temperature > 37.5°C] or history of fever within preceding 72 hours) plus ≥ one clinical marker of immediate organ dysfunction or locally predictive of poor outcome [15,16]: oxygen saturation < 90%; respiratory rate > 30 breaths/minute; systolic blood pressure < 90 mmHg; or Glasgow coma scale < 15. These selection criteria were chosen because they are applicable in our setting and regionally generalisable. Exclusion criteria were: participants lacking capacity to consent with no guardian available for proxy consent; participants speaking neither Chichewa nor English; and participants living > 30km from Blantyre city. Written informed consent was provided by

the participant or, if they lacked capacity, their accompanying guardian. All care and treatment decisions for enrolled participants remained with the usual clinical team. Study team members followed participants hourly for the first six hours of hospital admission, then daily whilst an inpatient then in person at days 28, 90 and 180.

Sampling and laboratory methods

Patients provided blood and urine at baseline and blood at day 28. Full details of tests/assays are in Supplementary Methods. In brief, blood was tested for HIV-1/2 antibodies, *P. falciparum* HRP-2 antigen, standard biochemical and hematologic analyses, CD4 cell count quantification, automated aerobic culture and mycobacterial culture (HIV-infected/HIV-unknown participants only). Sputum testing for tuberculosis using Xpert MTB/RIF was carried out when there was a suspicion of pulmonary tuberculosis and CSF microscopy, culture and lateral flow cryptococcal antigen testing when there was a suspicion of meningitis from the clinical team.

The following additional diagnostic tests were necessarily batched: urinary lipoarabinomannan (LAM, HIV-infected/HIV-unknown participants only) and testing of acute and convalescent sera for antibodies to Chikungunya, Dengue and Leptospira, and convalescent sera for spotted fever group and epidemic typhus group Rickettsioses. In addition, a subset of serum samples underwent PCR for 46 bacterial and viral pathogens (Supplementary methods). Case definitions are explained in Table 1. The study was designed and carried out before the WHO strong recommendation for LAM testing in seriously unwell inpatients with HIV in high TB burden settings[17]. HIV RNA testing was not available.

Statistical analysis

All analyses were carried out in R v4.0.2 (R Foundation for Statistical Computing, Vienna, Austria) and all models fitted with Stan v2.21.0 via the R *brms* v2.13.5 package[18,19].

The analysis aimed to identify modifiable treatment-related associations of sepsis mortality (full details in Supplementary Methods). In brief, we hypothesised a causal structure (Supplementary Figure E1) to identify which variables to control for to estimate a causal effect of treatments on outcome. We used principal component analysis (PCA) to reduce the dimensionality of host-severity variables (Supplementary Table E1 and Figure E8), and used these along with untransformed infection and treatment variables as covariates in Bayesian logistic regression models with death by 28-days as the outcome. Missing data (which were infrequent, Supplementary Figure E10) were imputed with chained equations. Model outputs are presented as odds ratios (OR) with a point estimate (posterior median) with 95% credible intervals (CrI), or marginal effect of the predictor on the probability of outcome with 95% credible intervals for nonlinear models.

Finally, Kaplan-Meier plots were used to estimate the survival function over the study period, stratified by HIV status with hazard ratios (posterior median and 95% CrI) for HIV infection vs no infection from Bayesian Cox proportional hazards model to quantify difference between the curves.

The study was approved by the University of Malawi College of Medicine (P.11/16/2063) and Liverpool School of Tropical Medicine (16-062) research ethics committees and is reported following the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines[20]. Data and code to replicate this analysis are available as the *BlantyreSepsis* R package at https://joelewis101.github.io/blantyreSepsis.

RESULTS

Baseline characteristics

Between 19th February 2017 and 2nd October 2018, 225 participants were recruited (Table 2, Supplementary Figure E2). 143/213 (67%) of participants were HIV-infected. Antiretroviral therapy (ART) coverage was high: of the HIV infected, 117/143 (82%) were on ART, 94% (110/117), the Malawian first-line regimen of efavirenz, lamivudine and tenofovir disoproxil, for a median of 29 (4-73) months. Despite this, CD4 counts were low for those on ART (median 98 [IQR 31-236]) and immunologic failure was common with 52/84 (62%) of participants on ART for longer than six months having a CD4 count below 200 cells /mL. HIV-infected participants were older than HIV uninfected participants, more likely to be female, been unwell for longer and with more severe disease at baseline as evidenced by a higher heart rate, lower blood pressure and less likely to be able to stand unaided (Supplementary Table E2).

