Community-acquired pneumonia in Malawian adults: Aetiology and predictors of mortality.

Thesis submitted in accordance with the requirements of the University of Liverpool for the degree of Doctor of Philosophy

Stephen James Aston

MBChB, BMedSc, MRCP, DTMH

August 2016

Declaration

I declare that this thesis was composed by me and that the work contained therein is my own, except where explicitly stated otherwise in the text. Any contribution of others is described briefly below and in detail at the beginning of relevant chapters. The work within this thesis has not been submitted in whole or in part for any other degree or professional qualification.

My supervisors Professor Stephen Gordon (Malawi Liverpool Wellcome Trust Clinical Research Programme (MLW), Malawi) Professor Robert Heyderman (University College London, UK) and Dr Henry Mwandumba (MLW) provided advice on all aspects of the design, conduct and analysis of the research presented here.

Professor Paul Garner (Liverpool School of Tropical Medicine, UK) advised on the methodology and analysis of the systematic review presented in chapter 2. Professor Charles Feldman (University of Witwatersrand, South Africa) independently reviewed all titles and corroborated study selection. Victoria Lutje (search strategist) advised on the search strategy and performed the database searches.

The Malawian adult lower respiratory tract infection severity, aetiology and outcome (MARISO) study presented in chapters 3, 4 and 5 was one of several concurrently recruiting adult respiratory infection projects based at MLW and Queen Elizabeth Central Hospital (QECH), Malawi. Recruitment to the MARISO study was nested within that of the Burden and Severity of HIV-associated Influenza (BASH-FLU) Study (Principal Investigator: Dr Antonia Ho) and integrated with that of the existing severe acute respiratory infection surveillance programme (Principal Investigators: Dr Dean Everett and Dr Ingrid Peterson). Some patients recruited to MARISO were also recruited to the Acute Infection of the Respiratory Tract (AIR) study (Principal Investigator: Dr Hannah Jary); a case-control study investigating the impact of exposure to indoor air pollution on the risk of developing pneumonia. Dr Antonia Ho, Dr Hannah Jary and myself jointly oversaw the integrated research team of clinical officers and nurses that performed study procedures. I designed the case record forms in conjunction with Dr Ho; we shared the tasks of data management and cleaning processes. The chest radiograph interpreting proforma was developed by Dr Sarah Heath (Liverpool School of Tropical Medicine, UK) under my supervision as part of Masters research project. Reading and grading of the radiographs was performed by two UK based radiologists, Dr Elizabeth Joekes and Dr Simon Greenwood (both Royal Liverpool University Hospital, UK), and myself. Professor Brian Faragher (Liverpool

School of Tropical Medicine, UK) advised on statistical analysis of the MARISO study; I undertook all analyses myself.

Dr Jacqueline Huwa (MLW) acted as study coordinator for the Addressing hypoxaemia in adult pneumonia (AHIP) study presented in chapter 6. She directly oversaw the clinical research team and completed the routine data management activities. In addition to my supervisors, Dr Jamie Rylance (Liverpool School of Tropical Medicine, UK), Dr Mulinda Nyirenda (QECH) and Dr Aylwin Chick (formerly QECH) provided useful comments in the development of the study protocol.

For both the AHIP and MARISO studies clinical specimens were processed at the MLW Clinical Diagnostic Laboratory under the supervision of its managers, Brigitte Denis and George Selemani, the MLW Molecular Laboratory under the supervision of senior laboratory technician, Mavis Menyere and the College of Medicine Tuberculosis Research Laboratory under the supervision of its manager, Aaron Mdolo.

For my father,

Robert Aston

1946-2010

Acknowledgements

Whilst it is my name alone on the cover, this work would not have been possible without the generous support of a large number of people.

Firstly, I want to express my gratitude to the patients and their guardians who willingly took part in the studies and generously donated their time. Also special thanks to the Wellcome Trust for awarding my Clinical PhD Fellowship that funded this work and giving me the incredible opportunity of living and working in Malawi.

It was a privilege to conduct my research at Queen Elizabeth Central Hospital and to work alongside many dedicated and talented clinicians in the Department of Medicine and the Adult Emergency and Trauma Centre. All were supportive and accommodating of my work. Particular thanks go to Dr Mulinda Nyirenda and Dr Jane Mallewa whose advice and assistance facilitated the smooth running of my studies.

The Malawi-Liverpool-Wellcome Trust Clinical Research Programme provided a supportive and motivating environment in which to work. I enjoyed and greatly benefitted from the exchange of ideas with my piers in the 'Junior Research Fellows Room'. My work was well supported by the operational, administrative and laboratory staff throughout the organisation. In particular I am grateful to Brigitte Denis, George Selemani, Aaron Mdolo, Neema Mtunthama and Vella Kdazu.

I was fortunate to arrive at MLW at a time of expansion in respiratory infection research. I had the great pleasure of working closely with Dr Antonia Ho (Principal investigator of the BASH-FLU Study) and Dr Hannah Jary (Principal Investigator of the AIR Study). I could not wish for better colleagues, co-investigators and friends. Our studies were well supported by the existing Influenza Surveillance Programme led by Dr Dean Everett and Dr Ingrid Peterson who generously shared staff and resources.

Special thanks go to my study team who grafted diligently and cheerfully on the frontline of clinical research for two years: Dan Chunda, Blessings Mkwaila, Collins Chilwawa, Rosaleen Ng'oma, Hannah Masangwi, Wezi Chimang'anga, Tiwonge Chinunda, Mike Magola and Chimwemwe Mtawali. It was my great pleasure to work with Dr Jacqueline Huwa who acted as a project coordinator for the AHIP study. She was meticulous and cheerful throughout, and a huge asset to the study team.

Thanks to Professor Charles Feldman for putting in many hours of hard work on the systematic review of pneumonia in Africa. Professor Paul Garner also provided

valuable input to its design and conduct. I'm grateful to the team of radiologists - Dr Liz Joekes and Dr Simon Greenwood - for generously giving their time in reporting study chest radiographs.

In Liverpool, Carolyn O'Leary and Matt Hanlon at the Wellcome Trust Tropical Centre provided invaluable logistical support. Professor Brian Faragher was consistently on hand to give clear and practical advice on statistical analysis. My advisory panel, Professor Bertie Squire and Dr Kevin Mortimer and my clinical supervisor Professor David Lalloo each gave timely encouragement during the long process of completing my research and compiling this thesis.

I want to express my sincere gratitude to my supervisors Professor Stephen Gordon, Professor Rob Heyderman and Dr Henry Mwandbumba. From the inception of this project to the final completion of this thesis, they have patiently provided support, encouragement and sage advice.

Finally, to my family - my loving and longsuffering wife, Ellen, and my wonderful boys, Noah and Reuben - my deepest love and gratitude.

Publications related to work presented in this thesis

Zar HJ, Madhi SA, **Aston SJ**, Gordon SB. Pneumonia in low- and middle- income countries: progress and challenges. *Thorax* 2013;68(11):1052-1056.

Wootton DG, **Aston SJ**, Gordon SB. The pathophysiology of pneumococcal pneumonia. In: Chalmers, Pletz MW, Aliberti S (Eds.). *European Respiratory Monograph: Community-acquired pneumonia* (Vol. 63). Sheffield, United Kingdom: European Respiratory Society; 2014, pp. 42-63.

Aston SJ. The role of rapid diagnostic tests in managing adults with pneumonia in low-resource settings. *Pneumonia* 2014;5:8-17.

Aston SJ, Rylance J. Community-acquired pneumonia in sub-Saharan Africa. *Semin Respir Crit Care Med* (in press).

Abstract

Background

Community-acquired pneumonia (CAP) is one of the commonest causes of adult hospitalisation in sub-Saharan Africa, but recent data describing its epidemiology, microbial aetiology and outcome are limited. Focusing particularly on Malawi, the overall aim of this thesis was to describe the aetiology and outcome of CAP in sub-Saharan African to determine the key predictors of mortality.

Methods

Firstly, a systematic review of studies of CAP in adults in sub-Saharan Africa was performed to describe CAP aetiology, estimate the mortality rate and identify risk factors associated with death. Secondly, a prospective observational study of adults hospitalised with clinically diagnosed CAP to Queen Elizabeth Central Hospital, Blantyre, Malawi was completed to describe microbial aetiology using modern diagnostic modalities, determine outcome and identify prognostics factors. Thirdly, having identified in preliminary analyses of the prospective cohort that hypoxaemia was an independent risk factor for mortality, a study of the effectiveness of supplemental oxygen delivery by oxygen concentrator to correct hypoxaemia in adults with suspected CAP was performed.

Results

In both the systematic review and the prospective cohort the predominant burden of hospitalised CAP was in young (average age 38 and 35, respectively) and HIV-positive (52% and 78%) patients with limited chronic cardiovascular and pulmonary comorbidity. *Streptococcus pneumoniae* (27% and 21%) and *Mycobacterium tuberculosis* (19% and 23%) were the most commonly identified causes. The overall mortality rate for hospitalised patients in the systematic review was 9.5%, but data describing prognostic factors were limited. In the prospective cohort (n=459), death by day 30 occurred in 14.6% and was associated with: male sex (aOR 2.57); pre-presentation symptom duration (aOR 1.11 per day increase); inability to stand (aOR 4.28); heart rate (aOR 1.02 per beat/minute rise); oxygen saturations (aOR 0.95 per % rise); white cell count (aOR 0.91 per 10^9/L rise); haemoglobin (aOR 0.90 per g/dL rise). A newly derived four parameter mortality risk prediction tool based on male sex, oxygen saturations <90%, inability to stand and heart rate ≥125 /min predicted 30-day mortality with reasonable accuracy (area under the receiver-operating curve (AUROC) 0.79) whilst existing tools performed poorly (CURB65: AUROC 0.60; SMRT-CO: AUROC

0.66). Hypoxaemia was corrected in 86.4% (n=59) of adults with suspected CAP with supplemental oxygen at standard flow-rate of 5 litres/minute. Failure to attain normoxaemia was associated with a more than four-fold increase in the risk of death (RR 4.25).

Conclusions

The major burden of hospitalised CAP in low-resource, sub-Saharan African settings is seen in young and HIV-positive adults, many of whom have TB. Extrapolating CAP assessment and treatment algorithms from well-resourced settings where the epidemiology and aetiology of disease is very different is flawed. If validated, locally derived severity assessment tools may provide a rational basis on which to stratify CAP management. Strategies to increase early detection and treatment of TB and to improve supportive care, in particular the correction of hypoxaemia, hold considerable promise for improving CAP outcomes and should be evaluated in clinical trials.

List of abbreviations

AETC	Adult Emergency and Trauma Centre
AFB	Acid-fast bacilli
AHIP	Addressing Hypoxaemia in adult Pneumonia Study
AIDS	Acquired immunodeficiency syndrome
AIR	Acute Infection of the Respiratory Tract Study
aOR	Adjusted odds ratio
ART	Antiretroviral therapy
ATS	American Thoracic Society
AUROC	Area under receiver operating characteristic curve
BAL	Bronchoalveolar lavage;
BASH-FLU	Burden and Severity of HIV-associated Influenza Study
BTS	British Thoracic Society
CAP	Community-acquired pneumonia
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
CMV	Cytomegalovirus
COPD	Chronic obstructive pulmonary disease
CRF	Case report form
CRP	C-reactive protein
CT	Computerised tomography
CURB65	Pneumonia severity assessment tool (see text)
CXCL8	Chemokine (C-X-C motif) ligand 8 (Interleukin 8 (IL8))
CXR	Chest radiograph
DAMP	Damage-associated molecular patterns
ESR	Erythrocyte sedimentation rate
FiO_2	Fraction of inspired oxygen
HAP	Hospital-acquired pneumonia
HDU	High dependency unit
HIV	Human immunodeficiency virus
hMPV	Human metapneumovirus
ICU	Intensive care unit
IDSA	Infectious Diseases Society of America
IF	immunofluorescence
IL1β	Interleukin 1 beta
IL6	Interleukin 6

ILI	Influenza-like illness
IPD	Invasive pneumococcal disease
IQR	Interquartile range
IRVS	Intensive respiratory or vasopressor support
LRTI	Lower respiratory tract infection
LSTM	Liverpool School of Tropical Medicine
LTBI	Latent tuberculosis infection
MARISO	Malawian Adult Lower Respiratory Tract Infection, Severity, Aetiology and Outcome Study
MDR	Multi-drug resistant
MLW	Malawi-Liverpool-Wellcome Trust Clinical Research Programme
MV/VS	Mechanical ventilation/vasopressor support
NIV	Non-invasive ventilation
NTS	Nontyphoidal *Salmonella*
OR	Odds ratio
PAMP	Pathogen-associated molecular patterns
PaO_2	Partial pressure of oxygen in arterial blood
PCP	*Pneumocystis jirovecii* pneumonia
PCR	Polymerase chain reaction
PCT	Procalcitonin
PSI	Pneumonia Severity Index
QECH	Queen Elizabeth Central Hospital
ROC	Receiver operating characteristic
RR	Risk ratio
RSV	Respiratory syncytial virus
SARI	Revere acute respiratory infection
SMART-COP	Pneumonia severity assessment tool (see text)
SpO_2	Peripheral capillary oxygen saturation measured by pulse oximetry
TB	Tuberculosis
TLR	Toll-like receptor
TNFα	Tumour necrosis factor alpha
UK	United Kingdom
US	United States
WBC	White blood cell
V/Q	Ventilation/perfusion
WHO	World Health Organization

Table of contents

List of figures

List of tables

1 Introduction: Community-acquired pneumonia in sub-Saharan Africa.

1.1 Preface and chapter overview

Pneumonia is an inflammatory process of the distal airspaces of the lung caused by infection that typically presents with cough, dyspnoea and fever. The inflammatory exudate that accumulates within the lung parenchyma may cause physical signs that are appreciable on clinical examination and/or is apparent as opacification on a chest radiograph. Left unchecked, the local inflammatory process may compromise gas exchange leading to respiratory failure; systemic spread of infection may result in sepsis and ultimately death. Pneumonia has been recognised for millennia as a common and important human ailment that remains - three-quarters of a century after the advent of modern antimicrobials - a leading cause of morbidity and mortality across the globe. The focus of the work presented in this thesis concerns the assessment and management of community-acquired pneumonia (CAP) in adults in Malawi where it is a leading cause of hospitalisation and death (SanJoaquin *et al.*, 2013).

In this introductory chapter I give an overview of the epidemiology, aetiology and pathogenesis of CAP, and highlight the important differences in the pattern of disease seen in sub-Saharan Africa compared to well-resourced settings, particularly with regard to the impact of HIV. With particular focus on a sub-Saharan African context, I discuss key issues in the management of CAP, namely: diagnosis and classification; microbiological investigation; severity assessment; antimicrobial and supportive treatment. I then provide a brief description of Malawi focusing on the healthcare system, before finally presenting a synopsis of this thesis and describing the key aims and objectives.

1.2 Epidemiology of CAP

1.2.1 Incidence

Globally, pneumonia is the commonest cause of infectious disease related death, the fourth commonest cause of death overall and the second leading cause of years of life lost (Lopez *et al.*, 2006; Lozano *et al.*, 2012). In 2010, it is estimated that lower respiratory tract infection (LRTI) accounted for 2.8 million deaths and the loss of 115 million disability-adjusted life years (Lozano *et al.*, 2012; Murray *et al.*, 2012).

The incidence of CAP in adults rises sharply with age. In Europe the overall incidence is 1.07-1.2 per 1000 person years, but is at least 10-fold higher in adults over 65

(Gutierrez *et al.*, 2006; Singanayagam *et al.*, 2014). This is reflected in hospitalised CAP cohorts where two-thirds of patients are over 65 (Ewig *et al.*, 2009). The rate of rise in CAP incidence accelerates with advancing age (Fry *et al.*, 2005; Millett *et al.*, 2013), such that in the United States, for example, approximately 1 in 20 persons aged 85 years or older will have a new episode of CAP each year (Jackson *et al.*, 2004). The incidence of CAP is increasing rapidly, as the proportion of older adults in the population grows, (Fry *et al.*, 2005; Millett *et al.*, 2013; Trotter *et al.*, 2008). In Portugal, for example, adult pneumonia admissions have increased by 28% in the last decade (Froes *et al.*, 2013).

In sub-Saharan Africa, there are an estimated 4 million episodes of pneumonia each year, resulting in 200,000 deaths (Scott *et al.*, 2012). The annual incidence of LRTI is estimated at 10 episodes per 1000 adults less than 60 years, but is at least several-fold higher in the elderly and HIV infected individuals (Lopez *et al.*, 2006). In Malawi, pneumonia is the commonest reason for adult hospitalisation (SanJoaquin *et al.*, 2013). The demographic structure of African populations and the dramatic impact of HIV are such that, in contrast to well-resourced settings, the predominant burden of pneumonia occurs in working age adults (Scott *et al.*, 2012).

1.2.2 Outcome

The mortality rate of CAP varies markedly with disease severity and treatment setting, ranging from less than 1% to nearly 50% (Welte *et al.*, 2012). Differences in patient demographics and comorbidity profile and clinical practice, particularly in terms of hospitalisation rate and intensive care referral, make direct comparison between cohorts difficult. In community cohorts from well-resourced settings, mortality rates typically range from 0-4% (Welte *et al.*, 2012; Yu *et al.*, 2012). Rates vary widely in hospitalised cohorts; mortality in recently published cohorts in high- and middle-income were: Argentina 13.3% (Isturiz *et al.*, 2010), Australia 5.7% (Charles *et al.*, 2008a), Germany 14.4% (Ewig *et al.*, 2009), United States 8.5% (Yu *et al.*, 2012) and Vietnam 9.8% (Takahashi *et al.*, 2013). In patients admitted to intensive care units, CAP mortality rates often exceed 25% (Welte *et al.*, 2012). Crude mortality rates of adults hospitalised with pneumonia in sub-Saharan Africa are comparable at 7-14%, but the average age of affected patients is typically much lower (Aderaye, 1994a; Onyedum *et al.*, 2011; Scott *et al.*, 2000; Sow *et al.*, 1996; Yone *et al.*, 2012).

Inpatient or 30-day mortality rates substantially underestimate total-pneumonia related mortality. Following apparent clinical resolution, survivors of CAP have an elevated risk of death for at least one year (Koivula *et al.*, 1999; Waterer *et al.*, 2004). In

well-resourced settings up to one-third of hospitalised CAP patients die within one year of hospital discharge (Kaplan *et al.*, 2003). This excess mortality is mainly related to decompensation of underlying comorbid illness, in particular cardiovascular disease (Musher *et al.*, 2007). Following an episode of CAP, hospitalisations for heart failure, acute coronary syndromes and arrhythmias are increased (Corrales-Medina *et al.*, 2011; Jasti *et al.*, 2008) and total cardiovascular mortality is elevated (Koivula *et al.*, 1999).

In long-term survivors, symptomatic recovery following an episode of CAP is surprisingly protracted, taking up to six months for most patients to attain premorbid levels of well-being (El Moussaoui *et al.*, 2006). There are no data on long-term mortality or symptomatic recovery following pneumonia in a sub-Saharan African setting.

1.2.3 Economic burden

CAP imposes a huge economic burden. In Europe, CAP is estimated to cost ~€10.1 billion annually, with inpatient care accounting for €5.7 billion and €3.6 billion in indirect costs from lost working days (Welte *et al.*, 2012). The total economic cost of treating CAP in the US is in excess of $17 billion (File *et al.*, 2010). Direct healthcare expenditure is dominated by inpatient care costs (Colice *et al.*, 2004; Guest *et al.*, 1997; Tichopad *et al.*, 2013); whilst treatment of outpatient episode of CAP is markedly cheaper the indirect costs resulting from sick leave and reduced productivity remain considerable (Scott *et al.*, 2004; Tichopad *et al.*, 2013). Healthcare costs remain elevated for at least two years following an episode of CAP (Thomas *et al.*, 2012). Data describing the overall healthcare costs associated with CAP in sub-Saharan Africa are lacking. At a household level, illness with an inpatient hospital stay may result in considerable – and potentially catastrophic – healthcare expenditure both in terms of out-of-pocket payments and subsequent lost income (Buigut *et al.*, 2015; Chuma *et al.*, 2012). The predominant burden of disease in working age adults in sub-Saharan African settings is likely to have substantial economic impact (Scott *et al.*, 2012).

1.2.4 Risk factors

After age, the dominant risk factors for CAP in well-resourced settings are: male sex (Ewig *et al.*, 2009; Gutierrez *et al.*, 2006); comorbid illness, particularly COPD congestive heart failure, cerebrovascular disease, dementia and diabetes (Almirall *et al.*, 2008; Jackson *et al.*, 2009; Klare *et al.*, 2002; Torres *et al.*, 2013; Welte, 2012; Yende *et al.*, 2013); and smoking (Almirall *et al.*, 1999). Excessive alcohol intake is an important risk factor particularly in middle-aged adults (Fernandez-Sola *et al.*, 1995).

Immunocompromise as a result of corticosteroid or other immunosuppressive medication use, underlying malignant disease or organ transplantation is an important and increasingly common risk factor in elderly patients (Sousa *et al.*, 2013). Even within high resource countries, CAP disproportionately affects the most deprived groups (Millett *et al.*, 2013).

Whilst all of the above are likely to pertain in sub-Saharan Africa, the epidemiology of pneumonia in this region is skewed by the dramatic impact of HIV. HIV infection increases the risk of pneumonia 17-fold (Gilks *et al.*, 1996) and that of pneumococcal bacteraemia up to 100-fold (Feikin *et al.*, 2004). Combination antiretroviral therapy (ART) reduces this risk (Saindou *et al.*, 2008), but pulmonary infections remain a leading cause of morbidity and mortality amongst patients with HIV (Benito *et al.*, 2012). Despite widespread rollout of ART, the burden of hospitalised pneumonia in many sub-Saharan African settings is still predominantly in young, HIV-infected patients (SanJoaquin *et al.*, 2013). Malnutrition, household crowding and exposure to indoor-air pollution from the use of biomass fuel may further contribute to the burden of pneumonia in the region (Almirall *et al.*, 2008; Ezzati *et al.*, 2001; Penner *et al.*, 2003).

1.2.5 Aetiology

A large number of microorganisms, including bacterial, viral and fungal pathogens, can cause CAP. In most well-resourced settings however, the majority of cases are caused by one of the following: *Streptococcus pneumoniae*; *Haemophilus influenzae; Mycoplasma pneumoniae; Chlamydophila pneumoniae*; respiratory viruses; *Legionella pneumophila; Staphylococcus aureus*; *Pseudomonas aeruginosa*; Gram-negative enteric bacilli. The relative frequency of each organism varies with disease severity, patient immune status and prior exposure to healthcare facilities and initial empirical management is adapted in light of these considerations (Charles *et al.*, 2008a; Isturiz *et al.*, 2010; Song *et al.*, 2011; Torres *et al.*, 2014; Welte *et al.*, 2012).

There are also important geographical variations in the aetiological profile of CAP whereby organisms outside the usual spectrum described above predominate locally. In areas of high incidence, *Mycobacterium tuberculosis* is common cause of acute CAP (Chon *et al.*, 2013; Liam *et al.*, 2006; Scott *et al.*, 2000). In South Africa and Taiwan, hypervirulent strains of *Klebsiella pneumoniae* are a common of cause severe bacteraemic CAP (Feldman *et al.*, 1991; Ko *et al.*, 2002; Lin *et al.*, 2010; Yu *et al.*, 2007). *Burkholderia pseudomallei*, the causative agent of melioidosis, is endemic in certain regions in South-East Asia and often presents as an acute pneumonic illness (Peto *et al.*,

2014; Song *et al.*, 2011). In areas of the southern United States, coccidioidomycosis may be account for nearly 30% of acute CAP presentations (Valdivia *et al.*, 2006).

In sub-Saharan Africa where many adults hospitalised with pneumonia are HIV-infected the array of potential pathogens is broadened further still (Benito *et al.*, 2012; SanJoaquin *et al.*, 2013). The available aetiological studies emphasise the importance of *M. tuberculosis* and *S. pneumoniae* as well as non-infective conditions such as pulmonary Kaposi's sarcoma masquerading as pneumonia (Allen, 1984; Hartung *et al.*, 2011; Scott *et al.*, 2000). The frequency of *Pneumocystis jirovecii* – the commonest cause of HIV-related opportunistic infection in well-resourced settings – as a cause of acute CAP in sub-Saharan Africa is unclear but is thought likely to be common (Aderaye *et al.*, 2007; Hartung *et al.*, 2011; Malin *et al.*, 1995; Nyamande *et al.*, 2006; Worodria *et al.*, 2003). There is a need for further studies to describe the aetiology of CAP in the region following the widespread use of co-trimoxazole prophylaxis and ART rollout.

1.3 Pathogenesis of pneumonia

1.3.1 Pathogen invasion and host response

Pneumonia refers to inflammation within the distal airspaces that is the result of infection and is typically characterised by the presence of intra-alveolar consolidation. The exact pathological features and underlying pathophysiological mechanisms vary with the causative organism. This brief discussion will focus on the pathogenesis of bacterial pneumonia, using the response to *S. pneumoniae* as a well-characterised example (van der Poll *et al.*, 2009; Wootton *et al.*, 2014).

Following acquisition by respiratory droplet spread or close contact, *S. pneumoniae* adheres to the upper respiratory tract epithelium to establish carriage within the nasopharynx (Bogaert *et al.*, 2004). In adults, colonisation is typically asymptomatic and usually terminated by adaptive host immune responses without disease (Li *et al.*, 2012; Zhang *et al.*, 2009). Propagation of colonising bacteria to the lower respiratory tract may occur by aspiration but is impeded by basic barrier functions (e.g. mucociliary escalator, airway bifurcations) and secreted bactericidal proteins (e.g. β defensin, lysozyme, lactoferrin) (Arnold *et al.*, 1980; Dajani *et al.*, 2005; Tecle *et al.*, 2010; Wootton *et al.*, 2014). The few bacteria that typically reach the alveolar spaces are phagocytosed by resident alveolar macrophages without activation of inflammatory pathways (Dockrell *et al.*, 2003).

When the number of pneumococci reaching the distal airspaces exceeds the capacity of alveolar macrophages to rapidly clear them, the cascade of inflammatory events that

result in pneumonia is initiated (Dockrell *et al.*, 2003). Rapidly multiplying bacteria release constituents such as lipoteichoic acid and bacterial DNA, so-called pathogen-associated molecular patterns (PAMPs), that activate toll-like receptor (TLR) pathways in macrophages and epithelial cells (Knapp *et al.*, 2008). Concurrently, cellular damage releases hyaluronic acid and host DNA – damage-associated molecular patterns (DAMPs) – that also activate TLR signalling (Jounai *et al.*, 2012). These dual signals trigger a switch in alveolar macrophage phenotype to an activated, pro-inflammatory state with up-regulation of multiple pro-inflammatory genes via NF-κB activation and release of TNFα, IL1β, IL6 and CXCL8 into the local milieu (Bordon *et al.*, 2012; McNeela *et al.*, 2010). Circulating neutrophils up-regulate integrins in response to CXCL8 and migrate to the alveolar space (Kadioglu *et al.*, 2011; Klesney-Tait *et al.*, 2013) Neutrophils phagocytose bacteria initially with complement components (C3b and iC3b) as opsonins and subsequently, as the adaptive immune response develops, via antigen specific immunoglobulin (Brown *et al.*, 2002; Yuste *et al.*, 2008). The intense local inflammatory response may precipitate severe sepsis - a systemic, dysregulated and maladaptive host response to infection that ultimately results in tissue hypoperfusion and organ dysfunction (Stearns-Kurosawa *et al.*, 2011).

If control over invading bacteria is achieved, the inflammatory response is de-escalated to avoid excessive collateral damage to host tissues. Macrophage phenotype switches to support tissue repair and undergo apoptosis and induce neutrophil apoptosis (Aberdein *et al.*, 2013; Dockrell *et al.*, 2003). Macrophage efferocytosis then clears apoptotic neutrophils to allow restoration of normal pulmonary architecture and function (McCubbrey *et al.*, 2013).

1.3.2 Respiratory failure

Gas exchange at the alveolus occurs by diffusion between the air spaces and pulmonary capillaries. Oxygen passes from inspired air, across the alveolar epithelium and capillary wall into the blood where it is largely carried bound to haemoglobin. Carbon dioxide - a highly soluble gas – diffuses freely along its concentration gradient from blood to alveolus (O'Driscoll *et al.*, 2008). In pneumonia, the alveolar airspaces become engorged with inflammatory exudate, reducing ventilation and compromising gas exchange. Auto-regulatory mechanisms within the pulmonary vasculature attempt to redirect blood flow to ventilated areas, but if overcome a ventilation-perfusion mismatch occurs. Since blood oxygen content is limited by haemoglobin concentration, reduced oxygen uptake in one area may not be compensated for by increase uptake in another, a substantial ventilation-perfusion mismatch often results in hypoxaemia (Gea *et al.*, 1991; O'Driscoll *et al.*, 2008).

1.4 Defining, diagnosing and classifying pneumonia

1.4.1 Pneumonia and other lower respiratory tract infections

The term lower respiratory tract infection (LRTI) refers to any infection of the respiratory tract distal to the larynx; it encompasses pneumonia, acute and chronic bronchitis, and acute exacerbations of COPD and bronchiectasis (Woodhead *et al.*, 2011). Whilst each of these specific infections give rise to a similar clinical presentation, differentiation is important since their microbial aetiology and prognosis - and hence treatment requirements - differ markedly.

Distinguishing pneumonia from acute bronchitis is a common diagnostic dilemma. Acute bronchitis, in contrast to pneumonia, is a typically a self-resolving and short-lived illness, for which antimicrobials are generally not effective or recommended (Gonzales *et al.*, 2000; Macfarlane *et al.*, 2001; Smith *et al.*, 2014; Wenzel *et al.*, 2006). Amongst adults presenting with an acute LRTI syndrome in a community setting, acute bronchitis is 20- to 30-times more common than pneumonia (Macfarlane *et al.*, 1993; Metlay *et al.*, 2003). The challenge for clinicians is to accurately identify the relatively infrequent cases of pneumonia, avoiding both delayed treatment initiation and unnecessary antimicrobial use.

1.4.2 Clinical versus radiological diagnosis

At a pathological level, pneumonia is distinguished from the other LRTI syndromes by the presence of alveolar inflammation. Demonstration of a new infiltrate on a chest radiograph is typically used as a proxy of alveolar inflammation and, in the context of a compatible clinical presentation, is the widely accepted diagnostic standard for pneumonia (Lim *et al.*, 2009; Mandell *et al.*, 2007; Metlay *et al.*, 2003; Woodhead *et al.*, 2011).

Radiographic pneumonia as defined by a plain chest radiograph, however, has important limitations as a diagnostic reference standard. Firstly, plain chest radiography has limited sensitivty. Computerised tomography (CT) scanning reveals pneumonic changes in 33-50% more patients with clinical pneumonia than plain chest radiograph (Claessens *et al.*, 2015; Syrjala *et al.*, 1998). The development of radiographic changes may lag behind clinical features and may alter with hydration status (Hagaman *et al.*, 2009; Hash *et al.*, 2000). Secondly, inter-observer agreement for the recognition of consolidation is only moderate at best, and for patients with underlying chronic lung disease is poor (Albaum *et al.*, 1996; Hopstaken *et al.*, 2004). Thirdly, confirmation of radiographic pneumonia does not necessarily usefully guide treatment decisions since it does not reliably distinguish between bacterial and viral

aetiologies (Graffelman *et al.*, 2008). In a recent cohort of US CAP patients with radiographic pneumonia, an isolated viral infection accounted for more than half of the cases in which an aetiology was determined (Jain *et al.*, 2015).

Many studies have unsuccessfully attempted to define a combination of clinical features that accurately and consistently identifies individuals with radiographic pneumonia (Metlay *et al.*, 1997). Auscultatory findings in isolation have poor diagnostic precision and high inter-observer variation (Hopstaken *et al.*, 2003; Melbye *et al.*, 1992; Wipf *et al.*, 1999). Specific symptoms such as lateral chest pain and severe dyspnoea have good specificity for pneumonia, but lack sensitivity (Melbye *et al.*, 1992). In community studies of adults with presumed LRTI, only around one-third of those with pneumonia will be identified on clinical assessment (van Vugt *et al.*, 2013; Woodhead *et al.*, 1987). Although studies of patients presenting to hospital emergency departments indicate the absence of any vital sign abnormality (tachycardia, fever, tachypnoea and hypoxaemia) excludes pneumonia with reasonable sensitivity (Khalil *et al.*, 2007; Nolt *et al.*, 2007; O'Brien *et al.*, 2006).

Despite the limitations of clinical diagnosis, many patients with suspected CAP are managed in community settings without a chest radiograph. The presence of focal signs and/or systemic features is used as an indicator of pneumonia, hence the need for antimicrobial treatment. British pneumonia guidelines advocate starting antibiotic treatment on the basis of a clinical diagnosis for patients with mild severity disease not requiring hospitalisation (Lim *et al.*, 2009). US pneumonia guidelines recommend routine chest radiography for all adult patients with suspected CAP (Mandell *et al.*, 2007).

1.4.3 Inflammatory biomarkers for CAP diagnosis

Inflammatory biomarkers may serve as a useful adjunct to clinical assessment. Combining values of procalcitonin (PCT) or C-reactive protein (CRP) with a standard clinical assessment improves accuracy for diagnosing radiographic CAP (Muller *et al.*, 2007). These markers may also be used to define the need for antibacterial therapy. Using a PCT-guided treatment algorithm, Christ-Crain *et al.* demonstrated that antibacterial use may safely be reduced amongst patients presenting to hospital with LRTI (Christ-Crain *et al.*, 2004; Schuetz *et al.*, 2009). In radiographic CAP specifically, antibacterial therapy may be withheld or substantially shortened on the basis of low PCT levels (Christ-Crain *et al.*, 2006).

1.4.4 Diagnostic considerations in sub-Saharan Africa

In sub-Saharan Africa, limitations in the availability of both adequately trained clinicians and diagnostic facilities further compound the problems associated with pneumonia diagnosis. In community settings, initial patient assessment will be made by lay-providers or first level health care workers who may, for example, not have been trained to perform chest auscultation (World Health Organization, 2009). Chest radiography would be reserved for patients requiring hospitalisation, but even then might be delayed or deliberately restricted for those failing to respond to treatment. WHO treatment guidelines indicate that in adults that present with cough or difficulty in breathing the diagnosis of pneumonia is made on the basis of fever, tachypnoea or chest pain (World Health Organization, 2009, 2011c).

In high prevalence settings, the influence of HIV on pneumonia aetiology and presentation will also be relevant to the diagnostic approach. For some pathogens, notably *M. tuberculosis*, HIV infection alters the characteristic radiographic appearances of pulmonary infection (Dawson *et al.*, 2010). For opportunistic pathogens such as *Pneumocystis*, the radiographic features may be subtle and not readily appreciated on plain chest radiograph (Richards *et al.*, 1996). PCT and CRP identify severe bacterial infection in children with reasonable accuracy (area under receiver-operating characteristic curve (AUROC) 0.81 and 0.86, respectively) and may help to distinguish bacterial from viral pneumonia (Carrol *et al.*, 2009; Diez-Padrisa *et al.*, 2010). In adults with radiographic CAP, PCT levels in bacterial CAP are approximately 5 times higher that for tuberculosis (TB) and 19 times higher that for *Pneumocystis jirovecii* pneumonia (PCP) (Cilloniz *et al.*, 2014; Nyamande *et al.*, 2006; Schleicher *et al.*, 2005), but there are no data examining the ability of inflammatory biomarkers to safely define antimicrobial therapy in Africa.

1.4.5 Pneumonia classification

If otherwise unspecified, a diagnostic label of 'pneumonia' is too imprecise to be clinically useful since the array of potentially causative organisms is very broad. Pneumonia is therefore classified on the basis of patient characteristics and clinical features in order to narrow the spectrum of likely pathogens and direct initial empirical treatment (Ewig, 2014). Pneumonia is typically classified on the basis of presumed site of pathogen acquisition as community-acquired pneumonia (CAP) or hospital-acquired pneumonia (HAP)(National Clinical Guideline Centre, 2014). This simple distinction usefully directs clinical management since the pathogens commonly implicated in CAP and HAP differ markedly (American Thoracic Society, 2005; Jain *et al.*, 2015; Torres *et al.*, 2014; Welte *et al.*, 2012). Pneumonia in immunocompromised patients, including in

HIV-positive patients, is generally considered separately (Lim *et al.*, 2009; National Clinical Guideline Centre, 2014). This so-called 'pneumonia triad' of CAP, HAP and pneumonia in the immunocompromised has formed the framework for studies and pneumonia management guidelines in well-resourced settings (Ewig, 2014; Lim *et al.*, 2009; Mandell *et al.*, 2007; National Clinical Guideline Centre, 2014).

1.4.6 Classification considerations in sub-Saharan Africa

In sub-Saharan Africa, the impact of HIV means that managing CAP in immunocompromised host is a daily reality. The challenge for pneumonia management guidelines in these settings is to appropriately direct care, but to do so with recourse to limited diagnostic laboratory facilities (World Health Organization, 2011c). The current South African guidelines advocate using a radiological classification scheme that divides patients into focal and diffuse pneumonic changes (Feldman *et al.*, 2007a). Giving the limitations of chest radiography discussed above (Claessens *et al.*, 2015; Nyamande *et al.*, 2007b), this might not be the most useful approach and alternative parameters such as CD4 count, ART use and duration of symptoms might be more appropriate (Benito *et al.*, 2012).

1.4.7 CAP and TB

M. tuberculosis is commonly identified amongst adults presenting with CAP in sub-Saharan Africa (Nyamande *et al.*, 2007a; Scott *et al.*, 2000). The terminology used to describe this group of patients is inconsistent: some authors distinguish TB from CAP (Aderaye, 1994a; Koulla-Shiro *et al.*, 1997; Sow *et al.*, 1996); others identify TB as a cause of non-responding pneumonia (Aderaye *et al.*, 2007; Malin *et al.*, 1995; Worodria *et al.*, 2003); whilst others report TB as a cause of CAP without further distinction (Albrich *et al.*, 2014b; Fiberesima *et al.*, 2007; Scott *et al.*, 2000).

Pulmonary TB may arise as a result of progressive disease following recent acquisition of infection or reactivation of latent infection (Dheda *et al.*, 2016; Getahun *et al.*, 2015). For TB arising from reactivation of latent infection, the community-acquired paradigm breaks down, however it can still cause an acute respiratory presentation compatible with the time-course of CAP due to other aetiologies (Fiberesima *et al.*, 2007; Scott *et al.*, 2000). In this sense it is reasonable to attribute causation of 'CAP' to *M. tuberculosis*.

1.5 CAP in the context of HIV

1.5.1 Epidemiology of respiratory infection in HIV

Respiratory infections are a leading cause of morbidity and mortality and one of the most frequent causes of hospitalisation in patients living with HIV (Benito *et al.*, 2012). In the pre-ART era, the incidence of CAP was 35-fold higher in HIV-infected individuals (Segal *et al.*, 2011). Use of ART and co-trimoxazole preventative therapy markedly reduces, but does not abolish, the excess risk. Respiratory infections continue to be a major burden of illness in patient groups with limited access to health services (Segal *et al.*, 2011). The impact of HIV status on acute CAP mortality is however unclear. Two international observational studies indicated no overall impact on CAP outcome (Christensen *et al.*, 2005; Malinis *et al.*, 2010). In bacteraemic pneumococcal CAP, HIV infection with reduced CD4 count was associated with increased mortality (Feldman *et al.*, 2007b).

Whilst HIV infection probably increases susceptibility to respiratory infection generally (Feikin *et al.*, 2004; Hirschtick *et al.*, 1995), the reported impact of HIV on the incidence of *Streptococcus pneumoniae*, TB and PCP is most dramatic and thoroughly described (DeRiemer *et al.*, 2007; Gilks *et al.*, 1996; Munoz *et al.*, 1993; Sonnenberg *et al.*, 2005).

1.5.1.1 Streptococcus pneumoniae

Streptococcus pneumoniae is the commonest cause of bacterial pneumonia in HIV-positive adults (Cilloniz *et al.*, 2014). In the pre-ART era, the incidence of pneumococcal pneumonia was increased 20-fold and that of invasive pneumococcal disease (IPD) by as much as 100-fold (Feikin *et al.*, 2004; Hirschtick *et al.*, 1995).

1.5.1.2 Mycobacterial pathogens

TB is the most important HIV-associated opportunistic infection globally and is the leading cause of HIV-associated mortality accounting for approximately 25% of such deaths (Lawn *et al.*, 2013b). In low-endemicity settings, most cases are due to reactivation of latent TB infection (LTBI) where the risk of developing TB is inversely proportional to CD4 cell count and remains elevated compared to HIV-negative patients even at CD4 counts up to 500 (Lawn *et al.*, 2009). ART curtails the risk of progression from LTBI, but even with robust immune recovery the risk of TB remains elevated (Girardi *et al.*, 2005; Lawn *et al.*, 2005).

1.5.1.3 *Pneumocystis jirovecii* pneumonia

The overall incidence of *Pneumocystis jirovecii* (formerly *P. carinii*) pneumonia (PCP) amongst patients with HIV living in well-resourced settings has fallen dramatically with the availability of effective ART (Furrer *et al.*, 1999; Moore *et al.*, 1999). However, it remains the commonest opportunistic infection in individuals with advanced HIV at presentation (Benito *et al.*, 2012; Cilloniz *et al.*, 2014; Serraino *et al.*, 2003). Despite being a ubiquitous organism, historically the reported burden of PCP in HIV-infected populations in sub-Saharan Africa has been by contrast low (Abouya *et al.*, 1992; Batungwanayo *et al.*, 1994; Fisk *et al.*, 2003; Wasserman *et al.*, 2013). This may in part be attributable to early mortality due to more virulent infections, but under-ascertainment due to lack of access to sensitive diagnostic tests is also likely (Atzori *et al.*, 1993; Lowe *et al.*, 2013). Recent bronchoscopy studies from African centres have demonstrated a considerable burden of PCP amongst HIV-infected patients with features of respiratory infection (Aderaye *et al.*, 2007; Hargreaves *et al.*, 2001; Hartung *et al.*, 2011; Malin *et al.*, 1995; Nyamande *et al.*, 2006; Worodria *et al.*, 2003).

1.5.2 Mechanisms of immunocompromise

Pneumonia occurs when pulmonary defence mechanisms are overwhelmed and invading microorganisms proliferate within the lung parenchyma. In immunocompetent patients, despite continual exposure of the upper respiratory tract to potentially pathogenic organisms, pneumonia is actually an infrequent occurrence owing to the effectiveness of the intricate system of host defence mechanisms present (see section 1.3.1)(Wootton *et al.*, 2014). Infections that established latency such as tuberculosis are held in check by an effective cellular immune response (Getahun *et al.*, 2015).

HIV infection is characterised by a combination of immune suppression and chronic inflammation that results in immune exhaustion and multiple defects that compromise the pulmonary response to infection (Huson *et al.*, 2015). Even in early, asymptomatic infection when peripheral blood CD4 cell counts are maintained, persistent inflammation at the respiratory mucosal surfaces, preferentially depletes mucosal lymphocytes and increases susceptibility to pathogen colonisation and ingress (Glennie *et al.*, 2011; Sepako *et al.*, 2014). Alveolar macrophage phagocytic and pathogen lysis function is impaired (Jambo *et al.*, 2014b). In addition macrophage pro-inflammatory cytokine response to infection is attenuated, in particular CXCL8 production is reduced leading to impaired neutrophil recruitment (Gordon *et al.*, 2005). Antigen-specific cellular and humoral responses against *S. pneumoniae*, *M. tuberculosis* and influenza are

also impaired and only partially restored by ART (Eagan *et al.*, 2007; Jambo *et al.*, 2014a; Jambo *et al.*, 2011; Sepako *et al.*, 2014).

1.5.3 Clinical assessment and management

The rational approach to managing pneumonia in HIV-infected patients depends upon the degree of immunosuppression. This is reasonably assessed by the peripheral CD4 cell count, since the sequence of pulmonary complications parallels the depletion of CD4 cells (Hirschtick *et al.*, 1995). Increasingly general CAP studies are including HIV-positive patients established on ART with well-preserved CD4 counts (Jain *et al.*, 2015).

In patients with advanced HIV, the assessment of apparent CAP is complicated by the broad array of pathogens potentially implicated. There are no evidence-based algorithms that define the best sequence of investigations to achieve an aetiological diagnosis (Figure 1.1). The radiological appearance (diffuse versus focal infiltrates) is frequently used to guide initial management and direct investigations, although the relatively lack of sensitivity of plain chest radiograph in immunocompromised patients should be considered (Feldman *et al.*, 2007a; Nyamande *et al.*, 2007b). Reported dyspnoea and hypoxaemia may also indicate PCP in favour of other aetiologies (Hargreaves *et al.*, 2001; Malin *et al.*, 1995). Substantially elevated inflammatory biomarker levels (i.e. PCT or CRP) are suggestive of bacterial CAP over PCP or TB (Cilloniz *et al.*, 2014; Nyamande *et al.*, 2006; Schleicher *et al.*, 2005). In highly immunocompromised patients, early bronchoscopy for diagnostic sampling is often recommended in well-resourced settings, particularly if response to empirical treatment is inadequate (Benito *et al.*, 2012).

