Developing an Antimicrobial Strategy for Sepsis in Malawi

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Thesis submitted in accordance with the requirements of the Liverpool School of Tropical Medicine for the degree of Doctor in Philosophy by Joseph Michael Lewis

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blah blah

Regression difficulties and solutions

colinearity/variable selection -> FAMD nonidentifiability (zero cells) -> bayesian regression with weakly informative priors

4.3 Results

4.3.1 Study population

Figure 4.1 shows flow through the study. 225 participants were recruited in 20 months between 19th February 2017 and 2nd October 2018. Participants were recuited, in general, soon after arrival in hospital, a median (IQR) of 1.5 (0.8-2.6) hours after fist attendance. In total, 4 participants (2%) were lost to follow up over the 180-day study period; 5 participants (2%) withdrew; and 7 participants (3%) transferred out of the study area before 180 days. Four of the five participants who withdrew gave a reason for their wish to withdraw, all that they no longer wished the inconvenience of being involved in the study. 15/225 (7%) participants had their final study visit before 180 days, and so were not included in the 180-day outcome analysis.

4.3.2 Symptoms and health-seeking behaviour

Table 4.1 shows the baseline characteristics of the recruited participants. They were young (median [IQR] age 36 [28-44]) and predominantly HIV-infected. Of those who were HIV-infected, the majority (117/143 [82%]) were on ART, almost exclusively the Malawian first-line regimen of efavirenz, lamivudine and tenofovir, and 88/117 (75%) had been taking ART for more than three months. Figure 4.2 shows the presenting symptoms of the participants. Almost all (221/225 [98%] of participants) experienced subjective fever. Participants had been unwell for some time, a median (IQR) of 7 (3-14) days; 32/225 (14%) of participants had been unwell for more than 4 weeks. 18/225 (8%) of participants had been admitted to hospital within the last 4 weeks. Over half (123/225 [55%]) of participants had sought care for their current ilness (Table 4.2), most commonly (101/123 [82%] of participants) at a government health centre, a median (IQR) of 2 (1-6) days previously. 60/225 (27%) of all participants had recieved an antimicrobial for their current illness: 7/60 (12%) of all prehospital antimicrobials were antimalarials, the remainder anitbacterial, most commonly co-trimoxazole or ciprofloxacin. Prehopsital intravenous or intramuscular antimirobials were administered in 16/60 (27%) participants recieving antimicrobials: ceftriaxone (n=6), benzylpenicillin (n=4), gentamicin (n=3) and artesunate (n=3).

Table 4.1: Participant Characteristics

Variable	Value
Demographics	
Age (years)	36 (28-44)
Male sex	114/225 (51%)
HIV/TB status	
HIV Reactive	143/225 (64%)
HIV Non Reactive	70/225 (31%)
HIV Unknown	12/225 (5%)
Ever treated for TB	37/225 (16%)
Of those, current TB treatment	10/37 (27%)
ART status*	
Current ART	117/143 (82%)
Months on ART	29 (4-73)
ART regimen: EFV/3TC/TDF	110/117 (94%)
ART regimen: other	7/117 (6%)
Current CPT†	98/141 (70%)
Tobacco/alcohol use	
Never tobacco	196/225 (87%)
Ex tobacco	17/225 (8%)
Current tobacco	12/225 (5%)

Table 4.1: Participant Characteristics *(continued)*

Variable	Value
Current alcohol	51/225 (23%)
Education	
Primary incomplete or complete	97/225 (43%)
Secondary school complete	48/225 (21%)
Some secondary education	47/225 (21%)
College or higher	17/225 (8%)
No formal schooling	16/225 (7%)
Employment	
Unemployed	82/225 (36%)
Currently employed	65/225 (29%)
Self-employed	56/225 (25%)
Student	21/225 (9%)
Retired	1/225 (0%)
Toilet facilities	
Pit latrine with slab +/- foot rest	104/225 (46%)
Hanging toilet/latrine	59/225 (26%)
Pit latrine with slab and cover +/- foot rest	45/225 (20%)
Flush Toliet (any type)	14/225 (6%)
No toilet	2/225 (1%)
Composting toilet	1/225 (0%)
Main water source	
Piped outside dwelling	69/225 (31%)
Tube well/borehole	64/225 (28%)
Public tap/standpipe	51/225 (23%)
Piped into dwelling	30/225 (13%)
Unprotected well/spring	5/225 (2%)
Surface water (including rainwater collection)	4/225 (2%)
Tube well with powered pump	2/225 (1%)
Electricty	
Electricity available in house	119/225 (53%)
Main cooking fuel	
Charcoal	161/225 (72%)
Wood	61/225 (27%)
Electricity	3/225 (1%)
Animals at home?	
Any animal	71/225 (32%)
Poultry	46/71 (65%)
Dogs	18/71 (25%)
Goats	12/71 (17%)
Dogs	18/71 (25%)
Other	11/71 (15%)

Table 4.1: Participant Characteristics *(continued)*

Variable	Value

Note:
ART = Antiretroviral therapy, CPT = Co-trimoxazole preventative therapy, EFV: Efavirenz, 3TC: Lamivudine, TDF: Tenofovir. Numeric values are median (IQR)) unless otherwise stated.
* ART status includes HIV reactive only as denominator
† Missing CPT data for two participants.

Table 4.2: Prehospital heathcare seeking and antimicrobial exposure

Variable	Value
Pre-hospital healthcare seeking	
Sought care prior to attendance at hospital	123/225 (55%)
At health centre	101/123 (82%)
At hospital	16/123 (13%)
At private doctor	8/123 (7%)
Somewhere else	1/123 (1%)
Days prior to today that participant sought care	2 (1-6)
Prehospital antimicrobial exposure	
Recieved any antimicrobial prior to attendance at hospital	60/225 (27%)
Co-trimoxazole	12/60 (20%)
Ciprofloxacin	10/60 (17%)
Amoxicillin	9/60 (15%)
Ceftriaxone	6/60 (10%)
Metronidazole	5/60 (8%)
Benzylpenicillin	4/60 (7%)
Artesunate	3/60 (5%)
Gentamicin	3/60 (5%)
Erythromycin	2/60 (3%)
LA	2/60 (3%)
SP	2/60 (3%)
Azithromycin	1/60 (2%)
Flucloxacillin	1/60 (2%)
Days prior to today that antimicrobials started	2 (1-5)
Method of transport to hospital	
Minibus	78/225 (35%)
Taxi	65/225 (29%)
Private car/truck	42/225 (19%)
Ambulance	37/225 (16%)
Other	2/225 (1%)
Walk	1/225 (0%)
Cost (MWK) of transport to hospital	1000 (275-3000)

Note:
LA = Lumefantrine-artemether, SP = Sulfamethoxazole-pyrimethamine, MWK = Malawian Kwacha. Numeric values are median (IQR)) unless otherwise stated.

