Developing an antimicrobial strategy for sepsis in Malawi

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Introduction

1.1 Chapter Overview

The syndrome of sepsis is an ancient one; from Hippocrates to Galen and Semmelweis, the potentially serious consequences of infection have long been recognized. Modern definitions of sepsis conceptualise it as a syndrome of life threatening organ dysfunction due to a deleterious and dysregulated host response to infection, but despite increased understanding of its pathogenesis, mortality from sepsis remains high. Progress has been made in improving sepsis mortality in high income settings through timely application of basic care: early appropriate antimicrobials, aggressive fluid resuscitation and organ support largely in a critical care environment. Limited data from low resource settings including sub-Saharan Africa (sSA) suggest that mortality remains high, and increasing evidence suggests that exporting high-income setting sepsis protocols to sSA has the potential to do harm. Data to guide sepsis management protocols for sSA are urgently needed.

Data on sepsis aetiology from sSA to guide antimicrobial strategies are lacking; currently, in Blantyre Malawi, for example, empirical management of sepsis is the norm and patients often receive prolonged empiric courses of broad spectrum antimicrobials – largely ceftriaxone, a third-generation cephalosporin antibiotic. The effects of this at an individual level are unknown, but on a population level invasive Escherichia coli and Klebsiella pneumoniae bacteria are showing an alarming increase in ceftriaxone resistance since the drug was introduced in Malawi in 2005. The majority of these resistant bacteria are so-called extended-spectrum beta lactamase producers (ESBL-producers) and are often untreatable with locally available antimicrobials. Novel antimicrobial strategies are needed to safely preserve ceftriaxone - a first and last line antibiotic - for those who need it.

It is the hypothesis of this thesis, then, that sepsis is Malawi is caused by a wide variety of infections that are currently unrecognised and untreated, and that this is contributing to high sepsis mortality. Conversely, prolonged ceftriaxone exposure in sepsis survivors is causing acquisition and carriage of resistant bacteria (principally ESBL Enterobacteriaceae, henceforth ESBL-E) and their transportation into the community. I will argue that sustainable antimicrobial strategies for sepsis in sSA can not only consider mortality; the unintended consequences in terms of antimicrobial resistance (AMR) acquisition in a setting where empiric management of infection is the norm must also be considered, and mitigated against where possible. In this chapter, I will review, firstly, the definitions, epidemiology, aetiology and management of sepsis, with a focus on aetiology and antimicrobial treatment; and secondly, the epidemiology and drivers of ESBL-E carriage, both with a focus on sSA.

1.2 Sepsis in sub-Saharan Africa

1.2.1 Search strategy

A review of the literature was undertaken to identify prospective cohort, case control studies or randomised controlled trials (RCTs) of sepsis in sub-Saharan Africa with the search terms sepsis AND ((Angola OR Benin OR Botswana OR Burkina Faso OR Burundi OR Cameroon OR Cape Verde OR Central African Republic OR Chad OR Comoros OR Republic of the Congo OR Congo Brazzaville OR Democratic republic of the Congo OR Cote d'Ivoire OR Djibouti OR Equatorial Guinea OR Eritrea OR Ethiopia OR Gabon OR The Gambia OR Ghana OR Guinea OR Guinea-Bissau OR Kenya OR Lesotho OR Liberia OR Madagascar OR Malawi OR Mali OR Mauritania OR Mauritius OR Mozambique OR Namibia OR Niger OR Nigeria OR Reunion OR Rwanda OR Sao Tome and Principe OR Senegal OR Seychelles OR Sierra Leone OR Somalia OR South Africa OR Sudan OR Swaziland OR Eswatini OR Tanzania OR Togo OR Uganda OR Western Sahara OR Zambia OR Zimbabwe) OR Africa). Pubmed and scopus were searched, yielding 5460 unique studies on 17 July 2018. Inclusion criteria were any prospective cohort, RCT or case-control studies of sepsis in sSA (defined as taking place in the countries listed in search terms panel) recruiting patients using sepsis 1,2 or 3 definitions. Abstract review was undertaken resulting in inclusion of 91 studies for full text review. Eleven publications providing data on eight prospective cohorts[1–8] and three intervention studies (two RCTs[9,10] and one before-after intervention[11]) were identified. These data inform the following review, alongside non-systematically searched studies examining sepsis in high-resource settings.

In order to put sepsis aetiology data in context, systematic searches of the Pubmed and Scopus databases for leptospirosis, brucellosis, Q fever, Rickettsioses, arboviruses (dengue, or chikungunya) and histoplasmosis prevalence in unselected sepsis or fever cohorts in sSA were undertaken. Because a recent systematic review has examined these pathogens up to 2013 (see "sepsis aetiology" below), the date of these searches were restricted the 2014 to the present. Any studies examining disease prevalence in cohorts of febrile adults or children were included; outbreaks were excluded. Studies where the inclusion criteria were not clear (including those with, for example, "suspected leptospirosis" with no further details) were excluded. Finally, systematic searches of Pneumocystis Jiroveci pneumonia (PCP) were made using the search terms below; because a recent systematic review has examined the role of PCP up to 2015, the date on this search was restricted to 2015 or later. Table 1.1 shows the search terms, number of of hits and number of included studies after full text review: nine studies provided data on Leptospirosis[12–20], seven on Brucellosis[21–27], seven on Q-fever[19,23,28–31] , six on Rickettsioses[19,28,32–35], eighteen on Dengue[13,15,19,20,28,34,36–47], thirteen on Chikingunya[15,20,34,37,40,42,44–50], three on Zika [43–45], two on Histoplasmosis[51,52] and none on PCP. Details of the included studies are provided below.

Table 1.1: Fever studies

Organism	Search	n_abstracts	n_included
Leprospirosis	Leptospir AND	187	9
Brucellosis	Brucell AND	123	7
Q-fever	((Q fever) OR (coxiella)) AND	315	7
Rickettsioses	(Ricketts OR typhus OR (spotted fever)) AND	375	6
Arboviruses	(dengue OR chikungunya OR arbovir) AND	1422	Dengue 18, Chikungunya 13, Zika 3
Histoplasmosis	Histoplasm AND	72	2
PCP	(((((PCP) OR pneumocystis) OR "pneumocystis carini*") OR "pneumocystis jiroveci")) AND	87	0

Note:
All searches inlcuded the sSA country list in addition to the disease-specific terms above.