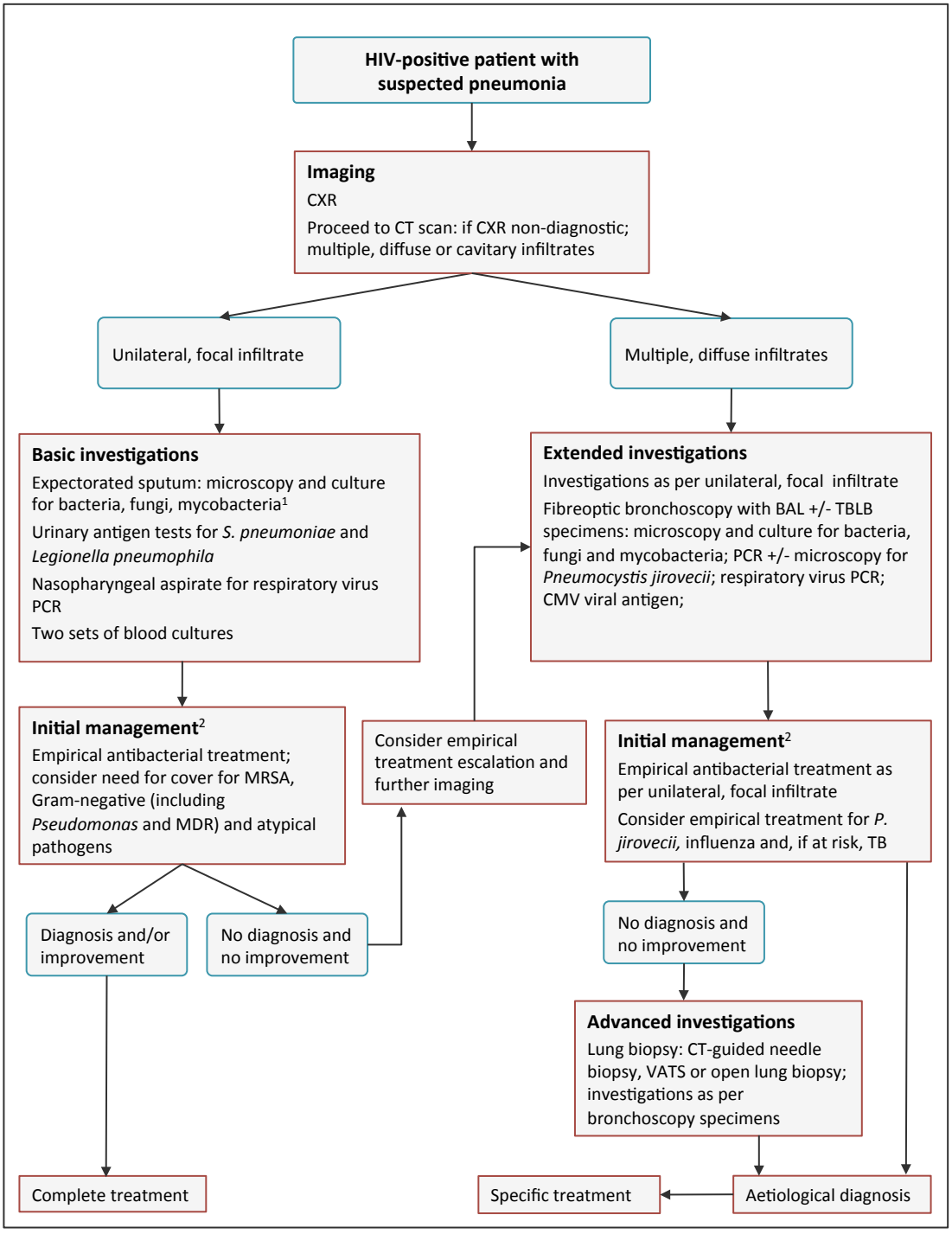

Figure 1.1 Diagnostic algorithm of pneumonia in HIV-infected patients in well-resourced setting. Adapted from (Benito et al., 2012).

CXR, chest radiograph; CT, computerised tomography; PCR, polymerase chain reaction; BAL, bronchoalveolar lavage; TBLB, transbronchial lung biopsy; CMV, cytomegalovirus; MRSA, methicillin resistant *Staphylococcus aureus*; MDR, multi-drug resistant; VATS, video-assisted thoracoscopic surgery

[1] Proceed to induced sputum for microscopy and culture for mycobacteria if standard sputum unavailable.

[2] Rationalised in light of investigations.

1.6 Establishing aetiological diagnosis in CAP

CAP may be caused by a broad array of pathogens. In well-resourced settings, the spectrum of potential pathogens is generally well defined and empirical treatment algorithms are devised to reliably provide adequate antimicrobial cover (Lim *et al.*, 2009). In clinical practice the use of extensive aetiological diagnostic tests is reserved for patients with severe disease or those that are failing to improve where the result of the test is likely to influence management. Although, even with extensive testing using multiple different assays, the aetiology of CAP may be established in fewer than half of patients (Jain *et al.*, 2015).

1.6.1 Standard bacteriological methods

Obtaining adequate specimens from the site of infection in pneumonia is often unachievable. Instead diagnosis by standard bacteriological methods is usually based on blood and expectorated sputum. Blood culture is highly specific, but has limited sensitivity particularly in patients that have already received antimicrobial treatment. Rates of bacteraemia as low as 6-7% have been reported in recent cohorts of hospitalised CAP (Charles *et al.*, 2008a; Jain *et al.*, 2015). In practice, blood cultures should restricted to patients with high severity illness, in whom they are likely to have a higher yield and also to influence management (Waterer *et al.*, 2001c).

Microscopy and culture of expectorated sputum specimens offer the potential of specific aetiological diagnosis. However, specimens are frequently contaminated by upper airway commensal organisms, many of which themselves are potential agents of CAP. Pre-treatment specimen collection, rapid processing and screening by microscopy to assess specimen adequacy may help (Bartlett, 2011). Alternative methods to obtain lower respiratory tract specimens such as induced sputum, bronchoscopy and transthoracic needle aspiration offer improved diagnostic yields but are invasive and are rarely performed in non-immunocompromised CAP patients that respond adequately to empirical treatment (Bartlett, 2011).

1.6.2 Serological assays

Serological assays were previously the mainstay of conventional diagnosis for *Legionella*, *Mycoplasma pneumoniae*, *Chlamydophila* spp. and respiratory viral pathogens in CAP. There was large selection of different assays available with variable diagnostic performance, but all with the intrinsic limitation of delayed diagnosis because of the requirement to demonstrate rising antibody titre in a convalescent specimen(Waterer *et al.*, 2001a). With the increasing availability specific molecular

diagnostics tests for atypical bacterial and viral pathogens, use of serological assays is declining (Jain *et al.*, 2015; Johansson *et al.*, 2010; Lim *et al.*, 2009).

1.6.3 Rapid diagnostic antigen based tests

The Alere BinaxNOW *Streptococcus pneumoniae* antigen card (BinaxNOW-SP) is a point-of-care immunochromatographic test that detects pneumococcal C-polysaccharide coat protein in urine (Kobashi *et al.*, 2007). Sensitivity and specificity for the diagnosis of pneumococcal pneumonia in adults are 74% and 97%, respectively (Sinclair *et al.*, 2013). In practice, when used in conjunction with classical microbiological methods, it gives an incremental improvement of around 13% for detection of pneumococcal pneumonia (Kobashi *et al.*, 2007). It has poor specificity in children owing to high rates of asymptomatic nasal carriage of *S. pneumoniae* (Adegbola *et al.*, 2001). The limited available data in adults indicate that specificity of BinaxNOW-SP is not affected by nasopharyngeal colonisation (Turner *et al.*, 2011). However, the impact of concurrent HIV infection and colonisation density has not been analysed.

An analogous urine antigen test is now widely used for the diagnosis of *Legionella*. The Alere BinaxNOW *Legionella* urinary antigen card has sensitivity of 80% and specificity of 99% for the detection of *L. pneumophila* serogroup 1 infection (Den Boer *et al.*, 2004; Helbig *et al.*, 2001). It is important to appreciate that infection with other serogroups or *Legionella* species will not be detected. However, more than 90% of *Legionella* infections are caused by *Legionella pneumophila* and amongst these over 80% are caused by serogroup 1 strains (Diederen *et al.*, 2006).

1.6.4 Molecular tests for atypical bacteria and viruses

Molecular assays based on multiplex polymerase chain reaction (PCR) have become the standard modality for determining the presence of *Mycoplasma pneumoniae*, *Chlamydophila* spp. and respiratory viral pathogens in CAP. A variety of different PCR platforms are available. For *Mycoplasma pneumoniae* and *Chlamydophila* spp., use of sputum specimens rather than nasopharyngeal or oral swabs is superior (Cho *et al.*, 2012). For most respiratory viral pathogens, detection is superior in nasopharyngeal specimens. Use of PCR assays gives an incremental improvement in sensitivity over standard techniques of approximately 50% for *M. pneumoniae* and respiratory viruses (Johansson *et al.*, 2010). Although definitively ascribing aetiological significance is often difficult since asymptomatic nasopharyngeal colonisation is well recognised for many respiratory viruses (Feikin *et al.*, 2012; Jain *et al.*, 2015; Pretorius *et al.*, 2012).

1.6.5 Diagnostic tests for TB

The gold-standard diagnostic test for pulmonary TB is the culture of pathogen from a respiratory tract specimen. Automated liquid-based culture techniques have improved the speed and sensitivity of culture, but still the delay to results is up to three weeks and too long to form the basis of acute treatment decisions (Cruciani *et al.*, 2004). Until recently, smear microscopy and chest radiography were the mainstay investigations for the acute diagnosis of TB. In HIV-associated TB, however, approximately only a third of cases are smear-positive and many have only very subtle changes on radiographs (Perlman *et al.*, 1997; Steingart *et al.*, 2006).

The last decade has seen renewed momentum in the area of TB diagnostics with several new assays being developed (Lawn *et al.*, 2013c; McNerney *et al.*, 2011). The Cepheid Xpert MTB/RIF platform is the single-most important recent advance. This fully integrated and automated diagnostics platform is capable of identifying *Mycobacterium tuberculosis* complex and the presence of mutations conferring rifampicin resistance in unprocessed sputum specimens in less than two hours (Lawn, 2013; Steingart *et al.*, 2013). Following WHO endorsement in 2010 the Xpert MTB/RIF platform has been rolled-out to many low- and middle-income countries where it is frequently the central pillar of TB diagnostics (Lawn *et al.*, 2013c; World Health Organization, 2014c). Compared to sputum culture, Xpert MTB/RIF has an overall sensitivity of 88% and specificity of 98%. The estimated sensitivity for smear-positive and smear-negative subgroups was 98% and 67%, respectively (Steingart *et al.*, 2013). The reported sensitivity of Xpert MTB/RIF in HIV-associated TB ranges between 58% and 92% (median 84%), but consistently gives a median increment in sensitivity over smear microscopy of approximately 30% (Lawn *et al.*, 2013c).

1.6.6 Diagnostic tests for PCP

Historically, definitive diagnosis of PCP has relied on direct visualisation of *Pneumocystis* organisms of bronchoalveolar lavage fluid and transbronchial tissue biopsy specimens. In recent years, molecular assays have begun to supersede direct visualisation techniques for the detection of *Pneumocystis jirovecii* (Durand-Joly *et al.*, 2005). The improved sensitivity of molecular assays based on PCR may permit the use of non-invasive specimens (where *Pneumocystis* organisms are present in lower concentrations) such as expectorated sputum (Cruciani *et al.*, 2002), nasopharyngeal aspirates (To *et al.*, 2013) and oral washes (Larsen *et al.*, 2004) for the diagnosis of PCP. However, all current PCP diagnostic assays are reliant on a robust laboratory infrastructure that is lacking in many low-resource, high HIV-burden settings.

1.6.7 Diagnostic approach in sub-Saharan Africa

The difficulties of managing CAP in HIV-infected patients were discussed in section 1.4.4. The additional challenge in low-resource settings is to manage this complicated group of patients with weak or limited diagnostic microbiology laboratory capabilities (World Health Organization, 2011c). The optimal diagnostic strategy in this setting is unclear and warrants further research. The use of point-of-care and other rapid diagnostic tests that require minimal laboratory infrastructure to perform may provide a feasible adjunct to guide the management of pneumonia in low-resource settings (Aston, 2014; Lawn, 2012; Zar *et al.*, 2013).

1.7 CAP outcomes and therapeutic endpoints

1.7.1 Overview

The outcome of CAP has often been described simply as the proportion of patients that die within a defined period. Whilst mortality is a highly relevant and objective outcome metric, since most patients with CAP do not die it does not provide any information on the clinical course of the majority of patients. Various attempts have been made to better conceptualise clinical outcomes in patients with CAP following the initiation of treatment. Broadly speaking, patients can get better – either quickly or slowly (i.e. early clinical stability or delayed clinical stability), get worse – either quickly or slowly (i.e. early or late clinical failure), or remain largely unchanged (i.e. non-responding pneumonia) (Aliberti *et al.*, 2014b; Wiemken *et al.*, 2013).

Early categorisations of treatment non-response aimed to group patients into distinct clinical phenotypes for which a list of most likely causes could be defined and thus provide clinicians with a framework to approach further diagnosis and management. The terms used were descriptive and relied heavily on radiographic changes. For example, delayed clinical and/or radiographic improvement was termed 'slowly resolving pneumonia,' persistent radiographic infiltrates as 'non-resolving pneumonia' and rapid clinical deterioration as 'progressive pneumonia' (Arancibia *et al.*, 2000).

More recent studies have sought to define early clinical endpoints that are more objective and reproducible, typically based on physiological criteria, and the attainment of which is prognostically significant, in that they themselves reflect a meaningful endpoint (e.g. mechanical ventilation) or are predictive of long-term outcome (e.g. death) (Barlow *et al.*, 2003). Increasingly surrogate endpoints such as attainment (or lack of attainment) of clinical stability or clinical failure are being used as the primary outcomes in CAP clinical trials since they permit detection of treatment effect in a study

population much smaller than that which would be required to detect differences in mortality (Garin *et al.*, 2014; Torres *et al.*, 2015).

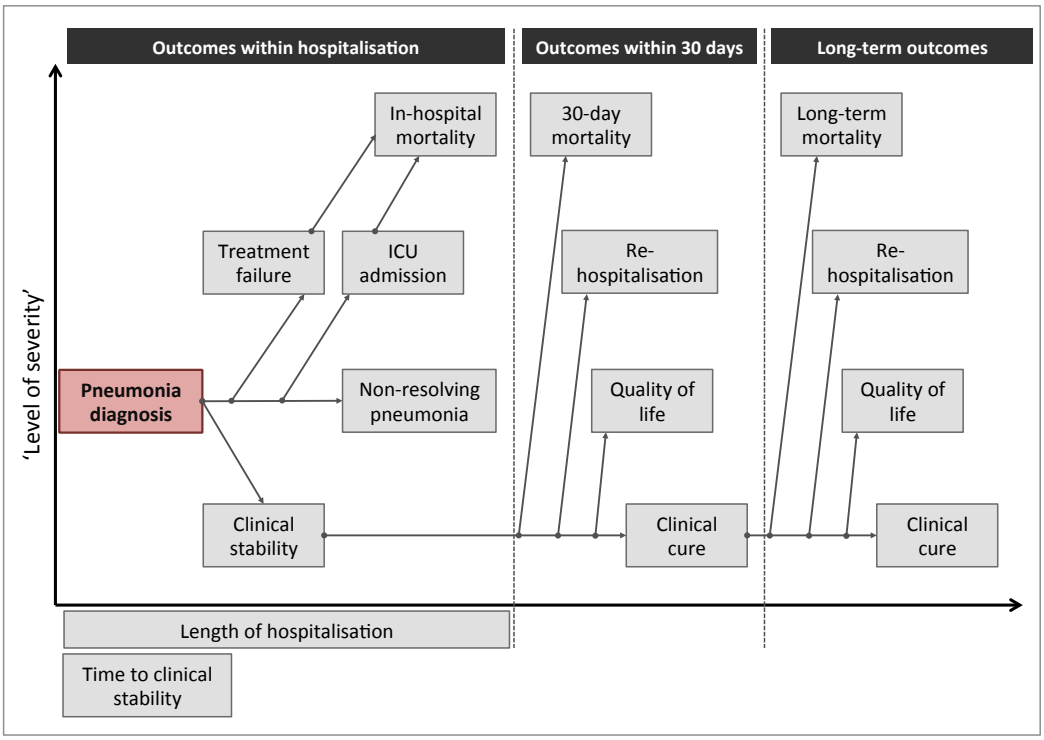

Figure 1.2 Chronology of outcomes for hospitalised patients with CAP.
Adapted from (Wiemken et al., 2013).

1.7.2 Mortality endpoints

Mortality data are usually readily obtainable and provide an objective measure of pneumonia outcome. Mortality at day 30 post diagnosis is the most commonly used time-point and is the outcome upon which many of the most widely recommended pneumonia severity assessment tools are based (Fine *et al.*, 1997a; Lim *et al.*, 2003). In-hospital mortality data may be more easily obtainable in some settings and approximates 30-day mortality but clearly misses early post-discharge mortality.

These relatively short-term outcomes arguably underestimate that true impact of CAP. Multiple studies have highlighted the excess mortality amongst short-term CAP survivors that persists for several years. The crude mortality rate at 5 years following an episode of CAP may be as high as 50% in apparent CAP survivors (Kaplan *et al.*, 2003; Koivula *et al.*, 1999; Restrepo *et al.*, 2013; Waterer *et al.*, 2004).

Only around half of deaths in the 3-months following an episode of pneumonia are directly attributable to pneumonia (i.e. due to respiratory failure, severe sepsis). Most of the remainder are attributable to complications of underlying comorbid illness. The

majority of pneumonia-related deaths occur within the first 30 days, whilst most unrelated deaths occur later (Mortensen *et al.*, 2002).

1.7.3 Treatment failure and related endpoints

Deterioration following the initiation of treatment - termed either treatment failure or clinical failure - occurs in 8-33% of hospitalised CAP patients (Aliberti *et al.*, 2008; Genne *et al.*, 2006; Hoogewerf *et al.*, 2006; Martin-Loeches *et al.*, 2014; Menendez *et al.*, 2004b; Roson *et al.*, 2004). Some authors distinguish treatment failure and clinical failure, using the former to refer to a presumed lack of response to antimicrobial therapy and the latter to describe clinical deterioration regardless of the underlying cause (e.g. treatment failure, super-imposed infection, exacerbation of comorbid condition) (Aliberti *et al.*, 2014b). However, this distinction is not consistently made and treatment failure is the more widely used term. Even after adjustment for baseline disease severity, treatment failure is strongly associated with an increased risk of further complications, prolonged hospital stay and subsequent death (Aliberti *et al.*, 2008; Hoogewerf *et al.*, 2006; Menendez *et al.*, 2004b; Roson *et al.*, 2004). Identified risk factors for treatment failure include: age, comorbid illness, raised inflammatory cytokines, high initial disease severity, infection with specific pathogens (e.g. *Legionella* and Gram-negative bacteria) and discordant antimicrobial therapy (Martin-Loeches *et al.*, 2014; Menendez *et al.*, 2008; Menendez *et al.*, 2004b; Roson *et al.*, 2004).

Several different definitions of treatment failure of varying complexity have been used (Table 1.1). Most are largely based on physiological variables to indicate the development of respiratory failure and/or haemodynamic instability. Most definitions categorise as treatment failure as early or late depending if it occurs within or beyond 72 hours of treatment initiation, respectively.

Several authors have attempted to define and categorise the causes of treatment failure (Aliberti *et al.*, 2008; Genne *et al.*, 2006; Menendez *et al.*, 2004b; Roson *et al.*, 2004). Broadly, early treatment failure is often directly pneumonia-related and commonly due to progressive respiratory failure and/or severe sepsis; nosocomial infection and other iatrogenic complications (e.g. drug toxicities) are common causes of late treatment failure; acute cardiovascular events, in particular acute heart failure, myocardial infarction, arrhythmia and pulmonary embolism are common throughout (Corrales-Medina *et al.*, 2011). In practice, it is often difficult to determine the cause of treatment failure and multiple simultaneous mechanisms may be implicated (Aliberti *et al.*, 2014b; Genne *et al.*, 2003).

Rather than using explicit treatment failure criteria, some studies have simply used admission to an intensive care unit (ICU) as an endpoint to describe severe pneumonia. However ICU admission practices vary widely between countries and institutions. Actual receipt of (or requirement for) intensive respiratory or vasopressor support is a more objective marker of CAP severity that may be more generalisable across settings (Charles *et al.*, 2008b).

1.7.4 Clinical stability and related endpoints

Attainment of clinical stability was initially proposed as a pragmatic clinical endpoint that could usefully guide management decisions in hospitalised CAP patients such as timing of switch from intravenous to oral antibiotics and timing of discharge from hospital (Akram *et al.*, 2013; Mandell *et al.*, 2007; Niederman *et al.*, 2001). Several definitions of clinical stability have been proposed with varying emphasis on symptomatic improvement, physiological observations and laboratory parameters (Table 1.2). Although varying slightly with the definition used, median time to clinical stability ranges from 2 to 4 days and is related to initial severity of pneumonia, presence of comorbid illness and antimicrobial regimen (Halm *et al.*, 1998; Menendez *et al.*, 2004a; Ramirez *et al.*, 1995).

Several prospective validation studies have confirmed the prognostic significance of clinical stability indicating that it may be a suitable surrogate endpoint in CAP trials, particularly in patient groups where the risk of mortality is low. Once clinical stability is attained, the risk of in-hospital mortality or deterioration requiring intensive care input is very low – generally less than 1% (Akram *et al.*, 2013; Aliberti *et al.*, 2013; Halm *et al.*, 1998). Although delayed attainment (i.e. greater than 3 days) is also associated with subsequent readmission or death (Aliberti *et al.*, 2011). Patients discharged from hospital without attaining clinical stability have substantially higher rates of death or readmission (Halm *et al.*, 2002).

Simple process of care variables such as time to intravenous to oral antimicrobial switch have been used to describe treatment response in hospitalised CAP patients, but interpretation is hampered by marked regional and individual differences in clinical practice. Length of hospitalisation similarly will vary with differences in style of practice, as well as with bed pressures and the availability of social care services. This limits its usefulness as an outcome to either describe the severity of CAP or evaluate the effectiveness of a treatment intervention (Barlow *et al.*, 2003)

Table 1.1 Definitions of treatment and clinical failure in CAP.

Reference	Endpoint	Definition
(Arancibia *et al.*, 2000)	Non-responding pneumonia	Persisting fever >38°C and/or clinical symptoms (malaise, cough, expectoration, dyspnea) after at least 72 hrs of antimicrobial treatment.
	Progressive pneumonia	Clinical deterioration with the development of acute respiratory failure requiring ventilatory support and/or septic shock after at least 72 hrs of antimicrobial treatment.
(Menendez *et al.*, 2004b)	Early treatment failure	Clinical deterioration within 72 hrs of treatment with one or more of: haemodynamic instability, respiratory failure, need for mechanical ventilation, radiographic progression, or the appearance of new metastatic infectious foci.
	Late treatment failure	Persistence/reappearance of fever and symptoms or haemodynamic instability, respiratory failure (PaO_2 <8 kPa or SpO_2 <90% when not receiving supplemental oxygen), radiographic progression, or the appearance of new infectious foci after 72 hrs of antimicrobial treatment.
(Roson *et al.*, 2004)	Early failure	Lack of response or worsening of clinical and/or radiologic status at 48 to 72 hrs, requiring either changes in antibiotic therapy and/or performance of invasive procedures for diagnostic and therapeutic purposes, including mechanical ventilation and chest tube drainage.
	Progressive respiratory failure	Increasing oxygen requirements or the necessity of mechanical ventilation during follow-up.
(Genne *et al.*, 2006)	Treatment failure	Any one of the following: fever for >3 days (or >6 days in bacteraemic pneumonia) with clinical deterioration (worsening of dyspnea with decrease of PaO_2 and/or increase of leucocyte count); clinical deterioration necessitating a change in the initial antibiotic therapy on the basis of the results of microbiological culture (concordant therapy) or the occurrence of a severe side effect (i.e. renal insufficiency, hepatic toxicity); death occurring after at least 48 h of antibiotic treatment.
(Hoogewerf *et al.*, 2006)	Early clinical failure	Assessed after 3 days and defined as: death; need for mechanical ventilation; respiratory rate >25/min; SpO_2 <90% or PaO_2 <55mm Hg; haemodynamic instability; altered mental state; fever (<1°C decline in temperature if >38.5°C on admission).

Reference	Endpoint	Definition
(Aliberti *et al.*, 2008)	Clinical failure	Occurrence of any of the following after initial stabilization: acute pulmonary deterioration requiring either invasive or noninvasive mechanical ventilation; acute haemodynamic deterioration with the need for aggressive fluid resuscitation (>40 mL/kg colloids or crystalloids), vasopressors, or invasive procedures (e.g. pericardial drainage or electrical cardioversion); in-hospital death up to 28 days after hospital admission. Classified as early if ≤3 days or late if >3 days after hospital admission.
(Menendez *et al.*, 2008)	Early treatment failure	Clinical deterioration within 72 hrs of treatment, as indicated by the need for mechanical ventilation and/or shock, or death.
	Late treatment failure	Persistence/reappearance of fever (>37.8°C), radiographic progression (>50% increase), including pleural effusion and/or empyema, nosocomial infection, worsening respiratory failure (defined as PaO_2/FiO_2<250 with respiratory rate ≥30/min), need for mechanical ventilation or shock after 72 hrs.
(Ott *et al.*, 2012)	Treatment failure	Need to switch to another antibiotic regimen with an expended antibiotic spectrum by addition of another agent or replacement of the initial antibiotic by another of the same class with a broader antibacterial spectrum after at least 72 hrs initial treatment,
(Martin-Loeches *et al.*, 2014)	Early treatment failure	Clinical deterioration within in 72 hrs of treatment, as indicated by development of shock, need for invasive ventilation or death.
	Late treatment failure	Radiographic progression (increase > 50% of pulmonary infiltrates compared to baseline), persistence of severe respiratory failure (PaO_2/FiO_2 < 200, with respiratory rate >30/min in non-intubated patients), development of shock, need for invasive mechanical ventilation, or death between 72 and 96 hrs after start of treatment.
(Torres *et al.*, 2015)	Early treatment failure	Clinical deterioration within 72 hrs of treatment (including development of shock, need for invasive mechanical ventilation not present at baseline, or death).
	Late treatment failure	Radiographic progression (increase of ≥50% of pulmonary infiltrates compared with baseline), persistence of severe respiratory failure (PaO_2/FiO_2 < 200 mmHg with respiratory rate ≥30/min in patients not intubated), development of shock, need for invasive mechanical ventilation not present at baseline, or death between 72 and 120 hrs after treatment initiation.

FiO_2 – fraction of inspired oxygen; PaO_2 – partial pressure of oxygen in arterial blood; SpO_2 – oxygen saturations by pulse oximetry;

Table 1.2 Definitions of clinical stability used in CAP.

Reference	Clinical stability definition
ATS 2001 (Aliberti *et al.*, 2013; Niederman *et al.*, 2001)	Attainment of all the following during the same day with reference to the previous day: improvement in cough and dyspnea; afebrile (<37.8°C) on two occasions at least 8 hrs apart; white blood cell count decreasing (at least 10% from previous day); functioning gastrointestinal tract with adequate oral intake.
(Halm *et al.*, 1998; Mandell *et al.*, 2007)	Attainment of all of the following on the same day: temperature ≤37.8°C; heart rate ≤100/min; respiratory rate ≤24/min; systolic blood pressure ≥90 mmHg, SpO_2 ≥90% or PaO_2 ≥60 mmHg when not receiving supplemental oxygen; normal mental status; normal oral intake.
(Menendez *et al.*, 2004a)	Attainment of all of the following on the same day: temperature ≤37.2°C; heart rate ≤100/min; respiratory rate ≤24/min; systolic blood pressure ≥90 mmHg; SpO_2 ≥90% or PaO_2 ≥60 mmHg when not receiving supplemental oxygen.
(Garin *et al.*, 2014)	Attainment of all the following, assessed on day 7: heart rate <100/min; systolic blood pressure >90 mm Hg: tympanic temperature <38.0°C; respiratory rate <24/min; SpO_2 >90% when not receiving supplemental oxygen.

PaO_2 – partial pressure of oxygen in arterial blood; SpO_2 – oxygen saturations by pulse oximetry

1.7.5 Non-resolving pneumonia

Non-resolving (or non-responding) pneumonia is an historic term that is poorly defined. Conceptually, it refers to the subgroup of patients with CAP who despite a prolonged period (at least 10 days) of antimicrobial treatment have persistent symptoms and/or radiographic infiltrates but who are not sufficiently clinically unstable to be classified as early treatment failure or 'progressive pneumonia' (Arancibia *et al.*, 2000; Low *et al.*, 2005). It overlaps considerably with more modern definitions of late treatment failure or delayed clinical stability. The causes of non-resolving pneumonia include: drug resistant pathogens (e.g. penicillin-resistant *S. pneumoniae*); pathogens not covered by empirical antimicrobial treatment (e.g. *M. tuberculosis*, *Pneumocystis jirovecii*); infectious complications (e.g. empyema, endocarditis, nosocomial pneumonia); non-infectious processes that mimic pneumonia (e.g. lung cancer, cryptogenic organising pneumonia). Rather than an objective, reproducible CAP endpoint, the usefulness of term non-resolving pneumonia is to describe a clinical phenotype with a recognised, albeit broad, differential diagnosis that prompts physicians to undertake further diagnostic procedures (Low *et al.*, 2005; Mandell *et al.*, 2007).

1.7.6 Defining severe CAP

Defining severe CAP in a clinically useful way has proved to be a major challenge. Intuitively, death following an episode of CAP appears to be a robust outcome and stratifying acute treatments on the basis of the risk of mortality initially seems reasonable (Lim *et al.*, 2009). However, since up to half the deaths in the first 90 days following an episode of CAP are not directly due to pneumonia – and as such *probably* not modifiable by acute treatment choices (e.g. parenteral versus oral antibiotics; combination versus monotherapy) – the usefulness of this endpoint is lessened (Mortensen *et al.*, 2002). Alternative composite endpoints that encompass respiratory failure, haemodynamic compromise as well as the risk of early death may prove more suitable in this regard (Chalmers, 2015; Kolditz *et al.*, 2015).

Current data describing outcomes of pneumonia in sub-Saharan Africa are largely limited to in-hospital mortality alone. Whether the risk of mortality is an adequate descriptor of severity to form the basis for acute management decisions will depend upon the predominant causes of death and the extent to which they are modifiable by targeted early interventions.

1.8 Prognostication in CAP

1.8.1 Importance of prognostication in management

The severity of illness and mortality rate of CAP is highly varied ranging from a nearly asymptomatic, spontaneously resolving infection to an acute fulminant illness complicated by respiratory failure and severe sepsis with a mortality rate approaching 50% (Welte *et al.*, 2012). Determining the severity of disease and risk of adverse outcome is therefore crucial to informing key management decisions such as site of care and antimicrobial therapy. Clinical judgement alone is not reliably predictive of CAP outcome; physicians may both over- and under-estimate disease severity with the resulting consequences of unnecessary hospitalisation and broad-spectrum antimicrobial treatment or inadequate treatment and delayed admission to ICU (Fine *et al.*, 1997b; Neill *et al.*, 1996; Tang *et al.*, 1993).

To support early clinical decisions, multiple CAP severity assessment tools have been developed (Table 1.3). These tools, that are all simply multivariable prognostic models, combine demographic, clinical and laboratory data to categorise the severity of CAP on the basis of the estimated risk of a specified adverse outcome (e.g. death, ICU admission etc.) (Sintes *et al.*, 2014). In the following section, I briefly describe the methodology used to derive multivariable prognostic models before reviewing in more detail some of the more widely used CAP severity assessment tools.

1.8.2 Prognostic models: Derivation, validation and evaluation

The estimate of the risk or probability of a particular outcome is rarely based on a single predictor. Multivariable prognostic models combine several risk factors to give a more accurate estimate of the risk of the outcome and have been widely used in studies of CAP prognosis (Moons *et al.*, 2015). The process of deriving a prognostic model begins by specifying *a priori* a set of candidate prognostic factors based on prior studies or biological plausibility. The aim is to identify those factors independently associated with the outcome of interest and then to define the simplest (or most parsimonious) model that adequately predicts the outcome of interest. Several different approaches to this variable selection process have been used (e.g. backwards elimination, forwards stepwise selection) and no consensus exists on the best method. Selection of predictors on the basis of significance testing as is commonly performed tends to produce selection bias and overly optimistic estimates of the predictive capability of the model as a result of overfitting (i.e. the model is too closely adapted to the data). Many studies also use a variable screening process based on univariable analysis prior to deriving the multivariable model that may further exacerbate bias (Royston *et al.*, 2009).

External validation is therefore essential to confirm that a prognostic model performs satisfactorily for patients other than those from whose data it was derived (Altman *et al.*, 2009; Collins *et al.*, 2015).

The two key measures of a model's prognostic capability are calibration and discrimination. Calibration refers to the agreement between observed outcomes and predictions; ideally observed and predicted event probabilities should agree over the whole range of probabilities. Discrimination refers to the ability of a prognostic model to distinguish between who will and will not develop the outcome of interest. The area under the Receiver Operating Characteristic (ROC) curve (or the equivalent concordance (*c*) index) is the most commonly used measure and equates to the probability that model will assign a higher probability of the outcome event to patients that go on to experience it (Altman *et al.*, 2000; Altman *et al.*, 2009; Royston *et al.*, 2009; Steyerberg *et al.*, 2010). These measures of statistical validity do not, however, equate to clinical validity since the requirements for calibration and discriminative capability will vary with the context of practice (Altman *et al.*, 2000).

The usefulness of a prognostic model in clinical practice does not solely relate to its accuracy. The information necessary to complete the model must be readily available in the clinical setting in which it is to be used (Moons *et al.*, 2009). For example, models to direct acute patient care in primary care settings cannot practically be reliant on laboratory indices. Similar considerations pertain in low-resource settings where laboratory indices are unavailable or delayed.

The underlying assumption in prognostics research is that by providing an objective measure to improve the accuracy of estimates of outcome (e.g. risk of death), clinicians' decision-making is improved and consequently patient outcome. Unfortunately, this aspect of prognostic model evaluation is often lacking, not least for many of the severity assessment tools derived for CAP (Moons *et al.*, 2009; Steyerberg *et al.*, 2013).

1.8.3 Prognostic factors in CAP

Multiple studies have assessed risk factors for adverse outcome in CAP and dozens of putative prognostic factors have been identified. The factors consistently identified with adverse outcome and therefore repeatedly used in severity assessment tools included: advancing age; presence of comorbid illness; raised respiratory rate; hypoxaemia and respiratory failure; low blood pressure; confusion; high or low white cell count; raised urea; multilobar or extensive chest radiograph changes (Fine *et al.*, 1996; Lim *et al.*, 2009; Lim *et al.*, 2000; Neill *et al.*, 1996).

Table 1.3 Commonly used severity assessment tools for prognosis in CAP.

Tool	Components and calculation	Interpretation and use	Derivation population	Initial validation
PSI (Fine *et al.*, 1997a)	Summation of points as listed in (): Age (1pt/yr; -10 if female) Nursing home residency (10) Neoplastic disease (30) Congestive heart failure (10) Cerebrovascular disease (10) Renal disease (10) Altered mental status (20) Heart rate ≥125/min (10) Resp. rate >30/min (20) Systolic BP < 90 mmHg (20) Temperature <35°C or ≥40°C (15) Arterial pH <7.35 (30) Urea ≥11 mmol/L (20) Sodium <130 mmol/L (20) Glucose ≥14 mmol/L (10) Haematocrit <30% (10) PaO_2 <60 mmHg (10) Pleural effusion (10)	*Predicted outcome:* 30-day mortality *Categorisation:* Class I, <50 yrs and no listed comorbidities or physical findings; Class II, <70 pts; Class III, 71-90 pts; Class IV, 91-130 pts; Class V, >130 pts. 30-day mortality estimates: Class I-II, 0.1-0.7%; Class III, 0.9-2.8%; Class IV-V, 4-27%. *Use:* Site of care decisions; antimicrobial choice	78 US hospitals; inpatients ≥18 years with coding diagnosis of CAP; n=14,199 *Exclusions:* HIV-positive; readmissions; transfers	Registry data from 193 US hospitals; inpatients ≥18 years with coding diagnosis of CAP; n=38,039 *Exclusions:* HIV-positive; readmissions; transfers Prospective cohort of outpatients and inpatients from 5 US centres with radiographic CAP; n=2287 *Exclusions:* HIV-positive
CURB65[a] (Lim *et al.*, 2003)	1 point for each component present Confusion Urea >7 mmol/L Resp. rate ≥30/min Sys. BP < 90 or dia. BP ≤60 mmHg Age ≥65 years	*Predicted outcome:* 30-day mortality *Categorisation:* Low, ≤1 pts (30-day mortality, 1.5%); Moderate, 2 pts (9.2%); Severe ≥3 pts (22%). *Use:* Site of care decisions; guide ICU admission; antimicrobial choice	4 hospitals in UK, New Zealand and Netherlands; adult inpatients with CAP; n=1068 (80% used for derivation) *Exclusions:* expected terminal event; TB; bronchiectasis; HIV or other immunocompromise; nursing home residents.	Internal using 20% of prospective cohort; n=214

Tool	Components and calculation	Interpretation and use	Derivation population	Initial validation
IDSA/ATS 2007[b] (Mandell *et al.*, 2007)	Summation of points as listed in (): Major criteria (2 points for each): Invasive mechanical ventilation Septic shock requiring vasopressors Minor criteria (1 point for each): Resp. rate ≥30/min PaO_2/FiO_2 ≤250 Multilobar infiltrates Confusion/disorientation Urea ≥7.1 mmol/L WBC <4 x10^9 cells/L Platelets <100 x10^9 cells/L Temperature <36°C Hypotension requiring aggressive fluid resuscitation	*Predicted outcome:* ICU admission *Categorisation:* 1 major or 3 minor criteria indicates high risk of ICU admission *Use:* Guide ICU admission	Expert consensus based on modification of existing severity assessment criteria	None initially
SMART-COP (Charles *et al.*, 2008a; Charles *et al.*, 2008b)[c]	Summation of points as listed in (): Major criteria (2 points for each): Sys. BP <90 mmHg Arterial pH <7.35 PaO_2 <70 mmHg, SpO_2 ≤93% or PaO_2/FiO_2 <333 if ≤50 yrs; PaO_2 <60 mmHg, SpO_2 ≤90% or PaO_2/FiO_2 <250 if >50 yrs Minor criteria (1 point for each): Multilobar involvement Albumin <3.5 g/dL Resp. rate ≥25/min if ≤50 years; ≥30/min if >50 years Heart rate ≥125/min Confusion	*Predicted outcome:* Need for IRVS *Categorisation*: Low, ≤2 pts (IRVS, low); Moderate, 3-4 pts (~13%); High, 5-6 (~33%); Very high, ≥7 (~66%). *Use:* Guide ICU admission	6 hospitals in Australia; patients >18 yrs seen in emergency departments with CAP; n=882 episodes *Exclusions:* withdrawal of active treatment; immunosuppressed; recent hospitalisation	Internal validation by bootstrap resampling External validation in 5 CAP databases; n=7464

Tool	Components and calculation	Interpretation and use	Derivation population	Initial validation
SCAP (Espana *et al.*, 2006)	Summation of points as listed in (): Major criteria: pH <7.30 (13) Sys. BP <90 mmHg (11) Minor criteria: Respiratory rate >30/min (9) Urea >11 mmol/L (5) Altered mental status (5) PaO_2/FiO_2 <250 (6) Age ≥80 (5) Multilobar/bilateral involvement (5)	*Predicted outcome:* Severe CAP, defined as in-hospital mortality, mechanical ventilation and/or septic shock. *Categorisation*: 0 pts (severe CAP, 0.2%); 1-9 pts (2.4%); 10-19 pts (9.3%); 20-29 (42.4%); ≥30 (75.9%). *Use:* Guide ICU admission; site of care decision	Teaching hospital in Spain; patients ≥18 years seen in emergency departments with radiographic CAP; n=1776 of which 1057 (60% used for derivation) *Exclusions:* expected terminal event; immunosuppressed	Internal using 40% of prospective cohort; n=719 External validation on retrospective cohort from 4 Spanish hospitals; n=1121

FiO_2 – fraction of inspired oxygen; IRVS – intensive respiratory or vasopressor support; PaO_2 – partial pressure of oxygen in arterial blood; SpO_2 – oxygen saturations by pulse oximetry; WBC – white blood cell

[a] Urea omitted for simplified tool for use in primary care (i.e. CRB65).

[b] For risk prediction, more commonly applied just using minor criteria since major criteria indicate current use of ICU.

[c] Albumin, arterial pH and PaO_2 omitted for simplified tool for use in primary care (i.e. SMRT-CO).

1.8.4 CAP severity assessment tools

1.8.4.1 Pneumonia severity index

Over the last two decades, many different CAP severity assessment tools have been derived. However, only a handful of these have been adequately validated and fewer still are widely used (Table 1.3). The Pneumonia Severity Index (PSI) is the archetypal severity assessment tool that predicts the risk of 30-day mortality. It was derived and validated with data on more than 50,000 CAP patients across a large network of US hospitals (Fine *et al.*, 1997a). In a meta-analysis of 33 cohorts, it had good to excellent discriminatory capability for the prediction of 30-day mortality (Table 1.4) (Chalmers *et al.*, 2010). It is particularly good at identifying patients at low-risk of death. Several impact studies have demonstrated that by using PSI to guide site-of-care decisions, the proportion of patients treated in the community can be safely increased (Aujesky *et al.*, 2008). With 20 parameters, however, the score is relatively complex to calculate and difficult to use in a busy emergency departments (Lee *et al.*, 2007). The PSI performs less well at predicting ICU admission or the need for respiratory or vasopressor support (Chalmers *et al.*, 2011a). Since it is heavily weighted by the presence of age and comorbid illness, elderly patients tend to be assigned to higher risk classes, but many may not be considered for ICU care (Sintes *et al.*, 2014). Some authors have suggested PSI underestimates disease severity in younger patients (Buising, 2008).

1.8.4.2 CURB65

The CURB65 score was also developed to predict 30-day mortality (Lim *et al.*, 2003). Despite being considerably simpler and more easily remembered than the PSI - being composed of only 5 parameters - it has overall comparable prognostic capability, although PSI may better at identifying low-risk patients (Chalmers *et al.*, 2010) (Table 1.4). It has been adopted internationally, and is incorporated into international CAP guidelines for severity assessment and, by extension, a basis for selecting antimicrobial therapy (see below) (Lim *et al.*, 2009). Use of CURB65 may decrease the use of broad-spectrum antimicrobials without compromising safety (Chalmers *et al.*, 2011b). The related CRB65 score, in which the requirement to measure urea is removed, performs comparably and may be used to assess CAP severity in primary care settings. A low CURB65 does not necessarily equate to suitability for community management; additional severity indicators (e.g. multilobar consolidation, acidosis) or social circumstances may mandate hospitalisation (Choudhury *et al.*, 2011). CURB65 notably does not include a direct assessment of oxygenation; the presence of hypoxaemia amongst patients with mild pneumonia as defined by CURB65 is associated with adverse outcome (Sanz *et al.*, 2011). As for the PSI, CURB65 performs less well in

predicting ICU admission or the need for respiratory or vasopressor support (Chalmers *et al.*, 2011a).

Table 1.4 Prognostic performance of CAP severity assessment tools for mortality, intensive care unit (ICU) admission, mechanical ventilation/vasopressor support (MV/VS) and clinical stability. Performance summarised as discriminative capability using area under ROC curve. When available, result of meta-analysis used (indicated by *), otherwise range of reported values given.

Score	30-day mortality	ICU admission	MV/VS	Clinical stability
PSI	0.81*	0.69*	0.69-0.73	0.65
CURB65	0.80*	0.69*	0.62-0.73	0.65
CRB65	0.79*	0.57-0.77	0.71	-
IDSA/ATS 2007	0.78-0.88	0.80-0.88	0.85	-
SMART-COP	0.71-0.85	0.72-0.87	0.83	-
SCAP	0.75-0.78	0.72-0.86	0.75	-

Sources: 30-day mortality, (Chalmers *et al.*, 2010; Sintes *et al.*, 2014); ICU admission, (Chalmers *et al.*, 2011a; Marti *et al.*, 2012); MV/VS, (Chalmers *et al.*, 2011c; Charles *et al.*, 2008b); clinical stability (Arnold *et al.*, 2010).

1.8.4.3 Tools predicting ICU requirement

In recognition that the likelihood of death alone is an inadequate descriptor of the severity of CAP, a series of alternative tools that predict ICU admission or the need for invasive mechanical respiratory or vasopressor support have been developed. The IDSA/ATS 2007 criteria and the SMART-COP score are the most widely used and have been more extensively validated.

The IDSA/ATS 2007 criteria were suggested by expert committee as reasonable indices of severe CAP for which ICU admission was indicated (Mandell *et al.*, 2007). The major criteria of use of mechanical ventilation or vasopressors would routinely mandate ICU admission and as such are not strictly predictive of requirement. The definition of severe CAP as three or more minor criteria has been shown to be accurately predictive of ICU admission and requirement for respiratory or vasopressor support, as well as 30-day mortality (Chalmers *et al.*, 2011c). Lim *et al.* used the IDSA/ATS 2007 minor criteria to identify patients with severe CAP for aggressive emergency department resuscitation and reported substantial mortality reduction (Lim *et al.*, 2014).

Recognising that ICU admission practices vary widely, the SMART-COP score was specifically developed to predict requirement for intensive respiratory or vasopressor support (Charles *et al.*, 2008b). Validation studies indicate comparable performance to

the IDSA/ATS 2007 minor criteria for the prediction of ICU admission (Chalmers *et al.*, 2011c), although evidence for the clinical of use of the score are as yet lacking (Sintes *et al.*, 2014). SMART-COP was derived in non-tropical Australia. A single study showed it to have comparable prognostic accuracy in a tropical population with a lower average patient age and different spectrum of causative pathogens (Robins-Browne *et al.*, 2012).