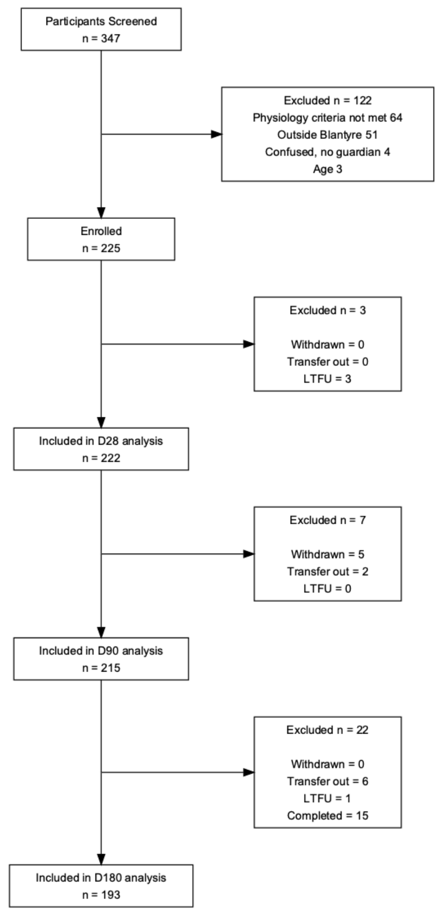

Figure 4.1: Study recruitment and follow up.

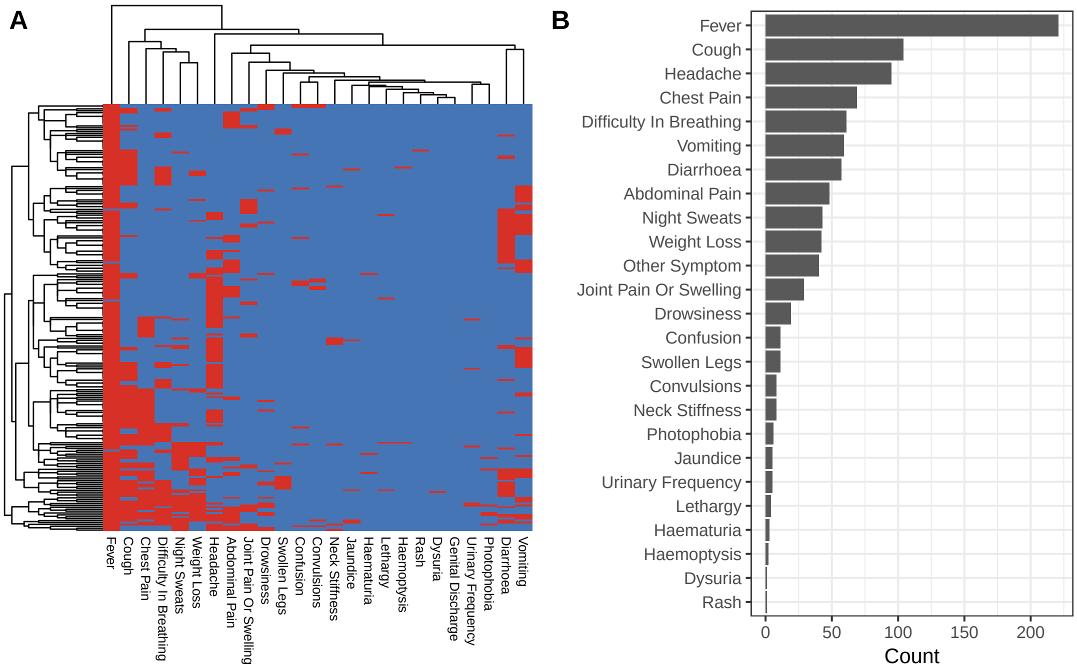

Figure 4.2: Symptoms of recruited participants. A: Row and column clustered heatmap of participant symptoms. Each row represents a patient. Red = presence, blue = absence. B: Frequency of occurence of symptoms

4.3.3 Admission physiology and laboratory investigations

Admission vital signs and laboratory investigations are shown in Table 4.3. Despite high ART coverage (117/143 [82%]) amongst HIV-infected participantsfor a median of 29 months, the median (IQR) CD4 count was low at 98 (31-236) cells μL^{-1}. 108/141 (70%) of participants had a CD4 count below 200 cells μL^{-1}. CD4 count was similar in participants who had started ART more than 6 months ago as compared to less than three months ago (median [IQR] 99 [27-260] vs 93 [39-137] cells μL^{-1} respectively) and 42/83 (51%) of participants who had been taking ART for more than 6 months had a CD4 count of less than 100 cells μL^{-1}, and would fulfil a WHO definition of immunological failure.

Table 4.3: Admission physiology, haematology and biochemistry

Variable	Value
Admission physiology	
Temperature (°C)	38.5 (37.9-39.0)
Heart rate (min^{-1}))	121 (102-132)
Systolic BP (mmHg)	99 (85-119)
Diatsolic BP (mmHg)	66 (56-76)
MAP (mmHg)	76 (65-89)
Respiratory rate (min^{-1})	34 (32-38)
Oxygen saturation (%)	96 (94-98)
15	204/225 (91%)
11-14	16/225 (7%)
< 11	5/225 (2%)
Unable to stand	63/225 (28%)
Admission CD4 count	
CD4 count* (μL^{-1})	98 (31-236)
Admission haematology	
Haemoglobin ($x10^9$ g dL^{-1})	10.8 (8.2-13.2)
White cell count ($x10^9$ L^{-1})	6.5 (4.4-11.4)
Neutrophil count ($x10^9$ L^{-1})	4.0 (2.1-7.5)
Platelet count count ($x10^9$ L^{-1})	218 (146-297)
Admission biochemistry	
Sodium (mmol L^{-1})	134 (130-137)
Potassium (mmol L^{-1})	4.0 (3.6-4.4)
Bicarbonate (mmol L^{-1})	19 (17-22)
Chloride (mmol L^{-1})	101 (97-104)
Urea (mmol L^{-1})	4.8 (3.5-8.0)
Creatinine (mmol L^{-1})	76 (59-103)
Lactate (mmol L^{-1})	3.4 (2.3-5.2)

Note:
GCS = Glasgow coma scale, BP = Blood pressure, MAP = Mean arterial blood pressure. Numeric values are median (IQR)) unless otherwise stated.

* CD4 count includes only HIV-infected participants; 2 values were missing.

4.3.4 Aetiology

In total, 51% (114/225) of the 225 participants had at least one infectious agent identified (Table 4.4), most commonly tuberculosis (76/225 [34%]) followed by bloodstream infection (24/225 [11%]) and malaria (21/225 [9%]). Table 4.5 shows the availability of test and proportion of positive tests across the cohort, stratified by HIV status. 2/225 patients (1%) had a missing aerobic blood culture; the remaining 223 patients had a total of 259 blood cultures performed. 15/259 (6%) blood cultures grew at least one contaminant, but 26 blood cultures from 24 patients were positive for a total of 28 pathogenic bacteria (Figure 4.3): *Salmonella* Typhi was the most commonly isolated pathogenic bacterium, and seemed to show an association with HIV-negative participants: all (8/8) of the participants from whom *S.* Typhi was isolated and whose HIV status was known were HIV noninfected. Of the 18 Gram negative bacteria isolated, 3/18 (17%) were cefpodoxime resistant on AST via disc diffusion testing, and likely ESBL producers: one *K. pneumoniae* and one *E. coli* (both from the same blood culture and same patient) and one *Acinetobacter baumannii.* Both *Staphyloccus aureus* isolates were oxacillin sensitive. The one *Streptococcus pneumoniae* cultured was penicillin intermediate on AST.