1.2.2 Defining sepsis

Sepsis is a heterogenous syndrome, with no diagnostic gold standard. In 1991 the first modern sepsis diagnostic criteria were defined in a consensus conference of key opinion makers[53] (Table 1.2). Sepsis was defined as the presence of the systemic inflammatory response syndrome (SIRS) plus infection, with a gradient of severity increasing through severe sepsis (sepsis plus organ dysfunction) to septic shock. These definitions were widely adopted as entry points into clinical trials, but ongoing concerns that SIRS was both insensitive and nonspecific for the diagnosis of sepsis led to an expansion of the diagnostic criteria in 2001[54] again by expert consensus. Despite these revised guidelines the SIRS criteria largely continued to be preferred both as the entry point to clinical trials of sepsis and in clinical practice until the development of the current sepsis-3 definitions in 2016[55].

The sepsis-3 definitions redefined sepsis as "life threatening organ dysfunction triggered by infection", a definition that rendered the sepsis-2 severe sepsis category obsolete. In contrast to the previous diagnostic criteria that had relied largely on expert opinion, the sepsis-3 criteria attempted to use a probabilistic approach to defining sepsis, by mandating that sepsis should be associated with excess mortality. The sequential organ dysfunction score (SOFA, Table 1.3), an organ-dysfunction score already in use in high income settings, and shown to be associated with mortality[56] was selected to operationalise the definition of sepsis. An acute change in SOFA of 2 or more points defines sepsis under sepsis-3.

Mindful that the SOFA score requires a large number of variables and is difficult to apply at the bedside, the consensus guideline group suggest the use of a simpler score, quick SOFA to identify patients who may have sepsis. Any two of: altered mental status, SBP $<$ 100mmHg or respiratory rate $>$ 22 defines a positive qSOFA score. qSOFA does not define sepsis; rather, under sepsis-3 patients with a qSOFA score of 2 or more are at increased risk of poor outcomes and should be screened for sepsis using a full SOFA score. The qSOFA was derived by identifying factors associated with mortality in large datasets of patients with infection from the United States and validated in further US and German datasets; in these datasets it showed good discriminant ability to predict mortality, equivalent to full SOFA score outside the intensive therapy unit (ITU)[57].

Finally, sepsis-3 defines septic shock as persistent hypotension requiring vasopressors to maintain mean arterial blood pressure (MAP) above 65mmHg and serum lactate greater than 2mmol /L. This definition was arrived at by a combination of consensus and systematic review to identify potential defining variables and validation in large datasets from the United States, where it was found to be strongly associated with mortality[58].

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

Application of the sepsis-3 definitions, both in terms of clinical use and as inclusion criteria for research studies in sub-Saharan African low resource settings, is problematic. Several of the domains of SOFA require the results of blood tests, which may not be available. In Blantyre, and elsewhere in sSA, intensive organ support with inotropes or mechanical ventilation (invasive or non-invasive) may not be available[59] or be difficult to access[60], yet use of these treatment modalities form components of the SOFA score. Both lactate measurement and inotropic support may be unavailable in some settings and yet these define septic shock. Five studies have validated the qSOFA score in sub-Saharan African settings[6,61–64] and found variable discriminant ability for mortality but it is not clear how this score should be deployed in this setting; no studies have been undertaken to link qSOFA score to clinical action, and it is not intended to define sepsis under sepsis-3. The optimal sepsis definitions (both clinical and for research) for sSA are therefore not clear.

1.2.4 Sepsis epidemiology in sub-Sahara Africa

1.2.4.1 Incidence

The changing case definition of sepsis over time hampers estimation of incidence even in high-income settings, furthermore sepsis is not included in global burden of disease estimates. Different methods of defining sepsis from disease registries can result in very different estimates[65], but a recent systematic review and meta-analysis of 27 studies from 9 high income countries found a recent population incidence rate of 437/100,000 person-years (95% CI 334-571) for sepsis and 270 (95% CI 176 – 412) for severe sepsis with an increasing incidence over time from 1979 to 2015[66]. Crudely extrapolating these estimates to the worldwide population would result in 20.7 million sepsis and 10.7 million severe sepsis cases a year, largely in low resource settings. However, no data are available from low or middle income settings and these estimates must be treated with caution.

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

In high-income settings, risk factors for sepsis have been identified, though once again changing definitions as well as a lack of large scale community based studies make it difficult to draw definitive conclusions. However, chronic diseases (including HIV) and immunosuppressive agents have been associated with increased sepsis incidence, as well as older age[67,68]. In the United States, male sex and black ethnicity (vs white) and poverty are associated with increased sepsis incidence and severity[69].

Though equivalent studies aiming to identify risk factors for sepsis in adults in sSA are lacking, it is clear from the available data that HIV-infection is the dominant risk factor there. Summary patient demographics from the 10 identified sepsis studies are shown in Table 1.4; of 2788 included patients with available HIV status, 69% (1809/2788) were HIV infected, and often with advanced disease; of 1278 HIV-infected patients from 5 studies the study median CD4 count ranges from 52-168 cells/μL. In keeping with the epidemiology of the HIV epidemic in Africa, these patients are young, with average ages (variably reported as mean or median) ranging from 30-39 across the studies. These studies recruited an equal proportion of males and females (1444/2812 males, 51%), suggesting that sex is not a risk factor.

These data contrast sharply with the sepsis population in high income settings, from whom the majority of sepsis data have been generated, and who are older and mostly HIV uninfected[67,70,71]. The need for data from sSA to guide sepsis treatment protocols, rather than extrapolating from the high-income setting sepsis population, is clear.

1.2.4.3 Outcomes

Summary outcomes for sepsis and severe sepsis in sSA from the identified studies are presented in Figure 1.1 below. Summary statistics of 28 or 30-day mortality were extracted from identified studies or, if 28- or 30-day data were not available, in-hospital mortality was used. For interventional studies, in order to reflect the "usual-care" mortality, only the usual care arms were included. Pooled mortality estimates were then generated using a random effect meta-analysis of proportions with a generalised linear mixed model (GLMM, the so called binomial-normal model) using the meta package in R. Exact binomial 95% mortality confidence intervals were used throughout.