Treatments received

The majority of participants (207/225 [92%]) were administered broad-spectrum antibacterial agents (median [interquartile range IQR] 5.3 (3.7-10.8) hours from initial ED attendance), usually ceftriaxone (181/207 [87%], Supplementary Table E3), but also antituberculous (63/225 [28%]), antifungal (26/225 [12%]) or antimalarial (12/225 [5%]) therapy. Median (IQR) duration of ceftriaxone was 5 (2-7) days. Only patients with a positive malaria rapid test received antimalarial therapy. 192/225 (85%) of participants received intravenous fluid: a median of 1.5L of fluid (IQR 1.0-2.0L) in the six hours following enrollment. None of the participants received inotropes, were intubated, or admitted to the intensive care unit. Only two patients were switched to second line ART during the 180-day study period.

Aetiology

A diagnosis was made 174 times in 144/225 (64%) participants (Table 3), most commonly tuberculosis, in 34% (95% confidence interval, CI 28-41%). Acute rickettsioses and leptospirosis (2% [95% CI 1-5%] and 1% [0.1-3.2%] of participants) were uncommon. Evidence of past exposure to spotted fever group rickettsioses, and Chikungunya however, was very common, with IgG detected in 61/147 (42% [95% CI 33-50%]) and 51/146 (35% [95% CI 27-43%]) convalescent serum samples, respectively (Supplementary Table E4, Supplementary Figure E3).

The commonest invasive bacterial pathogens identified on aerobic culture or PCR (43 pathogens in 38 participants, Supplementary Figures E4, E5) were *Streptococcus* spp. (13/38 participants, 6 of which were pneumococcus), non-Salmonella Enterobacterales (12/38), and *Salmonella* spp. (11/38). Results of antimicrobial sensitivity testing are given in Supplementary Figure E4. Considering only those HIV-infected participants, 14/97 (14%) of

those who reported taking CPT were diagnosed with an invasive bacterial infection, compared to 7/43 (16%) of those not reporting taking CPT. All invasive fungal disease was caused by *Cryptococcus,* either *C. neoformans* cultured from both blood and CSF (n=3), CSF alone (n=1) or detectible cryptococcal antigen in CSF (n=1). Of the 76 diagnoses of tuberculosis, two were pulmonary (positive Xpert MTB/RIF only), and the rest disseminated and all but one of the participants with tuberculosis were HIV-infected (Table 3). This patient group (disseminated tuberculosis) was clinically similar to the rest of the cohort (Supplementary Table E5). Of the 63 participants who received antituberculous therapy, 37/63 (59%) had a confirmed diagnosis of tuberculosis. Only 37/76 (49%) participants with tuberculosis received antituberculosis therapy.

HIV infection predicted sepsis aetiology (Table 4, Supplementary Table E6): malaria and arboviruses were more common in the HIV uninfected (malaria 17% vs 4% [difference 13% 95% CI 4-22]), arbovirus 27% vs 6% [difference 22% 95% CI 11-33] for HIV infected vs uninfected) whereas invasive fungal disease only occurred in in HIV infected participants, and TB was more common in HIV infected participants (1% vs 50% [difference 48% 95% CI 40-57%] HIV uninfected vs infected). Invasive bacterial infections occurred at similar proportions in HIV-infected and uninfected participants (20% vs 15% [difference 5% 95% CI -5-17]). Whilst there were some co-infections, most participants with a diagnosis had a single aetiologic agent, (113/145, 78%: Figure 1, Supplementary Figure E6). Of the patients with a microbiologically confirmed diagnosis, only 35/145 (24%) were predicted to be susceptible to ceftriaxone but 120/145 (83%) received it (Figure 1).

Outcome and associations of outcome

Median (IQR) follow up time was 182 (62-202) days, a total of 92 person-years. Case fatality ratio (CFR) was 39/222 (18% [95% CI 13-23]) at 28-days, and continued to increase thereafter to 51/215 (24% [95% CI 18-30%]) at 90-days and 60/194 (31% [95% CI 25-38%]) at 180-days; in-hospital CFR was 14% (95% CI 10-19%) and median (IQR) length of hospitalisation 5 (2-10) days. Early mortality was similar between HIV infected and noninfected participants, but diverged post-discharge (hazard ratio [HR] for death 2.0 [95% CrI 1.1-4.0] HIV infected vs uninfected, Figure 2). Mortality was similar across diagnoses though confidence intervals were wide (Table 5, Supplementary Figure E7). In an unadjusted analysis (Table 5), well recognized host and sepsis severity variables and inability to stand were associated with death. Receipt of antimalarials and antituberculous chemotherapy were associated with survival in univariable analysis.