1.8.5 Severity assessment tools for use in sub-Saharan Africa

The widely used CAP severity assessment scores were universally developed in well-resourced settings and routinely excluded immunosuppressed patients. In small studies from well-resourced settings, PSI and CURB65 remain reasonably predictive of CAP outcome in HIV-positive patients and may appropriately guide assessment and treatment of patients with CD4 cell counts of at least 200 cells/μL (Almeida *et al.*, 2015; Chew *et al.*, 2011; Curran *et al.*, 2008; Madeddu *et al.*, 2010). Data on the use of severity assessment tools in sub-Saharan Africa are limited. In small cohort of patients from Nigeria, Mbata *et al.* described comparable performance of CURB65 in terms of sensitivity and specificity to that previously described in other settings, but did not provide an overall estimate of the tests discriminative capability (Mbata *et al.*, 2013). Another study from Ethiopia described increasing mortality rates amongst hospitalised patients with CAP with increasing CURB65 score but did not provide any further analysis (Ahmedtaha *et al.*, 2014). In a large well-characterised cohort of patients from South Africa, Albrich *et al.* found no correlation of CURB65 with in-hospital mortality in either all CAP patients or those with confirmed pneumococcal pneumonia (Albrich *et al.*, 2014a).

In a cohort of patients with clinically-defined pneumonia from Malawi, of whom 80% were known to be HIV-positive, Birkhamshaw *et al.* reported that a novel severity score based on the presence of male sex, wasting, inability to stand, pyrexia/hypothermia and low blood pressure outperformed CRB65 in predicting in-hospital mortality had moderate discriminative capability (AUROC 0.87 vs. 0.65) (Birkhamshaw *et al.*, 2013). In a cohort of HIV-infected patients with cough for greater than two weeks and clinically suspected pneumonia, Koss *et al.* suggested an alternative severity assessment tool based on tachycardia, tachypnoea, hypoxaemia and low CD4 count (Koss *et al.*, 2015). Neither of these novel tools has been adequately validated.

1.9 Antimicrobial management of CAP

1.9.1 Principles of antimicrobial selection

Antimicrobial therapy is fundamental to the management of CAP. (Lim *et al.*, 2009). Antimicrobial selection in CAP is usually empirical since at the point of initial assessment the pathogen is rarely known and clinical features are not reliably predictive of specific pathogens. Given the diverse array of possible pathogens, selection of appropriate antibiotics is challenging. The need to give antimicrobial cover for the majority of potential pathogens must be weighed against the consequences of unnecessary use of broad-spectrum agents (e.g. *Clostridium difficile*-associated diarrhoea, antimicrobial resistance).

CAP management guidelines (summarised in Table 1.5) recommend that empirical antimicrobial treatment be selected on the basis of disease severity and/or site of care. Whilst *S. pneumoniae* is the commonest cause of pneumonia across all severity groups, *Staphylococcus aureus*, *Legionella* species and Enterobacteriaceae are over-represented in the most severely unwell patients.

1.9.2 Antimicrobial classes used in treatment of CAP

1.9.2.1 Penicillins and β-lactam antibiotics

Penicillins and other β-lactam antibiotics remain the backbone of the treatment of CAP of all severities in most regions of the world. They have excellent activity against *S. pneumoniae* but are not active against atypical bacteria (i.e. *Legionella* spp., *Chlamydophila* spp., *Mycoplasma pneumoniae*). Amoxicillin is the preferred oral agent because of its good oral bioavailability and favourable side effect profile. Reduced *in vitro* susceptibility to β-lactams is widespread in *S. pneumoniae* isolates and very common in several global regions including sub-Saharan Africa (Ginsburg *et al.*, 2013; Hackel *et al.*, 2013). However, in non-meningeal infections, the clinical impact of reduced β-lactam susceptibility is minimal providing adequate doses are used (Jinno *et al.*, 2012). The increasing prevalence of *Haemophilus influenzae* isolates that are resistant to β-lactams may pose greater problems and needs to be monitored (Ginsburg *et al.*, 2013; Tristram *et al.*, 2007).

1.9.2.2 Fluoroquinolones

Fluoroquinolones have a broad spectrum of antimicrobial activity against bacteria that commonly cause CAP including atypical pathogens and some Enterobacteriaceae. Concerns over the lack of anti-pneumococcal activity of older fluoroquinolones such as ciprofloxacin have largely been allayed with newer agents – the so-called respiratory

fluoroquinolones (i.e. moxifloxacin, levofloxacin, gemifloxacin) – that are highly active against *S. pneumoniae* including isolates that are resistant to multiple other classes of antimicrobial (Peterson *et al.*, 2009). They have excellent oral bioavailability and tissue penetration (Erard *et al.*, 2004; Pletz *et al.*, 2011; Yuan *et al.*, 2012). Concerns over their propensity to promote *Clostridium difficile*-associated diarrhoea and the potential ecological impact of their widespread use on the emergence of antimicrobial resistance has seen them relegated to second line agents in UK, European and South African CAP guidelines (Feldman *et al.*, 2007a; Hoffken *et al.*, 2010; Lim *et al.*, 2009; Spindler *et al.*, 2012; Woodhead *et al.*, 2011)

1.9.2.3 Macrolides

Macrolide antibiotics - notably azithromycin, clarithromycin and erythromycin - are widely used for the treatment of CAP. They act by inhibiting bacterial protein synthesis and offer broad-spectrum cover against Gram-positive and atypical bacteria and have reasonable oral bioavailability (Restrepo *et al.*, 2016). In addition to their direct antimicrobial effect, macrolides exert a broad array of immunomodulatory and anti-inflammatory effects that may contribute to their clinical efficacy in treating CAP (Kovaleva *et al.*, 2012; Lorenzo *et al.*, 2015). Safety concerns have been raised recently following registry data studies that have identified an apparent excess of cardiovascular-related deaths following the use of azithromycin and clarithromycin (Cheng *et al.*, 2015; Ray *et al.*, 2012; Wong *et al.*, 2016). *In vitro* resistance to macrolide in both *S. pneumoniae* and *Mycoplasma pneumoniae* is increasing but the clinical impact is not clear (Cilloniz *et al.*, 2015; Jenkins *et al.*, 2009; Principi *et al.*, 2013).

Table 1.5 Summary of antimicrobial recommendations in CAP management guidelines.

Guideline	Mild	Moderate	Severe
UK (Lim *et al.*, 2009)	Amoxicillin *Alt.* Doxycycline *or* clarithromycin	Amoxicillin *plus* clarithromycin *Alt.* Doxycycline *or* levofloxacin *or* moxifloxacin	Co-amoxiclav *plus* clarithromycin *Alt.* Benzylpenicillin *plus either* levofloxacin *or* ciprofloxacin; Cefuroxime *or* cefotaxime *or* ceftriaxone, *plus* clarithromycin
US (Mandell *et al.*, 2007)	Healthy and no risk factors DRSP: Macrolide[a] *Alt.* Doxycycline Comorbidities or recent antimicrobials: Fluoroquinolone[b] β-lactam *plus either* macrolide[a] *or* doxycycline	Fluoroquinolone[b] β-lactam (cefotaxime, ceftriaxone, ampicillin) *plus either* macrolide[a] *or* doxycycline	Cefotaxime *or* ceftriaxone *or* ampicillin-sulbactam, *plus either* azithromycin *or* fluoroquinolone[b] Suspected *Pseudomonas* infection[c]: Antipseudomonal β-lactam[d] *plus either* ciprofloxacin *or* levofloxacin
Europe (Woodhead *et al.*, 2011)	Amoxicillin *or* tetracycline *Alt.* Macrolide[e] *or* moxifloxacin *or* levofloxacin	Aminopenicillin ± macrolide[e] Aminopenicillin/β-lactamase inhibitor ± macrolide[e] Non-antipseudomonal penicillin Cefotaxime *or* ceftriaxone, ± macrolide[5] Levofloxacin *or* moxifloxacin Penicillin G ± macrolide	No risk factors for *Pseudomonas:*[f] Non-antipseudomonal cephalosporin *and* macrolide[e] Moxifloxacin *or* levofloxacin, ± non-antipseudomonal cephalosporin Risk factors for *Pseudomonas:*[f] Antipseudomonal β-lactam[d] *plus either* ciprofloxacin *or* macrolide[e] *and* aminoglycoside[g]
South Africa[h] (Feldman *et al.*, 2007a)	Young with no comorbid illness: Amoxicillin ± *either* macrolide[a] *or* doxycycline *Alt.* Fluoroquinolone[b] *or* telithromycin Elderly ≥65 yrs ± comorbid illness: Co-amoxiclav *or* 2nd generation cephalosporin[i] ± *either* macrolide[a] *or* doxycycline *Alt.* Fluoroquinolone[b] *or* telithromycin	Young with no comorbid illness: Penicillin G *or* amoxicillin, ± macrolide[a] *Alt.* Fluoroquinolone[b] Elderly ≥65 yrs ± comorbid illness: Co-amoxiclav *or* 2nd/3rd generation cephalosporin[i], ± macrolide[a] *Alt.* Fluoroquinolone[b]	Co-amoxiclav *or* 2nd/3rd generation cephalosporin[i], *plus* aminoglycoside[g] *and* macrolide[a] *Alt.* Fluoroquinolone[b] + another agent

Guideline	Mild	Moderate	Severe
Germany (Hoffken *et al.*, 2010)	Young with no comorbid illness: Amoxicillin *Alt.* Macrolide[j] *or* doxycycline Elderly ≥65 yrs ± comorbid illness: Co-amoxiclav *or* sultamicillin *Alt.* levofloxacin *or* moxifloxacin	Aminopenicillin/β-lactamase inhibitor ± macrolide; Cefuroxime *or* ceftriaxone *or* cefotaxime, ± macrolide *Alt.* Levofloxacin *or* moxifloxacin; Ertapenem ± macrolide	No risk factors for *Pseudomonas:*[c] Piperacillin/tazobactam *or* ceftriaxone *or* cefotaxime *or* ertapenem, *plus* macrolide[j] *Alt.* Levofloxacin *or* moxifloxacin; Risk factors for *Pseudomonas:*[c] Antipseudomonal β-lactam[d] *plus either* levofloxacin *or* moxifloxacin, *or* macrolide *and* aminoglycoside[g]
Sweden (Spindler *et al.*, 2012)	Penicillin G *or* Penicillin V Suspicion of DRSP: Penicillin G (high dose) *or* amoxicillin (high dose) Suspicion of *H. influenzae*: Penicillin G (high dose) *or* amoxicillin Suspicion of atypical aetiology: Erythromycin *or* doxycycline *Alt.* Erythromycin *or* doxycycline *or* clindamycin	Penicillin G Suspicion of DRSP: Penicillin G (high dose) During influenza season: Cefotaxime *or* penicillin G *and* cloxacillin Underlying lung disease: Piperacillin/tazobactam Suspicion of atypical aetiology: Erythromycin *or* doxycycline *Alt.* Levofloxacin *or* moxifloxacin *or* doxycycline	Cefotaxime *plus* erythromycin *Alt.* Penicillin G *plus either* levofloxacin *or* moxifloxacin Underlying lung disease: Piperacillin/tazobactam *plus either* erythromycin *or* levofloxacin *or* moxifloxacin *Alt.* Clindamycin *plus either* levofloxacin *or* moxifloxacin
Brazil (Correa Rde *et al.*, 2009)	Previously healthy: Azithromycin *or* clarithromycin *Alt*. Amoxicillin Comorbidities or use of antimicrobials in last 3 months: Levofloxacin *or* moxifloxacin; β-lactam *plus either* azithromycin *or* clarithromycin	Levofloxacin *or* moxifloxacin; β-lactam *plus either* azithromycin *or* clarithromycin	No risk factors for *Pseudomonas:*[c] Non-antipseudomonal β-lactam *plus either* azithromycin *or* clarithromycin *or* levofloxacin *or* moxifloxacin Risk factors for *Pseudomonas:*[c] Antipseudomonal β-lactam[d] *plus either* levofloxacin *or* moxifloxacin
Malawi (Zijlstra, 2006)	Amoxicillin	Amoxicillin	Ceftriaxone *or* penicillin G *and* chloramphenicol Consider erythromycin, gentamicin and/or treatment for PCP if no improvement at 48 hrs

Alt. – Alternative; DRSP – Drug resistant *Streptococcus pneumoniae*; PCP – *Pneumocystis jirovecii* pneumonia

[a] Azithromycin, clarithromycin or erythromycin

[b] Moxifloxacin, gemifloxacin, levofloxacin
[c] Any of the following: structural lung disease; frequent antimicrobial pre-treatment; frequent prior hospitalisation
[d] Piperacillin/tazobactam, cefepime, imipenem, meropenem
[e] Azithromycin, clarithromycin, erythromycin or roxithromycin
[f] At least two of the following: recent hospitalisation; frequent (>4 courses/year) or recent (≤3 months) administration of antimicrobials; severe lung disease (FEV_1 <30%); oral steroid use (>10mg/day of prednisolone in the last 2 weeks).
[g] Gentamicin, tobramycin or amikacin.
[h] Additional specific recommendations for hospitalised HIV-positive patients: If diffuse infiltrate, investigate and consider specific treatment for tuberculosis and *Pneumocystis jirovecii* pneumonia.
[i] 2nd generation: parenteral – cefuroxime; oral – cefuroxime axetil, cefpodoxime; 3rd generation: ceftriaxone, cefotaxime
[j] azithromycin, clarithromycin, roxithromycin

1.9.3 Antimicrobial therapy by CAP severity

1.9.3.1 Mild severity CAP

US guidelines diverge from those from other regions by mandating the coverage of atypical pathogens in all patients with mild pneumonia. Macrolides are recommended as first line agents and fluoroquinolones for patients with comorbid illness or recent antimicrobial use (Mandell *et al.*, 2007). Amoxicillin is the preferred first line agent in most guidelines with other antimicrobial classes reserved for patients that fail to respond.

1.9.3.2 Moderate severity CAP

The key questions of whether antimicrobial coverage for atypical bacterial infection is required for all hospitalised patients and, if so, whether a macrolide- or fluoroquinolone-based regimen is optimal continue to be hotly debated (An *et al.*, 2010; File *et al.*, 1997; Lee *et al.*, 2015; Querol-Ribelles *et al.*, 2005; Raz-Pasteur *et al.*, 2015; Vardakas *et al.*, 2008; Yuan *et al.*, 2012). Meta-analyses largely based on observational studies have yielded contrasting results. Eliakim-Raz *et al*. found no improvement in survival or clinical success with the use of atypical bacterial coverage (Eliakim-Raz *et al.*, 2012), whilst Nie *et al*. found that macrolide combination was associated with reduced mortality compared to β-lactam use alone (Nie *et al.*, 2014). Similarly, Asadi *et al* found that macrolide exposure was associated with a reduced mortality, but this benefit disappeared when the analysis was restricted studies comparing macrolides against other guideline concordant regimens (Asadi *et al.*, 2012). Two recent multi-centre randomised-controlled trials of hospitalised non-ICU patients designed to definitively address the issue of macrolide combination treatment yielded contrasting results: one indicated that β-lactam monotherapy was non-inferior to β-lactam-macrolide combination in terms of risk of 90-day mortality (Postma *et al.*, 2015), whilst the other failed to demonstrate non-inferiority of β-lactam monotherapy clinical stability at 7 days (Garin *et al.*, 2014).

In the absence of definitive results, antimicrobial choices are based on local epidemiological considerations (Gattarello, 2015; Lee *et al.*, 2016). High rates of macrolide resistance in *S. pneumoniae* isolates lead US CAP guidelines to recommend fluoroquinolone monotherapy as first choice (Mandell *et al.*, 2007). In other regions, fluoroquinolones are reserved as second line agents because of concerns over their propensity to promote *Clostridium difficile*-associated diarrhoea and drive antimicrobial resistance (Feldman *et al.*, 2007a; Hoffken *et al.*, 2010; Lim *et al.*, 2009; Spindler *et al.*, 2012; Woodhead *et al.*, 2011).

1.9.3.3 Severe CAP

In severe CAP, all major current guidelines recommend combination therapy with a β-lactam plus either a macrolide or fluoroquinolone. β-lactamase stable penicillins (e.g. co-amoxiclav) or 3rd generation cephalosporins (e.g. ceftriaxone, cefotaxime) are recommended to provide additional antimicrobial cover for *S. aureus*, Enterobacteriaceae and β-lactamase producing *Haemophilus influenzae*. European, US German and Brazilian guidelines advocate the choice of β-lactam in severe CAP is modified on the basis of the risk of infection with *Pseudomonas* (Hoffken *et al.*, 2010; Woodhead *et al.*, 2011).

Observational studies and a recent meta-analysis indicate that the use of macrolides confers a survival benefit (Martin-Loeches *et al.*, 2010; Restrepo *et al.*, 2009) (Gattarello *et al.*, 2014; Gattarello *et al.*, 2015; Metersky *et al.*, 2007) particularly in bacteraemic pneumococcal CAP (Sligl *et al.*, 2014; Waterer *et al.*, 2001b). The beneficial effects of macrolides remain evident in patients with disease caused by organisms resistant to macrolides indicating the potential importance of an anti-inflammatory or immunomodulatory role (Giamarellos-Bourboulis, 2008; Lorenzo *et al.*, 2015; Martin-Loeches *et al.*, 2010).

1.9.4 Antimicrobial considerations in sub-Saharan Africa

In any setting, CAP is a very common indication for antimicrobial use and the implications of treatment recommendations in terms of their cost and ecological impact need to be carefully assessed. In resourced-limited settings, both the cost of the drug and the broader implications of the treatment regimen in terms of the impact of dosing frequency on nursing time should be considered. In the absence of robust laboratory infrastructure, the development of antimicrobial resistance may go unnoticed until widespread treatment failures occur. Unrestricted antimicrobial use in low-resource settings is a major driver in the global emergence and spread of drug resistant bacteria (Kariuki *et al.*, 2014; Leopold *et al.*, 2014). For example, macrolide resistant *S. pneumoniae* isolates have emerged and rapidly spread in South Africa (Wolter *et al.*, 2008). The widespread use of azithromycin for trachoma control may accelerate spread in other areas of the continent (Coles *et al.*, 2013). Fluoroquinolones have potent anti-tuberculous activity and in high TB-burden settings empirical use of fluoroquinolones may lead to delayed diagnosis of pulmonary TB and a higher risk of subsequently developing fluoroquinolone-resistant TB (Chang *et al.*, 2010; Chen *et al.*, 2011).

In severe CAP, treatment guidelines from well-resourced settings advocate initial broad-spectrum antimicrobials to cover all of the probable pathogens and in tandem extended microbiological investigations to increase the chance that aetiology is established and the antimicrobial spectrum may be narrowed (Lim *et al.*, 2009). This approach cannot be replicated in many sub-Saharan African settings where microbiological diagnostics are lacking, hence treatment modifications often have to be made on the basis of clinical response. In addition, given the high burden of TB and other HIV-associated opportunistic infections, broad empirical treatment would have to include anti-tuberculous treatment and cover for PCP. A step-up approach is generally used in deteriorating patients (World Health Organization, 2011c), but the optimal clinical indicators and the consequences of delayed adequate treatment are unknown.

1.10 Supportive management of CAP

Pneumonia is frequently complicated by respiratory failure and severe sepsis (Aliberti *et al.*, 2014a). Successful management of severe CAP requires not only effective antimicrobial therapy to remove the causal pathogen, but supportive care to maintain adequate tissue perfusion and oxygenation.

1.10.1 Managing respiratory failure

Hypoxaemia is common feature of severe CAP and is independently associated with increased mortality (Fine *et al.*, 1996; Lim *et al.*, 2003). Although an established core component of CAP management, there is little empirical data that directly defines the indications for and therapeutic benefit of supplemental oxygen (Lim *et al.*, 2009; Mandell *et al.*, 2007; O'Driscoll *et al.*, 2008; Wijesinghe *et al.*, 2012). Hypoxaemia is generally defined as oxygen saturations (SpO_2) <90% (approximately equivalent to arterial oxygen tension of 60mmHg) since there is no known risk of hypoxic tissue injury above this level (Bowton *et al.*, 1994; O'Driscoll *et al.*, 2008). British CAP guidelines advise that SpO_2 should be maintained within a target range of 94-98% to give a wide margin of safety above the 90% threshold. In resource-limited settings, where supplemental oxygen provision is scare, it is usually reserved for patients with SpO_2 <90% (World Health Organization, 2011a). Potential adverse consequences of excessive oxygen administration are increasingly being recognised (Martin *et al.*, 2013). Amongst vulnerable patients such as those with advanced COPD, chest wall deformities or neuromuscular disease, excessive oxygen administration exacerbates V/Q mismatch and reduces ventilatory drive, resulting in hypercapnic respiratory failure (O'Driscoll *et al.*, 2008). Hyperoxaemia itself is associated with increased

peripheral vascular resistance, reduced coronary blood flow generation of reactive-oxygen species (e.g. hydrogen peroxide) that may cause direct cellular damage (Martin *et al.*, 2013).

Around 25% of hospitalised CAP patients develop acute hypoxaemic respiratory failure and approximately 10% require intubation and mechanical ventilation (Chalmers *et al.*, 2011a; Charles *et al.*, 2008b; Fine *et al.*, 1997a; Lim *et al.*, 2000). To avoid the complications associated with invasive mechanical ventilation (i.e. ventilator-associated pneumonia, ventilator-induced lung injury), non-invasive ventilation (NIV) techniques are increasingly used in patients with respiratory failure (Ferrer *et al.*, 2015). However, in contrast to other causes of acute respiratory failure such as acute pulmonary oedema and COPD exacerbations, NIV has not been consistently beneficial in CAP. Whilst small early randomised trials showed that NIV reduced rates of intubation and duration of ICU stay (Confalonieri *et al.*, 1999), subsequent larger observational cohorts indicate that NIV fails in up to 75% (Carron *et al.*, 2010; Murad *et al.*, 2015). The benefit of NIV in CAP is largely restricted to patients with underlying cardiorespiratory disease, particularly COPD, and immunosuppressed patients (Antonelli *et al.*, 2000; Hilbert *et al.*, 2001). NIV should be used very cautiously in other CAP patients since delays in intubation for mechanical ventilation are associated with increased mortality (Ferrer *et al.*, 2012; Hraiech *et al.*, 2013). Failure to improve after one hour of NIV is predictive of subsequent mortality (Carrillo *et al.*, 2012; Nicolini *et al.*, 2016).

1.10.2 Fluid resuscitation

Respiratory tract infections, particularly pneumonia, are the leading cause of severe sepsis. Around 20-30% of hospitalised CAP patients will develop severe sepsis, of whom around a quarter will die (Aliberti *et al.*, 2014a; Kellum *et al.*, 2007). Adequate fluid resuscitation to correct sepsis-induced hypoperfusion and ameliorate tissue injury is central to effective management (Dellinger *et al.*, 2013). Protocolised fluid resuscitation to achieve specific haemodynamic targets and/or normalisation of plasma lactate - termed early goal-directed therapy - has been shown to improve survival (Rivers *et al.*, 2001). Recent randomised controlled trials of early sepsis have called into question the additive benefit of invasive monitoring following adequate initial fluid volume resuscitation (Mouncey *et al.*, 2015; Peake *et al.*, 2014; Yealy *et al.*, 2014). The direct applicability of these findings to sub-Saharan Africa setting where critical care facilities are not available is uncertain. The FEAST trial of fluid resuscitation strategies in children with severe febrile illness found higher mortality in those treated with aggressive fluid management (Maitland *et al.*, 2012). Similarly, a small study from

Zambia of a simplified early goal-directed therapy protocol for adult sepsis was stopped early because of high overall mortality (Andrews *et al.*, 2014).

1.11 Study setting

1.11.1 Malawi: Country background

Malawi is a tropical, landlocked country in south-eastern Africa occupying a thin strip of land between Zambia and Mozambique. It is one of the world's poorest countries with a per capita gross domestic product (GDP) of only $226 that, in contrast to the rest of the region has fallen over the last four years. Total health expenditure is 8.3% of GDP, equating to approximately $19 per person per annum (World Bank, 2015).

It is one of sub-Saharan Africa's most densely populated countries with an estimated current population of 15.9 million and annual growth rate of 2.8%; 45.3% of the population are aged less than 15 years (United Nations Statistics Division, 2014). Life expectancy at birth has improved considerably over the last decade; from a nadir of 46 in 2000 to its a current level of now 55 (United Nations Statistics Division, 2014; World Bank, 2015). On the United Nations human development index, Malawi is ranked 174 of the 187 countries for which data were available (United Nations Development Programme, 2014).

There is a generalised HIV epidemic. At its peak in 1999, HIV prevalence amongst adults aged 15-49 was 16.6%. This declined steadily to 10.3% in 2013; currently there are approximately 1 million people living with HIV in Malawi. National ART scale-up began in 2004 and as of December 2013, there were approximately 500,000 people alive on ART with an estimated coverage of 83% of eligible individuals (Government of Malawi, 2014; Harries *et al.*, 2011).

1.11.2 Queen Elizabeth Central Hospital

Government-funded healthcare in Malawi is delivered via a three-tiered system consisting of community health centres, district hospitals and regional central hospitals. Queen Elizabeth Central Hospital is the largest hospital in Malawi with approximately 1200 beds and acts as a district level facility for Blantyre and surrounding areas (population approximately 1.2 million) and a referral facility for the entire Southern Region.

Patients referred to QECH are initialled assessed in the Adult Emergency and Trauma Centre (AETC) by a clinical officer (non-physician clinician licensed to practice independently following completion of 3-year diploma course) or doctor; those

requiring medical admission are initially seen by the medical intern or registrar and then generally reviewed by a consultant within 24 hours. Following admission, patients are seen twice weekly on consultant ward rounds and then variably at other times by interns, clinical officers or medical students depending on the availability of staff.

The Department of Medicine consists of two single-sex general medical wards each with approximately 60 beds and a mixed-sex TB ward of similar size. The bed capacity on the general wards is frequently exceeded, with patient numbers of greater than 100 on each ward not uncommon; when there are insufficient beds, patients are accommodated on mattresses on the floor. Each ward also has a 6-bedded high dependency unit (HDU) that is equipped with oxygen concentrators for supplementary oxygen delivery.

Each ward is staffed by two or three trained nurses supported by a variable number of student nurses; the nursing complement does not alter regardless of the patient load. Most personal care including feeding, washing and toileting is administered by a 'guardian' - a close relative or friend that remains with the patient during their hospitalisation. Nurses generally prioritise drug administration and performing phlebotomy for investigations; daily measurement of physiological observations is not routine outside the HDUs.

Medical care at QECH is provided in accordance with Malawi national treatment guidelines, but is frequently hampered by stockouts of essential medicines such as antibiotics, diuretics and insulin. Supplemental oxygen is available for only approximately one-third of hypoxic patients (Evans *et al.*, 2012). The available laboratory facilities support basic haematological and biochemical investigations and smear microscopy and latterly Xpert MTB/RIF for diagnosis of tuberculosis, but similarly are often disrupted by lack of reagents.

1.11.3 Malawi-Liverpool-Wellcome Trust Clinical Research Programme

The Malawi-Liverpool-Wellcome Trust Clinical Research Programme (MLW) was established in 1995 and is located adjacent to the QECH campus. Investigators based at MLW undertake a broad portfolio of clinical and basic science research with many projects recruiting patients from QECH. Since 2000 it has provided a routine diagnostic microbiology service to support clinical care, offering blood and cerebrospinal fluid culture (http://www.mlw.medcol.mw/).

1.12 Thesis synopsis

1.12.1 Aims and objectives

The overall aim of this PhD is to determine the clinical predictors of adverse outcome of CAP in Malawian adults. The intended outputs are two fold: firstly, to improve triage assessment of CAP; secondly, to identify modifiable risk factors for poor outcome that could be the target for future interventional studies. The underlying main hypothesis is that epidemiology and aetiology of CAP in Malawi and comparable sub-Saharan African settings is markedly different to that seen in well-resourced settings and accordingly that: clinical predictors of adverse outcome are different; CAP-severity assessment tools derived in well-resourced settings (e.g. CURB65) fail to predict outcome accurately; empirical therapy recommendations from well-resourced settings would fail to provide adequate antimicrobial coverage for the spectrum of pathogens encountered.

Key research questions to be addressed include:

1. What are the patient characteristics and clinical features of CAP in adults in sub-Saharan Africa in general and in Malawi in particular?
2. What are the common microbial causes of CAP in these settings?
3. What clinical factors evident at presentation predict adverse outcome?
4. Do CAP-severity assessment tools derived in well-resourced settings accurately identify individuals at risk of adverse outcome?
5. Are there potentially modifiable risk factors for adverse outcome that are rational targets for therapeutic interventions to improve CAP outcome?

This thesis sets out to address these questions in the following studies:

1. A prospective observational study of adults hospitalised with CAP to Queen Elizabeth Central Hospital called the Malawian Lower Respiratory Tract Infection, Severity, Aetiology and Outcome (MARISO) Study. The key objectives were:
    a. To determine the frequency of 30-day mortality and treatment failure in adults hospitalised with clinically diagnosed CAP;
    b. To identify the clinical and basic diagnostic laboratory characteristics associated with 30-day mortality and treatment failure;
    c. To describe the microbial aetiology using modern diagnostic modalities.

2. To set the results of the MARISO study in a broader regional context, a systematic review of CAP in adults in sub-Saharan Africa was completed. The key objectives were:
    a. To describe aetiology;
    b. To estimate mortality rate;
    c. To identify risk factors associated with death.
3. An interim analysis of the MARISO cohort showed that hypoxaemia was predictive of mortality. I therefore undertook a further study (Addressing Hypoxaemia in adult Pneumonia (AHIP) study) to assess the effectiveness of supplemental oxygen delivery by oxygen concentrator to correct hypoxaemia in CAP patients in this setting. The key objectives were:
    a. To determine the proportion of adults hospitalised with CAP that are hypoxaemic at presentation that attain normoxaemia with supplemental oxygen delivered by concentrator at a standard flow-rate of 5 L/min.
    b. To determine what proportion of those who fail to attain normoxaemia at a rate of 5 L/min, attain normoxaemia at a high flow-rate of 10 L/min.

1.12.2 Thesis overview

The systematic review of CAP in sub-Saharan Africa is presented in chapter 2. The detailed methods of the MARISO study are described in chapter 3 with the results presented in the two following chapters. In chapter 4, I describe the baseline characteristics, radiological features and aetiology of the MARISO cohort. In chapter 5, I describe the clinical outcomes in terms mortality, treatment failure and clinical stability and present the results of multivariable analyses examining risk factors for adverse outcome. The background, methods and results of the AHIP study are presented in chapter 6. In the final chapter I discuss the preceding results in light of recent data from other settings to suggest how outcomes from CAP in Malawi and other comparable settings may be improved and outline the immediate research priorities in this area.

2 Aetiology and outcome of community-acquired pneumonia in adults in sub-Saharan Africa: A systematic review

2.1 Introduction

Pneumonia is the commonest cause of infectious disease-related death globally (Lopez *et al.*, 2006). The burden of disease in African adults is high, particularly in sub-Saharan Africa where pneumonia is the among the commonest reason for adult hospitalisation (SanJoaquin *et al.*, 2013) and the cause of 200,000 deaths each year (Scott *et al.*, 2012). Effective management of community-acquired pneumonia (CAP) requires accurate assessment of disease severity followed by prompt initiation of appropriate empirical antimicrobials. The former aspect requires awareness of key prognostic factors that independently predict outcome and the latter knowledge of the likely causal pathogens based on local epidemiology (Lim *et al.*, 2009; Mandell *et al.*, 2007). To date, neither aspect has been systematically reviewed in CAP cohorts from sub-Saharan Africa.

Severity assessment of CAP is challenging since mortality rates for CAP vary markedly with the population studied (Welte *et al.*, 2012). In well-resourced settings, CAP outcomes have been studied extensively and the main risk factors for adverse outcome defined and often consolidated into readily usable clinical assessment tools (Charles *et al.*, 2008b; Fine *et al.*, 1996; Lim *et al.*, 2003; Welte, 2012). Outcomes are influenced substantially by patient demographics and underlying comorbidities (Fine *et al.*, 1997a; Lim *et al.*, 2003). Compared to well-resourced settings, CAP populations from sub-Saharan Africa are likely to have markedly different demographic and comorbidity profiles (Etyang *et al.*, 2013; Lopez *et al.*, 2006; Murray *et al.*, 2012). As such the clinical factors predictive of mortality in well-resourced settings may not apply in CAP cohorts in sub-Saharan Africa.

The aetiology of adult CAP has also been extensively studies in well-resourced settings in Europe, North America, Asia and Australia and summarised in several systematic reviews (Charles *et al.*, 2008a; Ewig *et al.*, 2009; Peto *et al.*, 2014; Torres *et al.*, 2014; Welte *et al.*, 2012). Whilst most cases of CAP are attributable to a relatively narrow spectrum of pathogens, these studies highlight significant regional variations in CAP aetiology that have important therapeutic implications. In high burden settings, like sub-Saharan Africa (World Health Organization, 2015a), tuberculosis (TB) may account for a substantial proportion of acute pneumonic presentations (Peto *et al.*, 2014). CAP aetiology in sub-Saharan Africa is also likely to differ as a result of the impact of HIV

that renders individuals susceptible to opportunistic pathogens (e.g. *Pneumocystis jirovecii*)(Benito *et al.*, 2012).

In this chapter, I present the methodology and results of a systematic review summarising the published literature on the aetiology and outcome of CAP in adults in sub-Saharan Africa.

2.2 Objectives

To summarise and appraise research that reports the aetiology and outcome of CAP in adults in sub-Saharan Africa. Specifically: to estimate the mortality rate; to identify risk factors associated with death and to quantify the strength of association; and to summarise the aetiology.

2.3 Contributors to this chapter

I devised the study, wrote the review protocol, reviewed all titles, extracted all data and performed the analyses. Professor Charles Feldman (University of Witwatersrand, South Africa) independently reviewed all titles and corroborated study selection. Professor Paul Garner (Liverpool School of Tropical Medicine, UK) advised on the development of the study methodology and analysis. Victoria Lutje (search strategist) helped to develop the search terms and performed the database searches.

2.4 Methods

The study was conducted according to MOOSE guidelines (meta-analysis of observational studies in epidemiology)(Stroup *et al.*, 2000).

2.4.1 Search strategy

The search consisted of three components: firstly, a search term for "pneumonia" or "respiratory tract infection"; secondly, a geographical term listing all the countries in sub-Saharan Africa along with "sub-Saharan Africa" and the relevant MeSH terms for Central, Western, Eastern and Southern Africa; and thirdly, limits excluding non-human and child or infant studies. The following electronic databases were searched: Medline (via OVID from 1st January 1960); Embase (via OVID from 1st January 1960); Science Citation Index Expanded and Conference Proceedings Citation Index (Web of Science); CINAHL (EBSCOhost); CAB abstracts and Global Health (CABI, Web of Science); Scopus; African Index Medicus. Studies published prior to 1960 were not considered for inclusion because of the non-systematic manner in which data are often presented in reports from this era and the lack of comparability of microbiological methods used to

determine aetiology. A full list of the searches terms used for each database is included in Appendix A. No restrictions of language or publication status were applied to the electronic searches. Non-English studies were translated using Google Translate (Google Inc.; California, USA; available at: https://translate.google.co.uk). The search results were merged using citation management software (Endnote X5, Thomson Reuters) and duplicate references removed. The reference lists of included articles were subsequently hand searched for additional relevant articles.

I reviewed all titles and extracted data from all papers. A second reviewer (Professor Charles Feldman) independently reviewed all titles and corroborated study selection. Disagreements over study eligibility were resolved by discussion.

2.4.2 Inclusion criteria

Studies that described the mortality rate and/or aetiological profile of CAP in adults (aged 12 years or older) resident in any sub-Saharan African country were included. Clinical trials and observational studies including cohort and case-control studies, and case series of 25 or more individuals were included. Additional abstracts or conference reports were included provided they contained sufficient detail to demonstrate they met the other eligibility criteria. Multicentre studies encompassing sites outside of Africa were only included if the data for patients recruited in Africa were presented separately.

2.4.3 Exclusion criteria

Review articles and small case series with fewer than 25 participants were excluded. Similarly for studies that presented aetiology or mortality data only as subgroups (e.g. by HIV status), subgroups with fewer than 25 participants were excluded. Studies that were not specifically focused on CAP such as surveillance studies or service improvement surveys that analysed records or patient registers were also excluded because of possible lack of precision of CAP diagnosis. Studies that did not provide an adequate description of the microbiological techniques used to assign aetiology were excluded from the aetiological analysis.

2.4.4 CAP case-definition

To produce a broad and inclusive review that comprehensively summarised available data, a precise CAP case definition was not mandated; studies were included regardless of whether they used a clinical or radiological case definition of CAP. However to ensure that the data related to populations with acute CAP, studies that recruited patients with nosocomial infection or studies that selected patients for recruitment on

the basis of prolonged duration of symptoms, failure to improve with initial treatment or clinical suspicion of PCP or TB were excluded. Studies describing the aetiology and outcome of severe acute respiratory infection (SARI) without otherwise specifying pneumonia were also excluded; similarly studies focusing on influenza-like illness (ILI) were excluded.

2.4.5 Data extraction

I independently reviewed each article and extracted data using a standardised paper form that was designed and piloted for this review. Data extracted included: details of the study size, design, population and dates of completion; patient demographics and recorded medical comorbidities; definition of CAP used; physiological and laboratory indices of disease severity; types and results of investigations to determine aetiology; frequency of mortality and other relevant clinical endpoints. Data on the risk of bias assessment of the second reviewer (Professor Charles Feldman) are also presented. The template for data extraction is shown in Appendix A.

2.4.6 Risk of bias assessment

In the absence of a generally accepted tool for observational studies, criteria adapted from the Cochrane Collaboration Tool to Assess Risk of Bias in Cohort Studies were used to assess the risk of bias and quality of studies included in this review (Cochrane Collaboration, 2014)(see Appendix A). The risk of bias for each of the three analyses – mortality, risk factors and aetiology – was considered separately for each study. For the mortality analysis, studies were considered to have a low risk of bias if each of the following criteria were satisfied: a radiographic definition of CAP was used; patient recruitment was not restricted to specific groups defined by age, comorbidity or disease aetiology; patient follow-up was greater than 90%. For the mortality risk factors analysis, studies were regarded to have a low risk of bias if the following additional criteria were met: prognostic factor data was collected prospectively using standardised methods and was available in at least 90% of patients analysed; the extent of missing outcome data was insufficient to have a clinically-relevant impact on reported associations; statistical analysis was performed according to pre-specified methods with all outcomes being reported and appropriate adjustment made for confounding variables. For the aetiology analysis, studies were considered to have a low risk of bias if clinical specimen collection was systematic and reasonably complete and the laboratory techniques used were adequately described.

2.4.7 Statistical analysis

For each study demographic data was summarised as the proportion of male patients and mean age with standard deviation. When unavailable mean age and/or standard deviation were estimated from the median, interquartile interval and range (Wan *et al.*, 2014). The overall frequency of common comorbid illnesses across all studies was estimated by meta-analysis. Mortality rates were directly extracted and 95% confidence intervals calculated. Estimated overall mortality rates by clinical setting were estimated by meta-analysis. When data on specific potential prognostic factors were provided their association with mortality was estimated by calculating univariable odds ratios (ORs) with 95% confidence intervals. Aetiological data was tabulated with the prevalence of specific pathogens reported as proportions. Weighted mean proportions for each main pathogen were calculated using data from all studies and only those with low risk of bias. The inter-observer variability of the risk of bias assessment between the two reviewers was assessed by calculating percentage agreement and kappa coefficient with estimated 95% confidence intervals.

2.5 Results

2.5.1 Summary of literature search

The literature search yielded 3546 citations after duplicates were removed, of which 200 were reviewed in full-text and 44 included in the review (Figure 2.1). A further 26 potentially relevant citations were identified through searching the reference lists of the included studies; 17 were reviewed in full and an additional 9 included in the review. The 53 reports described 47 studies: 39 studies were included in the mortality analysis, of which 18 were also included in the mortality risk factors analysis; 30 studies were included in the aetiology analysis.

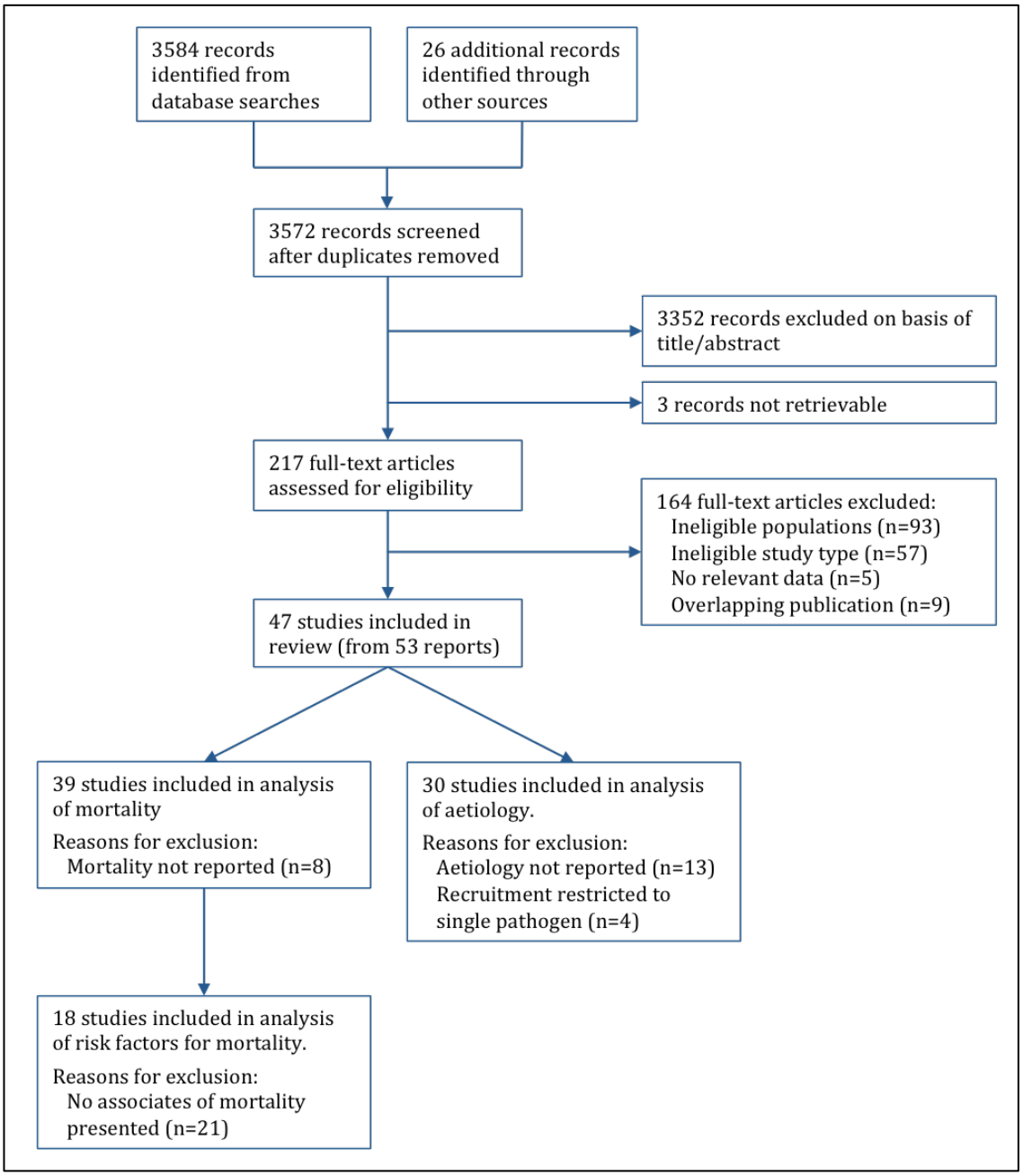

Figure 2.1 Flow diagram of study selection for systematic review

2.5.2 Characteristics of included studies

2.5.2.1 Distribution

The 47 studies were performed in 15 countries (Table 2.1). The geographical distribution across sub-Saharan Africa was uneven; studies from South Africa (12 studies), Kenya (6 studies), Nigeria (5 studies) and Côte d'Ivoire (5 studies) accounted for half of the total included. Within countries, most studies were conducted in major urban centres. 11 studies were completed prior to 1990. A further 15 were completed prior to 2000.

2.5.2.2 Design and setting

The majority of studies were hospital-based, mainly recruiting patients from general ward or emergency department settings. Three studies restricted recruitment to patients admitted to high dependency units (HDU) or intensive care units (ICU)(Feldman *et al.*, 1995; Hartung *et al.*, 2011; Potgieter *et al.*, 1992); only two studies were community based (Gilks *et al.*, 1996; Mwachari *et al.*, 2006).

Most studies were prospective observational studies in design. The median number of patients included was 100 (interquartile range: 81-121); 22 studies included fewer than 100 patients (Table 2.1). All studies combined included 6184 patients.

2.5.2.3 Patient selection

A pneumonia case definition was explicitly stated in all but 10 studies, but in these, requirement for radiographic confirmation was implied. Only three studies recruited patients based solely on a clinical case definition (Birkhamshaw *et al.*, 2013; Gordon *et al.*, 2002; Harries *et al.*, 1988b). Other exclusion criteria used included: prolonged symptom duration (Albrich *et al.*, 2012; Fiberesima *et al.*, 2008; French *et al.*, 2002; Mwachari *et al.*, 2006; Ouedraogo *et al.*, 2010; Scott *et al.*, 2000; Zoubga *et al.*, 2000); recent hospitalisation (Birkhamshaw *et al.*, 2013; Onyedum *et al.*, 2011; Rakotoson *et al.*, 2010); prior antibiotic use (Coulibaly *et al.*, 1986; Domoua *et al.*, 1993; Koffi *et al.*, 2001) and severe illness (Coulibaly *et al.*, 1986; Harries *et al.*, 1988b; Mwachari *et al.*, 2006).

HIV testing was performed in 25 of the studies overall and 24 of the 36 completed after 1990 (Table 2.3). Five studies focused specifically on HIV-positive patients (Domoua *et al.*, 1993; Gilks *et al.*, 1996; Schleicher *et al.*, 2005; Sire *et al.*, 2010; Vray *et al.*, 2008) whilst two specifically restricted analysis to HIV-negative patients (Fiberesima *et al.*, 2008; Sow *et al.*, 1996).