It is clear that there is significant heterogeneity in outcomes of sepsis and severe sepsis in sSA, likely reflecting diverse patient and pathogen populations and variation in availability of available resources. This heterogeneity means that summary estimates should be interpreted with extreme caution but severe sepsis (49% [95% CI 39-58]), as expected, seems to carry a higher mortality hazard than sepsis (23% [95% CI 12-38]). Data of outcomes beyond 30 days are absent.

How does this compare to high income settings? A recent meta-analysis of population level estimates in high income settings found that a pooled sepsis 30-day mortality estimate of 17% (95% CI 11-26%)[66],

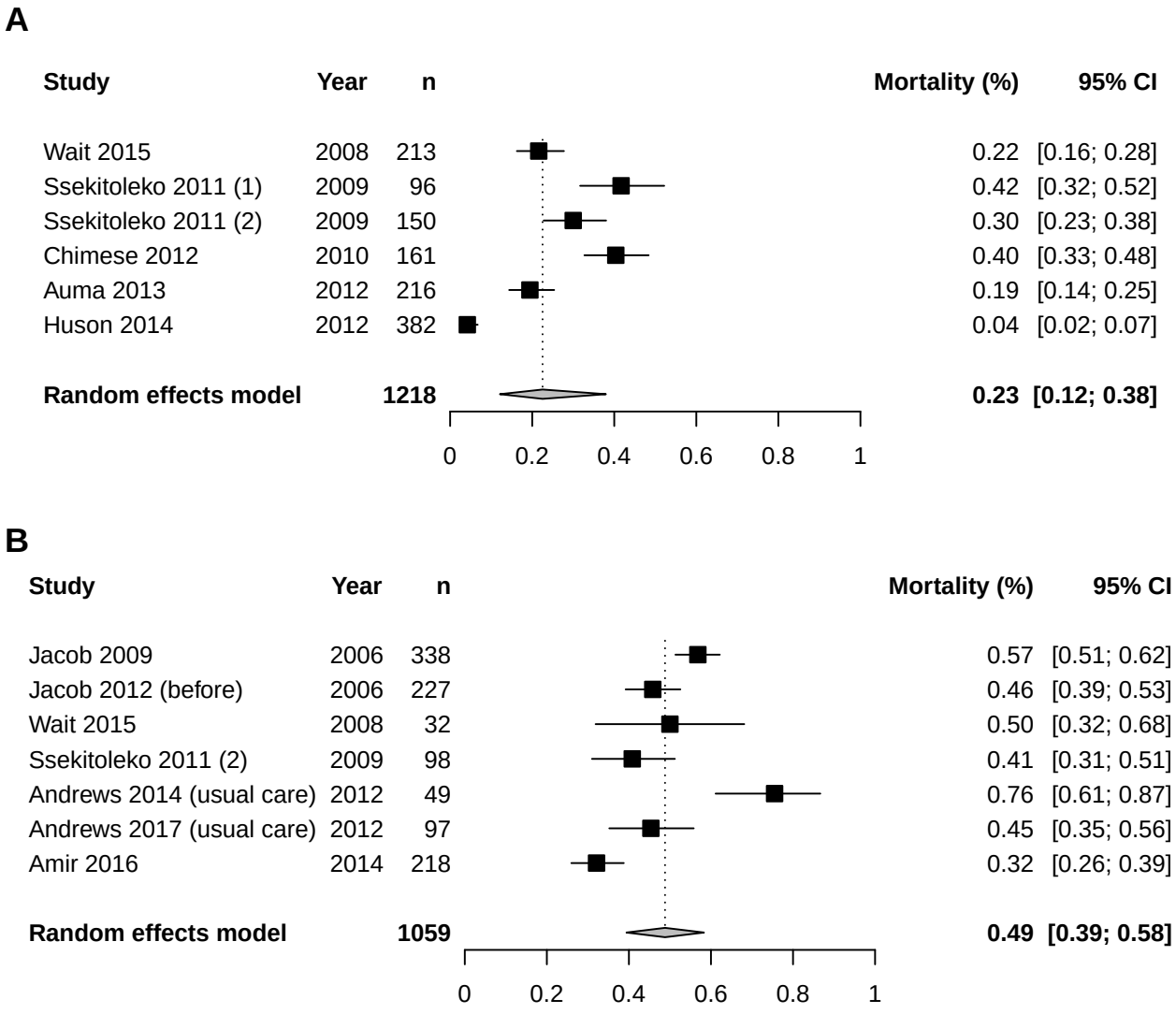

Figure 1.1: Pooled sepsis (A, top) and severe sepsis (B, bottom) inpatient mortality in sSA

though even older cohort studies as well as the more recent large sepsis-3 derivation cohorts have found considerably lower mortalities for sepsis (as defined by sepsis-2) ranging from 4-7%[57,72,73]. Most recent (largely post-2005) estimates of 30-day mortality from severe sepsis range from from 18-29%[65,66,71,74,75]. It seems likely therefore, that both sepsis and severe sepsis 30-day mortality is considerably higher in sSA than in high-income settings. The reasons for this are not clear, but are likely to be multifactorial; resource limitation is likely to play a part but the HIV epidemic in sSA, differing pathogen burden and lack of data and evidence based guidelines to inform optimal management in sSA may also play a role.

In the longer term, sepsis mortality continues to rise after the usual sepsis-study primary end point of 28 or 30 days, though data from sSA are absent. A systematic review in 2010 of long term sepsis mortality identified 26 studies (with none from low-resource settings) that reported long term sepsis mortality; 1 year mortality ranged from 22-72%, increasing to 45-75% at greater than 3 years[76]. Both short and long term morbidity is formidable also, though, once again, data from low income settings including sSA are absent. Cohort studies with no comparator group may not identify morbidity that is sepsis-specific (rather morbidity that is related to critical illness) but new, long-lasting reduction in physical and cognitive function with associated functional impairment have been identified in matched cohort studies in sepsis survivors[77,78]. Health-related quality of life in sepsis survivors in high-income settings have been found to be persistently below population norms[76]. Increased incidence of cardiovascular disease, renal failure and further episodes of infection are seen following a hospital discharge for sepsis[79–81]. Long term sepsis outcomes in sSA are unknown.