Lumbar puncture and CSF culture was carried out in 44 participants: 5/44 (11%) of samples grew a contaminent and no pathogenic bacteria were recovered from any sample. 4/44 (9%) had a detectable cryptococcal antigen (CRAG) in CSF. Malaria testing was missing for 6/225 (3%) of participants, but of the remainder, a positive malaria test was more likely in the HIV-uninfected (12/69 [17%] vs 6/138 [4%], p = 0.01 on pairwise Fisher's exact test). Positive aerobic blood culture showed no statistically significant association with HIV, nor did positive CSF testing, though in the latter case numbers were small and all positive tests (all positive CRAG) were in fact in the HIV-infected (Table 4.5).

Testing for TB, with the exception of sputum Xpert testing, was restricted to HIV-infected participants. Sputum Xpert was carried out in 44/225 (20%) of participants, and was more commonly carried out in the HIV-infected: 35/143 [24%] of HIV-infected participants had sputum testing performed vs 8/70 (11%) of HIV uninifected (p = 0.07 by Fisher's exact test). 53 sputum samples were sent in total from the 44 patients, and 8/44 (18%) diagnoses of TB made, all except one in HIV-infected participants. One sample identified a rifampicin resistance gene; the remainder of infections were rifampcin-sensitive.

155 participants were eligible for urinary lipoarabinomannan (uLAM) and mycobacterial blood culture testing, being either HIV-infected (n=143) or of unknown HIV status (n=12). Urine was available for 145/155 (94%) of those eligible, and 74/145 (51%) of samples were positive for uLAM. 150/155 (97%) of eligible participants had blood samples collected and cultured

Table 4.4: Final diagnosis of all participants

Diagnosis	Proportion of participants
Tuberculosis	76/225 (34%)
Bloodstream infection	24/225 (11%)
Malaria	21/225 (9%)
Meningitis	4/225 (2%)
No diagnosis	111/225 (49%)

Table 4.5: Positive diagnostic tests for all participants, stratified by HIV status.

	HIV status				
Test	Positive	Negative	Unknown	**All**	p
Number of participants	143	70	12	**225**	-
TB diagnostics					
Urinary LAM	70/136 (51%)	-	4/9 (44%)	**74/145 (51%)**	-
Sputum Xpert	7/35 (20%)	1/8 (12%)	0/1 (0%)	**8/44 (18%)**	0.835
TB blood culture	7/128 (5%)	-	1/10 (10%)	**8/138 (6%)**	-
Other diagnostics					
Aerobic blood culture	13/141 (9%)	9/70 (13%)	2/12 (17%)	**24/223 (11%)**	0.647
CSF culture or CRAG	4/31 (13%)	0/12 (0%)	0/1 (0%)	**4/44 (9%)**	0.445
Malaria RDT	6/138 (4%)	12/69 (17%)	3/12 (25%)	**21/219 (10%)**	0.007

Note:
LAM = Lipoarabinomannan, CSF = Cerebrospinal fluid, CRAG = Cryptococcal antigen, RDT = Rapid diagnostic test. p-values are chi-squared test across the three HIV status strata, and hence may be different from the pairwise exact Fisher's tests presented in the text. Urinary LAM and TB blood culture were not carried out in HIV negative participants.

for mycobacteria. 12/150 (8%) grew contaminents and are excluded from the denominators in Table 4.5; of the remainder 8/138 (6%) grew mycobacteria, all *M. tuberculosis*.

Figures 4.5 and 4.4 show the overlap of positive tests form the different diagnostic modalities. Of the 114 patients with at least one positive diagnosic test, 90/114 (79%) had only one positive diagnostic test. The exceptions to this were mycobacterial blood culture and sputum Xpert: patients who had TB diagnosed by these tests tended to also have a positive uLAM. 2/4 (50%) of patients with positive CSF testing (all of whom had detectible CRAG) had also grew *Cryptococcus neoformans* in aerobic blood culture. 111/225 (49%) of patients remained with no diagnosis.

4.3.5 Treatment

At least one antimicrobial drug was recieved by 95% (214/225) of the cohort during their admission (Table @ref:(time-to-ab-table)), most commonly an antibacterial (207/225 [92%]), but also a significant minority recieved antitubercular therapy (63/225 [28%]). Of those

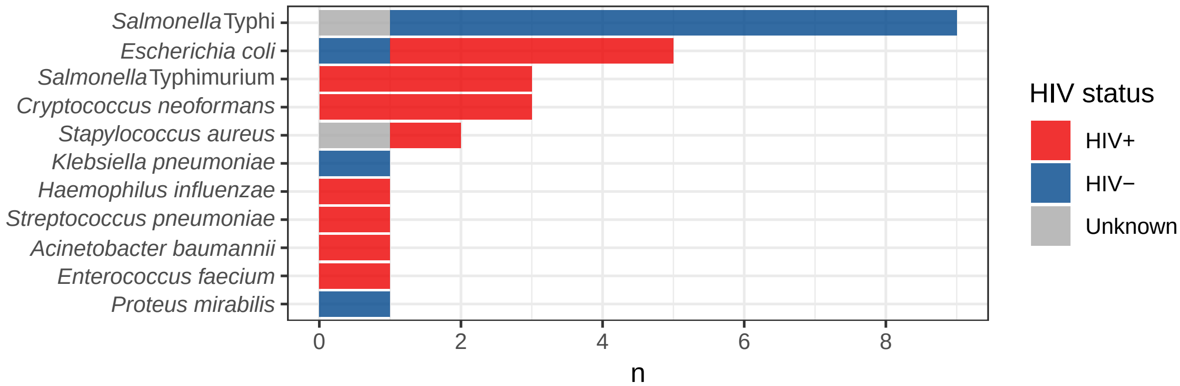

Figure 4.3: Pathogenic isolates recovered from aerobic blood culture. 26 blood cultures in 24 participants were positive for 28 pathogens in total

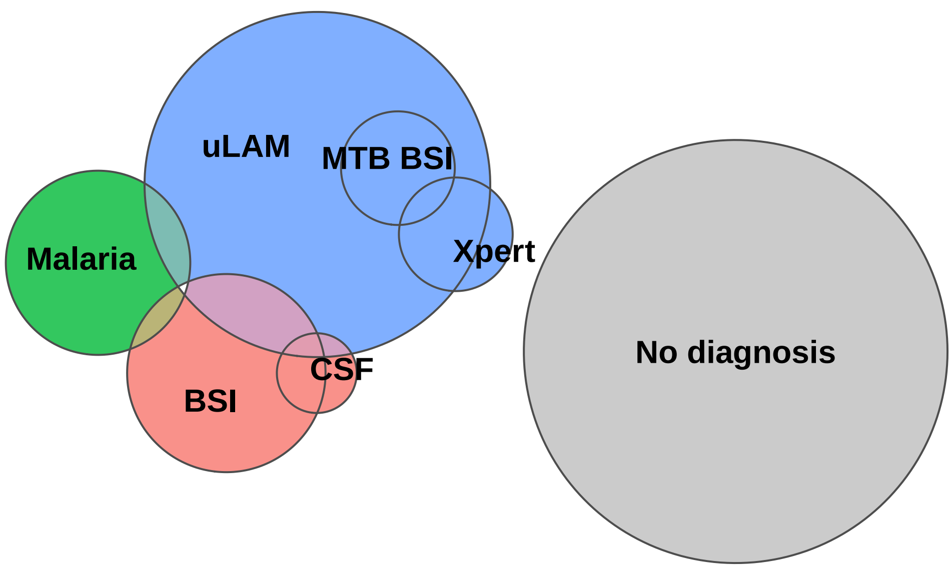

Figure 4.4: Venn diagram showing overlap of positive diagnostic tests; culture of blood and CSF shown in red, malaria in green and TB diagnostics in blue. The CSF variable in includes either a positive culture for a pathogenic bacteria or positive cryptococcal antigen, BSI a positive aerobic culture of pathogenic bacteria from blood and MTB BSI a positive mycobacterial culture of tuberculosis from blood. BSI: Bloodstream infection, CSF: Cerebrospinal fluid, CRAG: Cryptococcal antigen, mRDT: Malaria rapid diagnostic test, MTB BSI: Mycobacterium tuberculosis bloodstream infection, uLAM: urinary lipoarabinomannan.