We used Bayesian logistic regression with PCA-transformed host-severity variables (Supplementary Table E1) to estimate the effect of sepsis treatments received by study participants. Approximate leave-one-out cross validation showed that, comparing models with one to five PCA coordinates as predictors of death, three coordinates had the best out of sample predictive value (quantified by ELPD, Supplementary Table E7). This model (using PC1, 2 and 3) was used as the base model to assess the effect of sepsis treatments on mortality. Together PC1-3 explained 36% of the variance of the 18 included variables. PC1 defined an axis of HIV, immunosuppression and shock, PC2 included severe sepsis organ dysfunction (low oxygen saturation, low Glasgow coma score [GCS], high lactate and high creatinine), male sex and inability to stand and PC3 with thrombocytopenia, (Figure 3A, Supplementary Figure E9). All three transformed variables PC1-3 were associated with death by 28 days in the logistic regression models (Figure 3C, Supplementary Table E8).

Modelling the effect of different antimicrobial therapies found a convincing association only between antituberculous therapy and survival (adjusted odds ratio [aOR] of death by 28 days 0.17 [95% CrI 0.05-0.49] for receipt of antituberculous therapy), (Figure 3C, Supplementary Table E8). In linear models, the effect of an hour of antimicrobial delay on 28 day mortality was estimated to be aOR 1.02 (95% CrI 0.99-1.04) and the effect of a litre of IV fluid to be aOR 0.52 (95% CrI 0.29-0.91, Supplementary Table E7). Relaxing the linearity assumption and allowing these relationships to be nonlinear time found no convincing relationship between time to antimicrobial therapy and death (Figure 3D), but was suggestive of a lower mortality with increasing volume of administered fluid up to around 2L (Figure 3E).

DISCUSSION

We demonstrate that adults presenting with sepsis in Blantyre, Malawi, are young compared to high-income settings, predominantly HIV-infected, and that their illness is caused by a heterogeneous group of pathogens, the majority of which are not susceptible to ceftriaxone. HIV status is the key determinant of sepsis aetiology. Long term outcomes are poor, driven by late mortality in HIV-infection. These data suggest several strategies that could improve sepsis outcomes in sSA.

First, optimised antimicrobial strategies for sepsis in sSA are needed; ceftriaxone would be expected to be effective in only 24% of participants with a diagnosis, yet 83% received this drug (median 5 days). Ceftriaxone is a convenient, available drug in sSA, but widespread use in Malawi[21] and regionally has been associated increase in antimicrobial resistance[22,23]. Current diagnostic delays in establishing aetiology necessitate immediate broad spectrum antibacterial therapy. If, however, sepsis protocols for sSA can rapidly

establish alternate diagnoses – perhaps with rapid diagnostic tests – rapid de-escalation of therapy and reduction of reliance on broad spectrum antibacterials could be possible.

HIV status was the key determinant of sepsis aetiology, and represents a pragmatic starting point for management strategies. In particular, consideration of the need for antituberculous chemotherapy is indicated for HIV-infected people presenting with sepsis in high tuberculosis-burden settings. Tuberculosis was the most common diagnosis in this study, in 34% of participants, and receipt of TB therapy was associated with improved survival (aOR of death 0.17 [95% CrI 0.05-0.49]). A strategy of universal testing using lateral flow LAM testing of HIV-infected inpatients was shown to improve survival in the STAMP trial[24] and the WHO recommends testing in all seriously ill HIV-infected inpatients[17]. Even with expected improved sensitivity of the FujiLAM assay[25], however, LAM testing is likely to miss cases of disseminated tuberculosis. Furthermore it can be challenging to get urine samples from critically ill patients in low resource units, yet in the critically ill it may be that delaying antituberculous therapy is associated with poorer outcomes[8]. Whilst empiric tuberculosis treatment has previously been assessed and is yet to demonstrate improved outcomes[26–28], none of these studies recruited inpatients with critical illness or sepsis. Our data suggests there is a case for such interventional trials for critically unwell HIV-infected people, perhaps based on presumptive TB therapy with step down based on subsequent diagnostic testing.