1.2.5 Sepsis aetiology in sub-Saharan Africa

The 11 identified prospective sepsis studies in sSA carried out various combinations of diagnostic testing for malaria (either microscopy or rapid diagnostic test) and aerobic and mycobacterial blood culture; a summary is shown in Table 1.5 and 1.6 below. The commonest bloodstream infection (BSI) in all studies where mycobacterial blood cultures were carried out was tuberculosis – present in a higher proportion than of all BSI isolates from aerobic culture combined - though it is important to note that mycobacterial blood cultures in most studies were carried out in HIV infected people and bacteraemic tuberculosis is almost exclusively HIV-associated. The importance of bacteraemic tuberculosis as a cause of sepsis is further examined in an individual patient data meta analysis in chapter 3. With the exception of one study, malaria was less common than BSI, highlighting the importance of non-malarial fever in sSA as malaria control efforts reduce the burden of malaria.

1.2.5.1 Bacterial zoonoses, Rickettsioses and arboviruses

There are several reasons to suspect that aetiologic agents other than bacterial BSI and tuberculosis may be significant in sSA, though data in sepsis are sparse. Studies of febrile illness in sSA have implicated Rickettsioses, arboviruses and bacterial zoonoses as causes of fever, accounting for a third of fever in hospitalised adults in one study in Tanzania[82]. Historically, however, data on these pathogens have been lacking. A 2015 systematic review of fever aetiology in LMIC (considering studies from 1980-2013) found that small numbers of patients had been systematically screened for these pathogens: in sSA 40/453 (8.8%) of adults with fever fulfilled diagnostic criteria for Leptospirosis, 16/453 (3.5%) for Brucellosis, 36/450 (8.0%) for spotted fever group Rickettsiosis, 24/482 (5%) for Q-fever and 55/700 (7.9%) for Chikingunya[83].

Increasing interest in non-malarial fever, however, has meant that data are accumulating from different settings in sSA, post-2013, as identified by the systematic review of the literature performed for this thesis. Details of the studies identified from this review are shown below in Table 1.7. These data highlight, firstly, the heterogeneity in diagnostics which are used for these pathogens – a combination of serology, PCR and antigen testing (often not using gold-standard case definitions), and secondly, the spatial and temporal heterogeneity across the continent.

These studies also demonstrate an increase, post-2013, in the use of molecular tests, particularly multiplex PCR assays (TaqMan array cards or PCR macroarrays) to detect multiple pathogens in fever aetiology

studies. Despite the attractiveness of these assays – the ability to detect tens of pathogens in one assay on one body fluid sample – many infections will have only transiently detectable pathogen genetic material in blood and as such may have limited sensitivity. The post-2013 fever aetiology data strongly suggest paired sera will maximise the diagnostic yield of bacterial zoonoses and Rickettsioses: for example, in studies of leptospirosis using PCR only 23/2533 (0.9%) of samples were positive versus 75/1464 (5.1%) in studies using paired sera; for Q-fever 9/3811 (0.2%) of samples were positive in PCR only studies versus 25/370 (6.8%) for paired sera studies; for Brucellosis PCR only studies 15/1005 (1.5%) of samples were positive versus 39/562 (6.9%) for paired sera studies; and for Rickettsioses 55/1932 (2.8%) of samples were positive for PCR studies vs paired sera 63/364 (17%). Some care must be taken with this conclusion: there are no studies that aim to directly compare paired sera and PCR assays for diagnosis of febrile illness, so the possibility of confounding remains.

Available data therefore suggest that bacterial zoonoses, Rickettsioses and arboviruses are significant causes of febrile illness in sSA. Their role is sepsis however is unknown. Only two studies have directly addressed the question of sepsis aetiology beyond BSI, malaria and TB: the first[84] performed PCR for 43 pathogens (using a TaqMan array card) including viruses (including dengue, chikungunya, and causes of viral haemorrhagic fever), bacteria (including *S. pneumoniae*, *E. coli*, *Salmonella spp.*, *S. aureus* as well as *Coxiella burnetti*, *Rickettsia spp.*, *Brucella spp.* and *Leptrospira spp.*), Mycobacterial (including *M. tuberculosis* (MTB) and *M. avium* complex), fungal (*Cryptococcus* and *Histoplasma spp.*) and parasitic (including malaria) on a convenience sample of 336 stored plasma samples from a Ugandan sepsis study. In keeping with the original study, MTB was frequently identified as was pneumococcus and malaria. Cytomegalovirus (CMV) was detected in 139/336 (41%) of patients, and was found to be independently associated with death, a finding which has been seen in sepsis studies in high-income settings[85] and may be related to the immune paresis of sepsis and CMV viraemia rather than disease. This study had no pathologic specimens and could not address this question. Dengue was detected in 17/336 (5%) of patients; Rickettsia spp. in 6/336 (2%), Leptospira spp. in 2/366 (0.6%) and Coxiella burnetti and Brucella spp. in 1/336 (0.3%) each. The true burden of disease of these pathogens may be higher, given the potential for increased diagnostic yield fom serological assays.

The second study[86] is a retrospective analysis of a fever aetiology cohort from Tanzania, in which paired serology for bacterial zoonoses and Rickettsioses was carried out, as well as arboviral PCR. Of 423 enrolled adults, 25 were retrospectively classified as having septic shock, 37 severe respiratory distress without shock and 109 severe pneumonia by WHO Integrated Management of Adolescent and Adult Illness (IMAI) District Clinician Manual criteria[87]. These patients would likely fulfil sepsis criteria under sepsis-2 or 3 guidelines, and were found to have a variety of diagnoses, though not all patients had all diagnostic tests: Chikungunya (6/154 [3%]),Leptospirosis (5/82 [6%]), Coxiella burnetti (7/83 [8%]) and spotted fever group Rickettsioses (6/83 [7%]).