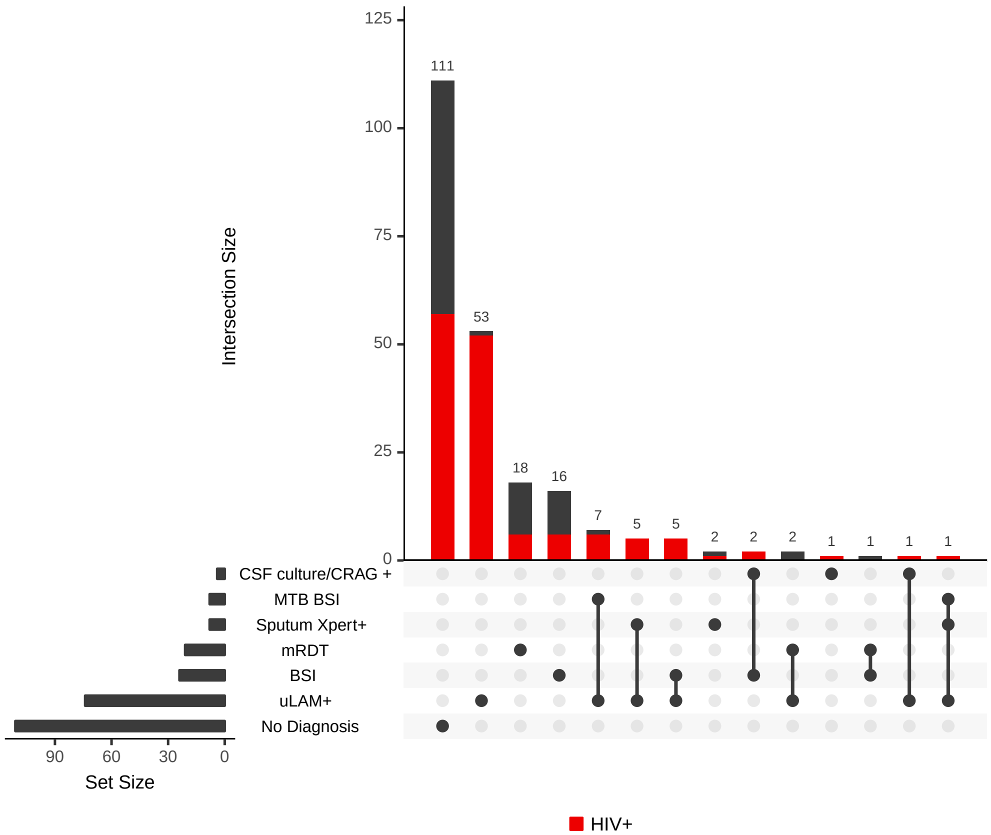

Figure 4.5: UpSet plot of overlap of positive diagnostic tests, showing that for the majority of participants, one test alone is positive. Red colour indicates HIV-infected; black is a composite of HIV-negative and unknown. The CSF variable in includes either a positive culture for a pathogenic bacteria or positive cryptococcal antigen, BSI a positive aerobic culture of pathogenic bacteria from blood and MTB BSI a positive mycobacterial culture of tuberculosis from blood. BSI: Bloodstream infection, CSF: Cerebrospinal fluid, CRAG: Cryptococcal antigen, mRDT: Malaria rapid diagnostic test, MTB BSI: Mycobacterium tuberculosis bloodstream infection, uLAM: urinary lipoarabinomannan.

Table 4.6: Door-to-antimicrobial times.

Antimicrobial class	No. participants	Median [IQR] time (hours)
Antibacterial	207/225 (92%)	5.3 (3.7-10.8)
Antitubercular	63/225 (28%)*	120.9 (63.7-171.0)
Antifungal	26/225 (12%)	47.7 (27.9-73.9)
Antimalarial	12/225 (5%)	4.5 (3.1-21.7)

* 10/63 participants who received antitubercular agents during admission were taking them prior to admission; they are excluded from the calculation of median door-to-antimicrobial time for this class.

receiving antitubercular therapy, 16% (10/63) were taking the medication prior to admission, and the remainder were initiated on therapy during admission. The first antibacterial agent administered was most often ceftriaxone, in 87% (181/207) of cases but ciprofloxacin (18/207 [9%] of participants), amoxicillin (6/207 [3%]) and metronidazole (2/207 [1%]) were also used. Median door to antimicrobial time was 5.3 (IQR 3.7-10.8) hours for antibacterials and 4.5 (IQR 3.1-21.7) hours for antimalarials but longer for antifungals at 47.7 (IQR 27.9-73.9) hours and longer still for antitubercular therapy at 120.9 (IQR 63.7-171.0). Cumulative incidence curves for administration of the different antimicrobial classess are shown in Figure 4.6A-D.

Of all participants, 85% (192/225) received any intravenous fluid in the first 6 hours of enrollment to the study; of these, most received 0.9% saline (160/192 [83%] of those recieving fluid) but 5% dextrose (91/192 [57%]) were also used; Ringer's lactate (6/192 [6%]) and blood (2/192 [1%]) were rarely administered. Of the 192 patients who were administered any fluid, a median of 1.5L (IQR 1-2L) was administered over the 6hr study period; fluid administration as a function of time is shown in Figure 4.6E.

4.3.6 Outcome

Median hospital stay was 4 (IQR 1-9) days. Mortality of the cohort was 18% (95% CI 13-23%) at 28 days, 24% (95% CI 18-30%) at 90 days and 31% (95% CI 25-38) at 180 days, and higher in HIV-infected participants at each time point (Table 4.7), though not statistically significant on pairwise Fisher's exact test (HIV-infected vs noninfected 19% vs 13%, [p = 0.14] at 28 days, 27% vs 17%, [p = 0.44] at 90 days and 36% vs 21% [p = 0.29] at 180 days). Kaplan-meier estimation of the survival function (Figure 4.7) showed a precipitous decline in survivorship to around day 30 but also continuous mortality therafter, to the end of the study period. Stratifying the analysis by HIV status revealed that early deaths (within the first 1-2 weeks) occur at similar rates in the two groups before the curves diverge; log-rank test suggested a significant difference in survival function between the two groups (p = 0.03).