Studies varied in the way they dealt with patients with TB. 15 studies specifically excluded all patients with TB including both those identified at presentation and those diagnosed subsequently during their work-up. Several other studies excluded patients with evidence of TB at presentation (typically on the basis of positive smear microscopy) but then performed systematic TB diagnostic testing on enrolled patients and presented the results in their aetiological descriptions (Albrich *et al.*, 2012; Fiberesima *et al.*, 2008; Mwachari *et al.*, 2006; Sire *et al.*, 2010; Vray *et al.*, 2008).

Table 2.1 Summary of studies included in systematic review. Studies classified by setting and grouped by country. Demographics shown as proportion male and mean ±standard deviation of whole cohort unless otherwise specified.

Reference	Country; region	Study period	Methodology	Population	Pneumonia case definition	Demographics		Analyses
						%male	Age	
Community-based studies								
(Gilks *et al.*, 1996)	Kenya, Nairobi	Oct 1989 – Sep 1992	Single centre, prospective, observational cohort study	Female sex workers under follow-up for IPD; n=719. 76 episodes of pneumonia in HIV-positive patients.	Acute cough and fever with new radiographic consolidation	0	29±7	Aetiology
(Mwachari *et al.*, 2006)	Kenya, Nairobi	Aug 2002 – July 2003	Multicentre, prospective, observational study	Consecutive patients ≥18 yrs with mild-moderate severity CAP; n=531. *Exclusions:* severe disease; suspected TB *Subgroups:* HIV-positive, n=193; HIV-negative, n=338	Acute illness (≤14 days) with cough, ≥1 other symptom and radiographic consolidation	51.6 HIV-pos., 43.0 HIV-neg., 56.2	33.7±11.4 HIV-pos., 33.2±8.7 HIV-neg., 34.1±12.7	Aetiology
Hospital-based studies								
(Zoubga *et al.*, 2000)	Burkina Faso, Bobo-Dioulasso	Feb 1997 - Jan 1998	Single centre, prospective, observational study	Hospitalised patients ≥15 yrs with signs of pneumonia and symptoms <1 month; n=106. *Exclusions:* positive AFB smear	Signs of pneumonia, symptoms <1 month and radiological confirmation	63.2	20-45, 67%	Mortality
(Ouedraogo *et al.*, 2010)	Burkina Faso, Bobo-Dioulasso	Jan 2005 – Dec 2006	Single centre, retrospective case series	Adults hospitalised with acute presumed bacterial pneumonia; n=239. *Exclusions:* suspected/confirmed TB; incomplete records	Pulmonary infection (<1 month) with CXR suggestive of bacterial pneumonia and neutrophilia	65.7	44.4	Mortality, aetiology
(Koulla-Shiro *et al.*, 1994)	Cameroon, Douala	March – June 1992	Single centre, prospective, observational study	Consecutive patients ≥15 yrs hospitalised with CAP; n=43.	Clinical features with pulmonary opacity on CXR	69.8	45; range 15-81	Mortality, aetiology
(Koulla-Shiro *et al.*, 1997)	Cameroon, Yaounde	Dec 1991 – Feb 1993	Multicentre, prospective, observational study	Consecutive patients ≥15 yrs hospitalised with CAP; n=91. *Exclusions:* TB; subsequent non-pneumonia diagnosis	Clinical features consistent with acute LRTI and radiographic confirmation	71.4	36.5±14.8	Mortality, prognostics, aetiology
(Yone *et al.*, 2012)	Cameroon, Yaounde	Jan 2008 – May 2012	Single centre, retrospective case series	Patients ≥15 yrs hospitalised with CAP; n=106. *Exclusions:* HIV status unknown	LRT signs, new alveolar opacity on CXR without alternative cause	48.1	Med. 40; IQR 31.75-53	Mortality, prognostics

Reference	Country; region	Study period	Methodology	Population	Pneumonia case definition	Demographics		Analyses
						%male	Age	
(Vray *et al.*, 2008)	Central African Republic, Bangui	Sep 2002 – Dec 2005	Multicentre, prospective, observational study	HIV-positive patients ≥18 yrs hospitalised with pneumonia; n=101. *Exclusions:* positive AFB smear; terminal AIDS	Clinical features of pneumonia with radiographic features compatible with infection: focal or diffuse opacities; lymphadenopathy	34.7	Med. 34; IQR 29-40	Mortality, aetiology
(Coulibaly *et al.*, 1986)	Cote d'Ivoire, Abidjan	1986[a]; 5 months	Single centre, prospective, non-comparative clinical trial	Hospitalised patients with acute presumed bacterial pneumonia; n=47. *Exclusions:* prior antibiotics; severe shock; penicillin allergy; concurrent meningitis	Clinician diagnosis with radiological confirmation; not otherwise specified	72.3	Range 16-57	Aetiology
(Domoua *et al.*, 1993)	Cote d'Ivoire, Abidjan	Jan – Oct 1990	Single centre, prospective, observational study	HIV-positive patients with acute pneumonia; n=70. *Exclusions:* prior antibiotics *Subgroups:* hospitalised patients, n=58; outpatients, n=12 (excluded).	Clinician diagnosis with radiological confirmation; not otherwise specified	-	33; range 22-59	Mortality, aetiology
(Koffi *et al.*, 1997)	Cote d'Ivoire, Abidjan	Jan 1994 – March 1995	Single centre, retrospective case series	Adults hospitalised with presumed bacterial pneumonia; n=96. *Exclusions:* positive AFB smear; confirmed/suspected PCP; HIV status unknown	Relevant symptoms with positive auscultatory findings and radiographic confirmation	71.9	31.5; range 15-45	Mortality, prognostics
(Koffi *et al.*, 2001)	Cote d'Ivoire, Abidjan	April 1998 – Oct 1999	Single centre, retrospective case series	Adults hospitalised with presumed bacterial pneumonia; n=100. *Exclusions:* positive AFB smear; pre-hospital antibiotics; death <72 hours of admission	Clinical features with radiographic consolidation and neutrophilia.	57.0	-	Mortality
(Horo *et al.*, 2009)	Cote d'Ivoire, Abidjan	2009[a]; 12 months	Single centre, prospective, observational cohort study	Patients ≥15 yrs hospitalised with (presumed bacterial) CAP; n=50. *Exclusions:* TB; HIV status unknown; interstitial shadowing on CXR; unable to afford investigations *Subgroups:* HIV-positive, n=29; HIV-negative, n=21	Clinical features with radiographic alveolar consolidation and leucocytosis or elevated CRP.	-	40.8 HIV-pos., 38.2 HIV-neg., 44.5	Mortality, prognostics

Reference	Country; region	Study period	Methodology	Population	Pneumonia case definition	Demographics		Analyses
						%male	Age	
(Aderaye, 1994a, 1994b)	Ethiopia, Addis Ababa	Aug 1987 – July 1989	Single centre, prospective, observational study	Consecutive patients ≥14 yrs hospitalised with CAP; n=110. *Subgroups:* HIV-positive, n=9; HIV-negative, n=101.	Acute illness with radiological pulmonary shadowing	56.3 HIV-pos., 77.8 HIV-neg., 54.5	35; range 14-75 HIV-pos., 30.5±8.1 HIV-neg., 35.5±15.4	Mortality, prognostics, aetiology
(Ahmedtaha *et al.*, 2014)	Ethiopia, Jimma	March 2008 – Feb 2009	Single centre, retrospective, observational study	Consecutive patients ≥15 yrs hospitalised with CAP; n=104.	Clinician diagnosis; not otherwise specified	71.2	<44, 66.3%	Mortality, prognostics
(Slack *et al.*, 1976)	Kenya, Nairobi	1976[a]	Single centre, prospective, observational study	Adults presenting to hospital emergency department and medical filter clinic with acute pneumonia; n=105.	Acute history with compatible symptoms, positive auscultatory findings and radiographic confirmation	72.4	Commonest age group 20-30 yrs	Mortality, aetiology
(Scott *et al.*, 2000)	Kenya, Coast Province	March 1994 – May 1996	Single centre, prospective, observational study	Consecutive patients ≥15 yrs hospitalised with acute pneumonia; n=281. *Subgroups:* HIV-positive, n=147; HIV-negative, n=134	Acute illness (≤14 days) with ≥2 respiratory symptoms and pulmonary consolidation on CXR	63.0	15-24, 23%; 25-34, 40%; 35-44, 22%; 45-54, 8%; 55-85, 8%	Mortality, prognostics, aetiology
(French *et al.*, 2002)	Kenya, Nairobi	2002[a]	Single centre, prospective, observational study	Consecutive adults hospitalised with pneumococcal pneumonia; n=122. *Subgroups:* HIV-positive, n=60; HIV-negative, n=62	Acute (≤28 days) febrile respiratory illness with LRT signs and parenchymal abnormality on CXR and *S. pneumoniae* isolated in blood or lung aspirate.	72.1 HIV-pos., 66.7 HIV-neg., 77.4	HIV-pos., med. 31; range 19-54 HIV-neg., med. 30; range 16-71	Mortality, prognostics
(Odera *et al.*, 2009)	Kenya, Nairobi	March – June 2007	Single centre, prospective, observational, case-control study	Patients ≥18 yrs admitted with provisional diagnosis of pneumonia; n=120. Aims to identify risk factors for *Legionella* pneumonia	Clinician diagnosis; not otherwise specified	60.8	38.7	Aetiology
(Rakotoson *et al.*, 2010)	Madagascar, Antananarivo	Sep 2006 – Aug 2007	Single centre, prospective, observational study	Patients ≥16 yrs hospitalised with CAP; n=96. *Exclusions:* positive AFB smear; prior hospitalisation within 7 days	Clinical features with radiographic consolidation and either neutrophilia or elevated CRP/ESR.	61.5	41.8; range 16-90	Mortality

Reference	Country; region	Study period	Methodology	Population	Pneumonia case definition	Demographics		Analyses
						%male	Age	
(Harries *et al.*, 1988b)	Malawi, Lilongwe	May – August 1986	Single centre, prospective, observational study	Hospitalised adults with clinically defined lobar pneumonia; n=100. *Exclusions:* positive AFB smear; prior pulmonary TB; complicating disease; severe illness	Compatible clinical features with unilateral chest signs	74.0	34; range 14-76	Mortality
(Gordon *et al.*, 2002)	Malawi, Blantyre	Oct 1997 – March 1999	Single centre, prospective, observational study	Consecutive adult patients hospitalised with IPD; n=217. Subset diagnosed with pneumonia, n=92.	Focal chest signs in patient with pneumococcal bacteraemia	57.6	33.9	Mortality, prognostics
(Birkhamshaw *et al.*, 2013)	Malawi, Blantyre	Feb – March 2010	Single centre, retrospective, observational study	All patients hospitalised with a clinical diagnosis of acute LRTI; n=240. *Exclusions:* known malignancy; prior hospitalisation within 14 days; illness duration >21 days	Clinician primary diagnosis of LRTI/CAP plus ≥2 recognised signs and symptoms of CAP	48.3	Med. 37; IQR 29-48; range 16-85	Mortality, prognostics
(Bos *et al.*, 2014)	Mozambique, Beira	April – June 2010	Single centre, prospective, observational study	Patients ≥16 yrs presenting to emergency room with LRTI; n=177. 86 with pneumonia	LRTI defined by fever plus ≥1 relevant symptom; pneumonia by radiographic confirmation	45.2	16-45, 85%	Aetiology
(Sofowora *et al.*, 1973)	Nigeria, Ibadan	1969 – 1971	Single centre, retrospective, observational study	Consecutive patients ≥15 yrs with pneumonia; n=88.	Clinician diagnosis; not otherwise specified	56.8	20-45, 75%; range 15-65	Mortality, aetiology
(Awunor-Renner, 1979)	Nigeria, Zaria	1979[a]	Single centre, retrospective, observational study	Adults hospitalised with pneumonia; n=73. *Exclusions:* prior antibiotics; 'reluctant to cooperate'	Relevant symptoms with positive auscultatory findings and radiographic confirmation	63.0	30.1; range 12-60	Mortality, aetiology
(Fiberesima *et al.*, 2007, 2008)	Nigeria, Port Harcourt	May 2002 – April 2003	Multicentre, prospective, observational study	Consecutive patients ≥15 yrs hospitalised with CAP; n=54. *Exclusions:* Known HIV-positive; known TB; COPD; illness duration >14 days	Clinical features with radiographic consolidation	55.6	38.1±17.6	Mortality, aetiology
(Onyedum *et al.*, 2011)	Nigeria, Enugu	July 2003 – July 2008	Single centre, retrospective case series	Hospitalised patients ≥18 yrs with final diagnosis of pneumonia; n=160. *Exclusions:* recent prior hospitalisation or hospitalised >48 hours; CXR unavailable	≥2 relevant symptoms with positive auscultatory findings and radiographic confirmation	55.0	52.9±19.0	Mortality, prognostics
(Mbata *et al.*, 2013)	Nigeria, Enugu	Dec 2008 – June 2009	Single centre, prospective, observational study	Consecutive patients ≥18 yrs with CAP seen in emergency department or medical outpatients; n=80.	Acute respiratory illness (≥2 symptoms) with acute infiltrates on CXR	48.8	56±18	Mortality, prognostics

Reference	Country; region	Study period	Methodology	Population	Pneumonia case definition	Demographics		Analyses
						%male	Age	
(Sow *et al.*, 1996)	Republic of Guinea, Conakry	March 1992 – March 1993	Multicentre, prospective, observational study	Patients ≥15 yrs diagnosed with CAP; n=218. *Exclusions:* HIV-positive; TB; nosocomial pneumonia	Compatible respiratory symptoms with fever and new densities on CXR	79.4	38±16	Mortality
(Sire *et al.*, 2010)	Senegal, Dakar	June 2003 – Dec 2004	Multicentre, prospective, observational study	HIV-positive patients ≥18 yrs hospitalised with pneumonia; n=70. *Exclusions:* positive AFB smear; terminal AIDS	Clinical features of pneumonia with radiographic features compatible with infection: focal or diffuse opacities; lymphadenopathy	55.7	Med. 39; IQR 32-47	Mortality, aetiology
(Prout *et al.*, 1983)	South Africa, Cape Town	Feb – June 1980	Single centre, retrospective, observational study	Consecutive adults with acute pneumonia presenting to the emergency unit; n=81. *Exclusions:* alternative final diagnosis; inadequate follow-up data.	Clinician diagnosis; not otherwise specified	67.9	39; range 14-85	Mortality, aetiology
(Maartens *et al.*, 1994)	South Africa, Cape Town	July 1987 – July 1988	Single centre, retrospective case series	Adults hospitalised with CAP; n=92. *Exclusions:* pulmonary TB; advanced immunosuppression; serology specimen unavailable	Acute respiratory illness with compatible shadowing on CXR	56.5	43.4	Aetiology
(Feldman *et al.*, 1996)	South Africa, Johannesburg	1996[a]	Single centre, prospective, observational case-control study	Patients hospitalised with CAP. *Subgroups:* General wards, n=47; ICU, n=19 (excluded)	Acute, pyrexial LRTI, acquired in the community and associated with clinical and radiological evidence of consolidation	ICU 89.5 Ward 66.0	ICU, range 18-62 Ward, range 15-71	Mortality, prognostics, aetiology
(Feldman *et al.*, 1999)	South Africa, Johannesburg	1999[a]; 2 yrs	Single centre, retrospective, observational study	Consecutive adult patients with bacteraemic pneumococcal pneumonia; n=112. *Subgroups:* HIV-positive, n=31; HIV-negative, n=81	Clinician diagnosis; not otherwise specified	73.9 HIV-pos., 58.3 HIV-neg., 79.6	37.7 HIV-pos., 32.8±2.9 HIV-neg., 39.6±1.7	Mortality, prognostics
(Mpe *et al.*, 2001)	South Africa, Medunsa	2001[a]; 12 months	Single centre, prospective, observational study	Consecutive adults hospitalised with CAP; n=123. *Exclusions:* TB	Acute, pyrexial LRTI acquired in the community with clinical and radiological evidence of consolidation	40.8	Range 13-85	Mortality, aetiology

Reference	Country; region	Study period	Methodology	Population	Pneumonia case definition	Demographics		Analyses
						%male	Age	
(Charalambous *et al.*, 2003)	South Africa, Free State	Feb 1998 – Feb 1999	Single centre, prospective, observational cohort study	Gold miners admitted to company hospital with bacterial pneumonia; n=108 with 124 episodes of pneumonia. *Exclusions:* confirmed TB. *Subgroups:* HIV-positive, n=119; HIV-negative, n=5	Clinical features with radiographic confirmation and either pathogen isolation or satisfactory response to treatment	100	<30, 9.3%; 30-39, 46.3%; 40-49, 39.8%; >50, 4.6%	Mortality, aetiology
(Schleicher *et al.*, 2005)	South Africa, Johannesburg	Jan 2001 – Oct 2003	Single centre, prospective, observational, case-control study	Hospital HIV-positive patients with CAP; n=67: Cases - confirmed pneumococcal CAP, n=33 (data presented); controls - confirmed pulmonary TB, n=34.	Clinical features of pneumonia and leucocytosis/leucopaenia and new infiltrate on CXR	51.5	32.5±10.5	Mortality
(Nyamande *et al.*, 2006; Nyamande *et al.*, 2007a)	South Africa, Durban	June 2000 – Oct 2001	Single centre, prospective, observational study	Consecutive patients ≥18 yrs hospitalised with CAP; n=430. *Exclusions:* bronchiectasis, interstitial lung disease; bronchial carcinoma *Subgroups:* HIV-positive, n=311; HIV-negative, n=71	Compatible respiratory symptoms and abnormal CXR with new infiltrate or consolidation	37.4	33; range 18-82	Mortality, prognostics, aetiology
(Xaba *et al.*, 2014)	South Africa, Pretoria	Jan 2010 – Jan 2012	Single centre, retrospective, observational cohort study	Random selection of patients ≥ 13 yrs diagnosed with CAP; n=200	Clinician diagnosis; not otherwise specified	67.5	43.6; range 14-89	Mortality
(Albrich *et al.*, 2012; Albrich *et al.*, 2014a; Albrich *et al.*, 2014b)	South Africa, Soweto	Dec 2005 – Sep 2007	Single centre, prospective, observational study	Patients ≥18 yrs hospitalised with acute pneumonia; n=370. *Exclusions:* Known TB *Subgroups:* HIV-positive, n=280	Relevant acute (≤14 days) symptoms with positive auscultatory findings and radiographic confirmation	41.8 HIV-pos., 37.1	38.4±12.2 HIV-pos., 36.5±9.7	Mortality, prognostics, aetiology
(Roe, 1968)	Uganda, Jinja	March 1966 – Aug 1967	Single centre, retrospective case series	Adults admitted with radiologically proven lobar or segmental pneumonia; n=101	Clinician diagnosis; not otherwise specified	78.2	-	Mortality, aetiology
(Yoshimine *et al.*, 2001)	Uganda, Kampala	Nov 1996 – March 1998	Single centre, prospective, observational study	Patients ≥18 yrs admitted with CAP; n=99. *Subgroups:* HIV-positive, n=74; HIV-negative, n=25	New pulmonary infiltrate on CXR with compatible clinical features or elevated white cell count or CRP	65.7 HIV-pos., 66.2 HIV-neg., 64.0	34.2 HIV-pos., 33.2±9.8 HIV-neg., 37.2±21.2	Aetiology

Reference	Country; region	Study period	Methodology	Population	Pneumonia case definition	Demographics		Analyses
						%male	Age	
(El-Amin, 1978)	Zambia, Solwezi	Jan – Oct 1976	Single centre, prospective, observational study	All patients with presumed bacterial pneumonia; n=109	Not otherwise specified; all patients had radiographic confirmation	54.1	34.4; range 20-65	Aetiology
High dependency or intensive care unit studies								
(Hartung *et al.*, 2011)	Malawi, Blantyre	Feb – Sep 2006	Single centre, prospective, observational study	Patients ≥18 yrs with clinical diagnosis of severe pneumonia; n=51. *Exclusions:* positive AFB smear; unsuitable for bronchoscopy	Clinical features with radiographic abnormality consistent with infection	54.9	35; range 17-88	Mortality, prognostics, aetiology
(Potgieter *et al.*, 1992)	South Africa, Cape Town	Jan 1987 – Dec 1989	Single centre, prospective, observational study	Patients with a diagnosis of acute pneumonia admitted to ICU; n=178. Data extracted for the subset of 95 with CAP. *Exclusions:* TB; major immunocompromise	Clinical (incl. pyrexia, cough, purulent sputum, crackles, bronchial breathing), leucocytosis/neutrophilia, and infiltrate on CXR	64.2	47; range 13-84	Mortality, aetiology
(Feldman *et al.*, 1989; Feldman *et al.*, 1995)	South Africa, Johannesburg	Jan 1982 – Dec 1992	Single centre, retrospective, observational study	Consecutive patients admitted to ICU with severe CAP; n=259. Mortality risk factors described in subset of 73 with lobar CAP *Exclusions:* TB.	Acute LRTI with clinical and radiological evidence of pulmonary consolidation	77.2	43.9; range 14-75	Mortality, prognostics, aetiology

AFB – acid fast bacilli; CAP – community-acquired pneumonia; CRP - C-reactive protein; CXR – chest radiograph; ESR – erythrocyte sedimentation rate; IPD – Invasive pneumococcal disease; LRT – lower respiratory tract; LRTI – lower respiratory tract infection; Med. – Median; IQR – interquartile range; TB – tuberculosis

[a] Study period not stated; publication year used.

[b] Considered the primary reference for studies described in multiple reports; used for subsequent citations.

.

2.5.2.4 Assessment of the risk of bias

The risk of bias was considered for the mortality, prognostics and aetiology analyses separately (Table 2.2).

Of the 39 studies included in the mortality analysis 11 were assessed to have a low-risk of bias on the basis of my assessment. The most common reason studies were judged to have high risk of bias was inadequate CAP case definition – either non-radiographic or not clearly defined. Inter-observer agreement with the second reviewer was fair (agreement 65.7%; kappa 0.37; 95% CI: 0.11-0.63).

Only two of the 18 studies included in the risk factors for mortality analysis were judged overall to have a low risk of bias (Albrich *et al.*, 2014a; Scott *et al.*, 2000) on the basis of my assessment. The two most common reasons for studies being assessed as having a high risk of bias were lack of prospective, systematically collected data on putative risk factors and a failure to control for confounding variables in statistical analysis. Inter-observer agreement with the second reviewer was perfect (agreement 100%; kappa 1.00).

For studies included in the aetiological analysis, 12 of 30 studies were considered to have a low risk of bias on the basis of my assessment. Inter-observer agreement with the second reviewer was slight (agreement 66.7%; kappa 0.12).

Table 2.2 Risk of bias assessment. Green, red and orange fields indicate a low, high and unclear risk of bias, respectively. Grey for non-applicable fields in bold in the three right-most columns indicate the overall risk of bias for the specified analysis (See section 2.5.6 and Appendix A for further details).

		Key indicator domains							Analyses		
Reference	**Country**	*Case definition*	*Generalisability*	*Follow-up*	*Exposure*	*Outcome data*	*Data analysis*	*Microbiology*	**Mortality**	**Prognostics**	**Aetiology**
Community-based studies											
(Gilks *et al.*, 1996)	Kenya										
(Mwachari *et al.*, 2006)	Kenya										
Hospital-based studies											
(Zoubga *et al.*, 2000)	Burkina Faso										
(Ouedraogo *et al.*, 2010)	Burkina Faso										
(Koulla-Shiro *et al.*, 1994)	Cameroon										
(Koulla-Shiro *et al.*, 1997)	Cameroon										
(Yone *et al.*, 2012)	Cameroon										
(Vray *et al.*, 2008)	CAR										
(Coulibaly *et al.*, 1986)	Cote d'Ivoire										
(Domoua *et al.*, 1993)	Cote d'Ivoire										
(Koffi *et al.*, 1997)	Cote d'Ivoire										
(Koffi *et al.*, 2001)	Cote d'Ivoire										
(Horo *et al.*, 2009)	Cote d'Ivoire										
(Aderaye, 1994a)	Ethiopia										
(Ahmedtaha *et al.*, 2014)	Ethiopia										
(Slack *et al.*, 1976)	Kenya										
(Scott *et al.*, 2000)	Kenya										
(French *et al.*, 2002)	Kenya										
(Odera *et al.*, 2009)	Kenya										
(Rakotoson *et al.*, 2010)	Madagascar										
(Harries *et al.*, 1988a)	Malawi										
(Gordon *et al.*, 2002)	Malawi										
(Birkhamshaw *et al.*, 2013)	Malawi										
(Bos *et al.*, 2014)	Mozambique										
(Sofowora *et al.*, 1973)	Nigeria										
(Awunor-Renner, 1979)	Nigeria										
(Fiberesima *et al.*, 2008)	Nigeria										
(Onyedum *et al.*, 2011)	Nigeria										
(Mbata *et al.*, 2013)	Nigeria										
(Sow *et al.*, 1996)	Rep. of Guinea										
(Sire *et al.*, 2010)	Senegal										
(Prout *et al.*, 1983)	South Africa										
(Maartens *et al.*, 1994)	South Africa										
(Feldman *et al.*, 1996)	South Africa										
(Feldman *et al.*, 1999)	South Africa										
(Mpe *et al.*, 2001)	South Africa										
(Charalambous *et al.*, 2003)	South Africa										
(Schleicher *et al.*, 2005)	South Africa										
(Nyamande *et al.*, 2007a)	South Africa										
(Xaba *et al.*, 2014)	South Africa										
(Albrich *et al.*, 2012)	South Africa										
(Roe, 1968)	Uganda										
(Yoshimine *et al.*, 2001)	Uganda										
(El-Amin, 1978)	Zambia										

Reference	Country	Key indicator domains							Analyses		
		Case definition	*Generalisability*	*Follow-up*	*Exposure*	*Outcome data*	*Data analysis*	*Microbiology*	**Mortality**	**Prognostics**	**Aetiology**
High-dependency or intensive care unit studies											
(Hartung *et al.*, 2011)	Malawi										
(Potgieter *et al.*, 1992)	South Africa										
(Feldman *et al.*, 1995)	South Africa										

2.5.3 Patient characteristics

2.5.3.1 Demographics

34 of the 42 studies describing the sex distribution of recruited patients reported a male majority (Table 2.1). The median proportion of males recruited was 61% (interquartile range (IQR): 54-71%). Based on 28 studies that presented sufficient information, the estimated age was 38.3 years (95% CI: 36.4-40.2).

2.5.3.2 Comorbid illness

The most commonly reported comorbidity was HIV (Table 2.3). In the 24 studies reporting HIV status, the mean proportion of patients infected was 55.0% (IQR: 34.6-75.0). Previous TB and lung disease were reported in 11.2% (IQR: 7.2-19.7; 6 studies) and 10.8% (IQR: 4.0-13.7%; 13 studies), respectively. Four studies reported the proportion of patients with any comorbid illnesses; the median proportion was 44.9% (IQR: 37.4-55.8%). Approximately 28% (IQR: 15.0-34.5%; 16 studies) of all patients reported being current smokers. There was marked heterogeneity between studies for the proportions of patients affected for nearly all comorbid conditions.

Table 2.3 Summary of comorbid conditions in CAP patients.

Comorbid condition	No. studies	Total patients	Summary		References
			Median, % (IQR)		
HIV[a]	24	3927	55.0	(34.6-75.0)	(Aderaye, 1994a; Ahmedtaha *et al.*, 2014; Albrich *et al.*, 2012; Birkhamshaw *et al.*, 2013; Bos *et al.*, 2014; Feldman *et al.*, 1999; French *et al.*, 2002; Hartung *et al.*, 2011; Horo *et al.*, 2009; Koffi *et al.*, 1997; Koffi *et al.*, 2001; Koulla-Shiro *et al.*, 1997; Koulla-Shiro *et al.*, 1994; Mbata *et al.*, 2013; Mwachari *et al.*, 2006; Nyamande *et al.*, 2007a; Odera *et al.*, 2009; Onyedum *et al.*, 2011; Ouedraogo *et al.*, 2010; Scott *et al.*, 2000; Xaba *et al.*, 2014; Yone *et al.*, 2012; Yoshimine *et al.*, 2001; Zoubga *et al.*, 2000)
Lung disease[b]	13	1730	10.8	(4.0-13.7)	(Aderaye, 1994a; Ahmedtaha *et al.*, 2014; Feldman *et al.*, 1999; Feldman *et al.*, 1995; Koffi *et al.*, 2001; Koulla-Shiro *et al.*, 1997; Maartens *et al.*, 1994; Mbata *et al.*, 2013; Mpe *et al.*, 2001; Onyedum *et al.*, 2011; Prout *et al.*, 1983; Sire *et al.*, 2010; Xaba *et al.*, 2014)
Previous TB	6	777	11.2	(7.2-19.7)	(Aderaye, 1994a; Ahmedtaha *et al.*, 2014; Charalambous *et al.*, 2003; Feldman *et al.*, 1995; Koffi *et al.*, 2001; Rakotoson *et al.*, 2010)
Heart disease[c]	7	1057	2.7	(1.3-5.3)	(Feldman *et al.*, 1999; Feldman *et al.*, 1995; Maartens *et al.*, 1994; Mbata *et al.*, 2013; Rakotoson *et al.*, 2010; Sow *et al.*, 1996; Xaba *et al.*, 2014)
Renal disease[d]	5	658	1.7	(1.5-5.2)	(Feldman *et al.*, 1995; Koffi *et al.*, 2001; Mbata *et al.*, 2013; Mpe *et al.*, 2001; Rakotoson *et al.*, 2010)
Diabetes	10	1260	4.2	(3.4-6.9)	(Feldman *et al.*, 1999; Feldman *et al.*, 1995; Koffi *et al.*, 2001; Koulla-Shiro *et al.*, 1997; Koulla-Shiro *et al.*, 1994; Maartens *et al.*, 1994; Mbata *et al.*, 2013; Mpe *et al.*, 2001; Onyedum *et al.*, 2011; Xaba *et al.*, 2014)
Neurological disease[e]	5	917	1.5	(1.3-7.9)	(Feldman *et al.*, 1995; Mbata *et al.*, 2013; Onyedum *et al.*, 2011; Sow *et al.*, 1996; Xaba *et al.*, 2014)
Malignant disease[f]	6	870	1.0	(0.2-1.7)	(Aderaye, 1994a; Feldman *et al.*, 1999; Feldman *et al.*, 1995; Koulla-Shiro *et al.*, 1997; Mbata *et al.*, 2013; Sow *et al.*, 1996)
Any comorbid illness	4	614	44.9	(37.4-55.8)	(Ahmedtaha *et al.*, 2014; Feldman *et al.*, 1995; Koulla-Shiro *et al.*, 1997; Onyedum *et al.*, 2011)
Smoking	16	2307	28.4	(15.0-34.5)	(Aderaye, 1994a; Albrich *et al.*, 2012; Birkhamshaw *et al.*, 2013; Charalambous *et al.*, 2003; Domoua *et al.*, 1993; Horo *et al.*, 2009; Koffi *et al.*, 2001; Koulla-Shiro *et al.*, 1997; Koulla-Shiro *et al.*, 1994; Mpe *et al.*, 2001; Odera *et al.*, 2009; Onyedum *et al.*, 2011; Ouedraogo *et al.*, 2010; Rakotoson *et al.*, 2010; Scott *et al.*, 2000; Yone *et al.*, 2012)

[a] Studies restricting recruitment to only HIV-positive or HIV-negative patients excluded. [b] Unspecified respiratory or chronic lung disease, COPD, asthma and bronchiectasis. [c] Unspecified cardiovascular or heart disease and cardiac/heart failure; excludes hypertension alone. [d] Unspecified renal disease, renal failure and chronic kidney disease. [e] Unspecified neurological or neuropsychiatric disease, epilepsy, cerebrovascular disease and stroke. [f] Two studies reported no patients with underlying malignant disease; one restricted to lung cancer only.

2.5.4 Mortality

Amongst general hospital inpatient populations mortality rates ranged from 0 – 22.7% (Table 2.4). The overall estimated median mortality rate was 9.8% (IQR: 4.1-18.7%). The median mortality rate was similar in the 11 studies with a low risk of bias at 9.8% (IQR: 2.6-13.4%; range 1.9-17%). In the three studies of HDU or ICU populations, mortality rates ranged from 21.6-45.2% (Feldman *et al.*, 1995; Hartung *et al.*, 2011; Potgieter *et al.*, 1992) with a median of 32.6% (IQR:). Neither of the two community-based studies reported on mortality (Gilks *et al.*, 1996; Mwachari *et al.*, 2006). Only nine studies specifically defined the time-point following admission at which mortality was recorded.

Table 2.4 CAP mortality by study setting and grouped by country.

Citation	Country	Mortality time point	No. deaths/ patients	Mortality rate (95% CI)
Hospital-based studies				
(Zoubga *et al.*, 2000)	Burkina Faso	Inpatient	10/106	9.4 (3.9-15.0)
(Ouedraogo *et al.*, 2010)	Burkina Faso	Inpatient	52/239	21.8 (16.5-27.0)
(Koulla-Shiro *et al.*, 1994)	Cameroon	Inpatient	0/43	0 (0-4.3)
(Koulla-Shiro *et al.*, 1997)	**Cameroon**	**Inpatient**	**7/91**	**7.7 (2.2-13.2)**
(Yone *et al.*, 2012)	Cameroon	Inpatient	13/106	12.3 (6.0-18.5)
(Vray *et al.*, 2008)	CAR	21 days	15/95	15.8 (8.5-23.1)
(Domoua *et al.*, 1993)	Cote d'Ivoire	Inpatient	12/52	23.1 (11.6-34.5)
(Koffi *et al.*, 1997)	Cote d'Ivoire	Inpatient	5/96	5.2 (0.8-9.7)
(Koffi *et al.*, 2001)	Cote d'Ivoire	Inpatient	5/100	5.0 0.7-9.3)
(Horo *et al.*, 2009)	Cote d'Ivoire	3 days	3/50	6.0 (0-12.6)
(Aderaye, 1994a)	**Ethiopia**	**6-8 weeks**	**11/110**	**10.0 (4.4-15.6)**
(Ahmedtaha *et al.*, 2014)	Ethiopia	Inpatient	21/104	20.2 (12.5-27.9)
(Slack *et al.*, 1976)	**Kenya**	**Inpatient**	**2/105**	**1.9 (0-4.5)**
(Scott *et al.*, 2000)	**Kenya**	**3 weeks**	**25/255**	**9.8 (6.2-13.5)**
(French *et al.*, 2002)	Kenya	Inpatient	12/122	9.8 (4.6-15.1)
(Rakotoson *et al.*, 2010)	**Madagascar**	**Inpatient**	**2/96**	**2.1 (0-4.9)**
(Harries *et al.*, 1988b)	Malawi	Inpatient	1/100	1.0 (0-3.0)
(Gordon *et al.*, 2002)	Malawi	Inpatient	18/92	19.6 (11.5-27.7)
(Birkhamshaw *et al.*, 2013)	Malawi	Inpatient	43/235	18.3 (13.4-23.2)
(Sofowora *et al.*, 1973)	Nigeria	Inpatient	20/88	22.7 (14.0-31.5)
(Awunor-Renner, 1979)	Nigeria	Radiological resolution	0/73	0 (0-2.5)
(Fiberesima *et al.*, 2008)	Nigeria	21 days	4/53	7.5 (0-14.7)
(Onyedum *et al.*, 2011)	Nigeria	Inpatient	19/160	11.9 (6.9-16.9)
(Mbata *et al.*, 2013)	**Nigeria**	**30 days**	**12/80**	**15.0 (7.2-22.8)**
(Sow *et al.*, 1996)	Rep. of Guinea	Inpatient	13/218	6.0 (2.8-9.1)
(Sire *et al.*, 2010)	Senegal	21 days	13/68	19.1 (9.8-28.5)
(Prout *et al.*, 1983)	South Africa	Inpatient (min. 14 days)	3/81	3.7 (0-7.8)
(Feldman *et al.*, 1996)	**South Africa**	**Inpatient**	**1/47**	**2.1 (2.0-6.3)**
(Feldman *et al.*, 1999)	South Africa	Inpatient	4/94	4.3 (0-8.3)
(Mpe *et al.*, 2001)	**South Africa**	**Inpatient**	**15/123**	**12.2 (6.4-18.0)**
(Charalambous *et al.*, 2003)	South Africa	Inpatient (min. 14 days)	5/124	4.0 (0.1-7.5)
(Schleicher *et al.*, 2005)	**South Africa**	**Inpatient**	**1/33**	**3.0 (0-8.9)**
(Nyamande *et al.*, 2007a)	**South Africa**	**Inpatient**	**73/430**	**17.0 (13.4-20.5)**
(Xaba *et al.*, 2014)	South Africa	Inpatient	39/200	19.5 (14.0-25.0)
(Albrich *et al.*, 2012)	**South Africa**	**Inpatient**	**52/357**	**14.6 (10.9-18.2)**
(Roe, 1968)	Uganda	Inpatient	2/97	2.1 (0-4.9)
				Median, % (IQR)
Overall				9.8 (4.1-18.7)
Low risk of bias studies				9.8 (2.6-13.4)

Citation	Country	Mortality time point	No. deaths/ patients	Mortality rate (95% CI)
High-dependency or intensive care unit studies				
(Hartung *et al.*, 2011)	Malawi	Inpatient	11/51	21.6 (10.3-32.9)
(Potgieter *et al.*, 1992)	South Africa	Inpatient	28/95	29.5 (20.3-38.6)
(Feldman *et al.*, 1995)	South Africa	Inpatient	117/259	45.2 (39.1-51.2)
				Median, % (IQR)
Overall				29.5 (25.6-37.4)

2.5.5 Risk factors for mortality

The description of risk factors for mortality was poor; only two studies had a low risk of bias (Table 2.2). A formal meta-analysis of morality risk factors was not attempted in view of the limited data available, variability in how risk features were defined (e.g. different blood pressure or respiratory rate thresholds to define abnormality) and the inability to adequately account for confounding factors. A narrative summary of the available data is provided.

2.5.5.1 Demographic

Five studies investigated the association between sex and Malawi. In a large cohort from Malawi, Birkhamshaw *et al.* reported significantly greater inpatient mortality amongst males in multivariable analysis (aOR 2.64; 95% CI: 1.07-6.51). This finding was not replicated in any of the other four studies (Feldman *et al.*, 1995; Hartung *et al.*, 2011), including two with low risk of bias (Albrich *et al.*, 2012; Scott *et al.*, 2000).

The relationship between age and risk of mortality was described in five studies. There was no consistent association with advancing age: two studies described increased risk (Ahmedtaha *et al.*, 2014; Scott *et al.*, 2000), one reduced risk (Birkhamshaw *et al.*, 2013), and two others found no significant association (Albrich *et al.*, 2012; Hartung *et al.*, 2011).

2.5.5.2 Comorbid illnesses

The relationship between mortality and HIV status was examined in 14 studies ranging in size from 50 to 430 patients. None demonstrated a significant association; estimated effect sizes ranged from OR 0.52 (95% CI: 0.28-0.94) to OR 4.44 (95% CI: 0.49-41.25). The two studies with low risk of bias estimated the OR for mortality at 1.23 (95% CI: 0.49-3.13)(Scott *et al.*, 2000) and 0.84 (95% CI: 0.33-2.15), respectively.(Albrich *et al.*, 2012).Three other studies examined the impact of *any* underlying comorbid illness (including HIV) on mortality, but again, none demonstrated a significant association. (Ahmedtaha *et al.*, 2014; Feldman *et al.*, 1995; Mbata *et al.*, 2013).

2.5.5.3 Clinical features

Whilst variably defined, hypotension was consistently associated with mortality in the three cohorts of general ward patients in it was assessed with effect sizes ranging from aOR 3.72 (95%: 1.51-9.13) to OR 10.4 (95% CI: 1.8-60.6)(Birkhamshaw *et al.*, 2013; Feldman *et al.*, 1996; Gordon *et al.*, 2002). Neither of the two studies from HDU settings reported a significant association of reduced blood pressure with mortality (Feldman *et al.*, 1995; Hartung *et al.*, 2011).

The association of tachypnoea (defined as a respiratory rate greater than 30 breaths/minute) with mortality was examined in three studies (Ahmedtaha *et al.*, 2014; Birkhamshaw *et al.*, 2013), one of which reported an increased risk of death but with very wide confidence intervals (OR 10.89; 95% CI: 1.23-96.08)(Feldman *et al.*, 1996). Two additional studies found no difference in mean baseline respiratory rates between patients who died and those who survived (Feldman *et al.*, 1995; Hartung *et al.*, 2011). A study from Kenya, however, found self-reported dyspnoea was strongly associated with mortality (OR 4.04; 95% CI: 1.34-12.14) (Scott *et al.*, 2000).

Four studies examined the association of heart rate with mortality (Feldman *et al.*, 1996; Feldman *et al.*, 1995; Hartung *et al.*, 2011; Scott *et al.*, 2000). Only Scott *et al*. found a significant association with tachycardia (aOR 1.64 for every 10 beats/min above 90 beats/min)(Scott *et al.*, 2000).

Oxygen saturations were only measured in two studies from Malawi and neither identified a significant association with mortality (Birkhamshaw *et al.*, 2013; Hartung *et al.*, 2011). A single study from Malawi examined the effect of temperature and found in multivariable analysis that an abnormal temperature (either high or low) was associated with increased mortality risk (Birkhamshaw *et al.*, 2013).

Both of the two studies that analysed the risk of mortality with cachexia found significant associations (Birkhamshaw *et al.*, 2013) aOR 6.61; 95% CI: 2.61-16.70. (Nyamande *et al.*, 2007a) RR 3.02; $P<0.001$. Non-ambulatory status was associated with mortality in multivariable analysis (aOR 2.46; 95% CI: 1.26-4.82)(Birkhamshaw *et al.*, 2013).

2.5.5.4 Radiological features

The single study with low risk of bias that presented data on radiographic changes described an approximate 4-fold increase in mortality with multilobar consolidation compared to unilobar involvement (OR 4.50; 95% CI: 1.65-13.5) (Scott *et al.*, 2000). Neither the general ward (Feldman *et al.*, 1996) nor the ICU cohort (Feldman *et al.*,

1995) from South Africa demonstrated a significant relationship of multilobar involvement with morality. Birkhamshaw *et al*., in a cohort from Malawi, found no association of either multizonal or bilateral radiographic changes with mortality, although chest radiographs were available for analysis in only 61% of patients (Birkhamshaw *et al.*, 2013).

2.5.5.5 Laboratory indices

A single study from Malawi found in univariable analysis haemoglobin was lower in non-survivors (Hartung *et al.*, 2011). Three of four studies described an association of white cell count with mortality: two showed reduced white cell count in non-survivors (Feldman *et al.*, 1996; Feldman *et al.*, 1995); one other showed an abnormal white cell count (either high (i.e. >18; OR 7.33; 95% CI: 1.2-42.9) or low (i.e. <4; OR 5.79; 95% CI: 1.43-27.4) was associated with mortality (Scott *et al.*, 2000).

Three studies reported on the relationship of biochemical parameters with mortality (Feldman *et al.*, 1996; Feldman *et al.*, 1995; Nyamande *et al.*, 2007a). Two described significant reduction in serum albumin and/or serum protein in non-survivors (Feldman *et al.*, 1995; Nyamande *et al.*, 2007a). An association of elevated creatinine and urea with mortality was described in one and two studies, respectively (Feldman *et al.*, 1996; Feldman *et al.*, 1995).

2.5.5.6 Severity assessment tools

The performance of CURB65 in predicting mortality was described in two studies. In a cohort of 88 patients from Nigeria, 30-day mortality rose with CURB65 and at a threshold score of 3 or more, sensitivity and specificity were 80% and 97%, respectively (Mbata *et al.*, 2013). Albrich *et al.* in a cohort of 280 HIV-infected patients from South Africa found CURB65 was not a useful discriminator of in-hospital mortality (Albrich *et al.*, 2012). CRB65 (the abbreviated version of CURB65 that does not require laboratory urea measurement) showed only moderate discriminative capability (i.e. CRB65 ≥2: sensitivity 36%; specificity 81%; positive predictive value 30%; negative predictive value 85%; AUROC 0.65) for predicting inpatient mortality in a cohort of patients from Malawi (Birkhamshaw *et al.*, 2013).

2.5.6 Clinical specimens and microbiological techniques

The clinical specimens collected and the microbiological techniques used to define CAP aetiology are summarised in Table 2.5. A combination of blood and expectorated sputum culture were performed in 16 of the 30 studies included in the analysis. Four studies used only sputum microscopy and culture (El-Amin, 1978; Mwachari *et al.*, 2006; Roe, 1968; Sofowora *et al.*, 1973). The adequacy of sputum quality control procedures was difficult to assess. Results were rarely disaggregated by site of pathogen isolation; thus it was not possible to consistently identify aetiologies assigned on the basis of sputum analysis alone versus those where an isolate was obtained from a sterile site.

Several studies used more invasive techniques to obtain lower respiratory specimens: four studies collected tracheobronchial aspirates; six studies collected bronchoalveolar (BAL) specimens. However, specimen collection was often not systematic (Domoua *et al.*, 1993; Feldman *et al.*, 1995) or restricted to a limited subset of patients related to their ability to tolerate the procedure (Hartung *et al.*, 2011) or because of lack of response to initial therapy (Nyamande *et al.*, 2007a; Ouedraogo *et al.*, 2010; Potgieter *et al.*, 1992). Transthoracic needle aspiration was systematically used in two studies as an alternative approach to obtaining lower respiratory tract specimens (Aderaye, 1994a; Scott *et al.*, 2000).

