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

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4.3.1 Study population

Figure 4.1 shows flow through the study. 225 patients were recruited in 20 months between 19th February 2017 and 2nd October 2018. In total, 4 patients (2%) were lost to follow up over the 180-day study period; 5 patients (2%) withdrew; and 7 patients (3%) transferred out of the study area before 180 days. Four of the five patients 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%) patients 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

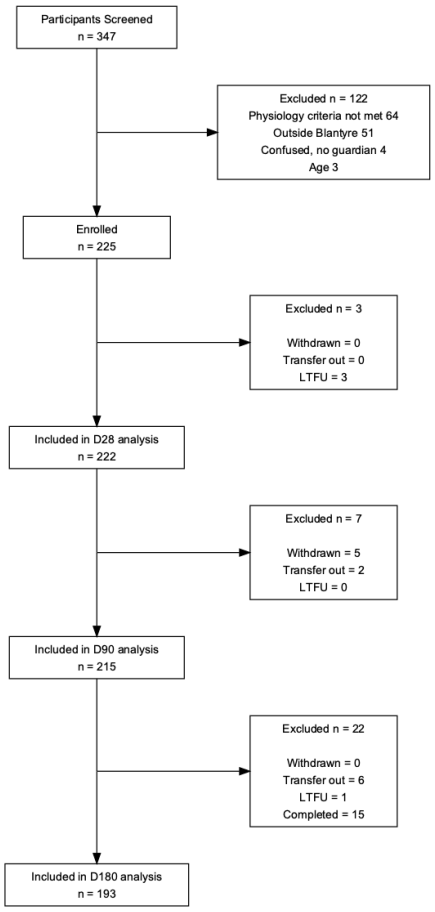

Figure 4.1: Study recruitment and follow up.

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) or 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%)
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%)

Table 4.1: Participant Characteristics *(continued)*

Variable	Value
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%)

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.

4.3.3 Admission physiology and laboratory investigations

Admission vital signs and laboratory investigations are shown in 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.

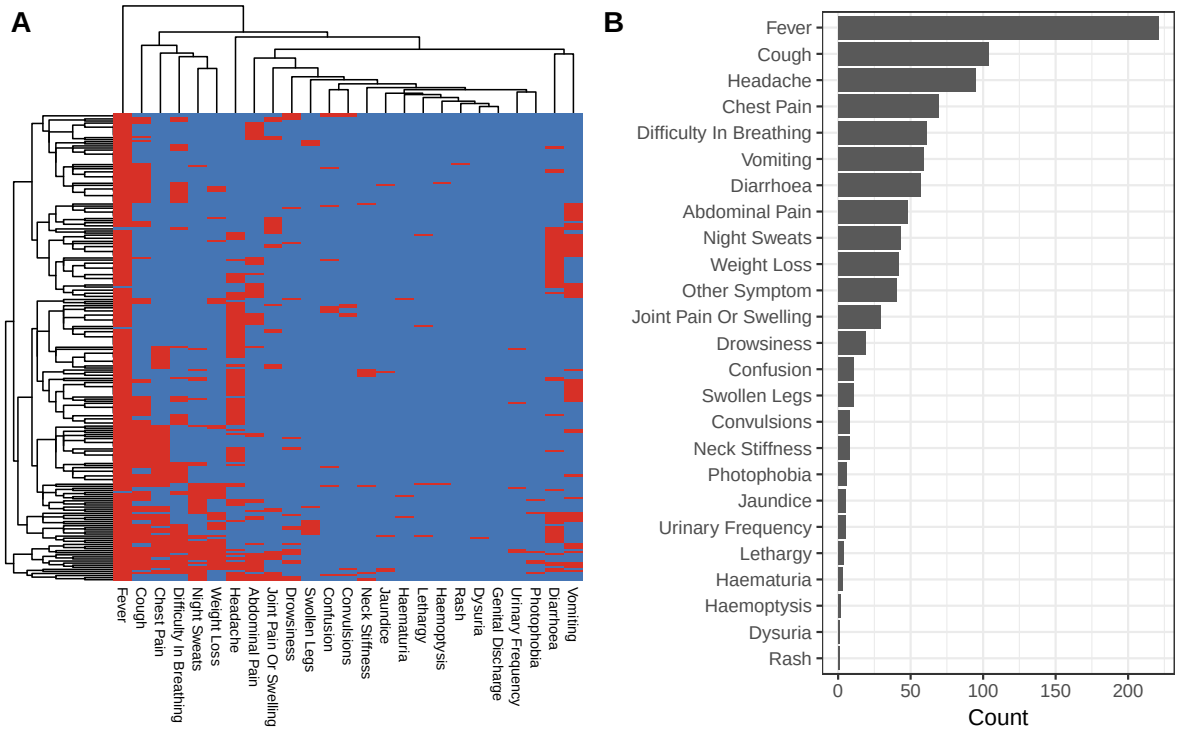

Figure 4.2: Symptoms of recruited participants. A: Row and column clustered heatmap of participant symptoms. Each row represents a patient. Red = presence, blue = absence. B: Frequency of occurence of symptoms