Health related quality of life measures, as assessed by EQ-5D-3L, are shown in Figure 4.8 for

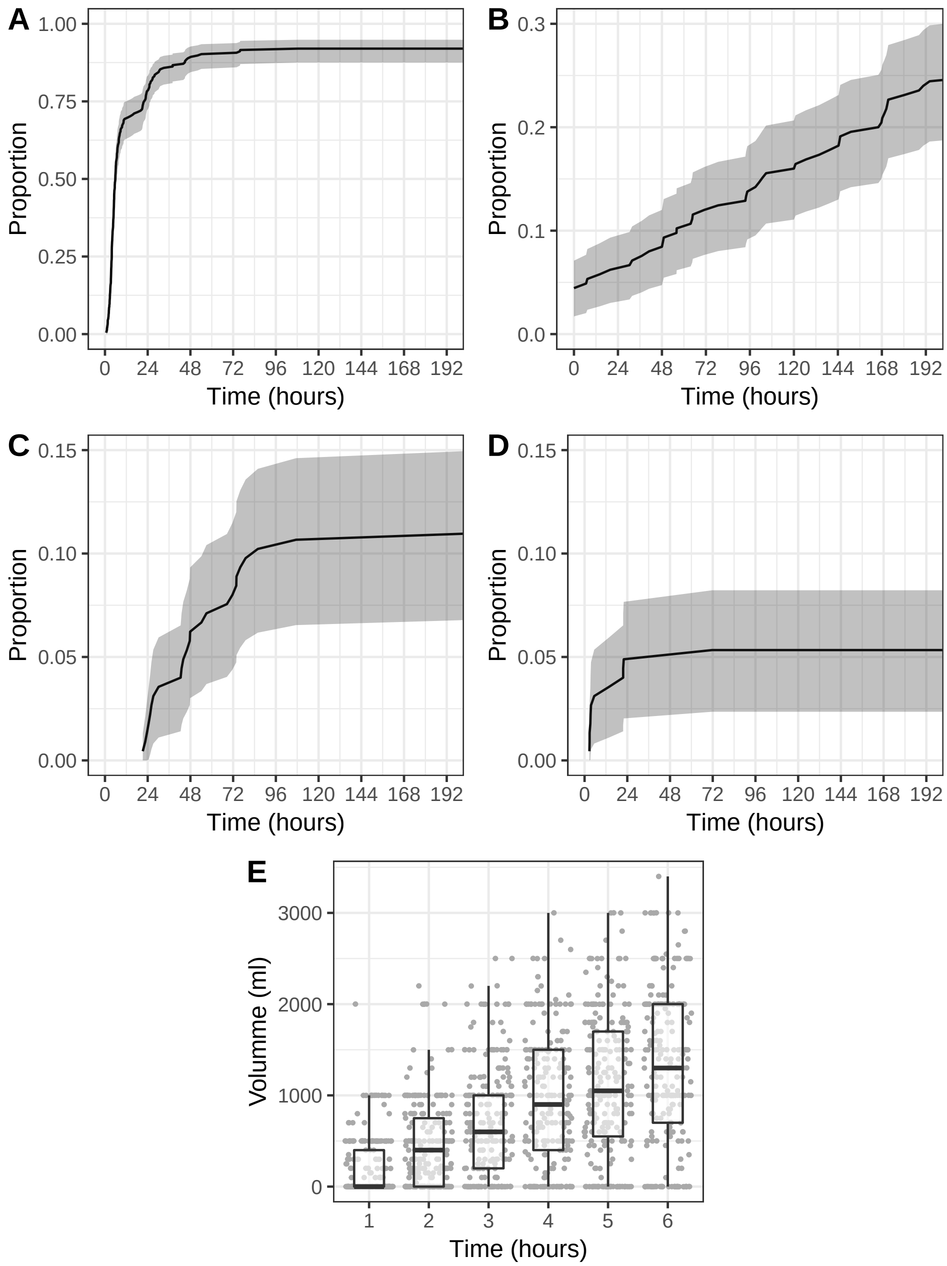

Figure 4.6: Timing of antimicrobial and fluid administration. A-D: Cumulative incidence of administration of antibacterial (A), antitubercular (B), antifungal (C) and antimalarial (D) agents as a function of time since arrival at hospital in hours. E: Total volumne of administered intavenous fluid as a function of time since enrollment to study in hours. Boxplots show median, quartiles box and 1.5 times interquartile range as whiskers. Points are jittered around the hour at which they were measured to show distribution.

Table 4.7: Day 28, 90 and 180 mortality stratified by HIV status

	HIV+		HIV-		HIV Unknown		Total	
	n	Mortality	n	Mortality	n	Mortality	**n**	**Mortality**
Day 28	143	19% (13-26)	67	13% (6-24)	12	25% (5-57)	**222**	**18% (13-23)**
Day 90	139	27% (19-35)	64	17% (9-29)	12	25% (5-57)	**215**	**24% (18-30)**
Day 180	125	36% (28-45)	58	21% (11-33)	11	27% (6-61)	**194**	**31% (25-38)**

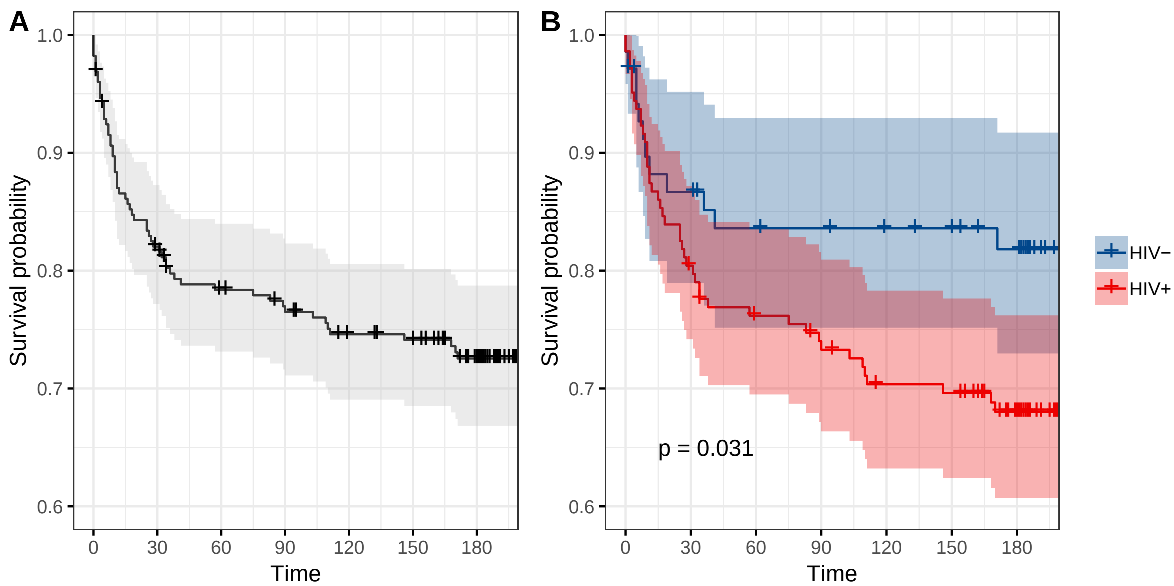

Figure 4.7: Kaplan-Meier survival curves of all included participants (A) and stratified by HIV status (B). Crosses indicate censoring. p value from log-rank test comparing survival of HIV-infected to HIV-noninfected participants shown (p = 0.03).

participants with sepsis and the community cohort as a comparator. Acutely, participants with sepsis reported were significantly disabled, reporting at least moderate impairment across all domains in the majority of cases, and over 90% of participants reporting at least moderate impairment in activities of daily living and experienceing at least moderate pain or discomfort. However, recovery following treatment in survivors was rapid. The mean EQ-5Q utility score (a measure of the weight compared to a health state compared to 1, perfect health) of healthy community controls was 0.910 (SD 0.102) at enrollment, significantly higher than participants with sepsis at enrollment (utility score 0.496 (SD 0.251), $p = < 0.0001$ versus community scores by t-test), but comparable to participants with sepsis at their 12 week assessment (0.913 (SD 0.147), $p = 0.903$ versus community enrollment scores).

