

# Developing an Antimicrobial Strategy for Sepsis in Malawi

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# Preface

Placeholder



# Chapter 1

## Introduction

Placeholder



## 1.1 Chapter Overview

## 1.2 Sepsis in sub-Saharan Africa

### 1.2.1 Search strategy

### 1.2.2 Defining sepsis

### 1.2.3 Applicability of sepsis-3 definitions in sub-Saharan Africa

### 1.2.4 Sepsis epidemiology in sub-Saharan Africa

#### 1.2.4.1 Incidence

#### 1.2.4.2 Risk factors: the sepsis population in sub-Saharan Africa

#### 1.2.4.3 Outcomes

### 1.2.5 Sepsis aetiology in sub-Saharan Africa

#### 1.2.5.1 Bacterial zoonoses, Rickettsioses and arboviruses

#### 1.2.5.2 HIV opportunistic infections: PCP, histoplasmosis and cryptococcal disease

### 1.2.6 Sepsis management

#### 1.2.6.1 Early goal directed therapy

#### 1.2.6.2 Evidence to guide antimicrobial therapy in sSA

#### 1.2.6.3 Evidence to guide intravenous fluid therapy in sub-Saharan Africa

## 1.3 ESBL-E in sub-Saharan Africa

### 1.3.1 Search strategy

### 1.3.2 Introduction: definition and classification of ESBL-E

### 1.3.3 Global molecular epidemiology of ESBL-E: an overview

#### 1.3.3.1 1980s-1990s: First identification of ESBL in nosocomial pathogens

#### 1.3.3.2 1990s-2010s: Emergence and globalisation of CTX-M



## Chapter 2

# Methods

Placeholder





## 2.1 Chapter Overview

## 2.2 Study site

### 2.2.1 Malawi

### 2.2.2 Queen Elizabeth Central Hospital

### 2.2.3 Participating Laboratories

#### 2.2.3.1 Malawi-Liverpool-Wellcome Clinical Research Programme

#### 2.2.3.2 Malawi College of Medicine Tuberculosis Laboratory

#### 2.2.3.3 Wellcome Trust Sanger Institute

## 2.3 Clinical Study

### 2.3.1 Entry Criteria

### 2.3.2 Study Visits and Patient Sampling

#### 2.3.2.1 Enrollment assessment and first six hours

#### 2.3.2.2 Subsequent visits

#### 2.3.2.3 Blood, urine, and stool, sputum and CSF collection

#### 2.3.2.4 Imaging: chest x-ray and ultrasound scanning

### 2.3.3 Outcomes and sample size calculations

## 2.4 Diagnostic Laboratory Procedures

### 2.4.1 Point of care diagnostics

### 2.4.2 Laboratory diagnostics

#### 2.4.2.1 Haematology and biochemistry

#### 2.4.2.2 Aerobic blood and CSF culture

#### 2.4.2.3 Mycobacterial blood culture

#### 2.4.2.4 Sputum Xpert



## Chapter 3

# *Mycobacterium tuberculosis* BSI: an IPD meta analysis



## Chapter 4

# Sepsis in Blantyre, Malawi

### 4.1 Chapter overview

### 4.2 Methods

blah blah

### 4.3 Results

#### 4.3.1 Study population

Figure 4.1 shows flow through the study. 225 patients were recruited in under 20 month, 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.

Table 4.1: Demographics

levels	value
<b>Demographics</b>	
Age (years)	36 (28-44)
Male sex	114/225 (51%)

Table 4.1: Demographics (*continued*)

levels	value
<b>HIV status</b>	
HIV Reactive	134/225 (60%)
HIV Non Reactive	47/225 (21%)
HIV Unknown	44/225 (20%)
<b>ART status</b>	
Current ART	115/134 (86%)
Months on ART	30 (4-73)
ART regimen: 5A	108/115 (94%)
ART regimen: other	7/115 (6%)
<b>CPT status</b>	
Current CPT	98/134 (73%)
<b>TB status</b>	
Ever treated for TB	37/225 (16%)
Of those, current TB treatment	10/37 (27%)
<b>Tobacco use</b>	
Never	196/225 (87%)
Ex	17/225 (8%)
Current	12/225 (5%)
<b>Alcohol use</b>	
Current	51/225 (23%)
<b>Education</b>	
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%)
<b>Employment</b>	
Unemployed	82/225 (36%)
Currently employed	65/225 (29%)
Self-employed	56/225 (25%)
Student	21/225 (9%)
Retired	1/225 (0%)
<b>Toilet facilities</b>	
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 Toilet (any type)	14/225 (6%)
No toilet	2/225 (1%)
Composting toilet	1/225 (0%)
<b>Main water source</b>	

Table 4.1: Demographics (continued)

levels	value
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%)
<b>Electricity</b>	
Electricity available in house	119/225 (53%)
<b>Main cooking fuel</b>	
Charcoal	161/225 (72%)
Wood	61/225 (27%)
Electricity	3/225 (1%)
<b>Animals at home?</b>	
Any animal	71/225 (32%)
Poultry	46/71 (65%)
Dogs	18/71 (25%)
Goats	12/71 (17%)
Other	11/71 (15%)