17 studies included at least one method of TB diagnostic testing, but in eight was smear microscopy alone. Testing for atypical bacterial pathogens was performed in nine studies using serological methods. An additional four studies used urinary antigen testing to identify *Legionella pneumophila* infection (Mpe *et al.*, 2001; Odera *et al.*, 2009; Sire *et al.*, 2010; Vray *et al.*, 2008). Molecular PCR-based diagnostic methods were only used in two studies (Albrich *et al.*, 2012; Hartung *et al.*, 2011).

Several studies deliberately used a restricted array of diagnostics only capable of detecting specific pathogens of interest: *S. pneumoniae* (Albrich *et al.*, 2012; Bos *et al.*, 2014), *L. pneumophila* (Odera *et al.*, 2009) or other atypical pathogens (Maartens *et al.*, 1994).

Table 2.5 Summary of microbiological techniques/specimens used for pathogen detection.

Specimen/test	Studies using technique, n (%)	Additional details	Citations
Blood culture	20 (67)		(Aderaye, 1994a; Albrich et al., 2012; Awunor-Renner, 1979; Charalambous et al., 2003; Domoua et al., 1993; Feldman et al., 1996; Feldman et al., 1995; Fiberesima et al., 2007, 2008; Gilks et al., 1996; Hartung et al., 2011; Koulla-Shiro et al., 1997; Mpe et al., 2001; Nyamande et al., 2007a; Ouedraogo et al., 2010; Potgieter et al., 1992; Prout et al., 1983; Scott et al., 2000; Sire et al., 2010; Slack et al., 1976; Vray et al., 2008)
Sputum Gram stain	16 (53)		(Aderaye, 1994a; Albrich et al., 2012; Charalambous et al., 2003; Feldman et al., 1996; Feldman et al., 1995; Koulla-Shiro et al., 1994; Mwachari et al., 2006; Nyamande et al., 2007a; Potgieter et al., 1992; Prout et al., 1983; Roe, 1968; Sire et al., 2010; Slack et al., 1976; Sofowora et al., 1973; Vray et al., 2008; Yoshimine et al., 2001)
Sputum culture	21 (70)		(Albrich et al., 2012; Awunor-Renner, 1979; Bos et al., 2014; Charalambous et al., 2003; El-Amin, 1978; Feldman et al., 1996; Feldman et al., 1995; Fiberesima et al., 2008; Gilks et al., 1996; Koulla-Shiro et al., 1997; Koulla-Shiro et al., 1994; Mwachari et al., 2006; Nyamande et al., 2007a; Potgieter et al., 1992; Prout et al., 1983; Roe, 1968; Sire et al., 2010; Slack et al., 1976; Sofowora et al., 1973; Vray et al., 2008; Yoshimine et al., 2001)
Sputum AFB microscopy	16 (53)		(Aderaye, 1994a; Albrich et al., 2012; Charalambous et al., 2003; El-Amin, 1978; Fiberesima et al., 2008; Gilks et al., 1996; Hartung et al., 2011; Koulla-Shiro et al., 1994; Mwachari et al., 2006; Nyamande et al., 2007a; Roe, 1968; Scott et al., 2000; Sire et al., 2010; Slack et al., 1976; Sofowora et al., 1973; Vray et al., 2008)
Sputum mycobacterial culture	7 (23)		(Charalambous et al., 2003; Gilks et al., 1996; Mwachari et al., 2006; Scott et al., 2000; Sire et al., 2010; Vray et al., 2008; Yoshimine et al., 2001)

Specimen/test	Studies using technique, n (%)	Additional details	Citations
Transthoracic needle aspiration	2 (7)	Bacterial microscopy and culture, pneumococcal antigen detection, AFB smear microscopy (both studies); mycobacterial culture (1 study).	(Aderaye, 1994a; Scott et al., 2000)
Tracheobronchial aspirate	4 (13)	Gram stain and culture (all studies); AFB microscopy, pneumococcal and *H. influenzae* antigen detection (1 study).	(Coulibaly et al., 1986; Domoua et al., 1993; Feldman et al., 1995; Potgieter et al., 1992)
Bronchoalveolar lavage	6 (20)	Investigations: bacterial microscopy and culture (6 studies); fungal microscopy and culture (5 studies); mycobacterial microscopy and culture (4 studies); P. jirovecii IF (4 studies); *Legionella* IF (2 studies); multiplex PCR for atypical bacteria and viruses (1 study).	(Hartung et al., 2011; Nyamande et al., 2007a; Ouedraogo et al., 2010; Potgieter et al., 1992; Sire et al., 2010; Vray et al., 2008)
Pleural fluid	3 (10)	Investigations: Gram stain and culture (2 studies); pneumococcal antigen detection (2 studies).	(Aderaye, 1994a; Koulla-Shiro et al., 1994; Ouedraogo et al., 2010)
Pneumococcal urine antigen test	7 (23)	Other studies tested for pneumococcal antigen in: sera (5 studies), sputum/bronchial aspirate (3 studies), pleural fluid (1 study), transthoracic needle aspirate (2 studies).	(Aderaye, 1994a; Albrich et al., 2014a; Bos et al., 2014; Nyamande et al., 2007a; Scott et al., 2000; Sire et al., 2010; Vray et al., 2008)
Legionella urine antigen test	5 (17)		(Mpe et al., 2001; Nyamande et al., 2007a; Odera et al., 2009; Sire et al., 2010; Vray et al., 2008)
Serology	9 (30)	Pathogens: *Legionella* spp. (4 studies); *M. pneumoniae* (9 studies); *C. pneumoniae* (5 studies); *C. psittaci* (3 studies); *C. burnetti* (4 studies); respiratory viruses (3 studies).	(Aderaye, 1994a; Feldman et al., 1996; Feldman et al., 1995; Koulla-Shiro et al., 1997; Maartens et al., 1994; Nyamande et al., 2007a; Potgieter et al., 1992; Prout et al., 1983; Scott et al., 2000)
Molecular	2 (7)	Multiplex PCR for atypical bacteria and respiratory viruses on nasopharyngeal aspirate with *S. pneumoniae* colonisation density (1 study) or on BAL (1 study).	(Albrich et al., 2012; Hartung et al., 2011)

AFB – acid-fast bacilli; BAL – bronchoalveolar lavage; IF – immunofluorescence; PCR – polymerase chain reaction

Table 2.6 Aetiology of CAP by HIV status in hospitalised patients. Percentages refer to the proportion of patients with specific pathogen identified; patients may have more than one pathogen and totals may exceed 100%. Overall weighted average combines data for HIV-positive, HIV-negative and HIV mixed/unknown studies. Studies with low risk of bias shown in bold. - indicates relevant diagnostic test not performed and ? that data not available or proportion is unclear. Qualifying information provided where possible in final column and indicated by * or ^.

			% with specified pathogen												
Citation	**Country**	**No. patients**	*S. pneumoniae*	*H. influenzae*	*S. aureus*	*K. pneumoniae*	Other Gram-negative bacilli[a]	*P. aeruginosa*	*M. pneumoniae*	*C. pneumoniae*	*Legionella spp.*	Viruses	*M. tuberculosis*	None identified	**Other pathogens or comments**
HIV positive															
(Vray *et al.*, 2008)[b]	**CAR**	**101**	**3**	**?***	**7**	**?***	**?***	**?***	**-**	**-**	**?***	**-**	**29**	**53**	*P. jirovecii* 2%* Total for all bacteria 24%
(Domoua *et al.*, 1993)	Cote d'Ivoire	70	1	0	1	1	11*	0	-	-	-	-	-	83	*Streptococcal* spp. 1%; * 10% due to *Salmonella* Enteritidis
(Scott *et al.*, 2000)	**Kenya**	**147**	**44**	**4**	**0**	**0**	**6***	**?^**	**3**	**0**	**0**	**8**	**13**	**33**	Nontuberculous mycobacteria 4%; * 4% due to *Salmonella*; ^ Not reported by HIV status; ~<1%
(Sire *et al.*, 2010)[b]	**Senegal**	**70**	**3**	**6**	**6**	**9**	**20**	**10**	**-**	**-**	**1**	**-**	**13**	**47**	*P. jirovecii* 4%. * Total for all bacteria 34%
(Yoshimine *et al.*, 2001)	**Uganda**	**74**	**23**	**12**	**5**	**4**	**4**	**0**	**-**	**-**	**-**	**-**	**3**	**45**	*M. catarrhalis* 11%; *Haemophilus* spp. 3%
(Charalambous *et al.*, 2003)	**South Africa**	**119**	**31**	**8**	**3**	**4**	**1**	**2**	**-**	**-**	**-**	**-**	**Excl.**	**52**	
(Nyamande *et al.*, 2007a)[c]	**South Africa**	**311**	**20**	**3**	**5**	**1**	**3**	**1**	**?***	**?***	**<1**	**-**	**23**	**?***	*C. neoformans* 1%; Chicken pox <1%. *P. jirovecii* 12% in subset.[c] * Not reported by HIV status: *M. pneumoniae* ~14%; *C. pneumoniae* ~4%; None identified ~48%
(Albrich *et al.*, 2012)	**South Africa**	**280**	**35 (54)***	**-**	**-**	**-**	**-**	**-**	**?^**	**-**	**-**	**?^**	**25**	**?**	* With molecular diagnostics tests; ^ 17% mycoplasma or viral infections
HIV positive weighted average															
High quality studies only		1102	26	5	4	2	5	2	-	-	<1	-	20	-	
All studies		1172	24	5	4	2	6	2	-	-	<1	-	20	-	

Citation	Country	No. patients	% with specified pathogen												Other pathogens or comments
			S. pneumoniae	*H. influenzae*	*S. aureus*	*K. pneumoniae*	Other Gram-negative bacilli[a]	*P. aeruginosa*	*M. pneumoniae*	*C. pneumoniae*	*Legionella spp.*	Viruses	*M. tuberculosis*	None identified	
HIV negative															
(Scott *et al.*, 2000)	**Kenya**	**134**	**49**	**3**	**3**		**1**	**?***	**2**	**0**	**0**	**4**	**5**	**37**	Nontuberculous mycobacteria 4%; Nocardia 1% * Not reported by HIV status; ~<1%
(Fiberesima *et al.*, 2008)[g]	Nigeria	54	17	0	4	15	7	6	-	-	-	-	20	57	
(Maartens *et al.*, 1994)[d]	South Africa	92	-	-	-	-	-	-	1	21	9	-	Excl.	?	*C. psittaci* 5%; *Coxiella burnetii* 0%
(Nyamande *et al.*, 2007a)	**South Africa**	**71**	**17**	**6**	**6**	**1**	**3**	**6**	**?***	**?***	**0**	**-**	**25**	**?^**	*Bacillus* spp. 3%; Chicken pox 1%; Anaerobes 1% * Not reported by HIV status: *M. pneumoniae* ~14%; *C. pneumoniae* ~4%; ^ Not reported by HIV status; overall ~48%
(Yoshimine *et al.*, 2001)	**Uganda**	**25**	**8**	**4**	**4**	**8**	**0**	**0**	**-**	**-**	**-**	**-**	**0**	**72**	*Haemophilus* spp. 5%
HIV negative weighted average															
High quality studies only		230	34	4	4	1	1	4	-	-	0	-	11	-	
All studies		376	31	3	4	4	2	5	2	8	3	-	11	-	
Mixed or unknown HIV status															
(Ouedraogo *et al.*, 2010)	Burkina Faso	239	6	0	3	4	10		-	-	-	-	Excl.	82	
(Koulla-Shiro *et al.*, 1994)	Cameroon	43	33	0	2	2	0	0	-	-	-	-	14	56	
(Koulla-Shiro *et al.*, 1997)	**Cameroon**	**91**	**24**	**2**	**7**	**6**	**0**	**0**	**9**	**5**	**-**	**-**	**Excl.**	**47**	*Coxiella burnetii* 9%; *M. catarrhalis* 2; *Strep. pyogenes* 2%
(Coulibaly *et al.*, 1986)	Cote d'Ivoire	47	72	36	2	9	2	0	-	-	-	-	-	?	Anaerobes 8.5%
(Aderaye, 1994a)	Ethiopia	110	69	0	6	2	5	2	3	-	0	7	6	?	*C. psittaci* 4%; *C. burnetti* 0%
(Slack *et al.*, 1976)	Kenya	105	49	0	1	2	1	0	-	-	-	-	1	45	

Citation	Country	No. patients	% with specified pathogen												Other pathogens or comments
			S. pneumoniae	*H. influenzae*	*S. aureus*	*K. pneumoniae*	Other Gram-negative bacilli[a]	*P. aeruginosa*	*M. pneumoniae*	*C. pneumoniae*	*Legionella spp.*	Viruses	*M. tuberculosis*	None identified	
(Odera *et al.*, 2009)[e]	**Kenya**	**120**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**9**	**-**	**-**	**91**	
(Bos *et al.*, 2014)[f]	**Mozambique**	**86**	**41**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**?**	
(Sofowora *et al.*, 1973)	Nigeria	88	14	0	0	7	21	11	-	-	-	-	2	41	
(Awunor-Renner, 1979)	Nigeria	73	52	3	0	0	0	0	-	-	-	-	-	41	
(Prout *et al.*, 1983)	South Africa	81	22	10	1	1	3	0	9	-	-	12	6	46	
(Feldman *et al.*, 1996)	South Africa	47	13	9	0	2	0	0	0	-	-	-	-	75	*S. viridans* 4%; *M. catarrhalis* 2%
(Mpe *et al.*, 2001)	**South Africa**	**120**	**11**	**0**	**3**	**3**	**2**	**0**	**-**	**-**	**2**	**-**	**Excl.**	**83**	
(Roe, 1968)	Uganda	101	19	0	30	11	0	7	-	-	-	-	-	?	*Strep. pyogenes* 30%
(El-Amin, 1978)	Zambia	109	27	4	20*	5	13	6	-	-	-	-	0	8	* Refers to Staphylococcal species
Overall weighted average															
High quality studies only		1797	27	4	4	2	4	1	8	2	2	-	19	-	
All studies		3056	27	3	5	3	5	2	7	5	2	7	14	-	

[a] Includes Enterobacteriaceae and lactose non-fermenters, but not *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Moraxella catarrhalis* or atypical pathogens.

[b] Excluded patients with positive AFB smear on spontaneously expectorated sputum specimen.

[c] 266 patients underwent more extended investigation with bronchoscopy (reported in Nyamande 2006); results not reported by HIV status.

[d] Study focused on atypical pathogens only.

[e] Study focused on *Legionella* spp. only; [f] Study focused on *S. pneumoniae* only.

[g] Patients known to be HIV-positive at presentation were excluded; 17% of recruited participants HIV-positive.

Table 2.7 Aetiology of CAP of patients admitted to ICU or HDU. Percentages refer to the proportion of patients with specific pathogen identified; patients may have more than one pathogen and totals may exceed 100%. Studies with low risk of bias shown in bold. - indicates relevant diagnostic test not performed and ? that data not available or proportion is unclear. Qualifying information provided where possible in final column and indicated by * or ^.

			% with specified pathogen												
Citation	**Country**	**No. patients**	*S. pneumoniae*	*H. influenzae*	*S. aureus*	*K. pneumoniae*	Other Gram-negative bacilli[a]	*P. aeruginosa*	*M. pneumoniae*	*C. pneumoniae*	*Legionella spp.*	Viruses	*M. tuberculosis*	None identified	**Other pathogens or comments**
(Hartung *et al.*, 2011)[b]	**Malawi**	**51**	**10**	**0**	**10**	**4**	**0**	**0**	**0**	**0**	**0**	**6**	**22**	**8**	*P. jirovecii* 27%; Pulmonary KS found in 16%
(Feldman *et al.*, 1995)	South Africa	259	29	1	3	19	6	<1	1	-	<1	1	Excl.	39	
(Potgieter *et al.*, 1992)[c]	South Africa	95	33	13	8	11	2	1*	1*	-	5	1	Excl.	25	Fungal 2%; other Gram-positive 4% * Identified to genus level only
HDU/ICU studies weighted average															
All studies		405	28	4	5	15	5	1	1	-	2	2	-		

[a] Includes Enterobacteriaceae and lactose non-fermenters, but not *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Moraxella catarrhalis* or atypical pathogens;

[b] 94% patients HIV-positive; excluded patients with positive AFB smear on spontaneously expectorated sputum specimen;

[c] Excluded patients with advanced immunosuppression; unclear if this refers to HIV infection.

2.5.7 Aetiology

Unless otherwise stated the narrative summary of results in this section is based on studies with low risk of bias for aetiology analysis. Figures quoted may vary from those presented in Tables 2.6 and 2.7 if an aggregate rather HIV-status-specific estimate is used.

2.5.7.1 Streptococcus pneumoniae

Streptococcus pneumoniae was the most commonly identified pathogen amongst hospitalised patients accounting for approximately one-quarter of all CAP cases. The proportion of CAP attributable to *S. pneumoniae* was higher amongst HIV-negative patients (34% *vs.* 26%), although the estimate for HIV-negative patients is numerically dominated by a single cohort (Scott *et al.*, 2000). A similar overall proportion of pneumococcal pneumonia was seen in the studies from HDU and ICU settings (Hartung *et al.*, 2011). Amongst the six studies with low risk of bias that included pneumococcal urinary antigen testing, proportions with pneumococcal CAP ranged from 3-46% (Albrich *et al.*, 2012; Bos *et al.*, 2014; Nyamande *et al.*, 2007a; Scott *et al.*, 2000; Sire *et al.*, 2010; Vray *et al.*, 2008). One study from South Africa incorporated a new diagnostic assay based on the density of pneumococcal nasopharyngeal colonisation and found 54% of CAP was attributable to *S. pneumoniae* (Albrich *et al.*, 2012).

2.5.7.2 Mycobacterium tuberculosis

Overall *Mycobacterium tuberculosis* was the second most commonly identified pathogen. In studies with low risk of bias that did not specifically exclude TB, it was identified in 19%. Rates in the HIV-positive group (20%) were almost double those of the HIV-negative group (11%). The proportion of cases attributable to TB was similar in the two studies that restricted recruitment to patients with illness duration of less than 14 days (13% (Scott *et al.*, 2000) and 25% (Albrich *et al.*, 2012)). The four studies that used microscopy and mycobacterial culture of BAL specimens identified TB in 13-29% of patients (Hartung *et al.*, 2011; Nyamande *et al.*, 2007a; Sire *et al.*, 2010; Vray *et al.*, 2008).

2.5.7.3 Other bacterial pathogens

Amongst general hospital inpatients, *Haemophilus influenzae, Staphylococcus aureus* and *Klebsiella pneumoniae* accounted for 4%, 4% and 2% of CAP cases, respectively. The relative proportion of cases due to each pathogen did not vary substantially with HIV status. The overall combined data from HDU or ICU settings indicated that *Klebsiella pneumoniae* occurred more frequently in severely ill patients (15%),

although this increase was most notable in the two studies from South Africa (Feldman *et al.*, 1995; Potgieter *et al.*, 1992).

Overall *Pseudomonas aeruginosa* was uncommon, accounting for only 1-2% of cases. However, there was substantial variation and in two studies *Pseudomonas* was identified in more than 10% of cases (Sire *et al.*, 2010; Sofowora *et al.*, 1973).

The combined group of other Gram-negative bacteria that included Enterobacteriaceae and lactose non-fermenters accounted for approximately 5% cases and did not vary markedly with disease severity. Studies varied in the extent to which the specific pathogens within this group were reported separately. Amongst HIV-positive patients, infection with nontyphoidal *Salmonella* (NTS) species (*S. enterica* serovar Enteritidis and *S. enterica* serovar Typhimurium) was noted (Domoua *et al.*, 1993; Scott *et al.*, 2000).

2.5.7.4 Atypical bacteria

Diagnostic testing for atypical bacterial pathogens was limited (Table 2.6); the estimates of the proportion of CAP attributable of *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* presented in Table 2.7 were each based on data from less than 1000 patients. With the exception of a study from Malawi that used a multiplex PCR assay on BAL fluid (Hartung *et al.*, 2011), diagnostic testing was based on serological diagnosis. Overall *M. pneumoniae* and *C. pneumoniae* accounted for 8% and 2% of CAP, respectively.

Testing for *Legionella pneumophila* was more comprehensive (Table 2.6). In cohorts from Kenya and South Africa, that systematically used the BinaxNOW *L. pneumophila* urinary antigen test, *Legionella* was identified in 9% and 2% respectively (Mpe *et al.*, 2001; Odera *et al.*, 2009). *Legionella* accounted for approximately 2% of cases in both general inpatient and high dependency settings.

2.5.7.5 Respiratory viruses

Diagnostic testing for respiratory viruses was performed in six studies, but systematically in only two (Hartung *et al.*, 2011; Scott *et al.*, 2000). Using serological testing alone, a viral aetiology was found in 6% of a Kenyan CAP cohort; influenza was the most commonly identified virus (Scott *et al.*, 2000). Using a multiplex PCR assay on BAL specimens, similar overall rates of viral disease were identified in a Malawian cohort with a mixed array of virus including influenza, parainfluenza, respiratory syncytial and rhinovirus but most frequently as a co-pathogen with bacterial or *Pneumocystis* pneumonia (Hartung *et al.*, 2011). The cases of viral disease identified by

Prout *et al.* in a South African cohort were also mainly as co-pathogens with bacterial pneumonia (Prout *et al.*, 1983).

2.5.7.6 Other causes

Immunofluorescence staining of BAL fluid for *Pneumocystis jirovecii* was performed in four studies. Three of these studies conducted in Central African Republic, Senegal and South Africa recruited general hospital inpatient cohorts of HIV-infected individuals and identified *P. jirovecii* in 2%, 2% and 12%, respectively (Nyamande *et al.*, 2006; Sire *et al.*, 2010; Vray *et al.*, 2008). The fourth study conducted in Malawi recruited a predominantly HIV-infected cohort (94%) admitted to the high dependency unit found 27% of patients to have confirmed or probable PCP (Hartung *et al.*, 2011). The latter study also identified a primary or associated diagnosis of pulmonary Kaposi sarcoma in 16% of patients.

2.6 Discussion

This is the first systematic review of CAP in adults in sub-Saharan Africa. It highlights important differences in the epidemiology, aetiology and outcome of CAP in sub-Saharan Africa compared to other global regions that are relevant to disease assessment and management.

2.6.1 Epidemiology

This review highlights that CAP populations in sub-Saharan Africa are dominated by young patients. This is in marked contrast to well-resourced settings where the burden of CAP, particularly in hospitalised cohorts, is in elderly patients (Ewig *et al.*, 2009; Fine *et al.*, 1996; Welte *et al.*, 2012). Although there are no high quality adult CAP incidence data from sub-Saharan Africa, the observed predominance of young adults in CAP cohorts is likely to reflect the true burden of disease in the population and probably relates both to the underlying population age structure and the dominant impact of HIV on CAP incidence (Benito *et al.*, 2012; Feikin *et al.*, 2004; Gilks *et al.*, 1996; Oxford Institute of Population Ageing, 2015; Segal *et al.*, 2011).

HIV was the dominant comorbid condition, present in around half of CAP patients. Much of the excess risk of CAP associated with HIV infection is preventable with anti-retroviral therapy (ART) and co-trimoxazole preventative therapy (Kohli *et al.*, 2006; Sullivan *et al.*, 2000; Suthar *et al.*, 2015). To date, ART has been started in more than 9 million patients in sub-Saharan Africa (World Health Organization, 2014b). Continued efforts to increase ART rollout coupled with strategies for HIV prevention and early

diagnosis represent important opportunities to markedly reduce the burden of adult CAP in the region.

In contrast to HIV, other chronic comorbid conditions such as COPD, heart failure and ischaemic heart disease - which are very common in hospitalised CAP cohorts from well-resourced settings and are an important driver of CAP-related mortality (Musher *et al.*, 2007; Welte *et al.*, 2012) - are currently present in a small minority of patients. The relative importance of these conditions is likely to increase as life expectancies across sub-Saharan Africa increase (Mathers *et al.*, 2006; World Health Organization, 2014a).

2.6.2 Mortality

The median mortality rates in general hospital ward and HDU/ICU patients were 9.8% and 29.5%, respectively, but rates varied markedly between cohorts. Variations in outcome are expected given differences in demographic and comorbidity profile, disease aetiology and management including the availability of higher level care. Although, observed mortality differences could be in part artifactual and related to differences in the duration of follow-up which for most cohorts was not standardised.

The overall mortality rates are comparable to those reported in well-resourced settings in Europe and US (Ewig *et al.*, 2009; Welte *et al.*, 2012; Yu *et al.*, 2012). The extent to which mortality is preventable with optimised management may differ between these settings. In well-resourced settings, a substantial proportion of total CAP-related deaths occurs in elderly individuals as a result of decompensated comorbid conditions, many of whom have limitations on the treatment interventions (e.g. do not attempt resuscitation orders) (Bauer *et al.*, 2013; Chalmers, 2015; Wunderink, 2015). Mortality may be more readily preventable in younger cohorts with limited cardiopulmonary comorbidity. Further studies are required to define the pattern of treatment response and causes of mortality following CAP in sub-Saharan Africa.

The assessment of risk factors for mortality was poor. 18 studies reported the relationship of mortality to at least one candidate risk factor. Formal meta-analysis was not undertaken. The observed association of hypotension and multilobar consolidation with mortality is consistent with previous studies from other settings (Charles *et al.*, 2008b; Fine *et al.*, 1996). General clinical status variables such as cachexia and inability to stand that are not widely used in well-resourced contexts were also associated with mortality (Birkhamshaw *et al.*, 2013; Nyamande *et al.*, 2007a). Inability to stand has also been identified as an independent risk factor for mortality in other unselected acute medical in-patient populations in Africa (Rylance *et al.*, 2009; Wheeler *et al.*,

2013). It may be useful as a component of a rapid assessment or triage tool, but its accuracy needs to be assessed in prospective studies.

The lack of consistent association between age and mortality risk is notable. Only two of five studies described increasing mortality with advancing age. In studies from high-income settings the increased risk of mortality with advancing age becomes apparent after the age of 40 (Ewig *et al.*, 2009; Fine *et al.*, 1997a). Given the size and age distribution of many cohorts, the power to detect an association with advancing age might be limited.

There was no evidence of an association between HIV status and mortality. Previous studies of the impact of HIV on CAP outcome from other settings have yielded variable results. Two international observational studies indicated no overall impact on CAP outcome (Christensen *et al.*, 2005; Malinis *et al.*, 2010). In bacteraemic pneumococcal CAP, HIV infection with reduced CD4 count is associated with increased mortality (Feldman *et al.*, 2007b). The implication for a resource-limited, sub-Saharan African context is that the presence of HIV alone should not be used as the basis for rationing care on the presumption of substantially worse prognosis.

2.6.3 Aetiology

In keeping with studies from other global regions, *Streptococcus pneumoniae* was the most commonly identified organism across all clinical settings, accounting for approximately 27% of cases. Based on the spectrum of diagnostic modalities used, this is likely to be a substantial underestimate of the true prevalence (Jokinen *et al.*, 2010; Said *et al.*, 2013). Future studies will be required to monitor changes in CAP aetiology following the widespread introduction of infant pneumococcal conjugate vaccination in Africa (Bar-Zeev *et al.*, 2015).

These data highlight the major importance of *Mycobacterium tuberculosis* as a cause of acute CAP in a sub-Saharan African setting. Given the limited array of TB diagnostic tests used in many of the studies and their limited sensitivity for HIV-associated TB in particular (Lawn *et al.*, 2013c), the overall estimate of 19% is likely to considerably underestimate the true frequency. In post mortem series, TB is the most prominent cause of death of HIV-infected patients with respiratory infection (Bates *et al.*, 2013). A recent study from South Africa using an array of conventional and molecular diagnostic tests identified TB in one-third of all acutely hospitalised HIV-infected adults (Lawn *et al.*, 2015). The optimal strategy for identifying TB in patients presenting with acute illness in low-resource settings, including the use of new rapid or point of care assays

(e.g. Xpert MTB/RIF, urinary lipoarabinomannan) is the focus of intense investigation (Peter *et al.*, 2016; Theron *et al.*, 2014).

The frequencies of atypical and Gram-negative enteric bacteria are important considerations when deciding upon appropriate empirical antibacterial therapy. In this review, the reported frequency of disease caused by atypical bacterial pathogens (i.e. *M. pneumoniae*, *C. pneumoniae*, *Legionella* spp.) was comparable to that seen in other global regions (Charles *et al.*, 2008a; Torres *et al.*, 2014). However diagnostic testing was often not systematic and relied on serological testing rather than newly developed more sensitive molecular assays. The necessity of antimicrobial cover for atypical bacterial pathogens amongst hospitalised adults is still unclear –as it is in well-resourced settings (Garin *et al.*, 2014; Postma *et al.*, 2015) – and further studies are needed.

The prevalence of CAP caused by individual species of Gram-negative enteric bacteria was often not reported separately. Amongst HIV-positive patients, a significant proportion of patients presenting with CAP have infection with NTS (Domoua *et al.*, 1993; Scott *et al.*, 2000). These organisms (*S. enterica* serovar Enteritidis and *S. enterica* serovar Typhimurium) are the commonest cause of bacteraemia in sub-Saharan Africa (Reddy *et al.*, 2010). Whether this represents true *Salmonella* pneumonia or disease caused by an undetected co-pathogen in patients with invasive salmonellosis is unclear, but the necessity to consider modifying empirical antimicrobial therapy is the same regardless (Feasey *et al.*, 2012).

Klebsiella pneumoniae – typically implicated as a cause of hospital-acquired pneumonia in well-resourced setting – was identified in 2-3% of hospitalised patients and up to 15% of patients in high dependency settings, although the latter estimation was dominated by studies from South Africa (Feldman *et al.*, 1995; Potgieter *et al.*, 1992). This finding also has implications for empirical antibiotic therapy, particularly for those patients with severe disease or that fail to improve on first line therapy.

Given the high prevalence of HIV, the potential for CAP attributable to opportunistic pathogens in sub-Saharan Africa is clear. *P. jirovecii* was identified in 2-12% of patients in general hospital cohorts (Nyamande *et al.*, 2006; Sire *et al.*, 2010; Vray *et al.*, 2008) and 27% of patients in the single study of high dependency unit patients (Hartung *et al.*, 2011). Diagnosis of *P. jirovecii* pneumonia (PCP) is difficult. It is not reliably distinguished from other causes of pneumonia on clinical or radiological grounds and microbiological confirmation has historically relied on microscopy of invasively obtained lower respiratory tract specimens that are often unobtainable in low-resource

settings (Malin *et al.*, 1995). Recently developed highly sensitive PCR assays may permit the use of more readily obtained clinical specimens (e.g. expectorated sputum, nasopharyngeal aspirate)(Cruciani *et al.*, 2002; To *et al.*, 2013).

The contribution of viruses to the aetiology of CAP has not been adequately addressed by the studies included in this review. Only five studies included diagnostic tests for respiratory viruses of which only two used modern molecular diagnostic assays. In a recent multicentre study of hospitalised adults with CAP in the US, rhinovirus was the most commonly identified pathogen (Jain *et al.*, 2015). Further studies are needed to define the burden of viral pathogens and their relationship with other pneumonia pathogens.

2.6.4 Notable excluded studies

The eligibility criteria for this systematic review were devised to capture studies that described acute CAP populations to give results that were generalisable to unselected adults presenting *de novo* with acute pneumonic illness. Studies that included children younger than 12 years were excluded. A large observational study of 502 patients with lobar pneumonia in Zambia that included children however found similar results: mortality occurred in 4% and associated with advanced age, leucopaenia, multilobar involvement, hypothermia and hypotension; *S. pneumoniae* and tuberculosis were the commonest causes (Allen, 1984).

Studies that selected patients on the basis of failure of response to first-line treatment, prolonged symptoms (e.g. more than 2 or 3 weeks) or that attempted to enrich the cohort for particular pathogens were excluded. Okwera *et al* studied HIV-infected, AFB-smear negative recurrent pulmonary TB suspects in Uganda with symptoms for two or more weeks and identified bacterial and PCP in 27% and 7% respectively, with TB only confirmed in 18% (Okwera *et al.*, 2013). Another study from Uganda in a similar population that also included analysis of BAL specimens found *P. jirovecii* to be the commonest cause of disease, present in 39% (Worodria *et al.*, 2003). Two acute pneumonia cohort studies from Ethiopia and Zimbabwe were excluded because they specifically selected patients with 'atypical' or diffuse radiographic changes. Both found that approximately one-third of cases were each caused by PCP and TB with the remainder attributable to bacteria, Kaposi's sarcoma or other opportunistic infections (Aderaye *et al.*, 2007; Malin *et al.*, 1995).

Studies that specifically recruited patients with SARI as defined by the World Health Organisation were also excluded. The SARI case definition - currently, acute respiratory infection with reported or measured fever, cough, onset within last 10 days and

requirement for hospitalisation - is designed to facilitate standardised reporting of respiratory illness and is mainly used for viral pathogen surveillance (World Health Organization, 2013b). A large SARI surveillance project in rural Kenya that was excluded from this review found a similar spectrum of aetiologies in hospitalised patients (23% pneumococcal disease; 3% NTS; 7% influenza A; 8% respiratory syncytial virus) and comparable 30-day mortality at 6% (Feikin *et al.*, 2012).

2.6.5 Strengths and limitations

This review has provided an inclusive and comprehensive summary of the published literature describing the aetiology and outcome of CAP in sub-Saharan Africa. The search strategy was broad and specifically aimed to access the African literature including that from Francophone countries by using databases such as CAB abstracts and Global Health (CABI, Web of Science) and African Index Medicus. The decision to restrict inclusions to studies describing acute CAP presentations was deliberate but resulted in the exclusion of several high quality studies. As such, this review does not provide specific data to address the important question of what is the aetiology and outcome of pneumonia amongst adults that fails to respond to initial narrow-spectrum antibacterial therapy.

The criteria used to assess the risk of bias and quality of the studies in the review were adapted from those used in the Cochrane Collaboration Tool to Assess Risk of Bias in Cohort Studies and as such were not validated. Several of the criteria, in particular those used to assess the risk of bias for the aetiology analysis, were subjective as demonstrated by the poor agreement between the assessors. Assessing the methodological quality of non-randomised studies is complicated by the range of study designs used and the varying approaches adopted to adjust for confounding. Numerous tools, scales and checklists have been developed for this purpose (Deeks *et al.*, 2003). The Downs scale, for example, lists 27 questions to assess reporting, external validity, bias and confounding. The Newcastle-Ottawa Scale uses a simple scoring system to assess studies across eight domains including representativeness of cohort and appropriateness of analyses. The inter-rate reliability of the tool has been established and it is recommended for use in systematic reviews (Deeks *et al.*, 2003; Wells *et al.*, 2014).

Additional limitations and potential for bias of this review relate mainly to the quality of the data of the included studies. Many studies were small and/or retrospective. Some studies did not describe the CAP case definition used and as such their generalisability is difficult to infer. The included studies were almost universally conducted in large

urban hospitals and as such might not be representative of other settings. In terms of the aetiological data, many of the included studies relied heavily on microscopy and culture of spontaneously expectorated sputum that is particularly susceptible to contamination; fewer than half described robust techniques for assessing the quality of sputum specimens. Only a small number of studies used more invasively obtained specimens such as bronchoalveolar specimens and peripheral lung aspirates. Shortcomings in laboratory testing were further compounded by incomplete and non-systematic specimen collection evident in many studies.

2.6.6 Future research

The description of CAP outcome in sub-Saharan Africa in studies conducted to date has largely been limited to inpatients mortality rate alone. Data from well-resourced settings highlight the persistently elevated risk of death for at least one year following an episode of CAP (Koivula *et al.*, 1999; Waterer *et al.*, 2004). Long-term follow up data from sub-Saharan Africa are needed to estimate the true impact of CAP on survival. Data from well-resourced settings also indicate that only half of all deaths following an episode of CAP are directly attributable to pneumonia itself (Mortensen *et al.*, 2002). Further detailed prospective observational studies are also needed to define the cause of death following CAP to develop appropriate management strategies.

The relative lack of high quality data describing risk factors for adverse outcome in CAP needs to be addressed. These data are necessary to improve prognostication and risk stratification in CAP patients. CAP severity assessment tools (e.g. CURB65, pneumonia severity index) should be prospectively assessed to determine their accuracy and utility in guiding CAP management sub-Saharan African populations.

The potential spectrum of pathogens implicated in CAP in sub-Saharan Africa is broad – particularly for HIV-infected patients – but laboratory infrastructure to support advanced microbiological investigations is often lacking. The utility of recently developed rapid or point-of-care diagnostic tests (e.g. Xpert MTB/RIF, urinary lipoarabinomannan) to effectively direct antimicrobial management in CAP should be examined.

2.7 Conclusions

The major burden of CAP in sub-Saharan Africa is in working age adults and associated mortality is considerable. HIV - the main driver of CAP in this region - is preventable and treatable: substantial reductions in the burden of CAP may be achievable with continued rollout of antiretroviral therapy across the continent. Further research is

required to determine the risk factors predictive of adverse outcome in CAP to both improve prognostication and identify opportunities for intervention. After *S. pneumoniae*, *Mycobacterium tuberculosis* is amongst the most commonly identified pathogens: strategies to improve early detection and treatment are needed.

3 Malawian Adult Lower Respiratory Tract Infection Severity, Aetiology and Outcome (MARISO) Study: Aims, design and methodology.

3.1 Introduction

Local surveillance data from Malawi show that pneumonia is the commonest reason for adult hospitalisation in Malawi (SanJoaquin *et al.*, 2013). However, there are limited recent data from prospective studies describing the outcome and aetiology of community-acquired pneumonia (CAP) in either Malawi or comparable sub-Saharan Africa settings.

I hypothesised that the epidemiology and aetiology of CAP in Malawi would be markedly different to that seen in well-resourced settings and accordingly that clinical predictors of adverse outcome would be different and empirical therapy recommendations from well-resourced settings would fail to provide adequate antimicrobial coverage for the spectrum of pathogens encountered.

The MARISO study was a prospective observational study of adults with clinically diagnosed CAP admitted to Queen Elizabeth Central Hospital (QECH), Blantyre, Malawi. The broad aim was to describe the clinical features, aetiology and outcome of CAP in adults in Malawi with a view to identifying the key risk factors for adverse outcome.

3.2 Objectives

i) To determine the frequency of 30-day mortality and treatment failure amongst adults hospitalised with clinically diagnosed CAP in Blantyre, Malawi and to identify the clinical and laboratory characteristics associated with these poor outcomes.

ii) To describe the microbial aetiology of clinically diagnosed CAP using microbiological culture, serological and molecular techniques.

iii) To determine the median time to clinical stability adults hospitalised with clinically diagnosed CAP

iv) To determine the utility of inflammatory biomarkers in predicting 30-day mortality and treatment failure in adults hospitalised with clinically diagnosed CAP.

3.3 Integration with other respiratory infection studies

The MARISO study was one of several concurrently recruiting projects based at QECH focusing on the clinical epidemiology and aetiology of respiratory infection. Recruitment to the MARISO study was nested within that of the Burden and Severity of HIV-associated Influenza (BASH-FLU) Study (Principal Investigator: Dr Antonia Ho). This case-control study recruited adults with mild (influenza-like illness) and severe (hospitalised LRTI) influenza-associated respiratory illness to determine the association of HIV with disease severity. The eligibility criteria used to define hospitalised LRTI were aligned with that of the MARISO study; patients recruited to the BASH-FLU study were invited to participate in the MARISO study that involved more detailed assessment and follow-up.

Recruitment to the MARISO study also integrated with that of the existing severe acute respiratory infection (SARI) surveillance programme at QECH that aimed to describe the local epidemiology of respiratory viral infections. Latterly, some patients recruited to MARISO were invited to participate in the Acute Infection of the Respiratory Tract (AIR) study (Principal Investigator: Dr Hannah Jary); a case-control study investigating the impact of exposure to indoor air pollution on the risk of developing pneumonia.

Recruitment to the studies was performed by an integrated respiratory infection research clinical study team. Laboratory and clinical data were shared between the respective studies. Recruitment was carefully coordinated so that there was no duplication of clinical specimen sampling and burden on participants was minimised.

3.4 Contributors to the MARISO Study

Patient recruitment and follow-up was performed by the integrated respiratory infection clinical research study team made up of clinical officers and research nurses. I and the principal investigators of the BASH-FLU and AIR studies, Dr Antonia Ho and Dr Hannah Jary, provided direct oversight of recruitment by regularly attending the study ward rounds and confirmed the eligibility of patients for recruitment and assured the quality of clinical data collection. For study participants that could not be reached after hospital discharge, community follow-up was undertaken by two study field workers.

Clinical specimens for haematology, biochemistry and bacteriology tests were processed in the MLW Clinical Diagnostic Laboratory under the supervisions of the laboratory managers, Brigitte Denis and George Selemani. Nasopharyngeal aspirate specimens for molecular respiratory pathogen diagnostic testing were processed at the MLW Molecular Laboratory under the supervision of senior laboratory technician,

Mavis Menyere. Specimens for mycobacterial microscopy and culture and Xpert MTB/RIF testing were process at the College of Medicine Tuberculosis Research Laboratory under the supervision of its manager, Aaron Mdolo.

Chest radiographs were photographed by Antonia Ho, Hannah Jary or myself. The chest radiograph interpreting proforma was developed by Dr Sarah Heath under my supervision as part of Masters research project. Reading and grading of the radiographs was performed by two UK based radiologists, Dr Elizabeth Joekes and Dr Simon Greenwood, and by myself.

I designed the case record forms (CRFs) used for the capture of clinical data in conjunction with Dr Ho. We also shared the tasks of CRF scanning, clinical data verification and cleaning processes.

I developed the statistical analysis plan and undertook all analyses myself with the guidance of Professor Brian Faragher.

3.5 Study design

The MARISO study was a prospective observational cohort study.

3.6 Clinical endpoints

i. 30-day mortality: death on or before the 30th day following hospital admission.

ii. 90-day mortality: death on or before the 90th day following hospital admission.

iii. Treatment failure was defined as clinical deterioration with death, respiratory failure (mechanical ventilation or oxygen saturations <90% without supplemental oxygen), haemodynamic instability (systolic blood pressure <90mmHg or fall by ≥40mmHg from baseline) or persistence/reappearance of fever (≥38°) at 72 hours following the commencement of antimicrobial treatment (Menendez *et al.*, 2008; Menendez *et al.*, 2004b).

iv. Clinical stability was defined as the achievement of all the following parameters: temperature ≤ 37.2°C; heart rate ≤100 beats per minute; respiratory rate ≤24 breaths per minute; systolic blood pressure ≥90mmHg; and oxygen saturations ≥90% without supplemental oxygen (Halm *et al.*, 1998; Menendez *et al.*, 2004a).

3.7 Ethical approval

The study protocol was independently reviewed and approved by the Research Ethics Committee of both the University of Malawi College of Medicine (Protocol No. P.11/12/1309) and the Liverpool School of Tropical Medicine (Protocol No. 13.02).

3.8 Setting

The study was conducted at Queen Elizabeth Central Hospital, Blantyre, Malawi (see section 1.11.2). Recruitment commenced on 15th May 2013 and continued until 31st January 2015. Participant follow-up was completed by 28th May 2015.

3.9 Study participants

The study recruited hospitalised adults with clinically diagnosed pneumonia.

3.9.1 Inclusion criteria

All of the following had to be present:

- Adults (aged 18 years or over)
- Reported or recorded fever (≥38°C)
- Reported cough or chest pain or breathlessness or haemoptysis
- Crepitations or pleural rub or bronchial breathing or percussive dullness or diminished breath sounds on clinical examination

3.9.2 Exclusion criteria

- Pre-admission diagnosis of terminal illness (e.g. metastatic malignancy, terminal AIDS)
- Current anti-tuberculous treatment
- Admitted to hospital more than 24 hours previously
- Symptoms for greater than 14 days
- Prior hospitalisation within last 4 weeks
- Suspected co-existent meningitis
- Prior participation in the study

3.10 Recruitment procedures

Patients were recruited in AETC and the adult medical wards.[1] In AETC, the study nurses were based at the triage station on weekdays between 8am and 3pm. All patients with any features of respiratory illness or infection were referred to the study clinical officers for formal screening against the eligibility criteria listed above. The study team also toured the medical wards each morning[2] to identify patients admitted within the previous 24 hours not previously seen in AETC and screened all those with features of respiratory illness or infection. Patient eligibility was determined by direct interview of the patient and/or their guardian and if necessary by reference to the medical notes. The physical examination to determine eligibility was performed by the study clinical officer.

Potentially eligible patients who were willing to consider participation in the study were given written and verbal information (in either English or Chichewa according to their preference) that provided an overview of the study and its objectives and describing the study procedures and associated risks and benefits. Written informed consent was obtained by a study team member from the patient or, in the case of incapacity, by proxy from their accompanying guardian.

3.11 Clinical assessment

3.11.1 Medical history

For each participant, the study clinical officer completed a thorough clinical assessment using standardised reporting forms (included in Appendix B). The medical history included details of the present illness, past medical and drug history, demographic details, social history and information about household characteristics. Information was obtained via direct questioning of the study participant (or accompanying guardian) and by reference to medical notes and health passport.

3.11.2 Physical examination

The initial physical examination consisted of cardiovascular, upper and lower respiratory tract and abdominal examinations. The examination findings were reported as the presence or absence of pre-specified features, rather than a non-directed description of findings. Level of consciousness was assessed using the AVPU scale (Kelly *et al.*, 2004). Using this simplified tool patients are assessed as "Alert", "Responsive to voice", "Responsive to pain" or "Unresponsive." In lieu of a validated

[1] Recruitment was initially restricted to the AETC. Ward-based recruitment began in May 2014 to allow the recruitment of patients admitted overnight.
[2] Ward-based recruited was extended to weekends from August 2014.

cognitive assessment tool that is not available in Malawi, the presence of confusion was determined using three standardised questions assessing orientation in time, place and person. For patients able to stand, weight and height were measured using mechanical floor scales (seca 761; seca, Birmingham, UK) and a wall-mounted measuring tape (seca 206; seca, Birmingham, UK).