In contrast, in HIV-uninfected people, malaria and arboviral infections are important causes of sepsis, and more common than proven invasive bacterial infection. Indeed the striking prevalence of Chikungunya IgG seropositivity in study participants is comparable to well described outbreak[29] and suggests widespread community transmission, in keeping with increased recognition of incidence of arboviral infections across sSA. The roll out of rapid

diagnostic tests for malaria has revolutionized the management of febrile illness in sSA; these data suggest that there may be a role for rapid arboviral tests as well.

Secondly, post-discharge deaths must be addressed. We demonstrate significant long term mortality following sepsis, driven by late deaths in HIV-infected participants, perhaps due to ART failure and opportunistic infection. To our knowledge these are the first estimates of case fatality ratios for sepsis in sSA beyond 30 days. ART coverage in this cohort was high compared to historical cohorts[16,30] and reflects the success of the Malawian ART programme, thus a sepsis presentation is likely to be a manifestation of ART failure[31], but rates of switching to second-line therapy during the study period were very low. This may reflect programmatic challenges of documenting serial viral loads before switching, per WHO guidance[32]. Structural interventions which optimize the identification of ART failure in acute illness, and rapidly switch to second line therapy should be investigated.

There are limitations to our study, especially around our ability to deliver comprehensive or real time diagnoses. It was only possible to carry out urinary LAM testing at the end of the study [17]. Serologic testing was largely carried out on convalescent sera and so we could not relate serologic diagnoses to survival. Testing IgG on paired sera would likely most accurately classify diagnoses, but was not possible because of resource limitations; serologic diagnoses of arboviruses and leptospirosis were based on IgM, which may be nonspecific. Rickettsial IgM particularly has poor specificity so an IgG based case definition was used, which may misclassify acute cases. Funding did not permit identification of some causes of febrile illness e.g. *Coxiella* serology for Q-fever or *Pneumocystis jiroveci*. We could not establish late causes of mortality, or provide HIV viral load testing. Malaria diagnosis used HRP-2 antigenaemia rather than smear for diagnosis, which could reflect recent but not current malaria, and a number of Streptococcal diagnoses were made through PCR, which

may have poor specificity[33]. Though we have used a principled modelling approach with an explicit hypothesized causal structure to identify associations of mortality, it is likely that residual confounding remains. The dataset is too small to model all treatments and diagnoses simultaneously, or to explore interaction effects (e.g. explore whether treatments are beneficial only in groups with confirmed disease). Though Blantyre is likely to be reasonably representative of an urbanising population in sSA, the study was carried out at a single centre.

In conclusion, sepsis in Blantyre, Malawi is caused by a diverse group of pathogens including *M. tuberculosis*, arboviruses, and malaria, yet management relies on prolonged courses of broad spectrum antibacterial agents, which would not treat these pathogens. HIV status is a key determinant of outcome and can assist clinicians in targeting antimicrobial therapy. Long term outcomes are poor and driven by late deaths in HIV-infected people. Understanding the reasons for these late deaths is of prime importance. Optimizing and operationalizing treatment solutions in sSA will require both randomized controlled trials and pragmatic implementation science approaches, but the high mortality in these patient populations represents an important opportunity to improve outcomes.

NOTES

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POTENTIAL CONFLICTS OF INTEREST

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TABLES

Table 1: Case definitions used in the study.

Diagnosis	Case definition
Invasive bacterial infection	**EITHER** **BLOODSTREAM INFECTION** defined by culture of pathogenic bacteria from aerobic blood culture (with coagulase-negative Staphylococci, *Bacillus* spp., diphtheroids and alpha-haemolytic Streptococci other than *S. pneumoniae* considered as contaminants) **OR** Detection of pathogenic bacterial DNA in blood by multiplex PCR **OR** **MENINGITIS** defined by culture of pathogenic bacteria from CSF (same

	definition of contaminants).
Invasive fungal infection	**EITHER** **BLOODSTREAM INFECTION:** Culture of fungus from blood or **OR** **MENINGITIS:** Culture of fungus from CSF **OR** Detectible cryptococcal antigen by lateral-flow assay in CSF
Tuberculosis*	**EITHER** *M. tuberculosis* cultured from blood **OR** *M. tuberculosis* detected in sputum with Xpert MTB/RIF **OR** Detectible urinary lipoarabinomannan in urine by Alere lateral flow assay
Possible spotted fever group Rickettsiosis	IgG convalescent serology titre ≥ 1:512
Possible epidemic Typhus group Rickettsiosis	
Chikungunya	Detectible IgM in either acute or convalescent serology or detectible pathogen DNA/RNA by PCR array
Dengue	
Leptospirosis	
All other diagnoses	Detectible pathogen DNA/RNA by PCR array (see supplementary methods for full list)