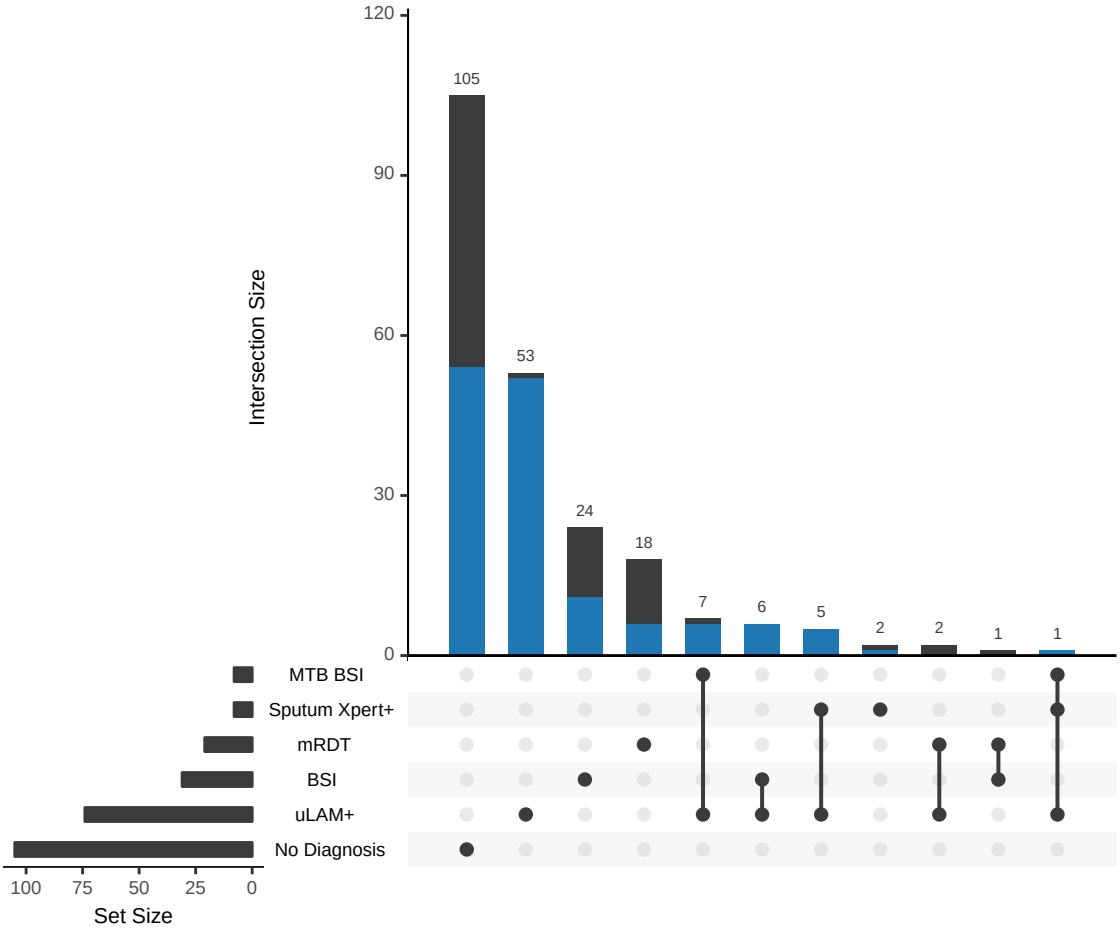

Figure 4.3: Symptoms of recruited participants. A: Row and column clustered heatmap of participant symptoms. Each row represents a patient. Red = presence, blue = absence. B: Frequency of occurence of symptoms