Table - demographics

Table - presentation

Table - health seeking behaviour

4.3.2 Aetiology

Table

Figure to show crossover

4.3.3 Treatment

Table: Time to antimicrobials Time to fluid Amount of fluid

4.3.4 Outcome

Table - 28 and 90 day mortality

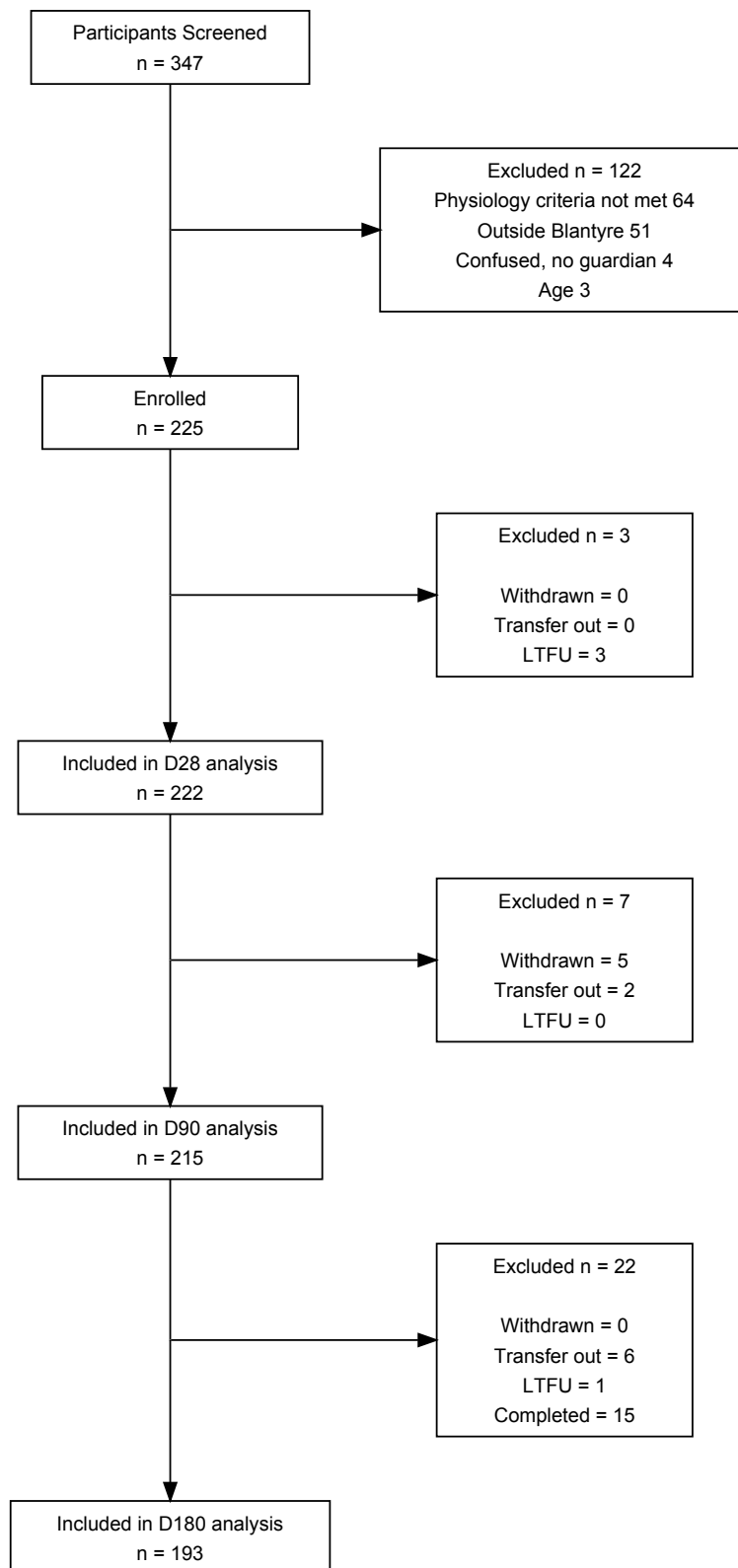


Figure 4.1: Study recruitment and follow up.



Figure - KM survival curve

Logistic regression - determinants of 28 day mortality

Morbidity -



## Chapter 5

# Early response to resuscitation 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





## 7.1 Chapter overview

## 7.2 Methods

### 7.2.1 Bioinformatic pipeline

### 7.2.2 Global *E. coli* collection

### 7.2.3 Statistical analysis

## 7.3 Results

### 7.3.1 Samples and quality control

### 7.3.2 Phylogroup, MLST and core genome phylogeny of study isolates

### 7.3.3 Study isolates in a global context

### 7.3.4 Antimicrobial resistance determinants

#### 7.3.4.1 $\beta$ -lactam resistance

#### 7.3.4.2 Quinolone resistance

#### 7.3.4.3 Aminoglycoside resistance

#### 7.3.4.4 Chloramphenicol, co-trimoxazole, tetracycline and other resistance determinants

#### 7.3.4.5 Clustering and lineage association of AMR determinants

### 7.3.5 Plasmid replicons

### 7.3.6 Testing metadata associations: SNP distance, hierBAPS sequence clusters and ESBL-clusters

#### 7.3.6.1 Hierarchical BAPS clustering of core gene pseudosequences

#### 7.3.6.2 ESBL-clusters

#### 7.3.6.3 Assessing for healthcare-associated lineages

#### 7.3.6.4 Assessing for within-patient conservation of lineage or MGE

## 7.4 Discussion



## References