*Pulmonary Tuberculosis = positive Xpert MTB/RIF, with no or negative urinary LAM and/or mycobacterial blood culture) All other identified tuberculosis = disseminated (positive urinary LAM and/or positive mycobacterial blood culture irrespective of sputum Xpert MTB/RIF).

Table 2: Characteristics of included participants.

Variable	Value
Demographics	
Age (years), median (IQR)	36 (28-44)
Male sex n/N (%)	114/225 (51%)
HIV/TB status	
HIV infected*, n/N (%)	143/213 (67%)
CD4 lymphocyte count (10^6/L), median (IQR)	156 (51-298)
Receiving antiretroviral therapy, n/N (%)	117/143 (82%)
Time on antiretroviral therapy (months), median (IQR)	29 (4-73)
Receiving co-trimoxazole preventative therapy, n/N (%)	98/141 (70%)
History of receiving TB treatment n/N (%)	37/225 (16%)
Of those, currently receiving TB treatment n/N (%)	10/37 (27%)
Physiology	
Temperature (°C), median (IQR)	38.5 (37.9-39.0)
Heart rate (beats/min), median (IQR)	121 (102-132)
Respiratory rate (breaths/min), median (IQR)	34 (32-38)
Systolic blood pressure (mmHg), median (IQR)	99 (85-119)
Diastolic blood pressure (mmHg), median (IQR)	66 (57-76)
Oxygen saturation (%), median (IQR)	96 (94-98)
Glasgow coma score < 15 n/N (%)	21/225 (9%)
Unable to stand unaided n/N (%)	63/225 (28%)
Length of time unwell for (days), median (IQR)	7 (3-14)
Laboratory parameters	
Haemoglobin (g/dL), median (IQR)	10.8 (8.2-13.2)
Platelets (10^9/l), median (IQR)	218 (146-297)
White cell count (10^9/l), median (IQR)	6 (4-11)
Sodium (mmol/L), median (IQR)	134 (130-137)
Potassium (mmol/L), median (IQR)	4.0 (3.6-4.4)

Bicarbonate (mmol/L), median (IQR)	19 (17-22)
Creatinine (mmol/L), median (IQR)	76 (59-103)
Lactate (mmol/L), median (IQR)	3.4 (2.3-5.2)

* HIV status missing for 12 participants

Table 3: Diagnoses in study participants and proportion of participants with positive results.

	Proportion of participants with positive result			**Cohort prevalence**		
Diagnosis	**n/N**	**%**	**95% CI**	**n/N**	**%**	**95% CI**
Bacterial infection (excluding mycobacteria)						
Bloodstream infection (culture)	24/224	11%	(7-15%)			
Bloodstream infection (PCR)	17/122	14%	(8-21%)			
Meningitis	0/44	0%	(0-8%)			

	Proportion of participants with positive result			Cohort prevalence		
Diagnosis	**n/N**	**%**	**95% CI**	**n/N**	**%**	**95% CI**
Any invasive bacterial infection	38/224	17%	(12-23%)	38/225	17%	(12-23%)
Possible Rickettsioses						
Spotted fever group	2/147	1%	(0-5%)			
Epidemic typhus group	0/147	0%	(0-3%)			
Any Rickettsiosis	2/147	1%	(0-5%)	2/225	1%	(0-3%)
Other						
Leptospirosis	2/179	1%	(0-4%)	2/225	1%	(0-3%)
Borreliosis	1/122	1%	(0-4%)	1/225	0%	(0-3%)
Mycobacterial infection						
Tuberculosis	76/162	47%	(39-55%)	76/225	34%	(28-41%)
Fungal infection						
Bloodstream infection	3/224	1%	(0-4%)			
Meningitis	4/44	9%	(3-22%)			
Any invasive fungal infection	5/224	2%	(1-5%)	5/225	2%	(1-5%)
Viral Infection						
Arboviral infection						
Chikungunya	17/176	10%	(6-15%)			
Dengue	14/180	8%	(4-13%)			
Any arbovirus infection	31/182	17%	(12-24%)	31/225	14%	(10-19%)
Other						