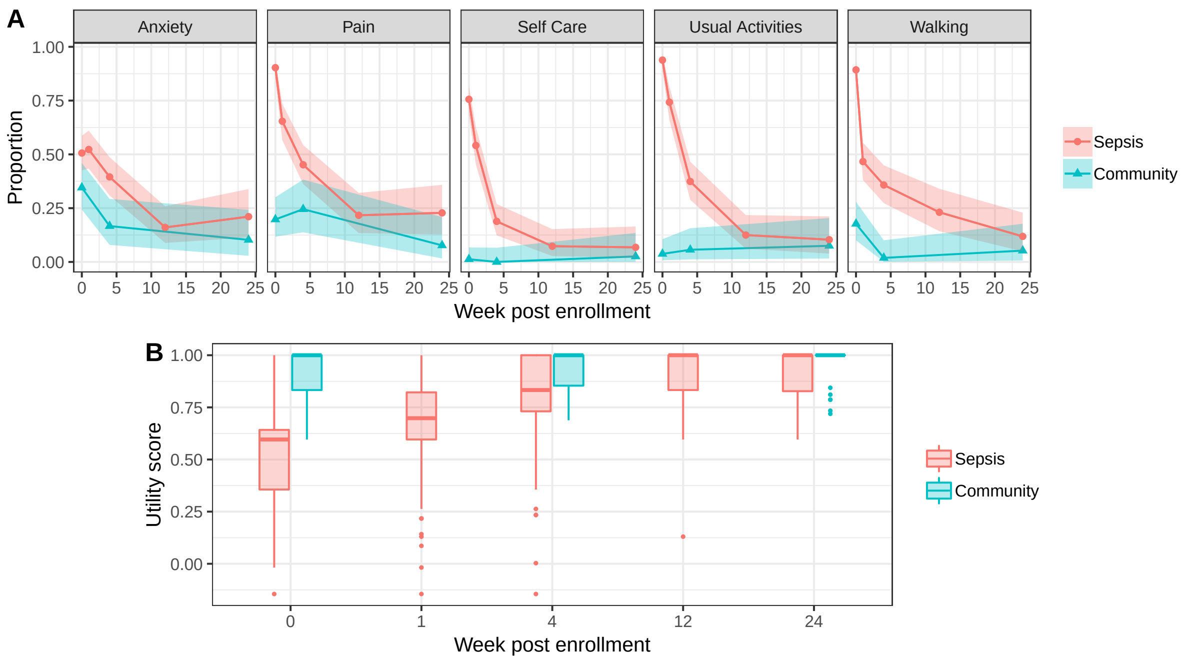

Figure 4.8: Health-related quality of life following sepsis admission, compared to community controls, showing a return to usual quality of life by 12 weeks following admission. A: proportion of participants across each of the five domains of the EQ-5D questionnaire who report at least moderate impariment. B: EQ-5D utility score derived using the Zimbabwean tariff set. The utility score is interpreted as the weight attached to a health state compared to perfect health, which is assigned a value of 1. By 12 weeks there is no statistically significant difference between sepsis and baseline community participant utility scores (p = 0.90 by t-test).

4.3.6.1 Determinents of mortality

Bivariate associations of mortality with host, disease severity and treatment variables are shown in **??**

4.3.6.2 Time to antimicrobial therapy

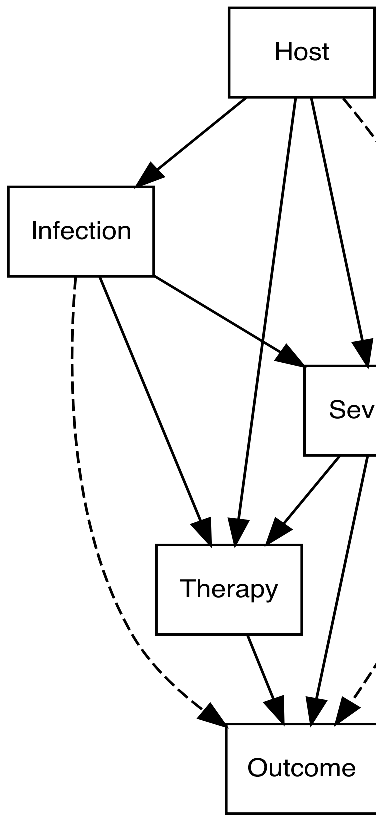

Figure 4.9: Hypothesised causal structre of death in sepsis. Host factors (e.g. age, sex, immune status) influence the type of infection; disseminated TB is more common in HIV, for example. Severity (variables quantifying e.g. shock or respiratory failure) is influenced by infection type and host factors. Therapy encodes which antimicrobials were administered and rapidity of administration of antimicrobials, and is influenced by disease severity (sicker patients may be given different therapies), host factors (HIV status may influence treatment) and the infection type (for example, malaria rapid diagnostic tests influenceing rapidity of malaria treatment). Dotted edges from host and infection to outcome are because it is not clear extita priori whether the effect of infection and host factors are entirely mediated by disease severity: in fact, even if this were the case in a theoretical sense, the available severity variables are unlikley to completely account for the causative effect of infection type on mortality and so conditioning on all available severity variables is likely to leave some residual causative effect of infection type. See text for further discussion