3.11.3 Measurement of physiological observations

The study team measured temperature, blood pressure, heart rate, respiratory rate and oxygen saturations at the point of recruitment.[3] Physiological observations were measured at rest and in accordance with a detailed standardised operating procedure, using study-specific equipment: temperature (Welch Allyn SureTemp Plus thermometer using an oral probe; Welch Allyn, Buckinghamshire, UK); blood pressure (A&D UA767 Digital Blood Pressure Monitor; A&D Instruments, Abingdon, UK); oxygen saturations (CMS50DL Pulse Oximeter or CMS60C Pulse Oximeter; Contec Medical Systems, Qinhuangdao, China). Heart rate was read from the pulse oximeter unless there was a discrepancy of greater than 5 beats/minute with the reading on the sphygmomanometer in which case it was counted manually. Respiratory rate was counted by direct chest visualisation over the course of a full 60 seconds.

3.11.4 Chest radiograph

A plain posteroanterior chest radiograph was requested for all study participants at the point of enrolment. Radiographs were performed in the Department of Radiology, QECH using standard techniques. During the period of the study, there was no functional portable radiograph machine available at QECH; consequently, radiographs were not performed in clinically unstable patients that could not be safely transferred to the radiology department.

3.12 Clinical management

Patient management was directed by the clinical team. Patients recruited by the study team in AETC prior to review by the clinical team were commenced on treatment in accordance with local guidelines for the management of pneumonia. The diagnostic work-up undertaken as part of the study was far more detailed than routinely available at QECH; the study team ensured that clinically relevant results were made available to the clinical team to aid management decisions.

[3] For patients recruited from the medical wards, the observations recorded on admission documented by the AETC triage team were used for the baseline assessment.

3.13 Clinical specimen collection

At the point of enrolment, a 25ml venous blood specimen was obtained for the following investigations: aerobic blood culture, full blood count, urea, creatinine, HIV test and CD4 cell count. Serum specimens were stored for delayed inflammatory biomarker and acute atypical bacteria serological assays.[4] A capillary blood specimen was obtained for point-of-care glucose measurement (Accu-Chek Aviva; Roche, UK) and malaria antigen test (First Response Malaria Ag. pLDH/HRP2 Combo Card Test; Premier Medical Corporation, Daman, India). For patients with productive cough, two spontaneously expectorated sputum specimens were collected for mycobacterial smear microscopy and culture and Xpert MTB/RIF assay (Cepheid; Sunnyvale, California, US). A nasopharyngeal aspirate specimen was collected for molecular testing for influenza viruses (CDC Human Influenza RT-PCR diagnostic panel; CDC Influenza Division, Atlanta, Georgia, US) and a real-time PCR multiplex assay for 33 respiratory pathogens (FTD Respiratory Pathogens 33; Fast-Track Diagnostics, Luxembourg). A urine specimen was collected for pneumococcal urinary antigen testing (BinaxNOW *Streptococcus pneumoniae* antigen card; Alere, Massachusetts, USA) and additional aliquots were stored. For patients with a clinically and radiologically apparent pleural effusion, diagnostic thoracocentesis was performed. Pleural fluid specimens were sent for Gram-stain microscopy and aerobic culture, mycobacterial smear microscopy and culture, and pneumococcal antigen testing (BinaxNOW *Streptococcus pneumoniae* antigen card).

For surviving inpatients, a further venous blood specimen was collected at day 3 and a serum specimen stored for repeated measurement of inflammatory biomarkers. This specimen was omitted for patients known to have a haemoglobin concentration of less than 8 g/dl. A convalescent serum specimen was obtained at approximately six weeks following enrolment for repeated serological assays.

[4] Specimens for acute and convalescent serology were collected for approximately the second half of the patient cohort recruited from 12th May 2014 onwards.

Table 3.1 Clinical specimens collected and investigations performed in MARISO study

Clinical specimen and investigation	
Venous blood	
Full blood count	Urea
HIV test	Creatinine
CD4 cell count	Atypical bacteria serology
Aerobic blood culture	Inflammatory biomarker assays
Finger prick capillary blood	
Glucose	Malarial rapid diagnostic test
Urine	
BinaxNOW Streptococcus pneumoniae antigen test	
Nasopharyngeal aspirate	
Multiplex molecular assays for influenza viruses and other respiratory pathogens	
Sputum	
AFB smear microscopy and mycobacterial culture	Cepheid Xpert MTB/RIF
Pleural fluid	
AFB smear microscopy and mycobacterial culture	BinaxNOW Streptococcus pneumoniae antigen test
Gram stain, microscopy and aerobic bacteriological culture	

3.14 Patient follow-up

Study participants were reviewed on a daily basis each morning. Level of consciousness and orientation, temperature, blood pressure, heart rate, respiratory rate and oxygen saturations were measured daily up to 14 days following hospital admission.[5] The clinical team were promptly informed of markedly abnormal findings that required immediate intervention. At the point of hospital discharge or inpatient death, the study team reviewed the clinical notes and recorded details of treatment administered and discharge diagnosis as determined by the clinical team.

Patients surviving to discharge were contacted at 30-days and 90-days post admission to determine vital status and hospital readmission. Two attempts were made to obtain

[5] Observation rounds were completed once daily in the morning. For patients recruited on the medical wards, the first day post-admission (termed day 1) observations were completed at the time of recruitment if more than 12 hours had elapsed since the time of admission.

this information by phone call to the patient or their guardian; if unsuccessful field workers visited the patient's home.[6]

3.15 Clinical specimen processing

Tuberculosis diagnostic tests were performed at the College of Medicine Tuberculosis Research Laboratory. All other specimen processing and investigations were performed at MLW Clinical Diagnostic and Molecular Laboratories which has an internal quality assurance programme with external quality control. These tests were done by a designated trained technician.

3.15.1 Haematology

Full blood count was performed on whole blood specimens using a Beckman Coulter HmX Haematology Analyser (Beckman Coulter, California, USA). CD4 cell counts were measured according to standard protocols using either a Becton Dickinson FACSCount (Becton Dickinson, California, USA) or Partec CyFlow CD4 Analyser (Sysmex Partec, Görlitz, Germany).

3.15.2 Biochemistry

Whole blood specimens for biochemical assays were centrifuged within 24 hours of collection. Urea and creatinine concentrations were measured in serum specimens using a Beckman Coulter AU480 Chemistry Analyser (Beckman Coulter, California, USA).

3.15.3 Blood culture

Blood cultures were performed using standard aerobic bottles in the BacT/ALERT 3D automated system (bioMérieux, Marcy-L'Etoile, France) as previously described (Everett *et al.*, 2011; Feasey *et al.*, 2014). All isolates were identified using standard diagnostic procedures (Barrow *et al.*, 1993). Coagulase-negative *Staphylococci*, *Bacillus* spp., *Micrococcus* spp. and diphtheroids were considered as contaminants.

3.15.4 HIV test

HIV testing was performed on whole blood specimens using rapid diagnostic test kits in a serial testing pathway in accordance with WHO guidelines (World Health Organization, 2004). Initial screening was performed using the Alere Determine HIV-1/2 Ag/Ab Combo assay (Alere, Massachusetts, USA); negative results were reported and positive results prompted confirmatory testing using the Uni-Gold Recombinogen

[6] Telephone follow-up alone was used for the first 100 patients but there was substantial loss to follow-up so a protocol amendment to permit home follow-up via field worker was made.

HIV-1/2 test (Trinity Biotech, Co Wicklow, Ireland). If results were discrepant a second confirmatory test was performed using a different assay (Bioline HIV-1/2 3.0; Standard Diagnostics, Gyeonggi-do, Republic of Korea).

3.15.5 Respiratory pathogen multiplex PCR

The nasopharyngeal aspirates were divided into aliquots and stored at -80°C in Universal Transport Medium (Copan, Brescia, Italy). These were batch-tested for influenza viruses by real-time reverse transcription polymerase chain reaction (qRT-PCR). Total nucleic acids were extracted from 300µl aliquots of each specimen with the Qiagen BioRobotÒ Universal System using the QIAamp One-For-All nucleic acid kit (Qiagen, Manchester, UK). 5 or 10 µL of nucleic acid extract was used in each qRT-PCR reaction. Both the CDC Human Influenza RT-PCR diagnostic panel (CDC Influenza Division) detecting influenza A and B and influenza A subtypes H1, H3 and H5, and the FTD respiratory pathogens 33 kit (Fast-track Diagnostics, Luxembourg) detecting influenza A, B and C, coronaviruses OC43, NL63, HKU1 and 229E, parainfluenza viruses 1-4; respiratory syncytial viruses (RSV) A and B; enterovirus; human metapneumovirus; rhinovirus; adenovirus; bocavirus; parechovirus; cytomegalovirus (CMV); *Bordetella pertussis*; *Chlamydia pneumoniae*; *Haemophilus influenzae*; *Klebsiella pneumoniae*; *Legionella* spp; *Moraxella catarrhalis*; *Pneumocystis jirovecii*, *Salmonella* species, *Staphylococcus aureus* and *Streptococcus pneumoniae* were used, in combination with the AgPath one-step RT-PCR reagents (Applied Biosystems, Foster City, California, USA). PCR conditions were according to the manufacturer's instructions. Appropriate negative and positive control specimens were run alongside each reaction. Samples with cycle threshold (Ct)-value <40 were recorded as positive.

3.15.6 BinaxNOW® Streptococcus pneumoniae Antigen Card

The BinaxNOW® *Streptococcus pneumoniae* Antigen Card (Alere, Massachusetts, USA) is a lateral flow rapid immunochromatographic assay for the detection of pneumococcal C-polysaccharide coat protein in the urine of patients with pneumonia. The assay was performed in accordance with the manufacturer's instructions (Alere, 2015). Briefly, the test kit swab was submerged in the urine sample and inserted into the specimen window of the assay cartridge, followed by three drops of the assay reagent. The test was read visually in ambient light at 15 minutes. An identical procedure was used for the pleural fluid specimens.

3.15.7 Tuberculosis diagnostic tests

3.15.7.1 Smear microscopy

Sputum and pleural fluid microscopy were performed according to standard procedures. Briefly, the most viscous part of the sputum specimen was aspirated and expelled onto a dry glass slide, spread to make a thin smear and stained using the Auramine O method. Pleural fluid specimens were concentrated by centrifugation at 2800 rpm for 10 minutes prior to smear preparation. Smear specimens were each examined twice by two independent readers using LED fluorescence microscopy and reported according to standard criteria; discordant results prompted review by a third reader. All sample smears graded as scanty, 1+, 2+, and 3+ were defined as smear-positive.

3.15.7.2 Mycobacterial culture

Mycobacterial culture was performed according to standard procedures using the BACTEC MGIT 960 Mycobacterial Detection System (Becton Dickinson Diagnostic Systems, Sparks, Maryland, USA) as previously described (Feasey *et al.*, 2013; Tortoli *et al.*, 1999). Briefly, following decontamination in sodium hydroxide and concentration by centrifugation, sputum and pleural fluid specimens were inoculated into mycobacterial growth indicator tubes (MGIT) tubes and incubated at 37°C in the BACTEC MGIT automated liquid culture system for up to 44 days. Cultured isolates identified as acid-fast bacilli on ZN microscopy were positively confirmed as *Mycobacterium tuberculosis* complex by microscopic cording and MPT-64 lateral flow assay (Capilia; TAUNS Laboratories, Numazu, Japan). Acid-fast bacilli (AFB) isolates that were negative on either confirmatory test were inoculated onto plain Löwenstein-Jensen (LJ) media and incubated at 25°C, 37°C and 45°C and onto paranitrobenzoic acid (PNB) and incubated at 37°C. Isolates that grew on LJ media at 37°C only were classified as *M. tuberculosis*. Those that grew at 25°C or 45°C or on PNB were classified as nontuberculous mycobacteria and not speciated further. Positive cultures that did not reveal AFB on microscopy were re-cultured using a stored aliquot of the primary specimen; if the same result was obtained, they were classified as contaminants or false positives.

3.15.7.3 Cepheid Xpert MTB/RIF

The Cepheid Xpert MTB/RIF assay (Cepheid, Sunnyvale, California, USA) is a self-contained, fully integrated, automated rapid diagnostic system that uses nested real-time PCR to detect *M. tuberculosis* genomic DNA in sputum and other clinical specimens (Lawn *et al.*, 2013c). The assay was performed in accordance with the manufacturer's

instructions (Cepheid, 2015). Briefly, unprocessed sputum specimens were mixed with the dedicated assay Sample Reagent and incubated at room temperature for 15 minutes. The liquefied specimen was then loaded into the Xpert MTB/RIF test cartridge and inserted into the GeneXpert machine for processing.

3.16 Chest radiograph photography and reporting

Plain chest radiograph films were photographed on a light-box using a standard light-reflex digital camera mounted on a tripod in a darkened room. Several high-resolution photographs at a range of exposure settings were taken of each radiograph to compensate for some of the variability in penetration of the original radiograph. All study radiograph reports were generated by review of the set of digital images rather than the original radiograph.

Chest radiographs were reported independently by two UK-based radiologists (Dr Elizabeth Joekes and Dr Simon Greenwood) and myself. All reporters were blinded to demographic and clinical data at the time of reporting. Radiographs were reported using a standardised form developed specifically for the study (see Appendix A). The form was accompanied with guidance notes containing definitions for radiological features based on the Fleischner Society: Glossary of terms for thoracic imaging (Hansell *et al.*, 2008). The form was piloted using a small number of non-study radiographs to ensure consistency of application of the agreed definitions.

The reporting form was based on fixed, categorical responses. Parenchymal abnormalities were categorised as consolidation, reticulonodular change, miliary appearance and cavitation. Consolidation was further characterised in terms of its quality (confluent or patchy), extent (segmental, lobar or multifocal) and distribution (lower, mid- and/or upper zone, or diffuse).

A consensus report was used for the main analyses. If there was disagreement between the three reporters, the majority opinion was used. Radiographic pneumonia was defined as the presence of consolidation or other parenchymal abnormality (including reticulonodular change, cavitation or miliary appearance) or pleural effusion (Jain *et al.*, 2015). Multilobar consolidation was not specifically reported on the form. Consolidation was considered to be multilobar if characterised as diffuse, present in two or more non-contiguous lung zones regardless of extent or present in two or more contiguous lung zones and characterised as multifocal. Multifocal consolidation within a single lung zone was not classified as multilobar.

3.17 Data management

Study participants were assigned a unique study number at the time of recruitment, under which all data were captured. The clinical data were collected in paper-based CRFs and subsequently converted to electronic form using Intelligent Character Recognition scanning software (TeleForm; Cardiff Software Developers, Cardiff, UK). Following verification the data were exported to a Microsoft Access database (Microsoft Corporation, Redmond, Washington, USA). Data were exported to a Microsoft Excel spreadsheet (Microsoft Corporation, Redmond, Washington, USA) and subsequently to Stata 12 (StataCorp LP, College Station, Texas, USA) for cleaning and analysis.

Prior to scanning the CRFs were checked by the clinical team and again by Dr Antonia Ho or myself. Discrepancies were queried and addressed; where possible missing fields were completed although frequently the patient had already been discharged. The TeleForm software automatically scans each CRF twice; any discrepant values or values outwith a range pre-specified by the user are highlighted for manual review. Further certain essential fields containing, for example, identifiers or key outcome variables were set for mandatory manual review.

The study database was hosted on the secure MLW server; access was restricted to the respiratory infection team lead investigators and the MLW data management and information technology groups. The corresponding paper records were held securely at MLW in a locked office. These records were pseudo-anonymised, identifiable by study number and initials only. The paper record containing the demographic data and contact details of the participants necessary for follow-up were held separately from the other CRFs in a secure locked cabinet only accessible to study team members.

3.18 Analysis

3.18.1 Sample size considerations

The intended analytic approach was to generate a multivariable logistic regression model to identify factors independently predictive of treatment failure and death. When using multivariable logistic regression, in order to avoid 'over-fitting' and type I (i.e. false positive) errors, a minimum number of 10 events per predictor variable is recommended (Peduzzi *et al.*, 1996). Assuming a treatment failure rate of 15%, a sample size of 433 would give 65 outcome events that should allow the inclusion of at least 6 predictor variables in a stable multivariable model. In univariable analyses, this sample size would give approximately 80% power to detect factors that are associated

with treatment failure with odds ratio of 2.2 or greater. In order to mitigate the effects of missing data and incomplete follow-up, I planned to recruit an additional 15% to give a target study patient population of 500.

3.18.2 Statistical methods

The statistical methods applicable to specific analyses are describes in detail in each of the respective results chapters. All statistical analyses were conducted using Stata version 12.1 (StataCorp; Texas, US).

4 Clinical characteristics, microbial aetiology and radiological features of community-acquired pneumonia in Malawi: A prospective observational cohort

4.1 Introduction

The clinical characteristics and aetiology of pneumonia in adults in Malawi, and sub-Saharan Africa more generally, are poorly described. With the exception of several cohorts from South Africa (Albrich *et al.*, 2012; Nyamande *et al.*, 2007a), the available studies of acute CAP in sub-Saharan Africa are either small (Fiberesima *et al.*, 2008; Hartung *et al.*, 2011; Horo *et al.*, 2009; Vray *et al.*, 2008), retrospective (Birkhamshaw *et al.*, 2013; Onyedum *et al.*, 2011; Ouedraogo *et al.*, 2010), completed prior to the HIV era or roll-out of ART (Scott *et al.*, 2000; Yoshimine *et al.*, 2001) or only used a restricted panel of investigations to define aetiology (Bos *et al.*, 2014; Odera *et al.*, 2009).

The Malawian Adult Lower Respiratory Tract Infection Severity, Aetiology and Outcome (MARISO) Study was a prospective observational study of adults hospitalised with clinically diagnosed community-acquired pneumonia (CAP) to Queen Elizabeth Central Hospital, Blantyre, Malawi between May 2013 and January 2015. Study participants underwent a standardised clinical assessment and laboratory work-up encompassing classical microbiological and molecular diagnostic techniques to define disease aetiology.

4.2 Objectives

In this chapter I describe the baseline characteristics, microbial aetiology and radiological features of the patient cohort. Clinical outcomes and severity assessment will be described in chapter 5.

4.3 Contributors to this chapter

The MARISO study was one of several prospective observational studies of respiratory tract infection occurring concurrently at Queen Elizabeth Central Hospital. The individuals that contributed to data collection are summarised in section 3.3. I have performed all analyses undertaken in this chapter independently.

4.4 Methods

4.4.1 Patient recruitment and assessment

The methods relevant to this chapter are described in full in chapter 3. Briefly, patients with features of respiratory illness or infection were screened within 24 hours of admission. Consenting patients with clinically diagnosed CAP as defined by the presence of reported or recorded fever, a relevant respiratory symptom and focal chest signs were recruited (see section 3.1.1 for full eligibility criteria). Patients underwent a standardised clinical assessment consisting of comprehensive medical history, targeted physical examination and measurement of physiological observations (see section 3.13).

Plain posteroanterior chest radiographs were performed as early as possible after hospital admission and independently reported by two radiologists and myself using a standardised form (section 3.14 and 3.18). Radiographic pneumonia was defined as the presence of consolidation or other parenchymal abnormality (including reticulonodular change, cavitation or miliary appearance) or pleural effusion (Jain *et al.*, 2015).

4.4.2 Clinical specimen collection

Blood was collected for aerobic culture, HIV testing, malaria rapid diagnostic antigen test and basic haematological and biochemical analysis (section 3.15). Non-induced sputum was collected for mycobacterial microscopy and culture and Xpert MTB/RIF assay (Cepheid; Sunnyvale, California, USA). Urine was collected for pneumococcal antigen testing (BinaxNOW *Streptococcus pneumoniae* antigen card; Alere, Massachusetts, USA). Nasopharyngeal aspirate (NPA) was obtained for molecular testing for influenza viruses (CDC Human Influenza RT-PCR diagnostic panel; CDC Influenza Division, Atlanta, Georgia, US) and a real-time PCR multiplex assay for 33 respiratory pathogens (FTD Respiratory Pathogens 33; Fast-Track Diagnostics, Luxembourg). When available pleural fluid specimens were collected for aerobic culture, mycobacterial smear microscopy and culture, and pneumococcal antigen testing. Diagnostic criteria for detection of specific microbial aetiologies are listed in table 4.1

4.4.3 Statistical analysis

The demographic features of enrolled and excluded patients were compared using χ^2 test and Mann-Whitney U test for categorical and continuous variables, respectively. The impact of an altered case definition of the demographics of the cohort was

estimated. Differences in baseline characteristics by HIV status, presence of radiographic pneumonia, symptom duration and timing of recruitment with respect to admission were explored by univariable logistic regression. The relationship of baseline parameters with antimicrobial and supportive treatment was examined by logistic regression. The impact of HIV on pathogen prevalence was assessed by comparing the proportion of HIV-positive and HIV-negative patients with each pathogen by χ^2 test and calculating odds ratios with 95% confidence intervals. The relationship between radiographic change and pathogen prevalence was assessed by comparing the proportion of those with and without radiographic pneumonia for each pathogen controlling for the effect of HIV status; χ^2 test was used and weighted odds ratios with 95% confidence intervals calculated directly by the Mantel-Haenszel method or estimated by logistic regression. The inter-observer variability of chest radiograph interpretation between the three readers was assessed by calculating average percentage agreement and kappa coefficient with estimated 95% confidence intervals. The kappa coefficient was interpreted as follow: <0, poor agreement; 0-0.2, slight agreement; 0.21-0.4, fair agreement; 0.41-0.6, moderate agreement; 0.61-0.8, substantial agreement; 0.81-1.0, almost perfect agreement.

Table 4.1 Diagnostic criteria for specific microbial aetiologies in MARISO study

Organism	Diagnostic criteria
Streptococcus pneumoniae	Positive blood or pleural fluid culture; positive BinaxNOW *S. pneumoniae* antigen card on either urine or pleural fluid
Mycoplasma pneumoniae *Chlamydophila pneumoniae* *Legionella* spp.	Positive result in NPA specimen on FTD 33 PCR assay[a]
Other bacteria	Positive blood or pleural fluid culture
Mycobacterium tuberculosis	Positive sputum or pleural fluid culture; positive Xpert MTB/RIF assay on sputum; positive AFB smear microscopy of sputum or pleural fluid (if results absent for sputum culture and Xpert MTB/RIF)
Nontuberculous mycobacteria	Positive sputum or pleural fluid culture
Influenza	Positive result in NPA specimen CDC Influenza PCR[b]
Adenovirus Bocavirus Coronavirus Enterovirus Metapneumovirus Parainfluenza Parechovirus Rhinovirus Respiratory syncytial virus	Positive result in NPA specimen on FTD 33 PCR assay[a]

[a] FTD Respiratory Pathogens 33 real-time PCR multiplex assay – Also detected influenza, *Pneumocystis jirovecii*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*, *Moraxella catarrhalis*, *Bordetella* spp., *Klebsiella pneumoniae*, *Salmonella* spp. but results not analysed

[b] CDC Human Influenza RT-PCR diagnostic panel

4.5 Results

4.5.1 Screening and recruitment

Between 13th May 2013 and 31st January 2015, 1711 adult patients were screened for inclusion in the study. Of 489 eligible patients, 472 (97%) were enrolled and 459 (94%) were included in the analysis (Figure 4.1). Due to the lack of radiograph developer solutions, patient recruitment was temporarily suspended between 28th October and 6th November 2013. Staffing and logistical issues also necessitated temporary suspension of recruitment from 16th December 2013 to 6th January 2014 and 16th December 2014 to 4th January 2015.

There was a male preponderance in both the excluded and analysed populations (57% and 62%, respectively; Table 4.2). Compared to the excluded patients, the analysed population was 1 year younger overall (median age 34.6 *vs.* 35.6 years; P=0.02),

although this difference was only significant for males (median age 35.4 *vs.* 36.8 years; $P<0.01$; Figure 4.2 and Table 4.2).

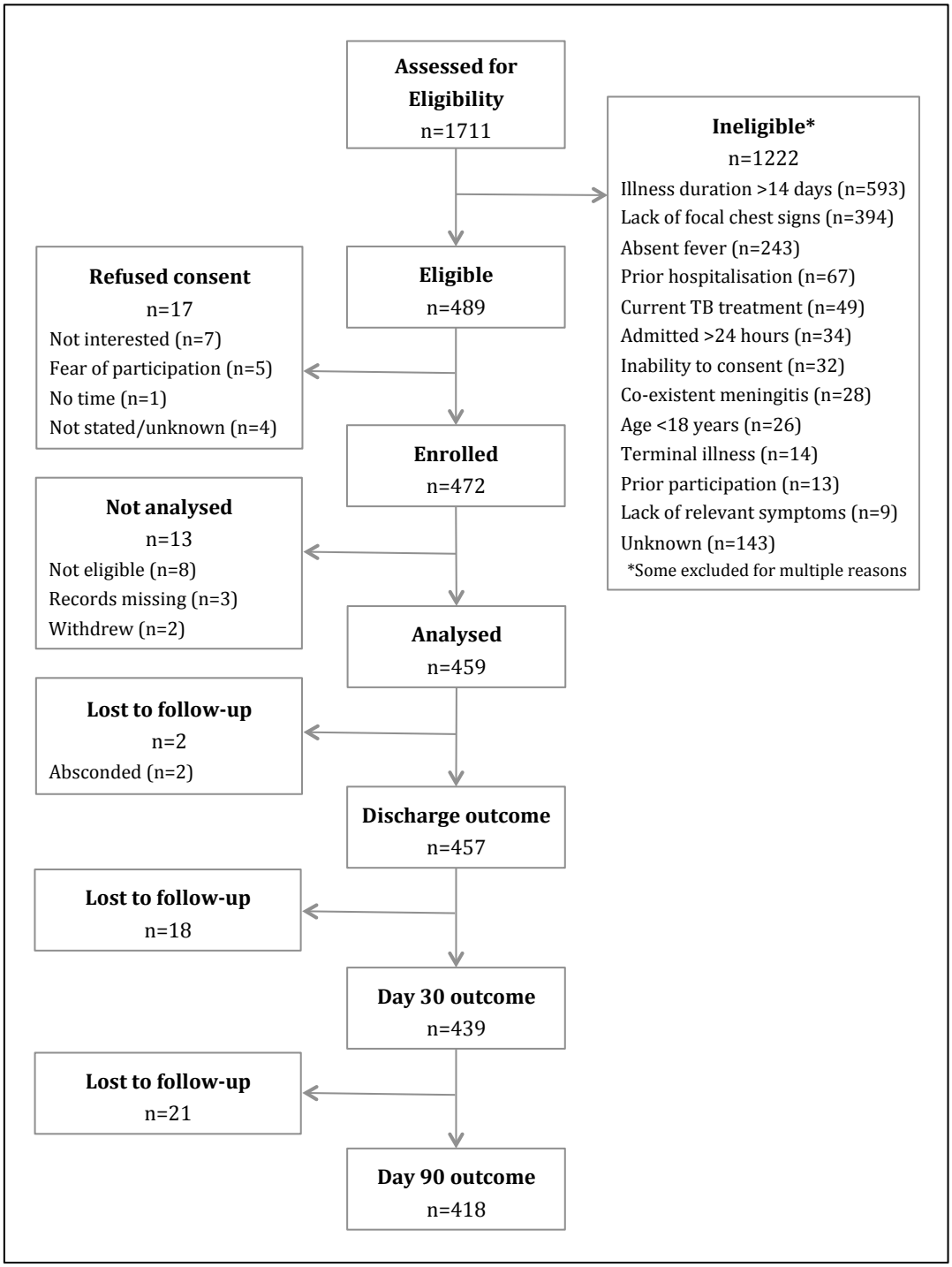

Figure 4.1 CONSORT diagram of screening, recruitment and follow-up in MARISO cohort.

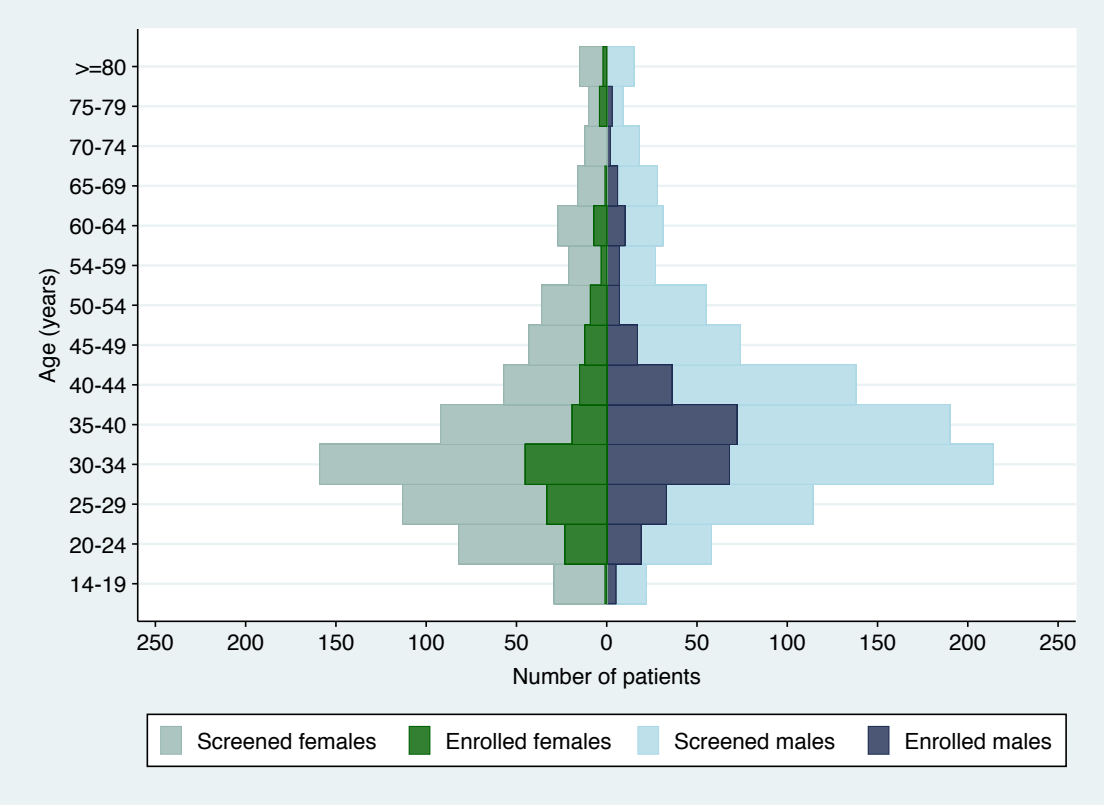

Figure 4.2 Age and sex distribution of screened and enrolled population in the MARISO cohort; displayed as opposing overlaid histograms.

Table 4.2 Comparison of the demographics of excluded and enrolled populations. Proportions of males compared by χ^2 test; age distributions compared using Mann-Whitney U test; odds ratios (with 95% confidence intervals) for enrolment in each age quartile estimated by logistic regression.

	Excluded[a] (n=1246)	**Analysed** (n=459)	**Comparative statistics**	
			OR (95% CI)	***P***
Male (n/%)[b]	708 (56.8)	285 (62.1)	1.24 (1.00-1.56)	0.05
Median age (IQR)	35.6 (29.6-46.0)	34.6 (29.6-41.9)	-	0.02
Males	36.8 (31.2-46.6)	35.4 (30.6-41.4)	-	0.009
Females	34.0 (27.5-45.1)	32.7 (27.7-42.1)	-	0.32
Age quartiles (n/%)[c]				
≤29	304 (72.7)	114 (27.3)	1	-
30-34	260 (69.7)	113 (30.3)	1.16 (0.85-1.58)	0.36
35-44	335 (70.2)	142 (29.8)	1.13 (0.84-1.51)	0.41
≥45	347 (79.4)	90 (20.6)	0.69 (0.51-0.95)	0.02

OR – odds ratio; NS – non-significant

[a] Includes 8 ineligible patients erroneously recruited; 6 patients that withdrew or with lost records not presented.

[b] Column percentage

[c] Row percentage

Illness duration greater than 14 days, lack of focal chest signs and absence of fever (either reported or measured) were, respectively, the three commonest reasons for ineligibility (Figure 4.1). Prolonged symptom duration and lack of focal chest signs frequently co-existed (Figure 4.3). If the symptom duration criterion were removed, at least an additional 338 patients would have been eligible for recruitment. Had these patients been included the expanded hypothetical cohort of 797 patients would have had broadly similar demographic characteristics (male sex 512/797 (64.2%); median age 35.8 (IQR: 29.6-46.8)). The reasons for exclusion varied with both age and sex (Table 4.3). Absence of fever (χ^2test for trend, $P<0.0001$) and inability to give consent (χ^2test for trend, $P=0.049$) were more common reasons for exclusion in the oldest quartile (patients ≥45 years). Male patients were more likely to be excluded on the basis of prolonged illness duration (OR 1.78; 95% CI: 1.38-2.29) and having features of terminal illness (OR 4.62; 95% CI: 1.02-42.67), whilst females were more likely to lack focal chest signs (OR 0.62; 95% CI: 0.48-0.81).

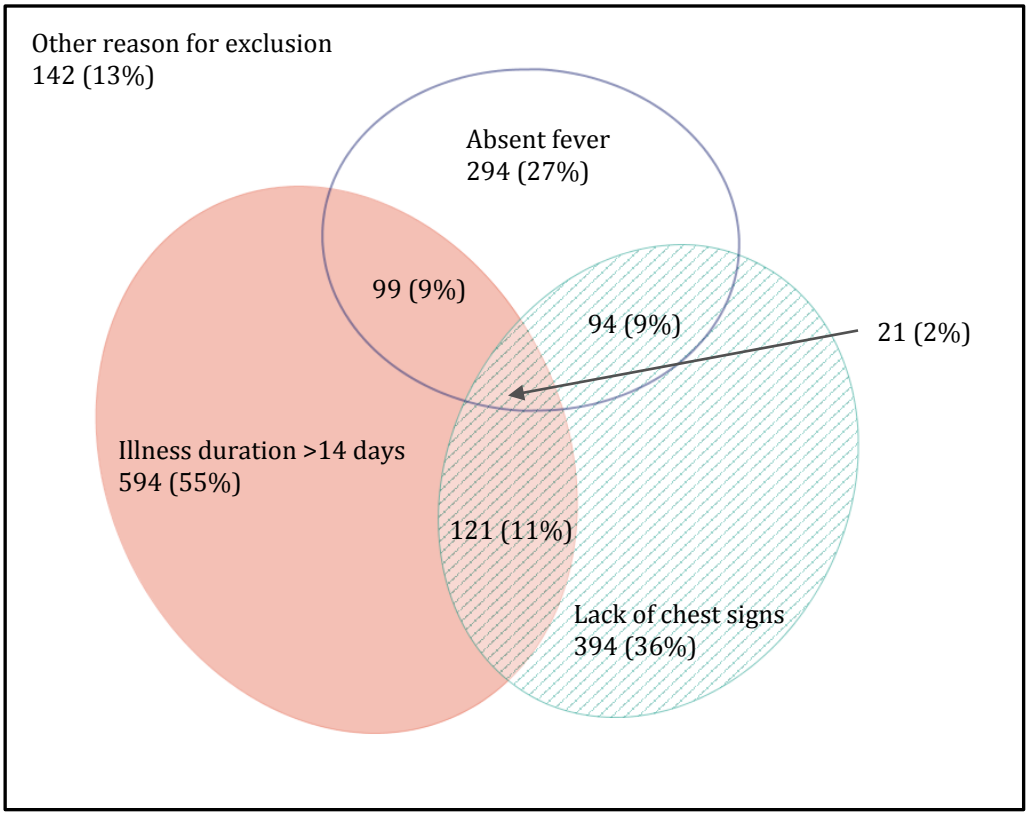

Figure 4.3 Inter-relationship of main reasons for exclusion from MARISO cohort. Proportional Venn diagram showing relationship of the three most frequent reasons for ineligibility for participation: illness duration greater than 14 days; lack of focal chest signs; absent fever. Percentages refer to proportion of all excluded patients for whom reason for exclusion is known (n=1079; 88% of all excluded patients).

Table 4.3 Reasons for exclusion from MARISO cohort stratified by sex and age. Proportions of males and females with each exclusion criteria compared using odds ratio (with 95% confidence intervals) and χ^2 test. Differences in proportions of patients within each (approximate) age quartile assessed using χ^2 test for trend. Owing to admission practice of 'adult' medical wards some patients less than 18 years were screened.

	Sex				Age (years)				
	Male (n=614)	**Female** (n=465)	**OR (95% CI)**	***P***	**≤29** (n=256)	**30-34** (n=231)	**35-44** (n=287)	**≥45** (n=305)	***P***
Illness duration >14 days	375 (61.1)	218 (46.9)	1.78 (1.38-2.29)	<0.0001	142 (55.5)	116 (50.2)	168 (58.5)	166 (54.8)	0.31
Lack of focal chest signs	195 (31.8)	199 (42.8)	0.62 (0.48-0.81)	0.0002	91 (35.6)	90 (39.1)	104 (36.2)	108 (35.7)	0.83
Absent fever	128 (20.9)	115 (24.7)	0.80 (0.60-1.08)	0.13	38 (14.8)	48 (20.8)	55 (19.2)	102 (33.4)	<0.0001
Prior hospitalisation,	35 (5.8)	32 (6.9)	0.82 (0.49-1.39)	0.43	20 (7.8)	13 (5.7)	15 (5.2)	19 (6.3)	0.63
Current TB Rx	28 (4.6)	21 (4.5)	1.01 (0.55-1.90)	0.97	8 (3.1)	12 (5.2)	18 (6.2)	10 (3.6)	0.26
Admitted >24 hours,	20 (3.3)	14 (3.0)	1.09 (0.52-2.35)	0.81	7 (2.7)	8 (3.5)	8 (2.8)	11 (3.6)	0.91
Inability to give consent	19 (3.1)	13 (2.8)	1.12 (0.52-2.49)	0.76	5 (2.0)	4 (1.7)	7 (2.5)	16 (5.3)	0.049
Co-existent meningitis	14 (2.3)	14 (3.0)	0.75 (0.33-1.73)	0.46	5 (2.0)	11 (4.8)	7 (2.4)	5 (1.7)	0.12
Age <18 years	10 (1.6)	16 (3.4)	0.46 (0.19-1.10)	0.05	-	-	-	-	-
Terminal illness	12 (2.0)	2 (0.4)	4.62 (1.02-42.67)	0.03	1 (0.4)	3 (1.3)	7 (2.4)	3 (1.0)	0.19
Prior participation	9 (1.5)	4 (0.9)	1.72 (0.48-7.70)	0.36	5 (2.0)	1 (0.4)	5 (1.7)	2 (0.7)	0.29
Lack of relevant symptoms	5 (0.8)	4 (0.9)	0.95 (0.20-4.80)	0.93	2 (0.8)	1 (0.4)	2 (0.7)	4 (1.3)	0.71

CI – confidence interval; OR – odds ratio

Over the 21 months of recruitment, a median of 74 patients was screened and 22 patients recruited each calendar month (Figure 4.4). During the first 13 months of the study, patient recruitment only occurred during weekdays. From 14th June 2014 recruitment was extended to weekends; the number of patients screened increased significantly (monthly median: 116 *vs.* 59; *P*=0.04), but without corresponding increase in recruitment (monthly median: 25 *vs.* 21; *P*=0.18) (i.e. the proportion of screened patients who were recruited fell from 32.6% to 21.8%). Extension of screening to weekends however, only made a modest impact on the total numbers of patients screened; a median of 15 (IQR: 11-19) patients were screened at weekends each month and 3 (IQR: 2-5) recruited. The proportion of patients recruited did not vary depending on whether screening occurred on weekdays or at weekends. Comparing patients that were screened before and after 7th June 2014, the only significant change in reasons for exclusion was that the proportion of patients that were excluded for being in hospital greater than 24 hours fell (23/460 (5.0%) *vs*. 11/618 (1.8%); *P* = 0.003). There was no obvious seasonal variation in the rate of recruitment, although it is not possible to robustly assess this given the study duration of less than 2 years.

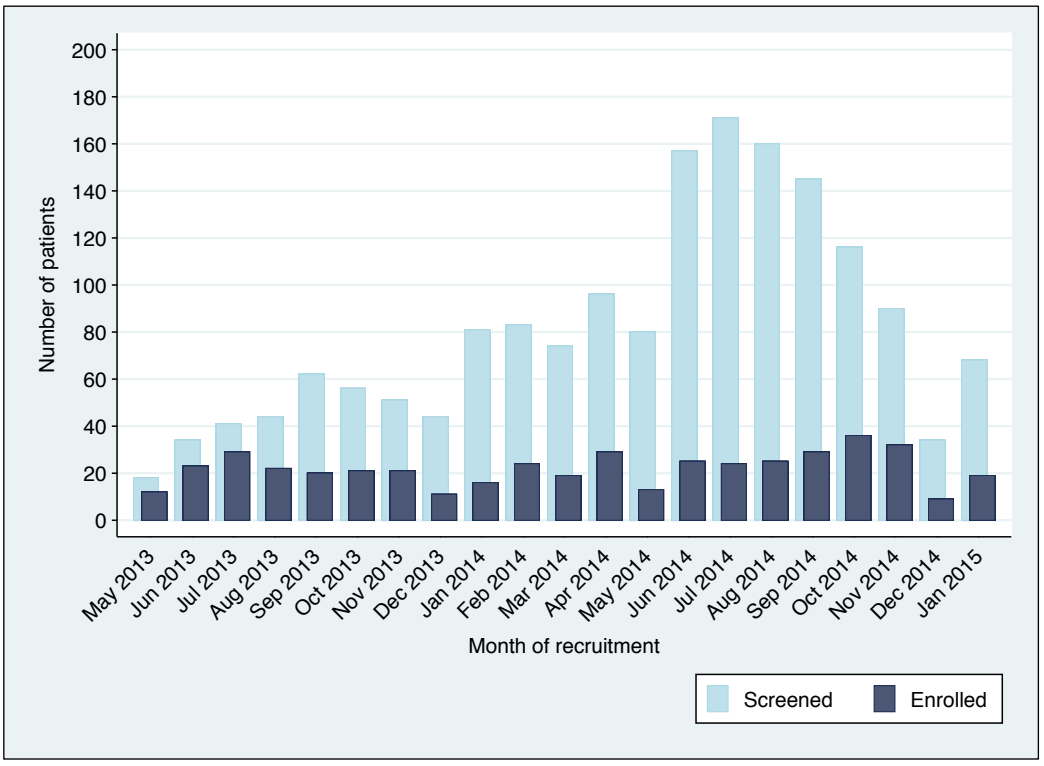

Figure 4.4 MARISO study patient screening and enrolment by month. Patient recruitment was temporarily suspended between 28th October and 6th November 2013, 16th December 2013 and 6th January 2014, and 16th December 2014 and 4th January 2015 (see section 4.3 for further details). Recruitment was extended to include weekends from 14th June 2014.

Most patients were recruited immediately upon presentation to hospital with initial assessment and management being undertaken by the study team. The median time from hospital admission to recruitment was 1.75 hours (IQR: 0.5-18.4). 162 (35.3%) patients were recruited the day following the day of admission and 188 (41%) recruited more than 4 hours after presentation.

4.5.2 Baseline characteristics

4.5.2.1 Demographic and social characteristics

The baseline characteristics of the 459 patients included in the analysis are summarised in Tables 4.4 – 4.8. There was a marked male preponderance (285; 62%) and the median age was 34.6 years (IQR: 29.6-41.9). 50 (11%) of patients were current smokers; an additional 20 (15%) reported smoking previously. 122 (27%) reported regular consumption of alcohol (i.e. drinking at least once a week), although exact quantification of alcohol consumption is precluded by the wide variation of alcohol concentration in the commonly consumed locally-brewed beers and spirits and uncertainty over volumes.

A basic assessment of socioeconomic status was undertaken by enquiring of details of employment status, educational attainment, food security and water usage (Table 4.4). Nearly one-third (137; 30%) of patients were in regular paid employment; an additional third (152, 33%) described themselves as self-employed. 164 (36%) had attended secondary school, but only 52 (12%) had attained a school-leavers qualification. More than half (237; 52%) reported frequent or occasional difficulties in obtaining sufficient food and these patients had lower median body mass index (19.3 *vs*. 20.6; $P<0.0001$; see Table 4.8). The vast majority of patients obtained water from a communal borehole/well (128; 28%) or standpipe (247; 54%). In keeping with previous reports of cooking fuel use in urban Blantyre, charcoal (298; 65%), and to a lesser extent, firewood (117; 26%), were the predominant fuel sources for cooking (Fullerton *et al.*, 2009).

Table 4.4 Demographics and social characteristics of MARISO cohort. Data presented as number and proportion of total episodes (n=459) unless indicated by * where median and interquartile range are shown. Denominator adjusted where data are unavailable.

Characteristic	No. (%) of episodes
Male sex	285/459 (62.1)
Age*	34.6 (29.6-41.9)
Current smoker	50/457 (10.9)
Regular alcohol intake	122/456 (26.8)
Employment status	
Paid employment	157/455 (34.1)
Self-employed	152/455 (33.4)
Unemployed	120/455 (26.4)
Other	26/455 (5.7)
Highest educational level attended	
None	45/451 (10.0)
Primary	242/451 (53.7)
Secondary	152/451 (33.7)
Higher	12/451 (2.7)
Water source	
River	3/458 (0.7)
Borehole/well	128/458 (28.0)
Public tap/standpipe	247/458 (53.9)
Piped to dwelling	80/458 (17.5)
Difficulty obtaining food	
Often	35/458 (7.6)
Sometimes	202/458 (44.1)
Never	221/458 (48.3)
Main cooking fuel	
Firewood	117/458 (25.6)
Charcoal	298/458 (65.0)
Paraffin	6/458 (1.3)
Electricity	37/458 (8.1)

4.5.2.2 Comorbid illness

HIV status was determined in 453 (99%) patients; 355 (78%) were HIV-positive, of whom 124 (35%) were newly diagnosed at presentation (Table 4.5). CD4 cell counts were measured on admission as a crude estimate of the degree of immunosuppression; results were available in 315 (89%). Median CD4 count was 100 cells/mm^3 (IQR: 44-193); 246 (78%) had CD4 counts of <200 cells/mm^3. Antiretroviral therapy (ART) coverage amongst patients with prior diagnosis of HIV was 83% (189/227) and 53% (189/355) overall. There was a trend to higher median CD4 counts in those patients receiving ART, but this difference was not statistically significant (106 *vs*. 76; *P*=0.10). In the absence of convalescent CD4 counts or HIV viral load measurements, it was not possible to definitively diagnose ART failure (World Health Organization, 2013a). Data on the use of co-trimoxazole preventative therapy (CPT) was available in only 188 (81.4%) of the known HIV-positive patients, of whom 151 (80.3%) reported current use.