	Proportion of participants with positive result			Cohort prevalence		
Diagnosis	**n/N**	**%**	**95% CI**	**n/N**	**%**	**95% CI**
Rift Valley fever	1/122	1%	(0.05%)	1/225	0%	(0-3%)
Protazoal infection						
Falciparum malaria	21/219	10%	(6-14%)	21/225	9%	(6-14%)

NB: The denominator in the proportion of participants with positive results is the number of participants who received any diagnostic test for the given diagnosis.

Table 4: Proportion of participants with diagnosis stratified by HIV status.

Diagnosis	HIV+	HIV-	Difference
Arboviral infection	8/143 (6%)	19/70 (27%)	22% (95% CI 11 to 33)
Invasive bacterial infection	21/143 (15%)	14/70 (20%)	5% (95% CI -5 to 17)
Invasive fungal infection	5/143 (3%)	0/70 (0%)	-3% (95% CI -7 to -1)
Malaria	6/143 (4%)	12/70 (17%)	13% (95% CI 4 to 22)
Tuberculosis	71/143 (50%)	1/70 (1%)	-48% (95% CI -57 to -40)

Difference is proportion in HIV-uninfected minus proportion in HIV-infected with bias-corrected bootstrap with 9999 replicates used to generate 95% confidence interval.

Table 5: Univariable associations with death by 28 days.

Variable	**Died**	**Survived**	**Difference**
Number of participants	39	183	-
Host Variables			
Age (years)	36.4 (31.5-46.0)	35.9 (27.4-42.9)	-0.5 (-8.1 to 3.2)
Male sex	19 (49%)	93 (51%)	2% (-16 to 19%)
HIV Infected*	27 (75%)	116 (67%)	-6% (-21 to 11%)
CD4 count 10^6 /L	**41 (17-225)**	**188 (69-302)**	**147 (46 to 186)**
Haemoglobin (x10^9} g/dL)	**9.1 (6.0-10.4)**	**11.0 (8.6-13.4)**	**1.9 (0.8 to 3.9)**
Severity Variables			
Temperature (C)	**38.1 (37.7-38.8)**	**38.5 (38.0-39.0)**	**0.4 (0.0 to 0.7)**
Heart rate (beats/min)	123 (105-139)	120 (102-131)	-3 (-13 to 6)
Systolic BP (mmHg)	89 (76-121)	99 (87-119)	10 (-1 to 16)
Diastolic BP (mmHg)	**60 (52-81)**	**67 (57-76)**	**7 (1 to 14)**
Respiratory rate (breaths/min)	34 (32-37)	34 (32-38)	0 (-2 to 2)
Oxygen saturation (%)	**95 (90-97)**	**97 (95-98)**	**2.0 (0 to 3)**

Variable	Died	Survived	Difference
GCS	15 (15-15)	15 (15-15)	0 (0 to 0)
Unable to stand	**27 (69%)**	**36 (20%)**	**-50% (-65 to -33%)**
Lactate (mmol/L)	**4.9 (3.0-10.6)**	**3.2 (2.1-4.5)**	**-1.7 (-6.2 to -0.1)**
White cell count (x10^9)	5.9 (3.5-11.0)	6.9 (4.6-11.5)	1.0 (-1.4 to 2.8)
Platelet count (x10^9 /L)	182 (87-301)	223 (148-297)	42 (-31 to 73)
Sodium (mmol /L)	131 (127-138)	134 (130-137)	3 (-1 to 6)
Bicarbonate (mmol /L)	**17 (14-21)**	**20 (17-22)**	**3 (0 to 5)**
Urea (mmol /L)	**7.8 (4.5-14.3)**	**4.5 (3.2-7.0)**	**-3.3 (-8.7 to -1.3)**
Creatinine (mmol /L)	90 (60-185)	73 (59-96)	-17 (-47 to 7)
Diagnosis			
Invasive bacterial infection	5 (13%)	32 (17%)	5% (-10 to 15%)
TB	15 (38%)	61 (33%)	-5% (-23 to 10%)
Malaria	**0 (0%)**	**21 (11%)**	**11% (7 to 16%)**
Invasive fungal infection	**3 (8%)**	**2 (1%)**	**-7% (-20 to -1%)**
Chikungunya	2 (5%)	15 (8%)	3% (-9 to 9%)
Dengue	2 (5%)	12 (6%)	1% (-10 to 7%)
No diagnosis	18 (46%)	64 (35%)	-11% (-29 to 6%)
Treatment Received			
Antibacterials	37 (95%)	167 (91%)	-4% (-10 to 7%)
Time to Antibacterials (hr)	4.7 (3.8-8.8)	5.3 (3.6-10.8)	0.6 (-1.1 to 1.7)
Antifungals	7 (18%)	19 (10%)	-8% (-23 to 3%)
Antimalarials	**0 (0%)**	**12 (7%)**	**7% (3 to 10%)**
Antimycobacterials	**6 (15%)**	**57 (31%)**	**16% (0 to 27%)**
IV fluid over 6hr (L)	1.4 (1.0-2.0)	1.3 (0.6-2.0)	-0.1 (-0.7 to 0.2)