Table 1.7: Causes of fever in sSA since 2013

Study	Year	Country	Setting	Patient Population	Test used	Case definition	Confirmed acute disease
Leptospirosis							
Zida 2018	2014-15	Burkina Faso	Central reference lab	Febrile Jaundice adults and children	In house IgM followed by MAT and PCR (acute only, > 1:400)	MAT > 1:400	27/781 (3.5%)
Guillebaud 2018	2014-2015	Madagascar	21 health-care centres	Febrile adults and children	PCR array	Positive PCR	1/682 (0.2%)

Table 1.7: Causes of fever in sSA since 2013 *(continued)*

Study	Year	Country	Setting	Patient Population	Test used	Case definition	Confirmed acute disease
Maze 2018	2012-2014	Tanzania	2 Referral Hospitals	Febrile adults and children	MAT (acute + conv)	MAT > 1:800 or fourfold rise	24/1239 (1.9%)
Gadia 2017		Central African Republic	Central reference lab	Febrile Jaundice adults and children	IgM ELISA (acute only)	Any IgM positive	0/198 (0%)
Hagen 2017	2011-2013	Madagascar	District Hospital	Adults and children FUO	PCR	Positive PCR	0/1009 (0%)
Biscornet 2017	2014-2015	Seychelles	Reference leptospirosis clinic	13 or above FUO, referred to central leptospirosis clinic	In house IgM followed by MAT and PCR (acute + conv)	MAT > 1:400 or fourfold rise	51/225 (23%)
Dreyfus 2017	2014	Uganda	2 Health centres	Any adult heath centre attendee	MAT (acute only)	MAT > 1:800	7/359 (1.9%)
Hercik 2017	2014-2015	Tanzania	District hospital	Febrile adults and children	Taqman PCR array	Positive PCR	22/842 (2.6%)
Chipwaza 2015	2014	Tanzania	District hospital	Outpatient febrile children	IgM IgG ELISA then MAT (acute only)	MAT > 1:160	26/200 (13%)
Q-fever							
Amoako 2018	2016-17	Ghana	2 distrct hospitals	Febrile children	Taqman PCR array	Positive PCR	1/166 (0.6%)
Hercik 2017	2014-2015	Tanzania	District hospital	Febrile adults and children	Taqman PCR array	Positive PCR	2/842 (0.2%)
Boone 2017	2011-13	Madagascar	Two public health care facilities	Febrile adults and children	PCR	Positive PCR	0/1005

Table 1.7: Causes of fever in sSA since 2013 *(continued)*

Study	Year	Country	Setting	Patient Population	Test used	Case definition	Confirmed acute disease
Njeru 2016	2014-15	Kenya	Two district hospitals	Febrile adults and children	Phase I/II IgG ELISA and IFA; PCR on subset (acute only)	Phase II IgG IFA titre > 1:128	163/1067 (15%), 10/448 (2.2%) PCR positive
Mourembou 2016	2013-14	Gabon	Four health centres	Febrile children	PCR	Positive PCR	0/410 (0%)
Maina 2016	2011-12	Kenya	District Hospital	Febrile children	IgM/IgG ELISA phase I and II (acute and conv)	Phase II IgG seroconversion	25/370 (8.9%)
Angelaksis 2014	2010-12	Senegal, Mali, Gabon	Six health centres	Febrile adults and children	PCR	Positive PCR	6/1388 (0.4%)
Brucellosis							
Cash-Goldwasser 2018	2012-14	Tanzania	Two referral hospitals	Febrile adults and children	MAT and blood culture (acute + conv)	Fourfold rise in MAT	39/562 (6.9%)
Gafiritia 2017	2014	Rwanda	District hospital	Adults, fever	Rose Bengal test	Positive test	10/198 (6.1%)
Boone 2017	2011-13	Madagascar	Two public health care facilities	Febrile adults and children	PCR	Positive PCR	15/1005 (1.5%)
De Glanville 2017	2012	Kenya	Referral hospital and private clinic	Febrile adults and children	Rose Bengal test	Positive test	8/825 (9.7%)

Table 1.7: Causes of fever in sSA since 2013 *(continued)*

Study	Year	Country	Setting	Patient Population	Test used	Case definition	Confirmed acute disease
Njeru 2016	2014-15	Kenya	Two district hospitals	Febrile adults and children	Rose bengal test, IgG/IgM ELISA, PCR (acute only)	Positive ELISA or PCR	146/1067 (13.7%)
Chipwaza 2015	2014	Tanzania	District hospital	Outpatient febrile children	IgM and IgG and tube agglutination (acute only)	Positive IgM	26/370 (7.0%)
Feleke 2015	2011	Ethiopia	Health centre	Febrile adults and children	Brucella antigen test	Positive test	3/280 (1%)
Rickettsioses							
Amoako 2018	2016-17	Ghana	2 distrct hospitals	Febrile children	Taqman PCR array	Positive PCR	5/166 (3.0%) RS
Hercik 2017	2014-2015	Tanzania	District hospital	Febrile adults and children	Taqman PCR array	Positive PCR	2/842 (0.2%) RF
Sothmann 2017	2012	Ghana	Referral hospital	Febrile Children	PCR	Positive PCR	6/431 (1.4%) RF
Maina 2016	2011-12	Kenya	District Hospital	Febrile children	IgG ELISA (acute and conv)	Fourfold rise in IgG titre	63/364 (22.4%) SFG 3/364 (1.1%) TG, 10/364 (3.6%) STG
Elfving 2016	2011	Zanzibar	District hospital	Febrile children with no diagnosis	PCR	Positive PCR	0/83 RS
Mourembou 2015	2013-14	Gabon	4 heath centres	Febrile children	PCR	Positive PCR	42/410 (10.2%) RF
Dengue							
Amoako 2018	2016-17	Ghana	2 district hospitals	Febrile children	Taqman PCR array	Positive PCR	2/166 (1.2%)