The presence of other chronic medical comorbid conditions was determined by direct questioning of the patient and by reference to their health passport. In contrast to HIV, other comorbidities were reported infrequently; overall, only 31 (7%) patients reported a non-HIV chronic comorbid condition. Chronic lung disease – which included asthma, COPD and bronchiectasis – was reported by 15 (3%) patients. Reported chronic lung disease did not correlate with current or previous smoking (OR 1.28; 95% CI: 0.34-4.09).

Prior pneumonia - defined as a history of a syndrome compatible with a lower respiratory tract infection reviewed in a health care facility and treated with antibiotics – was common (108/457; 24%) and associated with HIV (OR 2.91; 95% CI: 1.46-6.30). In addition, 84 (18%) of patients reported a prior history of tuberculosis, which again was associated with HIV (OR 3.49; 95% CI: 1.54-9.29)

Table 4.5 HIV and other comorbid illness of MARISO cohort. Data presented as number and proportion of patients unless indicated by * where median and interquartile range are shown. Data relating specifically to HIV-positive patients indicated by †. Denominator adjusted where data are unavailable.

Characteristic	No. (%) of episodes*	
HIV positive	355/453	(78.4)
Newly diagnosed†	124/355	(34.9)
CD4 cell count (cells/mm^3)†		
All HIV-positive*	99	(44-193)
Known HIV-positive*	100	(44-196)
On ART*	106	(45-203)
Not on ART*	90	(43-164)
Newly diagnosed HIV-positive*	93	(42.5-178.5)
CD4 <200 cells/mm^3†	246/315	(78.1)
On ART*	125/169	(74.0)
Not on ART*	121/146	(82.9)
ART use on admission†		
All HIV-positive	189/355	(53.2)
Known HIV-positive	189/227	(83.3)
ART duration		
<3 months†	34/157	(21.7)
3-12 months	35/157	(22.3)
>12 months	89/157	(56.1)
CPT use on admission†		
All HIV-positive	151/355	(42.5)
Known HIV-positive	151/188	(80.3)
Any other comorbid condition	31/451	(6.9)
Chronic lung disease[a]	15/452	(3.3)
Chronic heart disease[b]	3/452	(0.7)
Hypertension	8/452	(1.8)
Cancer	5/452	(1.1)
Chronic kidney disease	1/452	(0.2)
Liver disease	1/452	(0.2)
Stroke	5/452	(1.1)
Epilepsy	1/452	(0.2)
Dementia	2/452	(0.4)
Previous tuberculosis[c]	84/458	(18.3)
Previous pneumonia in last 5 years[d]	108/457	(23.6)
Pregnancy	2/174	(1.2)

ART – antiretroviral therapy; CPT – co-trimoxazole preventative therapy

[a] Chronic lung disease includes asthma, COPD and bronchiectasis

[b] Chronic heart disease includes congestive cardiac failure, cor pulmonale and dilated cardiomyopathy

[c] Any previous episode of treated tuberculosis regardless of site and confirmation

[d] Any prior episode within the last 5 years of a syndrome compatible with lower respiratory tract infection reviewed in a healthcare facility and treated with antibiotics

4.5.2.3 Prior treatment

The median duration of symptoms prior to presentation was 7 days (IQR: 5-12; Table 4.6). However, reported symptom duration was not smoothly distributed and clustered around 3, 7 and 14 days; 24% of patients reported symptoms for exactly 14 days. 283 (62%) patients had been seen at some form of healthcare facility prior to the current attendance at hospital. The majority (230/283; 81%) had attended a primary health centre, in keeping with the standard referral practice in operation at QECH whereby all but severely unwell patients must be referred. Prior review was not associated with longer duration of symptoms (7 days *vs.* 7 days; *P*=0.11). 280 (62%) patients had used antibiotics (excluding co-trimoxazole prophylactic treatment) in the two weeks prior to presentation. Prior use of antimalarials was also common (79/457; 17%). Whilst attendance at traditional healers was rare (2/283; 0.7%), 40 (9%) patients reported use of traditional remedies although these were not further characterised.

Table 4.6 Healthcare utilisation and prior treatment of MARISO cohort. Data presented as number and proportion of patients unless indicated by * where median and interquartile range are shown. Denominator adjusted where data are unavailable.

Characteristic	No. (%) of episodes*
Pre-admission symptom duration*	7 (5-12)
1-3 days	63/457 (13.8)
4-7 days	214/457 (46.8)
8-10 days	50/457 (10.9)
11-14 days	130/457 (28.5)
Travel time to hospital	
<1 hour	114/455 (25.0)
1-2 hours	245/455 (53.9)
>2 hours	96/455 (21.1)
Prior review	283/458 (61.8)
Primary health centre	230/283 (81.2)
Private clinic	49/283 (17.3)
Other hospital	7/283 (2.5)
Pharmacy	1/283 (0.4)
Traditional healer	2/283 (0.7)
Prior treatment	
Antibiotics	280/455 (61.5)
Antimalarials	79/457 (17.3)
Traditional remedies	40/456 (8.8)

4.5.2.4 Clinical features

The reported symptoms and clinical examination features evident at presentation are summarised in Table 4.7. The symptoms that formed a component of the clinical case definition – fever, cough, dyspnoea and chest pain – were all present in almost all patients. Despite the short maximal symptom duration of 14 days, weight loss was frequently reported (277/458; 61%). Similarly, night sweats were also commonly reported (299/457; 65%).

Audible crepitations were the most frequently detected focal chest sign (387/457; 85%). 79 (17%) patients had clinical evidence of pleural effusion. Cutaneous or palatal Kaposi's sarcoma was present in 3% (14/458) but did not associate with clinical pleural effusion. Acute confusion as assessed by orientation in time, place and person was judged to be present in only 5 patients (1%). Inability to stand - a feature previously used as a global assessment of illness severity in low-resource settings - was present in 87 (19%) (Rylance *et al.*, 2009).

Haemoptysis was reported more frequently amongst patients with radiographic pneumonia (21.2% *vs.* 10.6%; *P*=0.02) (see section 4.5.4). Amongst the recorded respiratory examination features, only clinically detected pleural effusion was significantly associated with radiographic pneumonia (22.5% *vs.* 5.8%; *P* <0.0001).

Weight loss (227/354 (64.1%) *vs.* 46/98 (46.9)), oral thrush (28/354 (7.9%) *vs.* 0/98 (0%)) and lymphadenopathy (40/355 (11.3%) *vs.* 2/98 (2.0%)) were present more frequently in HIV-infected patients. However, amongst HIV-infected patients, the clinical presentation did not vary with the use of ART. As reported earlier, there was substantial missing data on the use of CPT. Clubbing (6/37 (16.2%) *vs.* 7/151 (4.6%)) and confusion (2/37 (5.4%) *vs.* 1/150 (0.7%)) were present more frequently in patients not taking CPT, but there was no difference in the recorded respiratory features.

Physiological observations were considered as absolute values and as proportion of patients with a significant abnormality using thresholds described in previous validated CAP severity assessment tools (Table 4.8)(Charles *et al.*, 2008b; Fine *et al.*, 1997a; Lim *et al.*, 2003). Hypotension (systolic blood pressure <90 mmHg or diastolic blood pressure ≤60 mmHg), tachycardia (≥125 beats/min) and tachypnoea (≥30 breaths/min) were present in 35% (160/454), 38% (176/458) and 48% (213/446) of patients, respectively. Hypoxaemia as defined by peripheral oxygen saturations of <90% was present in 16% (73/449). Tachypnoea (≥30 breaths/min) was neither a sensitive (61.1%; 95% CI: 48.9%-72.4%) nor specific (54.9%; 95% CI: 49.6%-60.0%)

marker for the presence of hypoxaemia. Using a body mass index threshold of <18.5 kg/m^2, 30% (132/444) of patients were underweight (World Health Organization, 1995). A similar proportion (26%; 118/451) were classified as underweight/undernourished using a mid-upper arm circumference threshold of <230mm (Tang *et al.*, 2013).

For patients recruited from the medical wards on the day following admission, the physiological observations recorded at presentation by the routine AETC triage staff were used for analysis. The median recorded respiratory rate was lower in this group (27 *vs.* 30; P <0.0001) than for patients recruited directly from AETC whose initial observations were measured by the study team. There was no significant difference in temperance, blood pressure, heart rate or oxygen saturations.

The median haemoglobin concentration was 11.0 g/dL (IQR: 9.0-12.8). Using the WHO recommended threshold of 8 g/dL, 17% (74/449) of patients had severe anaemia (World Health Organization, 2011b). Pallor identified on clinical examination had excellent specificity (97.1%; CI: 94.8%-98.5%) but poor sensitivity for the diagnosis of severe anaemia (21.6%; CI: 12.9%-32.7%). Urea and creatinine were elevated in an estimated 30% and 17% of patients, respectively, however in the absence of baseline or interval values, determining whether this reflects acute kidney injury is not possible. Concurrent malaria was detected in only 2% (8/436).

The systemic inflammatory response syndrome (SIRS) criteria[7] of tachycardia, tachypnoea, fever or hypothermia, and high or low white blood are used to rapidly identify patient with potentially severe infection. SIRS was present in 396 (91%) patients in the MARISO cohort. Severe sepsis[8] – defined as the presence of SIRS with evidence of organ dysfunction (i.e. hypotension, respiratory failure, confusion, renal dysfunction, thrombocytopenia, jaundice) - was present in 179/412 (43%).

Since prolonged symptom duration was the commonest reason for exclusion from the cohort, the relationship between reported symptom duration and clinical features at presentation was examined (Table 4.9). Patients with reported symptom duration of 8-14 days compared to 1-7 days were more likely to be male and to report weight loss

[7] Systemic inflammatory response syndrome (SIRS) defined as ≥2 of: temperature <36°C or >38°C; heart rate >90/min; respiratory rate >20/min; white blood cell <4 or >12 x 10^9 cells/L (Bone *et al.*, 1992).
[8] Severe sepsis was defined as the presence of SIRS response with ≥1 of the followings signs of organ dysfunction: systolic blood pressure <90 mmHg or mean arterial blood pressure <65 mmHg; altered mentation; creatinine >164 μmol/L; platelet count <100 x 10^9/L; respiratory rate >40/min; jaundice (Andrews *et al.*, 2014) adapted from (Vincent *et al.*, 1996).

and night sweats. Recorded physiological observations and the proportion with radiographic pneumonia did not differ substantially.

4.5.3 Antimicrobial and supportive management

Details of the initial antibiotic treatment regimen were available in 435/459 (94.8%). Whilst overall 13 different initial antibiotic regimens were used, ceftriaxone monotherapy (n=306; 70.3%) and combination treatment with penicillin and chloramphenicol (n=100; 23.0%) accounted for more than 93%. An additional 10 (2.3%) patients received ceftriaxone in combination with other agents and 9 received (2.0%) penicillin monotherapy. Only 2 patients (0.5%) received atypical bacterial infection antimicrobial cover in the form of erythromycin (n=1) or doxycycline (n=1) in their initial treatment regimen. Only 4 (1.2%) patients were initially treated solely with oral antibiotics. The use of a ceftriaxone-based (n=316; 72.6%) versus an alternative antibiotic regimen (n=119; 27.4%) did not vary with sex, age, symptom duration, HIV status or oxygen saturations, but was more common amongst patients with low systolic blood pressure (<90mmHg, 67/80 (83.8%) *vs.* ≥90mmHg, 246/351 (71.9%); $P = 0.02$).

242 (79.1%) of patients with initial empirical ceftriaxone therapy completed treatment course with ceftriaxone monotherapy for a median duration of 5 days (IQR: 3-7) without a subsequent oral agent. 45 (14.7%) of patients initially treated with ceftriaxone monotherapy were stepped down to oral therapy after a median duration of ceftriaxone of 5 days (IQR: 2-7). Amoxicillin alone was used in 33 patients (10.8%); a single agent with atypical cover in 10 (3.3%); or a combination of both in 2 (0.7%).

Of the 100 patients initially commenced on penicillin and chloramphenicol, 67 (67%) stayed on this regimen throughout the treatment course for a median duration of 4 days (IQR: 3-6). 23 (23%) were switched to a treatment regimen containing ceftriaxone.

Intravenous fluids were commenced at the time of initial assessment in 278 (62.8%) of patients for whom data was available. Intravenous fluids were started more frequently in patients with low systolic blood pressure (<90mmHg , 70/81 (86.4%) *vs.* ≥90mmHg , 205/357 (57.4%); $P < 0.0001$) and low saturations (<90%, 58/73 (79.5%) *vs.* ≥90%, 215/360 (59.7%); $P = 0.002$).

Details on oxygen administration were available in 439 (95.6%) patients. Oxygen was commenced on initial assessment in 56 (12.8%) patients, including 43/70 (61.4%) of those with oxygen saturations of less than 90% at presentation.

There was no significant differences in antimicrobial selection, recorded oxygen or intravenous fluid use between patients recruited on the day of admission, whose initial management was usually overseen by the study team, and those recruited from the medical wards on the day following admission whose initial management was undertaken by the routine clinical team.

Table 4.7 Clinical features at presentation of MARISO cohort stratified by radiographic appearance. Data presented as number and proportion of patients. Denominator adjusted where data are unavailable.

Characteristic	No. (%) of episodes			
	Overall	No radiographic pneumonia	Radiographic pneumonia	*P*
Respiratory symptoms				
Cough	451/458 (98.5)	102/104 (98.1)	312/317 (98.4)	0.81
Sputum production	357/458 (78.0)	82/104 (78.9)	242/317 (76.3)	0.60
Dyspnoea	440/458 (96.1)	98/104 (94.2)	306/317 (96.5)	0.30
Chest pain	449/457 (98.3)	101/104 (97.1)	311/316 (98.4)	0.40
Haemoptysis	84/457 (18.4)	11/104 (10.6)	67/316 (21.2)	0.02
Rhinorrhoea	75/458 (16.4)	22/104 (21.2)	49/317 (15.5)	0.18
Sore throat	111/458 (24.2)	30/104 (28.9)	72/317 (22.7)	0.21
Respiratory exam^{n} features				
Crepitations	387/457 (84.7)	93/104 (89.4)	258/315 (81.9)	0.07
Bronchial breathing	167/458 (36.4)	39/104 (37.5)	111/316 (35.1)	0.66
Pleural rub	128/457 (28.0)	32/104 (30.8)	84/315 (26.7)	0.42
Pleural effusion	79/457 (17.3)	6/104 (5.8)	71/315 (22.5)	<0.0001
Wheeze	17/458 (3.7)	7/104 (6.7)	9/317 (2.8)	0.07
Other symptoms				
Fever	457/458 (99.8)	104/104 (100)	316/317 (99.7)	0.57
Weight loss	277/458 (60.5)	65/104 (62.5)	192/317 (60.6)	0.73
Night sweats	299/457 (65.4)	63/104 (60.6)	208/316 (65.8)	0.33
Collapse	8/457 (1.8)	3/104 (2.9)	5/316 (1.6)	0.40
Myalgia	371/458 (81.0)	87/104 (83.7)	254/317 (80.1)	0.43
Headache	217/458 (47.4)	58/104 (55.8)	143/317 (45.1)	0.06
Skin rash	36/458 (7.9)	7/104 (6.7)	26/317 (8.2)	0.63
Diarrhoea	75/456 (16.5)	25/104 (24.0)	43/315 (13.7)	0.01
Nausea and vomiting	73/457 (16.0)	22/103 (21.4)	44/317 (13.9)	0.07
Other exam^{n} features				
Confusion/disorientation	5/458 (1.1)	3/104 (2.9)	5/316 (1.6)	0.40
Inability to stand	87/459 (19.0)	20/104 (19.2)	51/317 (16.1)	0.46
Pallor	27/458 (5.9)	8/104 (7.7)	14/316 (4.4)	0.20
Oral thrush	28/458 (6.1)	8/104 (7.7)	16/315 (5.1)	0.32
Jaundice	3/457 (0.7)	1/103 (1.0)	2/316 (0.6)	0.72
Clubbing	27/459 (5.9)	7/104 (6.7)	16/317 (5.1)	0.51
Lymphadenopathy	43/459 (9.4)	16/104 (15.4)	22/317 (6.9)	0.009
Peripheral oedema	14/456 (3.1)	3/103 (2.9)	8/315 (2.5)	0.84
Kaposi's sarcoma	14/458 (3.1)	2/104 (1.9)	11/316 (3.5)	0.43
Hepatomegaly	22/457 (4.8)	3/103 (2.9)	16/315 (5.1)	0.36
Splenomegaly	16/456 (3.5)	3/103 (2.9)	10/315 (3.2)	0.89
Murmur	2/457 (0.4)	0/103 (0)	2/316 (0.6)	0.42

Table 4.8 Physiological observations and laboratory results at presentation of MARISO cohort. Data summarised as median and interquartile range and also in *italics* as number and proportion significantly abnormal using accepted thresholds. Denominator adjusted where data are unavailable.

Characteristic	Median (IQR) *No. (%) of episodes*
Physiological observations	
Temperature (°C)	37.9 (37.1-38.9)
<35 or ≥40	*14/459 (3.1)*
Systolic blood pressure (mmHg)	106 (93-121)
<90	*86/454 (18.9)*
Diastolic blood pressure (mmHg)	68 (59-78)
≤60	*143/454 (31.5)*
Systolic <90 and/or diastolic blood pressure ≤60 (mmHg)	*160/454 (35.2)*
Heart rate (beats/min)	118 (102-132)
≥125	*176/458 (38.4)*
Respiratory rate (breaths/min)	29 (26-34)
≥30	*213/446 (47.8)*
Oxygen saturations (%)	95 (91-98)
≤90	*101/449 (22.5)*
<90	*73/449 (16.3)*
Body mass index (kg/m^2)	19.9 (18.2-21.8)
<18.5	*132/444 (29.7)*
Mid-upper arm circumference (mm)	250 (220-260)
<230mm	*118/451 (26.2)*
Laboratory results	
Haemoglobin (g/dL)	11 (9.0-12.8)
<8	*74/449 (16.5)*
White blood cells (x 10^9 cells/L)	7.7 (5.0-11.4)
<4 or >15	*128/448 (28.6)*
Platelets (x 10^9 cells/L)	201 (127-304)
<100	*77/449 (17.2)*
Urea (mmol/L)	4.8 (3.3-8.0)
>7	*137/450 (30.4)*
Creatinine (µmol/L)	76 (59-100)
>120	*76/448 (17.0)*
Glucose (mmol/L)	5.6 (4.9-6.4)
≥11.1	*5/401 (1.2)*
Positive malaria rapid antigen test	*8/436 (1.8)*

Table 4.9 Baseline characteristics, clinical features and physiological observations stratified by reported symptom duration in MARISO cohort. Data summarised as median and interquartile range or in *italics* as number and proportion. Denominator adjusted where data are unavailable.

Characteristic	Symptoms 1-7 days		Symptoms 8-14 days		*P*
Male sex	*159/277*	*(57.4)*	*124/180*	*(68.9)*	*0.013*
Age	35.0	(29.1-41.9)	34.5	(30.0-41.3)	0.96
HIV positive	*219/275*	*(79.6)*	*135/176*	*(76.7)*	*0.46*
Crepitations	*237/276*	*(85.9)*	*149/176*	*(83.2)*	*0.45*
Bronchial breathing	*106/277*	*(38.2)*	*61/179*	*(34.1)*	*0.37*
Pleural effusion	*29/276*	*(10.5)*	*49/179*	*(27.4)*	*<0.0001*
Weight loss	*145/277*	*(52.4)*	*132/180*	*(73.3)*	*<0.0001*
Night sweats	*167/277*	*(60.3)*	*131/179*	*(73.2)*	*0.005*
Inability to stand	*57/277*	*(20.6)*	*29/180*	*(16.1)*	*0.23*
Pallor	*14/277*	*(5.1)*	*12/179*	*(6.7)*	*0.46*
Temperature (°C)	38.0	(37.2-39.0)	37.8	(37.0-38.8)	0.03
Systolic BP (mmHg)	105	(92-122)	106	(94-117)	0.82
Diastolic BP (mmHg)	68	(59-79)	68	(60-77)	0.90
Heart rate (/min)	118	(102-132)	120	(103-132)	0.49
Respiratory rate (/min)	30	(26-34)	28	(24-34)	0.05
Oxygen saturations (%)	95	(91-98)	95	(92-98)	0.59
Radiographic pneumonia	*194/255*	*(76.1)*	*122/165*	*(73.9)*	*0.62*

Table 4.10 Initial and final summary antimicrobial treatment regimens

Initial treatment group	*n*	Detailed initial regimen	*n*	Final treatment summary	*n*
Ceftriax.	306	-		Ceftriax.	242
				Ceftriax. & Amox.	33
				Ceftriax. & Atypical	10
				Pen. & Chloram.	5
				Ceftriax. & Gent. & Atypical	3
				Ceftriax., Amox. & Atypical	2
				Ceftriax., Pen. & Chloram.	2
				Ceftriax. & Gent.	1
Ceftriax.-based combination	10	Ceftriax., Pen. & Chloram.	5	Ceftriax.	3
		Ceftriax. & Atypical	2	Pen. & Chloram.	2
		Ceftriax. & Co-trimox.	1	Ceftriax., Pen. & Chloram.	2
		Ceftriax. & Metronid.	1	Ceftriax. & Amox.	1
		Ceftriax. & Pen.	1	Ceftriax. & Pen.	1
				Pen., Chloram. & Amox.	1
Pen. & Chloram.	100	-		Pen. & Chloram.	67
				Ceftriax., Pen. & Chloram.	10
				Ceftriax.	7
				Pen., Chloram.& Amox.	6
				Ceftriax. & Amox.	3
				Pen., Chloram., Amox. & Atypical	2
				Ceftriax., Pen., Chloram. & Amox.	1
				Ceftriax., Pen. & Gent.	1
Amox.	4	-		Amox.	3
				Amox. & Ceftriax.,	1
Other	15	Pen.	9	Ceftriax.	8
		Chloram.	3	Ceftriax., Pen. & Chloram.	2
		Pen., Chloram. & Metronid.	2	Pen. & Chloram.	2
		Pen. & Co-trimox.	1	Ceftriax., & Atypical	1
				Pen., Chloram. & Amox.	1
				Pen., Chloram. & Atypical	1

Amox. – Amoxicillin; Ceftriax. – Ceftriaxone; Chloram. – Chloramphenicol; Co-trimox – Co-trimoxazole; Gent. – Gentamicin; Metronid. – Metronidazole; Pen. – Pencillin;

4.5.4 Aetiology

4.5.4.1 Specimen collection

Blood for culture was obtained in 450 of the 459 patients (98%), urine for pneumococcal antigen detection from 433 (94%) and a nasopharyngeal aspirate (NPA) for multiplex respiratory pathogen PCR panel from 455 (99%; Table 4.9). Overall 322 (70%) patients submitted a sputum specimen for mycobacterial diagnostic testing. A result for smear microscopy was available in 305 (66%); valid results for Xpert MTB/RIF and mycobacterial cultures were available in 308 (67%) and 273 (59%), respectively. Pleural fluid sampling was performed in 35 patients (8%). Results for bacterial culture of pleural fluid were available in 31 (89%), for pneumococcal antigen detection in urine or pleural fluid in 31 (89%), and for smear microscopy and mycobacterial culture in 35 (100%). Overall at least one potential pathogen was identified in 310 (68%) patients or, if the results for *Legionella* spp. are discounted (see below), in 278 (61%).

Table 4.11 Organism identification by specimen type and diagnostic test stratified by HIV status. Data presented as number and proportion of specimens positive for specific organism.

Organism	All (n=459)	HIV-positive (n=355)	HIV-negative (n=98)
Blood cultures			
S. pneumonia	5/450 (1.1)	4/350 (1.1)	1/94 (1.1)
S. typhi	9/450 (2.0)	3/350 (0.9)	5/94 (5.3)
S. Typhimurium	6/450 (1.3)	6/350 (1.7)	0/94 (0)
S. Enteritidis	1/450 (0.2)	1/350 (0.3)	0/94 (0)
S. aureus	2/450 (0.4)	1/350 (0.3)	1/94 (1.1)
E. coli	2/450 (0.4)	2/350 (0.6)	0/94 (0)
E. cloacae	1/450 (0.2)	1/350 (0.3)	0/94 (0)
Pleural fluid culture			
S. typhi	1/31 (3.2)	1/19 (5.3)	0/11 (0)
M. tuberculosis	7/35 (20.0)	4/22 (18.2)	2/12 (16.7)
***S. pneumoniae* antigen test**			
Urine	95/433 (21.9)	67/333 (20.1)	28/94 (29.8)
Pleural fluid	3/31 (9.7)	1/20 (5)	2/10 (20)
Sputum mycobacterial diagnostic tests			
AFB smear microscopy	36/305 (11.8)	30/241 (12.4)	6/60 (10.0)
Sputum culture			
M. tuberculosis	60/273 (22.0)	54/217 (24.9)	6/52 (11.5)
NTM	8/273 (2.9)	5/217 (2.3)	3/52 (5.8)
Xpert MTB/RIF	56/308 (18.2)	46/244 (18.9)	10/60 (16.7)

Organism	All (n=459)	HIV-positive (n=355)	HIV-negative (n=98)
Multiplex PCR on nasopharyngeal aspirate			
Adenovirus	35/455 (7.7)	30/355 (8.5)	5/98 (5.1)
Bocavirus	13/455 (2.9)	13/355 (3.6)	0/98 (0)
C. pneumoniae	2/455 (0.4)	0/355 (0)	2/98 (2)
Coronavirus HKU	3/455 (0.7)	3/355 (0.9)	0/98 (0)
Coronavirus 229	19/455 (4.2)	16/355 (4.5)	3/98 (3.1)
Coronavirus 43	6/455 (1.3)	6/355 (1.7)	0/98 (0)
Coronavirus 63	5/455 (1.4)	5/355 (1.4)	0/98 (0)
Enterovirus	5/455 (1.1)	5/355 (1.4)	0/98 (0)
Influenza A	19/454 (4.2)	13/354 (3.7)	5/98 (5.1)
Influenza B	21/454 (4.6)	17/354 (4.8)	4/98 (4.1)
Legionella spp.	84/455 (18.5)	62/355 (17.5)	20/98 (20.4)
Metapneumovirus	9/455 (2)	8/355 (2.3)	1/98 (1.0)
M. pneumoniae	6/455 (1.3)	6/355 (1.7)	0/98 (0)
Parainfluenza 1	2/455 (0.4)	1/355 (0.3)	1/98 (1.0)
Parainfluenza 2	6/455 (1.3)	6/355 (1.7)	0/98 (0)
Parainfluenza 3	7/455 (1.5)	7/355 (2)	0/98 (0)
Parainfluenza 4	3/455 (0.7)	2/355 (0.6)	0/98 (0)
Parechovirus	5/455 (1.1)	5/355 (1.4)	0/98 (0)
Rhinovirus	17/455 (3.7)	15/355 (4.2)	2/98 (2)
RSV	8/455 (1.8)	4/355 (1.1)	3/98 (3.1)

NTM – nontuberculous mycobacteria; RSV – respiratory syncytial virus

4.5.4.2 Bacteria

At least one potential bacterial pathogen was identified in 182 (40%) patients or, if the results for *Legionella* spp. are discounted (see below), in 125 (28%). Overall, 26 patients (6%) were bacteraemic with a significant organism: *Salmonella typhi* (9 patients); nontyphoidal *Salmonella* (NTS)(7); *S. pneumoniae* (6); Gram-negative enteric bacteria (3); *Staphylococcus aureus* (2). A further 12 (3%) yielded contaminants: coagulase-negative *Staphylococci* (8); *Micrococcus* spp. (2); *Bacillus* spp. (2).

Streptococcus pneumoniae was the most commonly identified pathogen overall being present in 98 (21%; Table 4.10). Of these 92 (94%) were identified by detection of pneumococcal urinary antigen alone, 3 (3%) by both blood culture and urinary antigen, 2 (2%) by blood culture alone, and 1 (1%) by antigen detection in pleural fluid alone. Whilst 70% patients with pneumococcal disease were HIV positive, pneumococcal aetiology was more common in HIV-negative patients (30/98 (31%) *vs.* 68/355 (19%); *P*=0.01).

Salmonella spp. were the most commonly identified pathogens in blood culture. One additional case of *S. typhi* was identified on pleural fluid culture. *S. typhi* was identified more frequently in HIV-negative patients (5/94 (5%) *vs.* 3/350 (1%); *P*=0.01). All 7 cases of NTS infection (*S.* Typhimurium, 6 cases; *S.* Enteritidis, 1 case) occurred in HIV-positive patients.

Legionella spp. were identified by PCR in 84/455 (18%) of nasopharyngeal aspirate specimens. This prevalence greatly exceeds that reported in previous studies of adult CAP from either sub-Saharan Africa (see chapter 2) or other settings (Charles *et al.*, 2008a; Jain *et al.*, 2015; Peto *et al.*, 2014; Torres *et al.*, 2014). Pending further confirmatory testing the validity of this result is unclear and as such has not been included in combined aetiological analyses.

Infection with other 'atypical' bacterial pathogens was uncommon; only 6/455 (1%) cases of *Mycoplasma pneumoniae* and 2/455 (0.4%) cases of *Chlamydia pneumoniae* were identified overall. No association of atypical bacterial infection with HIV-status was detected.

4.5.4.3 Mycobacteria

Infection with *Mycobacterium tuberculosis* (TB) was determined on the basis of sputum AFB smear microscopy and mycobacterial culture, Xpert MTB/RIF assay and for those with an aspirated pleural effusion, pleural fluid smear microscopy and mycobacterial culture. Mycobacterial blood cultures were not performed. The result of a TB diagnostic test performed on a sputum specimen was available in 71% (326/459) of the whole patient cohort. Overall, TB was identified in 75 patients, representing 23% of those that submitted a sputum specimen and 16% of the overall cohort. TB was confirmed by culture in 65 (87%): sputum (n=65); pleural fluid (n=7); both (n=2). In the absence of a valid culture result, TB was diagnosed on the basis of Xpert MTB/RIF alone in 8 patients, sputum microscopy in 1 and pleural fluid microscopy in 1. Using a positive culture as reference standard, sputum Xpert MTB/RIF sensitivity was 68.4% (95% CI: 54.8%-80.1%) and specificity was 95.6% (95% CI: 91.8%-98.0%); smear microscopy sensitivity was 52.5% (95% CI: 39.3%-65.4%) and specificity was 99.1% (95% CI: 96.6%-99.9%).

Overall 64 (86%) of patients with TB were HIV-positive. TB was identified in 25% (64/257) of HIV-positive patients compared to 16% (10/64) of HIV-negative patients, although this difference was not statistically significant (OR 1.79; 95% CI: 0.84-4.17).

Nontuberculous mycobacteria infection was identified in 3% (8/273) of patients on the basis of sputum culture; sputum smear microscopy was negative in all but one case.

4.5.4.4 Viruses

Influenza viruses (encompassing influenza A and influenza B) were the most commonly identified viral pathogens (Table 4.10). Overall influenza was found in 9% (40/454) patients; influenza A and B occurred with approximately equal frequency. 75% (30/40) of patients with influenza were HIV positive; influenza did not associate with HIV status.

Adenovirus (35/455; 8%) and coronaviruses (31/455; 7%) were the two next most commonly identified viral pathogens; 86% (30/35) and 90% (28/31), respectively, were HIV positive. Rates of identification did not significantly vary with HIV status.

Table 4.12 Combined aetiological data stratified by HIV status. *S. pneumoniae* diagnosis based on blood and pleural fluid culture and antigen assay of urine and pleural fluid. *M. tuberculosis* based on sputum microscopy, culture and Xpert MTB/RIF and pleural fluid culture. Other organisms based on single test. Denominators indicate number of patients with at least one relevant test available. Association of specific pathogens with HIV status examined by χ^2 test and OR (with 95% CI) directly calculated or estimated by logistic regression *.

Organism	All (n=459)	HIV-positive (n=355)	HIV-negative (n=98)	OR (95% CI)	*P*
S. pneumoniae	98/459 (21.4)	68/355 (19.2)	30/98 (30.6)	0.53 (0.31-0.91)	0.01
S. typhi	10/450 (2.2)	4/350 (1.1)	5/94 (5.3)	0.21 (0.04-0.98)	0.01
Nontyphoidal *Salmonella*[a]	7/450 (1.6)	7/350 (2)	0/94 (0)	2.62 (0.39-∞)*	0.37
Other GNEB[b]	3/450 (0.7)	3/350 (0.9)	0/94 (0)	1.03 (0.11-∞)*	0.98
S. aureus	2/450 (0.4)	1/350 (0.3)	1/94 (1.1)	0.27 (0.00-21.14)	0.32
Legionella spp.[c]	84/455 (18.5)	62/355 (17.5)	20/98 (20.4)	0.83 (0.46-1.53)	0.50
Atypical bacteria[d]	8/455 (1.8)	6/355 (1.7)	2/98 (2)	0.85 (0.14-8.49)	0.82
M. tuberculosis	75/326 (23.0)	64/257 (24.9)	10/64 (15.6)	1.79 (0.84-4.17)	0.11
Nontuberculous mycobacteria	8/273 (2.9)	5/217 (2.3)	3/52 (5.8)	0.39 (0.07-2.57)	0.19
Influenza viruses[e]	40/454 (8.8)	30/354 (8.5)	9/98 (9.2)	0.92 (0.41-2.28)	0.82
Adenovirus	35/455 (7.7)	30/355 (8.5)	5/98 (5.1)	1.72 (0.63-5.82)	0.27
Coronaviruses[e]	31/455 (6.8)	28/355 (7.9)	3/98 (3.1)	2.71 (0.81-14.21)	0.09
Parainfluenza viruses[e]	17/455 (3.7)	15/355 (4.2)	1/98 (1)	4.28 (0.64-181.95)	0.13
Rhinovirus	17/455 (3.7)	15/355 (4.2)	2/98 (2)	2.12 (0.48-19.38)	0.31
Bocavirus	13/455 (2.9)	13/355 (3.6)	0/98 (0)	5.20 (0.85-∞)*	0.08
Metapneumovirus	9/455 (2)	8/355 (2.3)	1/98 (1)	2.24 (0.29-100.22)	0.44
RSV	8/455 (1.8)	4/355 (1.1)	3/98 (3.1)	0.36 (0.06-2.51)	0.17
Enterovirus	5/455 (1.1)	5/355 (1.4)	0/98 (0)	1.87 (0.25-∞)*	0.59
Parechovirus	5/455 (1.1)	5/355 (1.4)	0/98 (0)	1.87 (0.25-∞)*	0.59
No pathogen detected[c]	181/459 (39.4)	137/355 (38.6)	42/98 (42.9)	0.84 (0.52-1.36)	0.44

CI – confidence interval; GNEB – Gram-negative enteric bacilli; OR – odds ratio; RSV – respiratory syncytial virus.

[a] *S.* Enteritidis and *S.* Typhimurium combined; [b] *E. coli* and *Enterobacter cloacae* combined; [c] *Legionella* spp. not included in combined total of detected pathogens; [d] *C. pneumoniae* and *M. pneumoniae* combined; [e] subtypes of influenza, parainfluenza and coronavirus combined into single category for each virus species.

4.5.4.5 Co-infection

Co-infection relationships were investigated in the 307 (67%) patients from whom a complete set of investigations was performed (i.e. blood culture, pneumococcal urine antigen testing, sputum mycobacterial culture and/or Xpert MTB/RIF, nasopharyngeal aspirate multiplex PCR). In view of the uncertainties over their accuracy, results for *Legionella* spp. were excluded from this analysis

In this subset at least one potential pathogen was identified in 206 (67%) patients. The overall pattern of pathogens was similar to that describe in the overall cohort with *S. pneumoniae* (73/307; 24%), *M. tuberculosis* (68/307; 22%) and influenza (31/307; 10%) being the most commonly identified pathogens. Overall a single organism was identified in 139 (45%): single bacterial pathogen in 45 (15%); single virus in 50 (16%); single mycobacterial infection in 44 (14%; Figure 4.7). In the patients with multiple identified organisms, the combination of a bacterial viral co-infection was most frequently observed (28/307; 9%), followed by a mycobacterial viral co-infection in 18 (6%).

Amongst the 73 patients with *S. pneumoniae*, it was present as sole pathogen in 40 (55%) patients and in combination with *M. tuberculosis* in 7 (10%), adenovirus in 7 (10%), influenza in 6 (8%) and rhinovirus in 6 (8%; Table 4.11). *M. tuberculosis* occurred as a sole pathogen in 42 (62%) patients and in co-infection was most commonly detected with adenovirus (8/68; 12%), *S. pneumoniae* (7/68; 10%) and parainfluenza viruses (4/68; 6%). Influenza was detected as in isolation in 19 (61%) patients and in co-infection was most commonly associated with *S. pneumoniae* (6/31; 19%), coronavirus (3/31; 10%) and *M. tuberculosis* (2/31; 6%).

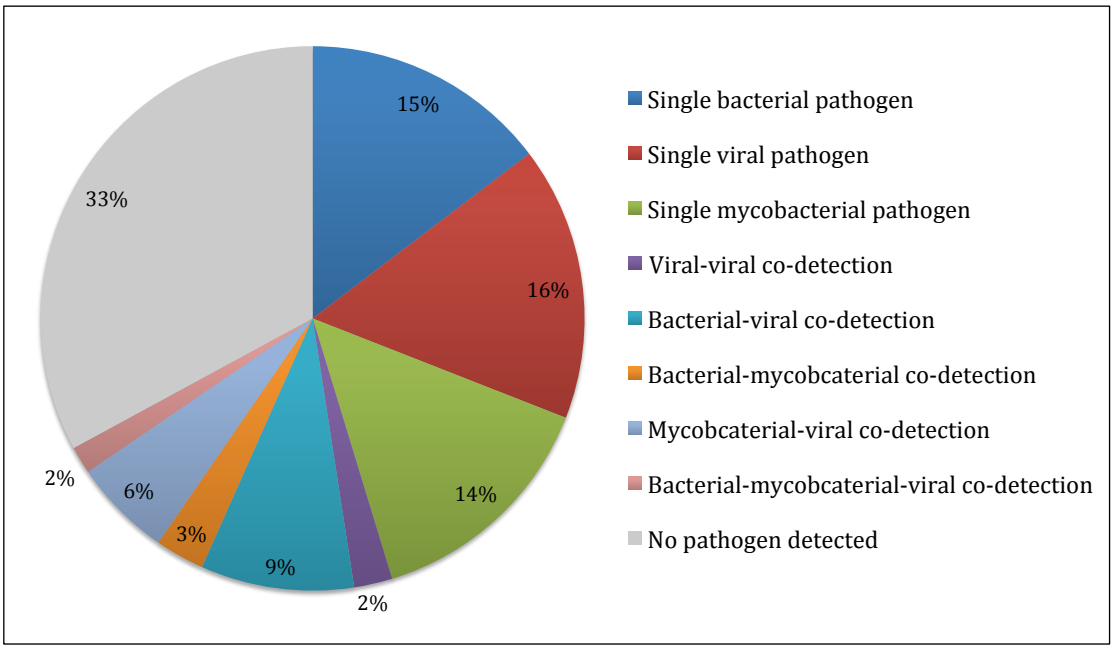

Figure 4.5 Bacterial, viral and mycobacterial infection in isolation and combination in MARISO cohort. Analysis restricted to 307 patients with results available for blood culture, pneumococcal urine antigen testing, sputum mycobacterial culture and/or Xpert MTB/RIF, nasopharyngeal aspirate multiplex PCR.

Table 4.13 Matrix showing co-infection combinations in MARISO cohort.
Analysis restricted to 307 patients with complete results available for blood culture, pneumococcal urine antigen testing, sputum mycobacterial culture and/or Xpert MTB/RIF, nasopharyngeal aspirate multiplex PCR. Shaded squares indicate mono-infection.

	S. pneumoniae	*S. typhi*	NTS	Other GNEB	*S. aureus*	Atypical bacteria	*M. tuberculosis*	NTM	Influenza	Adenovirus	Coronaviruses	Parainfluenza	Rhinovirus	Bocavirus	Metapneumovirus	RSV	Enterovirus	Parechovirus	**TOTAL**
S. pneumoniae	40	0	0	0	0	0	7	2	6	7	5	4	6	1	3	2	0	0	**73**
S. typhi		2	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	**4**
NTS			2	0	0	0	0	2	0	1	1	1	0	0	0	0	0	0	**5**
Other GNEB				0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	**1**
S. aureus					0	0	0	0	1	0	0	0	0	0	0	0	0	0	**1**
Atypical bacteria						1	1	0	0	0	0	1	0	0	0	0	0	0	**3**
M. tuberculosis							42	0	2	8	3	4	3	1	2	1	0	0	**68**
NTM								2	0	2	2	1	1	0	0	0	0	0	**8**
Influenza									19	1	3	1	1	1	0	1	0	0	**31**
Adenovirus										8	1	1	0	0	1	0	0	0	**23**
Coronaviruses											10	0	2	3	0	0	0	0	**25**
Parainfluenza												4	2	0	1	0	0	0	**14**
Rhinovirus													3	0	0	0	1	1	**13**
Bocavirus														3	0	2	0	0	**8**
Metapneumovirus															1	0	0	0	**6**
RSV																2	0	0	**7**
Enterovirus																	0	1	**1**
Parechovirus																		0	**1**

GNEB – Gram-negative enteric bacilli; NTM – nontuberculous mycobacteria; NTS – nontyphoidal *Salmonella*; RSV – respiratory syncytial virus.

4.5.5 Radiology features

4.5.5.1 Overview

A chest radiograph was available for review in 421 (91.7%) patients. Radiographs were unavailable for analysis due to: early death in 14; hospital discharge without radiograph in 10 (including at least 4 where radiographs were not possible due to the lack of processing chemicals); discharge prior to photograph in 8; unknown reason in 5.

Each radiograph was independently assessed by three readers (two radiologists and myself); a consensus view based on the majority opinion of the three readers was used to define the presence of specific radiological features for use in analysis (see sections 3.14 and 3.18 for detailed methods). Radiographic pneumonia - defined as the presence of consolidation or other parenchymal abnormality or pleural effusion - was identified in 322 (77%), 297 (71%) and 314 (75%) patients, respectively, by the three readers giving a consensus value of 317 (76%). Applying a more restrictive definition of radiographic pneumonia based on parenchymal abnormalities alone, the proportion with radiographic pneumonia was 67%. There was substantial agreement between the three reporters for the identification of radiographic pneumonia (kappa coefficient 0.71; 95% CI: 0.65-0.78).

Consolidation was identified in 251 (60%) patients. Inter-reader agreement was substantial for the presence of consolidation (kappa 0.65; 95% CI: 0.59-0.70), but only moderate for its quality (kappa 0.46; 95% CI: 0.37-0.55) and extent (kappa 0.49; 95% CI: 0.42-0.55). Multilobar involvement was present in 73/250 (29%) of those with consolidation. Other parenchymal abnormalities such as reticulonodular change (35/418; 8%), cavitation (20/418; 5%) and miliary appearance (2/417; 0.5%) were less common and inter-reader agreement was moderate at best. Pleural effusion was identified in 118/417 (28%) with substantial inter-reader agreement (kappa 0.49; 95% CI: 0.42-0.55). The presence of pleural effusion was the sole grounds of defining radiographic pneumonia in 38/322 (12%).

The proportion of patients with radiographic pneumonia did not vary with HIV status (HIV-positive 247/324 (76%) *vs.* HIV-negative 66/91 (73%); *P*=0.47). Similarly the frequencies of the following features did not associate with HIV status: any parenchymal abnormality (222/318 (70%) *vs.* 57/90 (63%); *P*=0.24); consolidation (199/317 (63%) *vs*. 49/90 (54%); *P*=0.15); cavitation (15/321 (5%) *vs.* 5/91 (5%); *P*=0.75); reticulonodular change (27/321 (8%) *vs.* 8/91 (9%); *P*=0.91); pleural effusion (93/319 (29%) *vs.* 23/91 (25%); *P*=0.47). Amongst HIV-positive patients, the frequencies of the following features did not alter with CD4 count: radiographic

pneumonia (CD4 <200 cells/mm^3 176/225 (78%) *vs.* CD4 ≥ 200 cells/mm^3 49/64 (77%), *P*=0.78); consolidation (139/219 (63%) *vs.* 39/64 (61%), *P*=0.71); cavitation (10/223 (4%) *vs.* 4/64 (6%), *P*=0.56); reticulonodular change (17/223 (8%) *vs.* 6/64 (9%), *P*=0.65); pleural effusion (64/221 (29%) *vs.* 18/64 (28%), *P*=0.90).

Table 4.14 Radiological features and inter-reader agreement. Data presented as number and proportion of patients. Overall proportion with radiographic pneumonia in top row, then proportions for specific features shown below. Average agreement and three-way kappa (estimated 95% confidence intervals) calculated for all assessors. Consensus values used in later analyses calculated by majority rating of all assessors. Radiologist 1, radiologist 2 and clinician considered 2, 14 and 4 radiographs, respectively, as uninterpretable.