4.3.4 Aetiology

4.3.5 Treatment

Table: Time to antimicrobials Time to fluid Amount of fluid

4.3.6 Outcome

Table - 28 and 90 day mortality

Figure - KM survival curve

Logistic regression - determinants of 28 day mortality

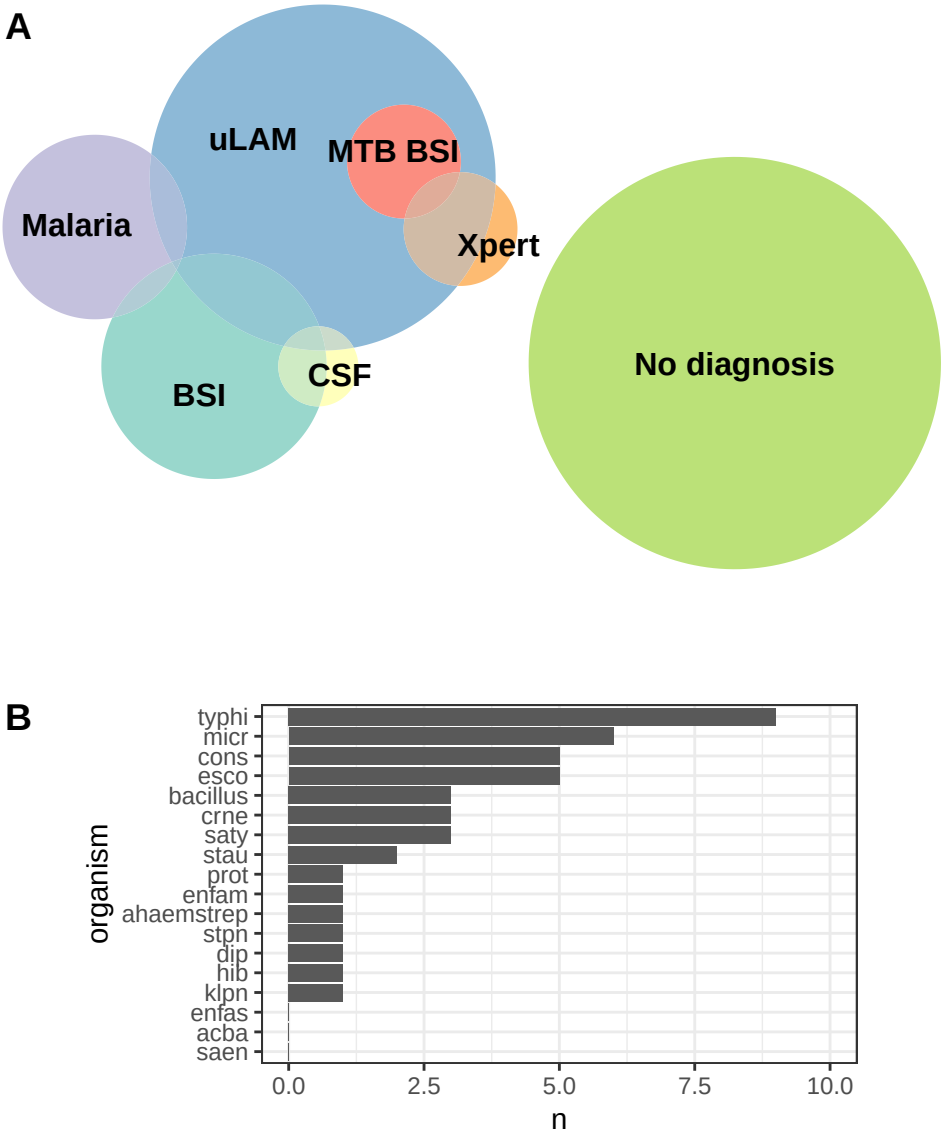

Figure 4.4: Symptoms of recruited participants. A: Row and column clustered heatmap of participant symptoms. Each row represents a patient. Red = presence, blue = absence. B: Frequency of occurence of symptoms

Morbidity -

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.

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 blood pressure (mmHg)	99 (85-119)
Diatsolic blood pressure (mmHg)	66 (56-76)
Respiratory rate (min^{-1})	34 (32-38)
Oxygen saturation (%)	96 (94-98)
GCS	
15	204/225 (91%)
11-14	16/225 (7%)
< 11	5/225 (2%)
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. Numeric values are median (IQR)) unless otherwise stated.
* CD4 count includes only HIV-infected participants; 2 values were missing.

Table 4.4: Final diagnosis of all participants

Diagnosis	Proportion of participants
Tuberculosis	76/225 (34%)
Bloodstream infection	31/225 (14%)
Malaria	21/225 (9%)
Meningitis	4/225 (2%)
No diagnosis	105/225 (47%)

Note:
Tuberculsosis includes and positive tuberculosis diagnostic test; bloodstream infection includes any patient with at least one positive blood culture, excluding contaminants; meningitis includes any positive CSF culture, excluding contaminents, or positive cryptococcal antigen test in CSF

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

Test	HIV Positive	HIV Negative	HIV Unknown	p
TB diagnostics				
Urinary LAM	70/136 (51%)	-	4/9 (44%)	-
Sputum Xpert	7/35 (20%)	1/8 (12%)	0/1 (0%)	0.835
TB blood culture	7/128 (5%)	-	1/10 (10%)	-
Other diagnostics				
Aerobic blood culture	17/141 (12%)	12/70 (17%)	2/12 (17%)	0.665
CSF culture or CRAG	4/31 (13%)	0/12 (0%)	0/1 (0%)	0.445
Malaria RDT	6/138 (4%)	12/69 (17%)	3/12 (25%)	0.007

Note:
LAM = Lipoarabinomannan, CSF = Cerebrospinal fluid, CRAG = Cryptococcal antigen, RDT = Rapid diagnostic test. P-values are chi-squared test across three HIV status strata. Urinary LAM and TB blood culture were not carried out in HIV negative participants.

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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References