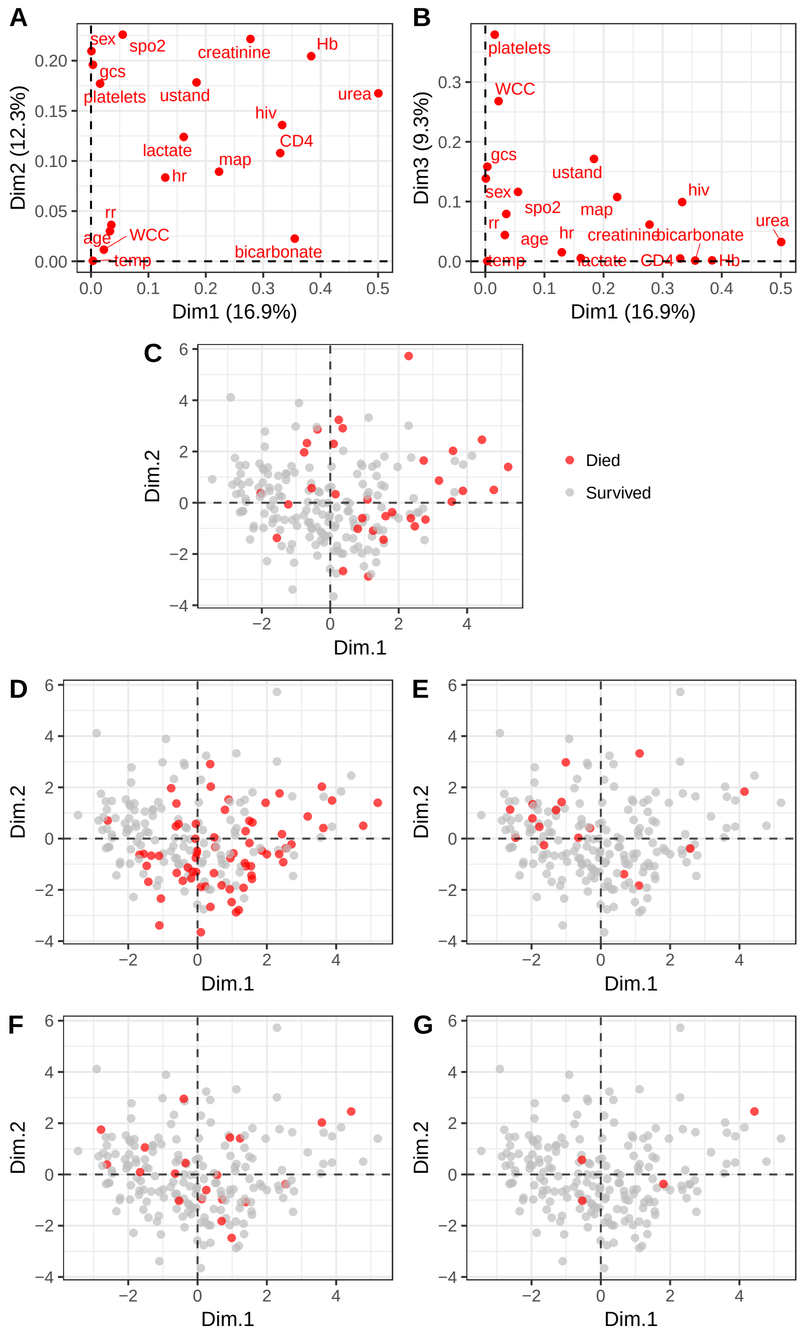

Figure 4.10: Dimensionality reduction of dataset using factor analysis of mixed data (FAMD); this is a combination of principal components analysis (PCA) for continuous variables and multiple correspondence analysis (MCA) for categorical variables, resulting in a new orthogonal coordinate system which maximises explained variance in each FAMD axis. A and B show the squared correlation ratio (for categoriacal variables) and the squared correlation coefficient (for continuous variables) with dimensions 1 and 2 (A) or 1 and 3 (B), along wih the proportion of variabce explained by each axis. C shows the location of all individuals in the FAMD space, with patients who died by 28 days coloured red to show that Dim.1 is associated with mortality. E-H show idividuals colored by diagnosis: TB (E), malaria (F), BSI (G) and meningtis (H) to show that malaria and tb seperate somewhat in Dim.1 and 2 with malaria patients clustering in top left and TB patients in bottom right

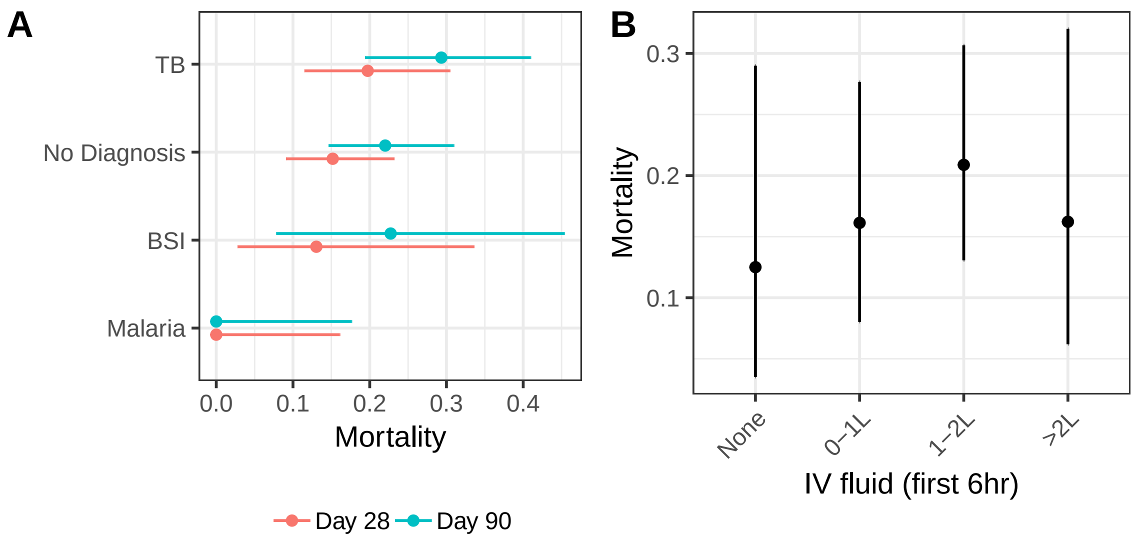

Figure 4.11: A; Day 28 and 90 mortality stratified by diagnosis, B: Day 28 mortality stratified by IV fluid volume recieved in first 6hr of hospital admission.

Table 4.8: Bivariate associations with death by 28 days

Variable	Died	Survived	p
Host Variables			
Age (years)	36.4 (31.5-46.0)	35.9 (27.4-42.9)	0.252
Male sex	19/39 (49%)	93/183 (51%)	0.861
HIV Infected*	27/36 (75%)	116/174 (67%)	0.433
Taking ART†	21/27 (78%)	96/116 (83%)	0.582
CD4 count† (μL^{-1})	**28.5 (9.5-124.5)**	**103.0 (43.5-251.0)**	**0.007**
Haemoglobin (x10^{9} g dL^{-1})	**9.1 (6.0-10.4)**	**11.0 (8.6-13.4)**	**<0.001**
Severity Variables			
Temperature (°C)	**38.1 (37.7-38.8)**	**38.5 (38.0-39.0)**	**0.024**
Heart rate (min^{-1}))	123.0 (104.5-138.5)	120.0 (102.0-131.0)	0.510
Systolic BP (mmHg)	**89.0 (76.0-106.0)**	**99.0 (86.5-118.5)**	**0.047**
Diastolic BP (mmHg)	**59.0 (51.0-72.0)**	**67.0 (57.0-75.5)**	**0.040**
Mean arterial BP (mmHg)	**69.7 (60.0-81.3)**	**78.7 (67.0-89.2)**	**0.035**
Respiratory rate (min^{-1}))	34.0 (32.0-36.5)	34.0 (32.0-38.0)	0.720
Oxygen saturation (%)	**95.0 (89.5-97.0)**	**97.0 (95.0-98.0)**	**0.019**
GCS	**15.0 (15.0-15.0)**	**15.0 (15.0-15.0)**	**0.044**
Unable to stand	**27/39 (69%)**	**36/183 (20%)**	**<0.001**
Lactate (mmol L^{-1})	**4.6 (3.0-10.6)**	**3.2 (2.1-4.5)**	**0.001**
White cell count (x10^{9} L^{-1})	5.9 (3.5-11.0)	6.9 (4.5-11.5)	0.165
Platelet count (x10^{9} L^{-1})	181.5 (86.8-300.8)	223.0 (148.0-296.5)	0.291
Bicarbonate (mmol L^{-1})	**17.0 (14.0-21.0)**	**20.0 (17.0-22.0)**	**0.007**
Urea (mmol L^{-1})	**7.8 (4.5-14.3)**	**4.5 (3.2-7.0)**	**<0.001**
Creatinine (mmol L^{-1})	90.0 (60.0-185.0)	73.0 (59.0-96.0)	0.100
Diagnosis			
BSI	3/39 (8%)	20/183 (11%)	0.773
TB	15/39 (38%)	61/183 (33%)	0.579
Malaria	**0/39 (0%)**	**21/183 (11%)**	**0.030**
Meningitis	**3/39 (8%)**	**1/183 (1%)**	**0.018**
No diagnosis	21/39 (54%)	88/183 (48%)	0.598
Treatment Recieved			
Antibacterials	37/39 (95%)	167/183 (91%)	0.746
Time to Antibacterials (hr)	4.7 (3.8-8.8)	5.3 (3.6-10.8)	0.648
Antifungals	7/39 (18%)	19/183 (10%)	0.180
Time to Antifungals (hr)	68.5 (45.0-72.7)	47.6 (26.6-76.4)	0.665
Antimalarials	0/39 (0%)	12/183 (7%)	0.132
Time to Antimalarials (hr)	NA (NA-NA)	4.5 (3.1-21.7)	NA
Antimycobacterials	**4/39 (10%)**	**49/183 (27%)**	**0.037**
Time to Antimycobacterials (hr)	107.3 (23.6-138.7)	99.0 (37.0-169.4)	0.778
IV fluid (ml)	1450.0 (1000.0-2000.0)	1300.0 (625.0-2000.0)	0.368