* 12 participants had unknown HIV status and are excluded from the denominator to calculate proportion; 3 died and 9 survived to 28 days. Numeric variables are presented as

median (IQR) and categorical variables as proportions. Difference column shows difference in medians or difference in proportions with bias-corrected bootstrapped 95% confidence intervals. Variables shown in bold are those for which the 95% confidence intervals do not cross 0.

FIGURE LEGENDS

Figure 1: UpSet plot of diagnoses. Black circles in the lower half of the plot show diagnoses: either a single diagnosis (single circle) or two or more diagnoses (black circles linked by lines), with the large bar chart (top right) showing the number of participants with the indicated diagnosis or diagnoses. Only participants who had a diagnosis are included in this plot, and the five most frequent diagnoses shown, demonstrating that most participants had only one diagnosis. Red colour of bar indicates receipt of antibacterial therapy, showing that almost all participants received antibacterial therapy despite no demonstrated invasive bacterial infection in many cases.

Figure 2: Kaplan-Meier estimate of survival function following sepsis admission, stratified by HIV status.

Figure 3: Determinants of sepsis mortality. A: Host-severity principal components 1 and 2 showing that PC1 defines an axis of HIV, immunosuppression (low CD4 count and anaemia) and shock (tachycardia, low blood pressure and bicarbonate) whereas PC2 is associated with sepsis-related organ dysfunction, age, and male sex. **B:** Participants projected onto PC1 and 2 showing that participants who die (red circles) tend to have immunosuppression and shock (upper right), other sepsis related organ dysfunction (lower left), or both (lower right). **C-E:** Outputs of models predicting death by 28 days. Adjusted odds ratios and 95% credible intervals of effect of different antimicrobial therapies (C),

predicted mortality as a function of time to antibacterial therapy (D) or volume of intravenous fluid received (E).