Table 1.7: Causes of fever in sSA since 2013 *(continued)*

Study	Year	Country	Setting	Patient Population	Test used	Case definition	Confirmed acute disease
Guillebaud 2018	2014-2015	Madagascar	21 health-care centres	Febrile adults and children	PCR macroarray	Positive PCR	0/682 (0%)
Kayiwa 2018	2014-2017	Uganda	District hospital	Febrile adults and children	PCR	Positive PCR	1/384 (0.26%)
Makiala-Mandanda 2018	2003-2012	Democratic Republic of Congo	Central lab	Febrile Jaundice, yellow fever IgM negative	PCR	Positive PCR	16/453 (3.5%)
Muianga 2018	2014	Mozambique	Not clear	Febrile adults and children	IgG, IgM and PCR (acute only)	Positive PCR	37/99 by PCR (37.4%)
Mugabe 2018	2016	Mozambique	Five health centres	Febrile adults and children	IgM, IgG, PCR (acute only)	Positive PCR	PCR 0/163
Hercik 2018	2014-2015	Tanzania	District hospital	Febrile adults and children	Taqman PCR array	Positive PCR	1/191 (0.5%)
Gadia 2017		Central African Republic	Central reference lab	Febrile Jaundice adults and children	IgM (Acute only)	Positive IgM	0/198 (0%)
Vu 2017	2014-2015	Kenya	Two health centres	Febrile children	PCR	Positive PCR	82/1104 (7.4%)
Waggoner 2017	2014-2015	Kenya	Two health centres and two district hospitals	Children with fever	PCR	Positive PCR	0/385 (0%)
Kolawole 2017	2016	Nigeria	Two heath centres	Adults and children with fever	IgM, IgG, PCR (Acute only)	Positive PCR	11/176 (6.2%)
Nasir 2017	2016	Nigeria	Teaching hospital	Adults and children with fever	NS1 antigen	Positive antigen	15/171 (8.8%)

Table 1.7: Causes of fever in sSA since 2013 *(continued)*

Study	Year	Country	Setting	Patient Population	Test used	Case definition	Confirmed acute disease
Ngoi 2016	2014-2015	Kenya	Five health clinics, one district hospital	Adults with fever, negative for acute HIV and malaria	PCR	Positive PCR	43/489 (8.8%)
Onoja 2016	2014	Nigeria	One district hospital	Adults and children with fever	IgM (Acute only)	Positive IgM	64/274 (23.3%)
Kajeguka 2016	2013-2014	Tanzania	Three district hospitals	Probable Dengue (on clinical and IgM)	PCR	Positive PCR	0/381 (0%)
Elfving 2016	2011	Zanzibar	District hospital	Febrile children with no diagnosis	PCR	Positive PCR	0/83
Sow 2016	2009-2013	Senegal	Seven health-care facilities	Adults and children with fever	IgM, PCR (acute only)	Positive PCR	3/13,845 (0.02%)
Chipwaza 2014	2013	Tanzania	One district hospital	Children with fever	IgM, PCR (acute only)	Positive PCR	29/364 (8.0%)
Chikingunya							
Kayiwa 2018	2014-2017	Uganda	District hospital	Febrile adults and children	PCR	Positive PCR	19/384 (4.9%)
Makiala-Mandanda 2018	2003-2012	Democratic Republic of Congo	Central lab	Febrile Jaundice, yellow fever IgM negative	PCR	Positive PCR	2/453 (0.4%)
Muianga 2018	2014	Mozambique	Not clear	Febrile adults and children	IgG, IgM (acute only)	Positive IgM	8/114 by IgM (7%)
Antonio 2018	2015-16	Mozambique	Eight health centres	Undifferentiated fever	IgM, IgG (Acute only)	Positive IgM	6/392 (1.5%)
Mugabe 2018	2016	Mozambique	Five health centres	Febrile adults and children	IgM, IgG, PCR (Acute only)	Positive PCR	PCR 0/163, IgM 17/163 (10.4%)
Sow 2017	2009-2010	Senegal	Fiver health centres and four schools	Febrile adults and children	IgM, IgG, PCR (Acute only)	Positive PCR	20/1049 (1.4%)

Table 1.7: Causes of fever in sSA since 2013 *(continued)*

Study	Year	Country	Setting	Patient Population	Test used	Case definition	Confirmed acute disease
Gadia 2017		Central African Republic	Central reference lab	Febrile Jaundice adults and children	IgM (Acute only)	Positive IgM	0/198 (0%)
Olajiga 2017	2015-2016	Nigeria	Seven hospitals	Fever or joint pain or rash, over 10 years	IgM, IgG (acute only)	Positive IgM	66/172 (38.4) by IgM
Waggoner 2017	2014-2015	Kenya	Two health centres and two district hospitals	Children with fever	PCR	Positive PCR	32/385 (8.3%)
Ngoi 2016	2014-2015	Kenya	Five health clinics, one district hospital	Adults with fever, negative for acute HIV and malaria	PCR	Positive PCR	0/489 (0%)
Kajeguka 2016	2013-2014	Tanzania	Three district hospitals	Probable Chikungunya (on clinical and IgM)	PCR	Positive PCR	11/263 (4.2%)
Elfving 2016	2011	Zanzibar	District hospital	Febrile children with no diagnosis	PCR	Positive PCR	0/83
Sow 2016	2009-2013	Senegal	Seven health-care faciities	Adults and children with fever	IgM, PCR (acute only)	Positive PCR	13/13,845 (0.1%)
Chipwaza 2014	2013	Tanzania	One district hospital	Children with fever	IgM (acute only)	Positive IgM	17/364 (4.7%)
Zika							
Kayiwa 2018	2014-2017	Uganda	District hospital	Febrile adults and children	PCR	Positive PCR	5/384 (1.3%)
Makiala-Mandanda 2018	2003-2012	Democratic Republic of Congo	Central lab	Febrile Jaundice, yellow fever IgM negative	PCR	Positive PCR	0/453 (0%)
Sow 2016	2009-2013	Senegal	Seven health-care faciities	Adults and children with fever	IgM, PCR (Acute only)	Positive PCR	9/13,845 (0.1%)

Note:
RS = Rickettsia spp., RF = R. felis, SFG/TG/STG = spotted fever/ typhus/scrub typhus group

1.2.5.2 HIV opportunistic infections: PCP, histoplasmosis and cryptococcal disease

The burden of HIV opportunistic infections in sepsis in sSA (including PCP, cryptococcal disease and including here Histoplasmosis as an opportunistic infection) is unclear. Beyond blood culture identification of *Cryptococcus neoformans* (present in 20/365 of positive blood cultures in the sepsis studies identified in this review) none of these pathogens have been systematically sought in sepsis cohorts in sSA, and their role as causative agents of sepsis is far from clear. Cryptococcal disease most commonly manifests as cryptococcal meningitis, is common in HIV infection and is thought to account globally for 15% of AIDS-related deaths[88]. It is likely therefore to contribute significantly to aetiology of sepsis; of the 11 identified sSA sepsis cohorts, three[4,5,9] provide data on suspected site of infection, and CNS infection accounts for 14-31% of the total, of which cryptococcal disease is likely to be responsible for a large proportion. One study2 performed CSF examination on 41/213 patients for suspected meninigoencephalitis. Of these, 3/41 cultured *C. neoformans*.