Note:
BP = Blood pressure, GCS = Glasgow coma scale. Numeric variables are presented as median (IQR) and categoric variables as proportions. P-values are from Kruskal-Wallace test for continuous variables and Fisher's exact test for categorical variables.
* Participants with HIV status unknown not included in this row
† Includes only HIV-infected participants

Table 4.9: Adjusted odds ratios (aOR) for death by 28 days for complete case analysis (CCA) and multiply imputed data

	Adjusted Odds Ratio	
Variable	CCA	Imputed
FAMD composite variables		
FAMD Dimension 1	2.39 (1.70-3.55)	2.58 (1.85-3.81)
FAMD Dimension 2	1.36 (1.00-1.86)	1.28 (0.95-1.72)
FAMD Dimension 3	1.18 (0.84-1.66)	1.10 (0.79-1.52)
Diagnosis		
TB	0.74 (0.27-1.94)	0.70 (0.26-1.76)
Malaria	0.06 (0.00-1.55)	0.04 (0.00-0.76)
BSI	0.17 (0.01-0.93)	0.24 (0.04-1.09)
Meningitis	17.46 (1.22-679.98)	16.10 (1.08-595.67)
Therapies recieved		
TB Therapy	0.18 (0.04-0.62)	0.14 (0.03-0.48)
Antifungals	1.11 (0.28-4.11)	1.05 (0.29-3.48)
Antimalarials	0.24 (0.00-12.08)	0.31 (0.00-17.08)
IV Fluid Recieved (per L)	0.62 (0.32-1.14)	0.65 (0.35-1.16)

Note:
FAMD = Factor Analysis of Mixed Data, BSI = Bloodstream infection, TB = Tuberculosis, CCA = Complete case analysis

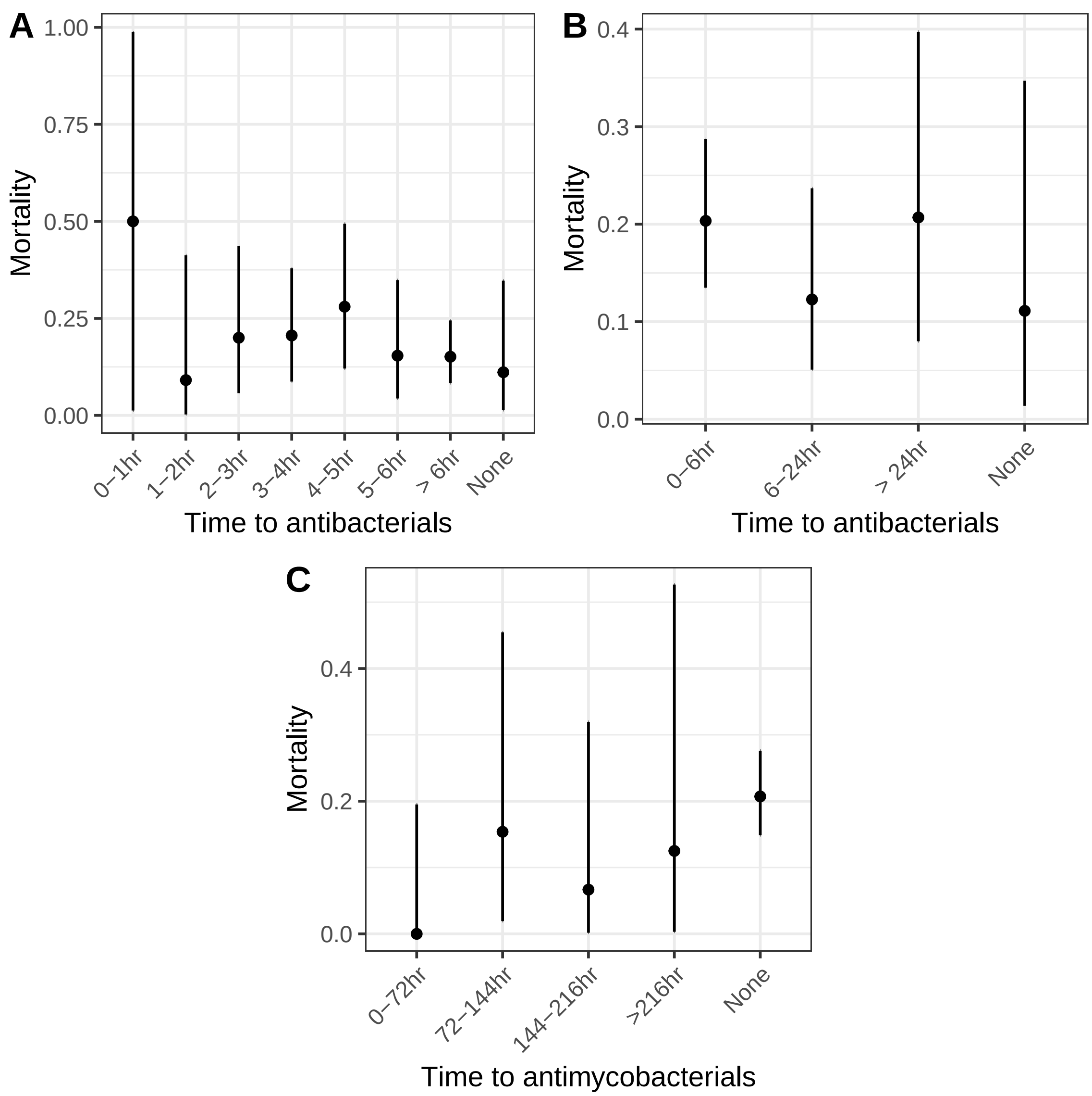

Figure 4.12: Day 28 mortality stratified by time-to-antimicrobials in hours (A-C). A and B show mortality stratified by time-to-antibacterial with different bin sizes to focus on the first 6hr (A) and afterwards (B). C shows mortality stratified by time to antituberculous therapy. In view of the small number of patients receiving antimalarial or antifungal therapy, this analysis was not repeated for those agents.

Chapter 5

Early response to resusitation in sepsis

Chapter 6

Gut mucosal carriage of ESBL-E in Blantyre, Malawi

Chapter 7

Whole genome sequencing of ESBL *E. coli* carriage isolates

Placeholder

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7.2.2 Global *E. coli* collection

7.2.3 Statistical analysis

7.3 Results

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7.3.4.5 Clustering and lineage association of AMR determinants

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7.3.6.1 Hierarchical BAPS clustering of core gene pseudosequences

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7.3.6.4 Assessing for within-patient conservation of lineage or MGE

7.4 Discussion

References