Figure 1

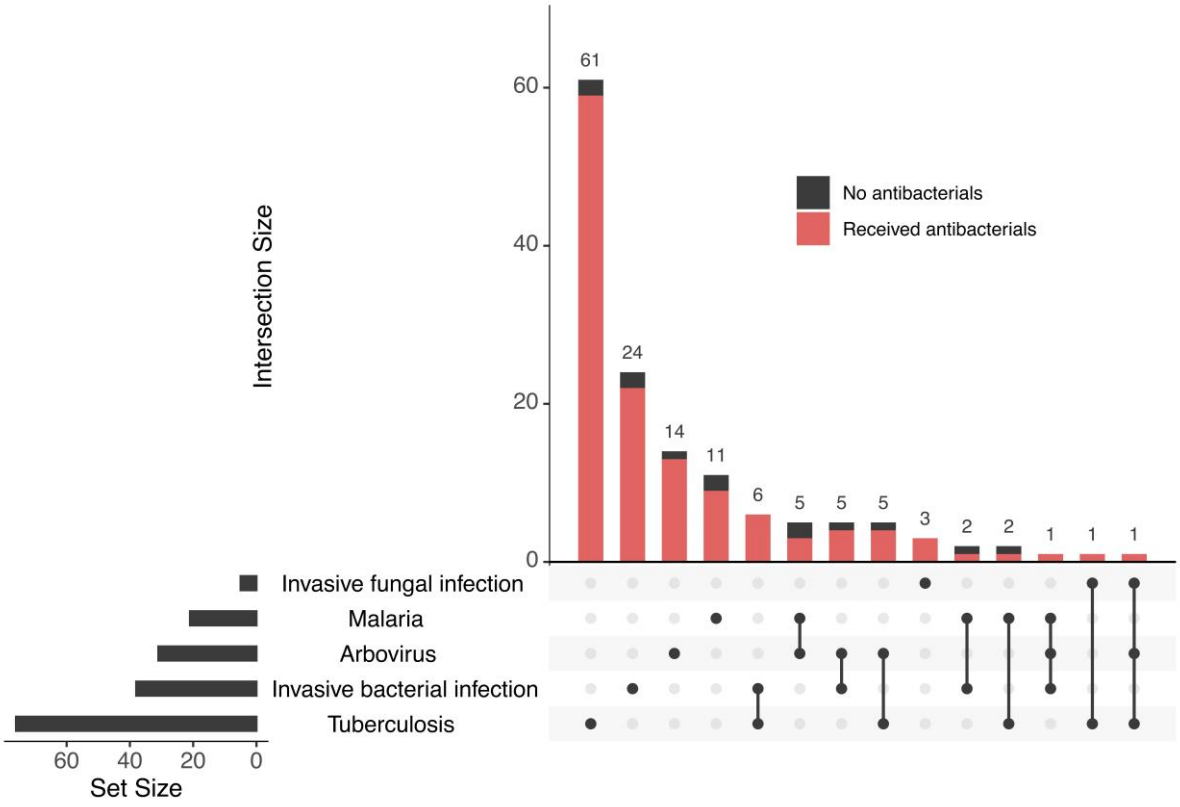

Figure 2

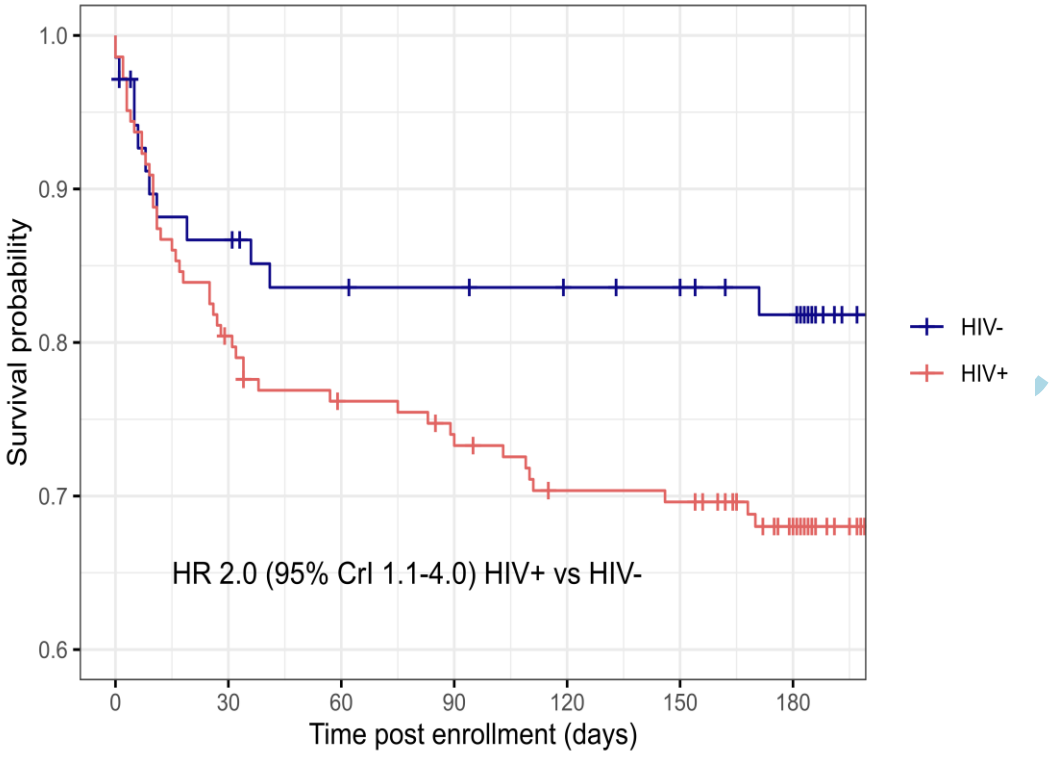

Figure 3