No study has attempted to define the burden of PCP in sepsis in sSA, though a 2016 systematic review[89] addressed the prevalence and attributable mortality of PCP. Searches were limited to post-1995; 48 studies were identified comprising 6884 individuals from 18 countries, with a varying patient population including inpatients and outpatients with respiratory presentation or clinical or radiological community acquired pneumonia, often sputum smear negative for TB, and some autopsy studies. A number of diagnostic tests including bronchoscopy and bronchoalveolar lavage were carried out. Many of the inpatient cohorts would include patients with sepsis; the pooled prevalence of PCP in inpatients (n = 2593, 23 studies) was 22% (90% CI 17 – 27%) in random effect meta-analysis. Clearly there are significant difficulties with obtaining lower respiratory tract specimens in unwell hypoxic, shocked or obtruded patients; newer serologic tests (1,3, beta-d glucan) which have reasonable diagnostic characteristics for PCP in high-income settings[90] and may have a role to play, but no study in sSA has attempted to use or validate this assay in any condition.

Data examining the role of Histoplasmosis as a cause of fever or sepsis in sSA are sparse. A 2015 systematic review[83] identified only one study up to 2013 which Histoplasma urine antigen testing in 628 febrile adults and children in Tanzania and acute serum testing on a subset of 200, finding 9/628 (1%) probable cases, 6/9 of whom were HIV infected. Since then, two studies have addressed histoplasma prevalence in varying conditions: the first, in Uganda, enrolled HIV-infected patients with suspected meningitis[51] and found 0/151 patients had detectable IgM to *Histoplasma capsulatum* and no Histoplasma antigen was detected in serum (n = 57), urine (n = 37) or CSF (n=63). The second study in Cameroon[52] recruited HIV infected patients with CD4 < 200 cells/μL, chronic cough and Histoplasmosis like skin manifestations. Histopathologic examination and culture found Histoplasmosis in 7/56 (13%) of patients over 3 years.

1.2.6 Sepsis management

The cornerstone of sepsis management is rapid administration of appropriate antimicrobial therapy, source control of any infectious focus and normalisation of tissue perfusion using intravenous fluids and, if necessary, inotropes, with other organ support as necessary (e.g. intubation and mechanical ventilation and renal replacement therapy). Several international guidelines for sepsis care are available; this section will examine these and specific guidance for sepsis in adults in sSA followed by a review of the evidence to inform these guidelines.

The surviving sepsis campaign has published four editions of comprehensive guidance on the management of sepsis in adults, which are endorsed by all the major critical care organisation in high income settings and form the basis of most sepsis care in high income settings; selected major recommendations of the latest guidance[91] are shown in table 11 below.

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Table 1.2: Sepsis diagnostic criteria

Definition	Diagnosis	Criteria
Sepsis-1 (1991)	SIRS	Two or more of: Temperature > 38°C or < 36°C, Heart rate > 90 /min, Respiratory rate > 20 /min or PaCO2 < 32mmHg (4.3 kPa), White blood cell count > 12 x 10-9 /Lor < 4 x 10-9 /L or > 10% immature forms
	Sepsis	SIRS plus proven or suspected infection
	Severe Sepsis	Sepsis plus acute organ dysfunction
	Septic shock	Sepsis with persistent hypotension after fluid resuscitation
Sepsis-2 (2001)	Sepsis	Infection documented or suspected and some of the following General variables: temperature > 38°C or < 36°C, heart rate > 90 min-1 or > SD above normal for age, tachypnoea, altered mental status, significant oedema or positive fluid balance (> 20ml/kg over 24hrs), hyperglycaemia > 7.7mmol /L Inflammatory variables: white blood cell count > 12 x 10-9 /L or < 4 x 10-9 /L or > 10% immature forms, plasma C-reactive protein > SD above normal, plasma procalcitonin > 2 SD above normal Haemodynamic variables: arterial hypotension (SBP < 90 mmHg or MAP < 70 mmHg or SBP decrease > 40mmHg in adults or 2SD below normal range, SvO2 > 70%, Cardiac index > 3.5
	Severe sepsis	Sepsis plus organ dysfunction Organ dysfunction variables: arterial hypoxaemia (PaO2 / FiO2) < 300, acute oliguria (urine output < 0.5 ml kg-1 hr -1 for at least 2 hours), creatinine increase > 0.5mg/ dL, coagulation abnormalities (INR > 1.5 or aPTT > 60s), ileus, thrombocytopenia (platelet count < 100,000 /mL, hyperbilirubinaemia (plasma bilirubin > 4mg /dL or 70 mmol /L
	Septic shock	Sepsis plus hypotension SBP < 90mmHg or MAP < 60mmHg or reduction in SBP of 40mmHg from baseline despite adequate volume resuscitation
Sepsis-3 (2016)	Sepsis	Infection plus life threatening organ dysfunction defined by an acute change in SOFA score of 2 or more
	Septic shock	Persisting hypotension requiring vasopressors to maintain MAP 65mmHg AND serum lactate below 2mmol /L

Note:
SIRS = Systemic Inflammatory Response Syndrome, SD = Standard deviation, SBP = Systolic blood pressure, MAP = Mean arterial blood pressure

Table 1.3: Sequential organ failure assessment (SOFA) score

	Score				
System	0	1	2	3	4
Respiratory					
Pao2 / FiO2 mmHg (kPa)	400 (53.3)	< 400 (53.3)	< 300 (40)	< 200 (26.7) with respiratory support	< 100 (13.3) with respiratory support
Coagulation					
Platelets x100,000/ mL	150	< 150	< 100	< 50	< 20
Liver					
Bilirubin mg /dL (mmol/ L)	<1.2 (20)	1.2-1.9 (20 – 32)	2.0 – 5.9 (33-101)	6.0 – 11.9 (102 – 204)	> 12.0 (204)
Cardiovascular					
Cardiovascular	MAP > 70mmHg	MAP < 70mmHg	Dopamine < 5 or dobutamine any dose	Dopamine 5.1 – 15 or epinephrine < 0.1 or nore-pinephrine < 0.1	Dopamine > 15 or epinephrine > 0.1 or nore-pinephrine > 0.1
CNS					
Glasgow coma scale	15	13-14	10-12	7-9	< 6
Renal					
Creatinine mg/dL (mmol /L)	< 1.2 (110)	1.2 – 1.9 (110 -170)	2.0 – 3.4 (171 – 299)	3.5 – 4.9 (300 – 440)	> 5.9 (440)
Urine output (ml /day)				< 500	< 200

Note:
PaO2 = Arterial partial pressure of oxygen, FiO2 = Inspired fraction of oxygen, MAP = mean arterial blood pressure, CNS = Central nervous system. All doses of inotropes are micrograms/kg/min

Table 1.4: Characteristics of patients recruited to sSA sepsis studies

Study	Type	Year	Country	Inc. criteria	n	Male	Age	HIV infected	Median CD4
Jacob 2009	Cohort	2006	Uganda	Severe sepsis	382	156/382 (41%)	34.8 (11.2)	320/382 (85%)	52 (16-131)
Jacob 2012	Before-after	2006	Uganda	Severe sepsisc	245	95/245 (39%)	34 (28-41)	207/245 (86%)	43 (11-178)
		2008-09			426	207/426 (49%)	34 (27-40)	362/426 (85%)	63 (15-178)
Waitt 2015	Cohort	2008-09	Malawi	Sepsis	213	87/213 (41%)	30 (25-39)	161/213 (76%)	NR
Ssekitoleko 2011 (1)	Cohort	2009	Uganda	Sepsis	96	193/418 (46%)	35.1 (12.0)	331/418b (83%)	NR
Ssekitoleko 2011 (2)	Cohort	2009	Uganda	Sepsis	150	94/150 (63%)	35 (13)	96/150 (64%)	NR
Chimese 2012	Cohort	2010	Zambia	Sepsis	161	79/161 (49%)	39 (15.6)	110/138 (80%)	NR
Andrews 2014	RCT	2012	Zambia	Severe sepsis	112	58/109 (53%)	35 (1.4)	88/109 (81%)	NR
Auma 2013	Cohort	2012	Uganda	Sepsis	216	106/216 (49%)	32 (27-43)	122/216 (56%)	NR
Andrews 2017	RCT	2012-13	Zambia	Severe sepsis	209	117/209 (56%)	36.7 (12.4)	187/209 (89.5%)	66 (21-143)
Huson 2014	Cohort	2012-13	Gabon	Sepsis	384	142/382 (37%)	34 (25-46)	77/384 (20%)	168 (61-438)
Amir 2016	Cohort	2014-15	Uganda	Severe sepsis	218	110/218 (50%)	35 (26-50)	125/218 (57%)	78 (20-202)

Note:
RCT = randomised controlled trial. All studies use a modified sepsis-2 definition of sepsis or severe sepsis. Age is given as median (IQR) or mean (SD). Units of CD4 count are cells/microlitre. Jacob 2012 includes two cohorts of patients – results shown for both separately - and includes data from patients included in Jacob 2009. The n here includes those not included in this publication but the summary estimates include all patients as they cannot be disaggregated

Table 1.5: Aetiology of sepsis in sSA

Study	BSI	MTB BSI	Malaria
Jacob 2009	48/382 (13%)	156/382 (22%)	34.8 (15%)
Jacob 2012	83/671 (12%)	104/576 (18%)	83/671 (12%)
Waitt 2015	33/213 (15%)	ND	26/213 (12%)
Ssekitoleko 2011 (1)	ND	ND	ND
Ssekitoleko 2011 (2)	39/150 (26%)	ND	7/150 (5%)
Chimese 2012	27/161 (17%)	ND	ND
Andrews 2014	26/109 (24%)	32/81 (40%)	2/109 (2%)
Auma 2013	41/216 (19%)	ND	9/216 (4%)
Andrews 2017	29/209 (14%)	43/187 (23%)	3/47 (6%)
Huson 2014	39/384 (10%)	NR	130/384 (33%)
Amir 2016	ND	ND	ND
TOTAL	**365/2493 (15%)**	**234/1093 (21%)**	**311/2139 (15%)**

Table 1.6: BSI isolates in sepsis in sSA

Organism	N
S. aureus	109
Non-Typhoidal Salmonellae	84
S. pneumoniae	67
Non-salmonellae Enterobacteriaceae	46
Cryptococcus spp.	20
S. Typhi	6
Other	33
TOTAL	**365**

Note:
Excluded are coagulase-negative Staphylococci, alpha-haemolytic Streptococci other than Pneumococcus, Bacillus spp. and Micrococci as likely contaminants.

Table 1.8: Surviving sepsis campaign guidelines

Recommendation	Strength of recommendation	Quality of evidence
Resusitation		
Administer 30ml/kg of intravenous crystalloid solution, within 3hr of diagnosis of sepsis	Strong	Low
Use frequent reassessment to guide further fluid	BPS	BPS
Use dynamic variables to assess fluid responsiveness (e.g. cardiac output)	Weak	Low
Use vasopressors in patients who remain hypotensive despite adequate fluid resuscitation; target a MAP of 65mmHg	Strong	Moderate
Use noradrenaline as first-line vasopressor	Strong	Moderate
Measure lactate and use lactate normalisation to guide resuscitation in patients with elevated lactate	Weak	Low
Antimicrobials		
Administer broad spectrum antibiotics within 1hr of diagnosis of sepsis	Strong	Moderate
Adjunctive therapies		
Use hydrocortisone 200mg IV per day if adequate fluid resuscitation and vasopressor therapy are unable to restore haemodynamic stability	Weak	Low

Note:
BPS = best practice statement