	Individual scorers assessment			Consensus assessment	All scorers agreement	
	Radiologist 1 (n=420)	Radiologist 2 (n=420)	Clinician (n=421)		Avg. agree (%)	Kappa (95% CI)
Radiographic pneumonia	322 (76.7)	297 (70.7)	314 (74.6)	317 (75.7)	89.0	0.71 (0.65-0.78)
Any parenchymal abnormality	299 (71.2)	266 (63.3)	268 (63.7)	282 (67.3)	85.9	0.68 (0.62-0.74)
Consolidation	244 (58.1)	251 (59.8)	260 (61.8)	251 (59.9)	83.2	0.65 (0.59-0.70)
Quality						
Confluent	158 (64.8)	135 (53.8)	161 (61.9)	145 (62.2)	74.4	0.46 (0.37-0.55)
Patchy	85 (34.8)	116 (46.2)	99 (38.1)	88 (37.8)		
Extent						
Segmental	77 (31.6)	78 (31.1)	83 (31.9)	62 (27.7)	66.1	0.49 (0.42-0.55)
Lobar	72 (29.5)	73 (29.1)	89 (34.2)	72 (32.1)		
Multifocal	95 (38.9)	99 (39.4)	88 (33.8)	90 (40.2)		
Multilobar	85 (26.4)	65 (21.9)	76 (24.2)	73 (23.6)	83.5	0.55 (0.47-0.63)
Cavitation	27 (6.4)	26 (6.2)	15 (3.6)	20 (4.8)	94.9	0.51 (0.36-0.65)
Reticulonodular change	140 (33.3)	35 (8.3)	24 (5.7)	35 (8.4)	76.8	0.14 (0.06-0.23)
Miliary appearance	2 (0.5)	2 (0.5)	8 (1.9)	2 (0.5)	98.4	0.17 (-0.02-0.32)
Pleural effusion	111 (26.4)	106 (25.2)	155 (36.8)	118 (28.2)	83.8	0.61 (0.54-0.68)
Pneumothorax	2 (0.5)	1 (0.2)	3 (0.7)	2 (0.5)	99.3	0.32 (-0.02-0.49)
Mediastinal lymphadenopathy	40 (9.5)	34 (8.1)	50 (11.9)	28 (6.8)	87.3	0.30 (0.19-0.39)
Volume loss	76 (18.1)	35 (8.3)	44 (10.5)	30 (7.2)	84.3	0.27 (0.16-0.38)
Bronchiectasis	31 (7.4)	8 (1.9)	3 (0.7)	3 (0.7)	93.8	0.04 (-0.03-0.12)

Table 4.15 Consolidated aetiological data stratified by radiological appearance and HIV status in MARISO cohort. Data presented as number and proportion of patients with given aetiology. Association of specific organisms with radiological appearance controlling for effect of HIV assessed by χ^2 test with weighted OR (95% CI) calculated by Mantel-Haenszel method or estimated by logistic regression (*).

	Radiographic pneumonia (n=317)			No radiographic pneumonia (n=104)				
Organism	**All**	**HIV-pos.**	**HIV-neg.**	**All**	**HIV-pos.**	**HIV-neg.**	**OR (95% CI)**	***P***
S. pneumoniae	83/317 (26.2)	56/247 (22.7)	27/66 (40.9)	9/104 (8.7)	6/77 (7.8)	3/25 (12)	3.93 (1.86-8.29)	<0.001
S. typhi	2/309 (0.6)	1/243 (0.8)	0/62 (0)	8/103 (7.8)	2/76 (2.6)	5/25 (20)	0.09 (0.02-0.48)	<0.001
NTS[a]	1/309 (0.3)	1/243 (0.4)	0/62 (0)	5/103 (4.9)	5/76 (6.6)	0/25 (0)	0.06 (0.01-0.53)	<0.001
Other GNEB[b]	2/309 (0.7)	2/243 (0.8)	0/62 (0)	1/103 (1)	1/76 (1.3)	0/25 (0)	0.62 (0.06-6.99)	0.70
S. aureus	1/309 (0.3)	0/243 (0)	1/62 (1.6)	0/103 (0)	0/76 (0)	0/25 (0)	0.40 (0.01-∞)	1.00*
Legionella spp.[c]	63/314 (20.1)	47/247 (19.0)	15/66 (22.7)	13/103 (12.6)	10/77 (13.0)	2/25 (8)	1.85 (0.95-3.60)	0.06
Atypical bacteria[d]	5/314 (1.6)	4/247 (1.6)	1/66 (1.5)	1/103 (1)	0/77 (0)	1/25 (4)	1.70 (0.18-15.64)	0.64
M. tuberculosis	58/232 (25)	47/186 (25.2)	10/42 (23.8)	13/70 (18.6)	13/52 (25)	0/17 (0)	1.39 (0.71-2.72)	0.33
NTM	3/194 (1.6)	2/158 (1.3)	1/33 (3)	4/59 (6.8)	2/43 (4.7)	2/15 (13.3)	0.23 (0.05-1.15)	0.05
Influenza[e]	25/313 (8)	20/246 (8.1)	4/66 (6.1)	11/103 (10.7)	9/77 (11.7)	2/25 (8)	0.68 (0.32-1.45)	0.32
Adenovirus	22/314 (7)	19/247 (7.7)	3/66 (4.5)	7/103 (6.8)	5/77 (6.5)	2/25 (8)	1.01 (0.42-2.46)	0.97
Coronaviruses[e]	22/314 (7)	19/247 (7.7)	3/66 (4.6)	9/103 (8.7)	9/77 (11.7)	0/25 (0)	0.76 (0.33-1.71)	0.51
Parainfluenza[e]	10/314 (3.2)	9/247 (3.6)	1/66 (1.5)	6/103 (5.8)	5/77 (6.5)	0/25 (0)	0.62 (0.21-1.86)	0.39
Rhinovirus	11/314 (3.5)	9/247 (3.6)	2/66 (3)	5/103 (4.9)	5/77 (6.5)	0/25 (0)	0.69 (0.23-2.03)	0.50
Bocavirus	9/314 (2.9)	9/247 (3.6)	0/66 (0)	3/103 (2.9)	3/77 (3.9)	0/25 (0)	0.93 (0.25-3.54)	0.92
Metapneumovirus	9/314 (2.9)	8/247 (3.2)	1/66 (1.5)	0/103 (0)	0/77 (0)	0/25 (0)	4.07 (0.63-∞)	0.16*
RSV	4/314 (1.3)	1/247 (0.4)	2/66 (3)	3/103 (2.9)	2/77 (2.6)	1/25 (4)	0.34 (0.07-1.69)	0.17
Enterovirus	2/314 (0.6)	2/247 (0.8)	0/66 (0)	1/103 (1)	1/77 (1.3)	0/25 (0)	0.62 (0.06-6.97)	0.70
Parechovirus	2/314 (0.6)	2/247 (0.8)	0/66 (0)	1/103 (1)	1/77 (1.3)	0/25 (0)	0.62 (0.06-6.97)	0.70
No pathogen detected[c]	123/317 (38.8)	95/247 (38.5)	26/66 (39.4)	40/104 (38.5)	28/77 (36.4)	12/25 (48)	0.98 (0.62-1.56)	0.94

CI – confidence interval; GNEB – Gram-negative enteric bacilli; NTM – nontuberculous mycobacteria; NTS – nontyphoidal *Salmonella*; OR – odds ratio; RSV – respiratory syncytial virus.

[a] *S.* Enteritidis and *S.* Typhimurium combined; [b] *E. coli* and *Enterobacter cloacae* combined; [c] *Legionella* spp. not included in combined total of detected pathogens; [d] *C. pneumoniae* and *M. pneumoniae* combined; [e] subtypes of influenza, parainfluenza and coronavirus combined into single category for each virus species.

4.5.5.2 Radiological features by aetiology

In this cohort of patients with clinically defined pneumonia the relationship of aetiology with radiological change was investigated (Table 4.13). The overall rankings of the most commonly identified organisms in the subgroup of patients with radiographic pneumonia reflected those of the whole cohort with *S. pneumoniae* (83/317; 26%)*, M. tuberculosis* (58/232; 25%) and influenza (25/313; 8%) being identified most frequently. In the subgroup lacking radiographic pneumonia, *M. tuberculosis* (13/70; 19%) and influenza (11/103; 11%) were the most frequently identified pathogens. Having controlled for any effect of HIV, detection of *S. pneumoniae* was positively associated with radiological pneumonia (83/317 (26%) *vs*. 9/104 (9%); OR 3.93; 95% CI: 1.86-8.29). Both *S. typhi* (2/309 (1%) *vs*. 8/103 (8%); OR 0.09; 95% CI: 0.02-0.48) and NTS (1/309 (<1%) *vs*. 5/103 (5%) OR 0.06; 95% CI: 0.01-0.53) were negatively associated with the presence of radiographic pneumonia. The relative abundance of all other organisms did not vary significantly with the presence of radiological change.

The radiographic appearance of the three commonest organisms (*S. pneumoniae*, *M. tuberculosis* and influenza) was analysed in more detail (Table 4.14). For patients with radiographic pneumonia, confluent consolidation was associated with *S. pneumonia*e (OR 2.41; 95% CI: 1.29-4.51) and patchy consolidation with *M. tuberculosis* (OR 2.12; 95% CI: 1.06-4.29). Multilobar involvement (OR 2.37; 95% CI: 1.23-4.56), reticulonodular change (OR 3.98; 95% CI: 1.74-9.12) and mediastinal lymphadenopathy (OR 4.91; 95% CI: 1.77-13.64) were more common with *M. tuberculosis* infection. Pleural effusion was common across all aetiologies. There were no significant associations between specific radiological features and influenza. As described above, inter-observer agreement was substantial for identification of pleural effusion, moderate for consolidation quality and multilobar involvement, fair for mediastinal lymphadenopathy and only slight for reticulonodular change (Table 4.12).

Table 4.16 Description of radiological appearance for three commonest causal organisms: *S. pneumoniae*, tuberculosis and influenza. Analysis restricted to patients with radiographic pneumonia.

Radiographic feature	Organism		
	S. pneumoniae **(n=82)**	***M. tuberculosis*** **(n=58)**	**Influenza (n=25)**
Any parenchymal abnormality	79 (96.3)	50 (86.2)	25 (100)
Consolidation	75 (91.5)	47 (81.0)	20 (80.0)
Quality			
Confluent	56 (75.7)	21 (47.7)	10 (55.6)
Patchy	18 (24.3)	23 (52.3)	8 (44.4)
Extent			
Segmental	13 (18.8)	5 (11.4)	3 (20)
Lobar	29 (42.0)	12 (27.3)	5 (33.3)
Multifocal	27 (39.1)	27 (61.4)	7 (46.7)
Multilobar	23 (28.4)	22 (37.9)	4 (18.2)
Cavitation	2 (2.4)	6 (10.3)	0 (0)
Reticulonodular change	5 (6.0)	14 (24.1)	4 (16)
Miliary appearance	0 (0)	0 (0)	0 (0)
Pleural effusion	26 (31.3)	23 (40.4)	7 (28.0)
Mediastinal lymphadenopathy	3 (3.7)	10 (17.2)	2 (8.3)

4.6 Discussion

4.6.1 Study recruitment

The broad objective of the MARISO study was to recruit a cohort representative of patients hospitalised with acute CAP in Malawi. Of 1711 patients with features of respiratory illness or infection that were screened, only 489 were assessed as eligible with the clinical case definition of CAP used. The primary reason for non-eligibility was prolonged symptom duration (>2 weeks), present in more than a third of excluded patients. Delayed presentation, in particular in male patients, may reflect that the study was completed in a referral hospital setting where prior review in primary care was mandated or other barriers to healthcare-seeking behaviour present in Malawi (e.g. transportation costs). Also, women were more frequently excluded for lack of chest signs and older patients for absent fever. The case definition of pneumonia used may substantially impact the demographic composition of study cohorts and, by extension, the aetiological spectrum and outcome.

The proportion of screened patients who were recruited varied over the course of the study with a notable fall in June 2014 as screening numbers increased. The explanation for this is not immediately clear and can only be speculated because of the limited information available about non-recruited patients. However, it is possible that in an

attempt to maximise recruitment the study team screened more broadly (i.e. interpreted the screening criterion of features of respiratory illness or infection more liberally) whilst continuing to comply the eligibility criteria consistently.

4.6.2 Baseline characteristics

The study population was predominantly young, male and HIV-positive. The age profile reflects that of acute adult medical admissions to QECH, but is on average younger than the local community; adults aged 30 to 40 years make up 27% of the urban population of southern Malawi compared to 44% of the study cohort (National Statistical Office of Malawi, 2008; SanJoaquin *et al.*, 2013). The male preponderance, however, is not observed in overall admission figures and has not been seen in other recent local cohorts of sepsis (Waitt *et al.*, 2015), meningitis (Scarborough *et al.*, 2007) or tuberculosis (Feasey *et al.*, 2013). A male preponderance is a consistent finding of CAP cohorts in both sub-Saharan Africa (Aderaye, 1994a; Albrich *et al.*, 2014a; Birkhamshaw *et al.*, 2013; Nyamande *et al.*, 2007a; Scott *et al.*, 2000) and well-resourced settings (Ewig *et al.*, 2009; Gutierrez *et al.*, 2006) and reflects a genuine increased incidence in men, although the reasons for this are incompletely understood.

The high rate of HIV is consistent with the overall prevalence of HIV amongst medical inpatients at QECH (SanJoaquin *et al.*, 2013), comparable to that of other CAP cohorts from the region and reflects its role as a key driver of pneumonia incidence (Aderaye, 1994a; Albrich *et al.*, 2014a; Birkhamshaw *et al.*, 2013; Nyamande *et al.*, 2007a; Scott *et al.*, 2000). More than one-third of HIV infected patients were newly diagnosed at presentation and disease was typically advanced (median CD4 cell count of 100 cells/mm^3). These data suggest that there are still considerable gains to be made in reducing CAP incidence through earlier diagnosis and treatment of HIV. The impact of the recent shift in to WHO policy to recommending universal ART upon diagnosis of HIV (regardless of CD4 count) should be observed (Siedner *et al.*, 2015; World Health Organization, 2015b).

In keeping with previous CAP cohorts from sub-Saharan Africa, other chronic comorbid conditions such as COPD, congestive heart failure, and cerebrovascular disease were rarely reported, presumably reflecting the age profile of patients (Feldman *et al.*, 1995; Koulla-Shiro *et al.*, 1997; Onyedum *et al.*, 2011). By contrast, in well-resourced settings typically more than two-thirds of hospitalised CAP patients are over 65 and more than half have chronic cardiopulmonary or neurological comorbidities (Ewig *et al.*, 2009; Gutierrez *et al.*, 2006; Jackson *et al.*, 2004). Differences in demographics and comorbidity profile mean that strategies for CAP prevention, severity assessment and

management need to be locally adapted. Severity assessment tools derived in well-resourced settings that predict CAP mortality and give weight to advanced age and comorbid illness are unlikely to be accurate in Malawi (Albrich *et al.*, 2014a; Fine *et al.*, 1997a).

4.6.3 Aetiology

Using a combination of blood culture, pneumococcal urinary antigen testing, multiplex PCR on nasopharyngeal aspirate and TB diagnostic tests on sputum and pleural fluid, a potentially causal organism was identified in 61% of patients. This yield is comparable to other recent high quality pneumonia aetiology studies (Charles *et al.*, 2008a; Johansson *et al.*, 2010). A recent CDC study of adult pneumonia in the US identified a potential causative organism in only 38% of patients (Jain *et al.*, 2015).

Streptococcus pneumoniae was commonest organism identified, present in 21% overall. This is comparable to the 27% reported in a recent South African cohort of HIV-infected adults that used similar diagnostic tests (Albrich *et al.*, 2012). Higher proportions have been obtained with more invasive sampling techniques (e.g. percutaneous transthoracic needles aspirates)(Scott *et al.*, 2000). Pneumococcal pneumonia occurred more frequently in HIV negative patients. Given the strong positive association between HIV and pneumococcal disease this result initially appears counter-intuitive (Gilks *et al.*, 1996), but has also been observed in recent South African cohort (Albrich *et al.*, 2012). Potential explanations include: differential under-ascertainment of *S. pneumoniae*; aggressive disease course leading to early (pre-recruitment) death; relatively higher burden of other opportunistic pathogens.

Nearly all cases of pneumococcal infection were based on a positive BinaxNOW *S. pneumoniae* urinary antigen test; only 1% of patients had pneumococcal bacteraemia. This may reflect under-ascertainment as a result of high rates of pre-presentation antibiotic use (Jokinen *et al.*, 2010). Alternatively, it may indicate a genuine shift to less invasive pneumococcal serotypes, perhaps as an indirect result of universal infant pneumococcal vaccination (Bar-Zeev *et al.*, 2015). BinaxNOW *S. pneumoniae* has poor specificity in children because of high rates of asymptomatic nasopharyngeal carriage of *S. pneumoniae* (Adegbola *et al.*, 2001). Limited data indicate that specificity in adults is not compromised by nasopharyngeal colonisation (Boulware *et al.*, 2007; Sinclair *et al.*, 2013; Turner *et al.*, 2011). The combined effect of nasopharyngeal colonisation and HIV-infection on test accuracy has not been examined.

M. tuberculosis was overall the second most commonly identified organism. Traditional teaching has attuned clinicians to suspecting pulmonary TB in patients with prolonged

symptoms - typically a cough for longer than 2 weeks (World Health Organization, 2013c). These results highlight the high prevalence of TB in patients with CAP and short reported illness duration. Previous CAP studies in the region have consistently identified a substantial burden of TB when adequate diagnostic tests have been performed (Hartung *et al.*, 2011; Nyamande *et al.*, 2007a; Scott *et al.*, 2000; Vray *et al.*, 2008). Recent studies from South Africa, Zambia and Malawi using rigorous TB diagnostic algorithms with intensive specimen collection estimate that up to one-third of all HIV-positive acute medical inpatients have TB (Bates *et al.*, 2012; Gupta *et al.*, 2015; Lawn *et al.*, 2015). A post mortem series of medical inpatients in Zambia found TB in 62% with concurrent pyogenic pneumonia present in approximately one third (Bates *et al.*, 2015).

Improved diagnostic tests for TB that facilitate early treatment are urgently needed. In many low-resource settings, TB diagnosis is still largely reliant on smear microscopy and chest radiography despite their limited diagnostic accuracy . The development and rollout of the Xpert MTB/RIF platform represents a major step forward in TB diagnostics in low-resource settings (Lawn *et al.*, 2013c). However, as seen in this cohort, sputum specimens are frequently unobtainable in acutely unwell patients. New diagnostic modalities based on urine specimens (e.g. Alere Determine urinary lipoarabinomannan assay) show some promise to improving outcomes (Peter *et al.*, 2016).

Invasive salmonellosis was the commonest cause of bacteraemic disease. Whether these cases were true pneumonic disease directly attributable to *Salmonella* spp. or primarily bacteraemic diseases with pulmonary features due to other pathogens is uncertain. It is notable that most patients with invasive salmonellosis lacked radiographic change. NTS is the commonest cause of bacteraemia in African adults and up to 30% of patients have an apparent focal lower respiratory tract infection (Feasey *et al.*, 2012). In a cohort of Kenyan adults with radiographic pneumonia, invasive *Salmonella* infection was present in 4% of HIV-infected patients (Scott *et al.*, 2000). Regardless of the exact nature of infection, the therapeutic implications of the need for broader spectrum antibacterials are the same.

The burden of so-called atypical bacterial infections (including *Legionella* spp., *Mycoplasma pneumoniae* and *Chlamydophila* spp.) in sub-Saharan Africa is poorly described. The low prevalence of infection with *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* observed in the current study based on multiplex PCR of NPA specimens is consistent with previous studies based on serology that estimated

prevalence, respectively, at 0-9% and 0-21% (Koulla-Shiro *et al.*, 1997; Maartens *et al.*, 1994; Nyamande *et al.*, 2007a; Prout *et al.*, 1983; Scott *et al.*, 2000).

The multiplex PCR detected *Legionella* spp. in 19%. The primers and probes used in the FTD 33 kit have been designed to target the 16S rRNA gene of *L. pneumophila* and *L. longbeachae*. Validation experiments by the manufacturer report excellent (100%) specificity although sequence analysis by BLAST predicts possible cross reactivity with *L. worsleiensis*, which has been implicated as a rare cause of nosocomial pneumonia (Berger *et al.*, 2006). Previous studies from Kenya and South Africa estimated *Legionella* prevalence in CAP patients at 2-9% based on BinaxNOW *L. pneumophila* urinary antigen assay (Mpe *et al.*, 2001; Odera *et al.*, 2009). The substantial difference may be due to infection with non-serogroup 1 *L. pneumophila* or non-*pneumophila* species that are not detected by the urinary antigen test. There is considerable geographical variation in the predominance of particular *Legionella* species and serogroups (Isenman *et al.*, 2016; Waterer *et al.*, 2001a). In a recent CAP cohort from rural Thailand, for example, legionellosis was identified by serological methods in 5% of patients, with all cases caused by *L. longbeachae* (Phares *et al.*, 2007).

There are possible reasons for false positive results that require further investigation. The automated PCR process used the Qiagen QIAamp One-For-All nucleic acid extraction kit. Previous reports have suggested that the silica-gel membrane component of the extraction columns produced by this company may be contaminated with *Legionella* species during the manufacturing process (Evans *et al.*, 2003; van der Zee *et al.*, 2002). It is unclear whether this problem has been addressed in current versions of the extraction kit. All samples were however run alongside a negative control of manufacturer provided nuclease free water that should have identified contamination during the extraction step. In analysing the PCR curves, no cut-off value of cycle thresholds was applied; all specimens with evidence of an amplification curve within the 40 cycles of the reaction were reported as positive. Amplification artefacts or non-specific cross-reactivity at high cycle threshold values may account for some of the positive results.

Respiratory viruses were frequently detected with influenza, adenovirus and coronavirus being most common. Viral detection was more common than described in previous dedicated CAP cohorts from sub-Saharan Africa, presumably reflecting the increased sensitivity of molecular detection methods compared to serological or viral culture techniques (Aderaye, 1994a; Prout *et al.*, 1983; Scott *et al.*, 2000). Whether the isolated viruses were the primary pathogen, were permissive to the action of the co-pathogen or were simply bystanders is uncertain. In severe acute respiratory illness

(SARI) surveillance in Kenya, influenza and rhinovirus/enterovirus were each identified in 23%, adenovirus, RSV and parainfluenza each in approximately 7% and human metapneumovirus (hMPV) in 3%; when compared against asymptomatic controls however, only influenza, RSV and hMPV were associated with clinical disease (Feikin *et al.*, 2012). Rhinovirus, RSV, influenza and adenovirus were similarly most frequently detected in South African SARI surveillance (Pretorius *et al.*, 2012). A recent US CAP cohort that used a similar multiplex PCR assay of upper respiratory tract specimens found one or more viruses in 23% of patients; rhinovirus, influenza and human metapneumovirus were most common (Jain *et al.*, 2015). The finding of high frequencies of viral infection is in keeping with previous studies, but further work is needed to define their contribution to clinical disease in this setting and also whether this may be mitigated by vaccination or treatment strategies.

4.6.4 Radiological features

In contrast to most studies of CAP, this study used a clinical rather than radiological definition of pneumonia. This approach was used for several reasons. Firstly, to recruit a study population that was representative of that treated as CAP in low-resource settings where chest radiography may not routinely available or is used selectively in patients that deteriorate. Secondly, to avoid selection bias given the lack of portable radiography facilities at QECH that may hamper chest radiography in the sickest patients. Thirdly, recognising that although commonly used as the gold standard to diagnose CAP, plain chest radiography has inherently limited sensitivity and specificity, particularly in advanced immunosuppression (Claessens *et al.*, 2015; Nyamande *et al.*, 2007b; Syrjala *et al.*, 1998).

Using a broad definition that included pleural effusion, radiographic pneumonia was identified in 76%. However, the usefulness of plain chest radiography for directing therapy appears limited. Using a simple binary classification (i.e. presence or absence), radiographic pneumonia was positively associated with *S. pneumoniae*, negatively associated with *Salmonella* spp., but had no bearing on the likelihood of detecting any other organism. The analysis of patterns of radiographic change to infer aetiology was compromised by inter-observer variability in interpretation. Reticulonodular change and mediastinal lymphadenopathy were most strongly associated with TB, but agreement for identifying these features was only fair or slight. South African CAP guidelines recommend a management algorithm for HIV-positive patients based on the presence of diffuse infiltrates or focal consolidation (Benito *et al.*, 2012; Feldman *et al.*, 2007a). The current findings indicate that this recommendation could not be applied consistently by clinicians and may be of limited value.

Variability in chest radiograph interpretation is well recognised and is accentuated by differences in reader experience and training (Albaum *et al.*, 1996; Moncada *et al.*, 2011; Sakurada *et al.*, 2012). Standardised reading protocols and computer-assisted diagnosis may improve the consistency of radiographic interpretation (Breuninger *et al.*, 2014; Pinto *et al.*, 2013), but radiological features are rarely sufficiently characteristic to accurately differentiate between CAP of different aetiologies and are a questionable basis for therapeutic decisions (Assefa *et al.*, 2011).

How best to characterise and manage patients with a clinical diagnosis of CAP but lacking radiographic change (24% of patients in this study) is unclear and has received scant attention. These patients may have pneumonia that is not appreciable on plain chest radiograph or an alternative - non-pneumonia - diagnosis. In a CAP cohort from Canada, patients lacking radiological change were older and had a different microbiological spectrum of disease (Basi *et al.*, 2004). In well-resourced settings, chest tomography scanning is often used in immunosuppressed patients with a clinical impression of pneumonia but negative plain chest radiography (Benito *et al.*, 2012). Potential options for further evaluation in a resource-limited setting include an interval chest radiograph, chest ultrasound (Cortellaro *et al.*, 2012; Reissig *et al.*, 2012) and inflammatory biomarkers (Pfister *et al.*, 2014; Schuetz *et al.*, 2009).

4.6.5 Strengths and limitations

The MARISO study is the largest prospective observational study of acute CAP in hospitalised adults in sub-Saharan Africa, outside of South Africa, conducted in the last thirty years. Patients were recruited according to a case definition reflective of that used in clinical practice in low-resource settings and were thoroughly characterised and prospectively observed with minimal loss to follow-up. The panel of microbiological investigations used to identify causal pathogens was broad and with the exception of sputum specimens for mycobacterial investigations, specimen collection was reasonably complete.

There are several important limitations. There is potential for selection bias in the study population that was entirely recruited at a single central, teaching hospital. Restriction of patient recruitment to weekdays in the early phase of the study may further compound any bias. Although reflective of clinical practice, the use of a clinical case definition based on clinical signs is likely to miss a substantial proportion with radiographic CAP (Hopstaken *et al.*, 2003; van Vugt *et al.*, 2013). The medical history of the patients was based on that recorded in the health passports. Given limitations in access to care and lack of availability of diagnostics, under-diagnosis of comorbid

conditions is possible. The study relied on spontaneously expectorated sputum specimens for TB diagnostics and up to 30% failed to produce a specimen. At most a single specimen for culture and Xpert MTB/RIF was sent, meaning that the burden of TB is probably underestimated. The diagnostic panel for detecting other opportunistic pathogens, in particular PCP and cytomegalovirus was lacking. Further, the lack of a healthy control population limits interpretation of the significance of the results of multiplex PCR panel, in particular for respiratory viruses.

4.6.6 Future research

The current results suggest opportunities for CAP prevention that should be evaluated in future studies. HIV infection was highly prevalent. Whether the occurrence of CAP represented delayed initiation of ART or ART failure should be investigated in longitudinal studies. The potential role of exposure to indoor air pollution as a modifiable cause of CAP is the focus of a current case-control study based at QECH (Jary *et al.*, 2015). CAP due to *S. pneumoniae* and influenza is potentially preventable with vaccination (Bonten *et al.*, 2015; French *et al.*, 2010; Madhi *et al.*, 2011). Serotype-specific urinary antigen assays that are able to define pneumococcal serotype in CAP in the absence of bacterial isolate have recently been developed (Pride *et al.*, 2012; Sheppard *et al.*, 2011). Defining the serotype distribution of adult pneumococcal CAP would complement current surveillance studies monitoring the effect of universal infant PCV vaccination (Bar-Zeev *et al.*, 2015).

A more comprehensive understanding of CAP aetiology is required to support empirical therapy decisions. This study highlighted the large burden of TB, but also exposed the difficulties of diagnosis based on sputum specimens alone. The role of new urine based diagnostic methods (e.g. urine lipoarabinomannan, urine Xpert MTB/RIF) should be investigated (Lawn *et al.*, 2013a; Peter *et al.*, 2012; Peter *et al.*, 2016). Questions remain about the burden of PCP amongst HIV-positive patients with acute CAP in this setting (Lowe *et al.*, 2013). New tests based on quantitative PCR of nasopharyngeal aspirates and detection of fungal antigens in serum that remove the need for invasively-obtained lower respiratory tract specimens should be evaluated (Durand-Joly *et al.*, 2005; Karageorgopoulos *et al.*, 2013; To *et al.*, 2013).

The need to include antimicrobial cover for atypical bacteria in empirical treatment is also unresolved. Additional investigation to confirm the high detection rate of *Legionella* spp. by the multiplex PCR assay is needed. In the first instance, the multiplex PCR data will be re-examined to identify the proportion that occurred at high cycle-threshold values, possible suggestive of non-specific amplification. The potential role of

contamination during the extraction process will be further examined. Stored nasopharyngeal specimens are available for repeat processing. BinaxNOW *Legionella* urinary antigen testing will be performed on stored urine specimens, although this will not address the potential role of non-serogroup 1 *L. pneumophila* or non-*pneumophila* species. Convalescent serum specimens are available in 88 patients for serological testing. Indirect immunofluorescence antibody testing can distinguish between *L. pneumophila* serogroups and non-*pneumophila* species, although cross reactivity has been reported and seroconversion may be attenuated in highly immunocompromised patients (Ditommaso *et al.*, 2008; Mercante *et al.*, 2015).

4.7 Conclusions

The major burden of hospitalised community-acquired pneumonia in Malawi is in young, HIV-positive patients and is most commonly caused by *S. pneumoniae*, tuberculosis and influenza. The epidemiology and aetiology of disease differs markedly from that seen in well-resourced settings; accordingly strategies for prevention, assessment and treatment should be locally adapted. There are potentially substantial gains to be made in the prevention of CAP through early HIV diagnosis and initiation of ART and vaccination. Further studies are required to define how to optimally use basic laboratory and radiological investigations to diagnose CAP and to make best use of available therapies.

5 Risk factors for 30-day mortality and treatment failure in adults with community-acquired pneumonia in Malawi: A prospective observational cohort

5.1 Introduction

Community-acquired pneumonia (CAP) varies in severity from a mild, short-lived illness that settles with little or no treatment to an acute, fulminant disease complicated by respiratory failure and severe sepsis (Welte *et al.*, 2012). Understanding the determinants of outcome is crucial. Firstly, accurately assessing CAP outcome allows early aggressive treatment to be initiated in those at risk of deterioration or, conversely, avoidance of unnecessary treatment or prolonged hospitalisation in those with mild disease. Secondly, it identifies opportunities for therapeutic innovation to improve outcome. In the setting of limited resources, identifying factors most strongly associated with adverse outcome provides a rational basis on which to target interventions.

Data describing the outcome of CAP in sub-Saharan Africa are limited and as such the risk factors for adverse outcome are poorly described. CAP in sub-Saharan Africa differs from that seen in many well-resourced settings in terms of aetiology and the demographics and comorbidity profile of the patients affected (see chapters 2 and 4). The same risk factors therefore cannot be assumed to apply. CAP severity assessment tools (e.g. CURB65, PSI, SMART-COP) aid physicians in making early management decisions by estimating the risk of adverse outcome increased (Aujesky *et al.*, 2008; Chalmers *et al.*, 2011b; Charles *et al.*, 2008b). These tools have almost exclusively been derived in CAP populations from well-resourced settings. Their prognostic performance in sub-Saharan Africa is largely unknown (Aliberti *et al.*, 2014a).

As described previously,[9] the Malawian Adult Lower Respiratory Tract Infection Severity, Aetiology and Outcome (MARISO) Study was a prospective observational study of adults hospitalised with clinically diagnosed CAP to Queen Elizabeth Central Hospital. The broad aim was to describe the clinical features, aetiology and outcome of CAP in adults in Malawi with a view to identifying the key risk factors for adverse outcome.

[9] The baseline characteristics, radiological features and aetiology of the MARISO cohort have been described in detail in chapter 4. Unless required for clarity of the current analysis, the results will not be repeated.

5.2 Objectives

In this chapter I describe the outcome of CAP in Malawi in terms of 30-day mortality, treatment failure and clinical stability and present analyses that identify the clinical and basic diagnostic laboratory characteristics associated with these outcomes. I also describe the accuracy of existing CAP severity assessment tools for predicting 30-day mortality (CURB65 and CRB65 (Lim *et al.*, 2003); SMART-CO (Charles *et al.*, 2008b); IDSA/ATS 2007 minor criteria (Mandell *et al.*, 2007); SWAT-Bp (Birkhamshaw *et al.*, 2013)) and the derivation of a novel severity assessment tool based on clinical characteristics evident at presentation.

5.3 Contributors to this chapter

As described in section 3.3, the MARISO study was a one of several prospective observational studies of respiratory tract infection occurring concurrently at Queen Elizabeth Central Hospital. The individuals that contributed to data collection are summarised in that section.

I have performed all analyses undertaken in this chapter. Professor Brian Faragher (Liverpool School of Tropical Medicine) advised on the development of the analysis methodology and interpretation.

5.4 Methods

5.4.1 Patient recruitment and assessment

The methods of the MARISO study are described in full in chapter 3. Briefly, patients with features of respiratory illness or infection were screened within 24 hours of admission. Consenting patients with clinically diagnosed CAP as defined by the presence of reported or recorded fever, a relevant respiratory symptom and focal chest signs were recruited (see section 3.1.1 for full eligibility criteria). Patients underwent a standardised clinical assessment consisting of comprehensive medical history, targeted physical examination and measurement of physiological observations (see section 3.13). Plain posteroanterior chest radiographs were performed as early as possible after hospital admission and independently reported by two radiologists and myself using a standardised form (section 3.14 and 3.18). Radiographic pneumonia was defined as the presence of consolidation or other parenchymal abnormality (including reticulonodular change, cavitation or miliary appearance) or pleural effusion (Jain *et al.*, 2015). Blood was collected for HIV testing and basic haematological and biochemical analysis (section 3.15). In addition, blood, urine and respiratory tract

specimens were collected for microbiological investigations to determine disease aetiology (section 3.15).

5.4.2 Clinical endpoints

Patients were followed through their hospital admission with daily physiological observations recorded for up to 14 days. Following discharge patients were followed-up by telephone, or where necessary by field worker visit, to determine vital status at 30 and 90 days post admission. The clinical endpoints were defined as follows:

i. 30-day mortality: death on or before the 30th day following hospital admission.

ii. 90-day mortality: death on or before the 90th day following hospital admission.

iii. Treatment failure was defined as clinical deterioration with death, respiratory failure (mechanical ventilation or oxygen saturations <90% without supplemental oxygen), haemodynamic instability (systolic blood pressure <90mmHg or fall by ≥40mmHg from baseline) or persistence/reappearance of fever (≥38°) at 72 hours following the commencement of antimicrobial treatment (Menendez *et al.*, 2008; Menendez *et al.*, 2004b).

iv. Clinical stability was defined as the achievement of all the following parameters: temperature ≤ 37.2°C; heart rate ≤100 beats per minute; respiratory rate ≤24 breaths per minute; systolic blood pressure ≥90mmHg; and oxygen saturations ≥90% without supplemental oxygen (Halm *et al.*, 1998; Menendez *et al.*, 2004a).

5.4.3 Statistical methods

Candidate risk factors for adverse outcome were selected *a priori* based on a review of the literature (Birkhamshaw *et al.*, 2013; Fine *et al.*, 1996; Lim *et al.*, 2009; Lim *et al.*, 2000; Neill *et al.*, 1996; Scott *et al.*, 2000). Univariable analyses were performed using logistic regression to explore associations between these risk factors and (a) 30-day mortality, (b) treatment failure and (c) death within 24 hours. Multivariable logistic regression analyses were performed in stages using all variables that had prevalence of at least 5% and for which data were available in more than 95% of patients. Firstly, preliminary analyses were performed to identify variables showing multicollinearity that were then excluded. Secondly, two intermediate models were generated in which clinical and laboratory variables were grouped together. A backwards elimination procedure was used with removal of variables that had $P > 0.2$. Variables retained in these intermediate models were combined in a full model and the backwards

elimination procedure was repeated using *P* >0.1 to derive a final multivariable model (Moons *et al.*, 2015; Steyerberg *et al.*, 2013). Age, sex and HIV status were retained in all models regardless of *P* value. Subgroup analyses of HIV-infected patients (both overall and those known to be infected at admission) and those with radiographic pneumonia were completed. The impact of delayed recruitment (i.e. using baseline observations extracted from clinical notes rather than directly obtained by the study team) on multivariable models for each of the endpoints was examined.

The clinical stability endpoint was analysed in patients surviving to discharge. Time to clinical stability was measured in whole days from the date of admission to the date of the first occurrence of clinical stability. Kaplan-Meier analyses were performed to identify baseline variables associated with delayed clinical stability. Survival curves were compared by log-rank test.

A severity assessment tool was derived based on the clinical features shown to be associated with 30-day mortality. Continuous variables were dichotomized at standard thresholds to form binary indicator variables. The backwards elimination process was repeated using *P* >0.1. As a strategy to avoid overfitting, 1000 bootstrap replications of the selection procedure were performed and only those variables present in at least 60% of the replications were included in the final multivariable model (Austin *et al.*, 2004). A simplified tool was derived by assigning points based on the strength of association of individual variables with mortality: 1 point for variables with a β coefficient of ≤1.2 and 2 points if β coefficient of >1.2 (Han *et al.*, 2016; Moons *et al.*, 2015; Steyerberg *et al.*, 2013). The prognostic performance of the tool was compared against that of existing CAP severity assessment tools by calculating sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratios and area under the receiver-operating characteristic curve (with 95% confidence intervals). Subgroup analyses were performed to assess prognostic performance in HIV-infected patients (both overall and those known to be infected at admission) and in delayed recruitment patients. In exploratory analyses, the effect of altering the thresholds at which heart rate, respiratory rate, oxygen saturation and systolic blood pressure were dichotomized to form binary indicator variables was examined. The severity assessment tool was re-derived based on thresholds that maximized Youden's index for each of the component parameters. Population attributable fractions for mortality were calculated for potentially modifiable parameters. All statistical analyses were conducted using Stata version 12.1 (StataCorp; Texas, US).

5.5 Results

5.5.1 Recruitment and follow-up

The baseline characteristics and details of the screened and recruited population are detailed in the previous chapter (sections 4.3 and 4.4) and summarised in figure 5.1. Of the 472 patients initially recruited, data from 459 was available for analysis. Outcome at hospital discharge, at 30-days and at 90 days was determined in 457 (99.6%), 439 (95.6%) and 418 (91.1%), respectively. The response to treatment at 72 hours was determined in 454 (98.9%) patients. Amongst the 408 patients surviving to hospital discharge, the daily observation record was adequate in 399 (97.8%) to determine the attainment of clinical stability. Overall patient outcomes are summarised in table 5.1 and described in detail in the following sections.

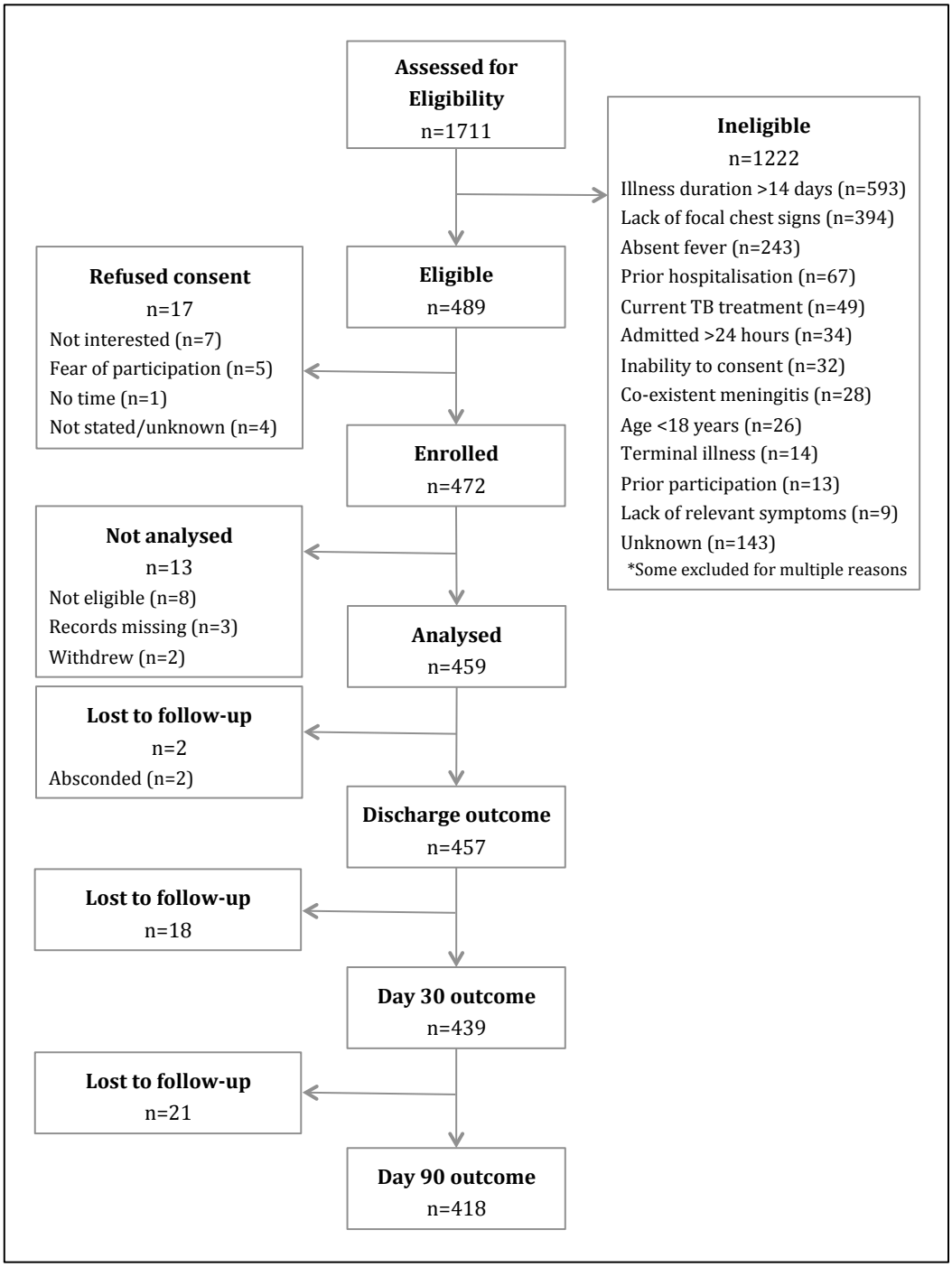

Figure 5.1 CONSORT diagram of screening, recruitment and follow-up in MARISO cohort.

Table 5.1 Summary of patient outcomes in MARISO cohort. Treatment failure defined as death or hypotension, hypoxia or fever at 72 hours post admission; clinical stability endpoint attained if normal temperature, heart rate, respiratory rate, systolic blood pressure and oxygen saturations recorded on single day.

Outcome	No. (%) of episodes
Inpatient mortality[a]	51/457 (11.2)
Day 30 mortality[a]	64/439 (14.6)
Day 90 mortality[a]	87/418 (20.8)
Treatment failure at 72 hours[b]	109/454 (24.0)
Death	16/454 (3.5)
All non-death treatment failure[c]	93/454 (20.5)
Systolic BP <90 or fall ≥40 mmHg	60/454 (13.2)
Oxygen saturations <90%	32/454 (7.1)
Temperature ≥38°C	26/454 (5.7)
Clinical stability attained[d]	
Survivors to discharge	242/399 (60.7)
All patients[e]	254/451 (56.3)

[a] Vital status missing at discharge in 2, at day 30 in 20, and at day 90 in 41.
[b] Data missing for 5 patients.
[c] Components of non-death treatment failure exceed total since hypotension, hypoxia and fever may coexist.
[d] Data missing for 8 patients.
[e] Clinical stability attained in 12 patients that subsequently died prior to hospital discharge.

5.5.2 30-day mortality

5.5.2.1 Overall cohort

64 (14.6%) of the 439 patients followed to 30 days died. Of these, 51 (79.7%) died during hospitalization, including 15 (23.4%) within 24 hours of admission, 16 (25%) within the first 3 days and 31 (48.4%) within the first 7 days following admission. A further 23 patients died between day 30 and day 90, giving an overall 90 day mortality rate of 20.8% (87/418). Amongst patients surviving to day 30, the mortality rate over the following 60 days was 6.5% (23/354).

The association of the candidate clinical risk factors to 30-day mortality is shown in table 5.2. Seven variables were retained in the final multivariable analysis as independently predictive of mortality: male sex (aOR 2.57; 95% CI: 1.23-5.39); pre-presentation symptom duration (aOR 1.11 per day increase; 95% CI 1.02-1.20); inability to stand (aOR 4.28; 95% CI: 2.14-8.57); heart rate (aOR 1.02 per beat/minute rise; 95% CI: 1.00-1.04); oxygen saturations (aOR 0.95 per % rise; 95% CI: 0.92-0.98); white cell count (aOR 0.91 per 10^9/L rise; 95% CI: 0.84-0.98); haemoglobin (aOR 0.90 per g/dL rise; 95% CI: 0.80-1.01). Reduced blood pressure was associated with 30-day

mortality in univariable analysis and in the intermediate multivariable model of clinical predictors, but was eliminated from the final multivariable model. Confusion was strongly associated with mortality in univariable analysis (OR 9.15; 95% CI: 1.50-55.87), but was identified in only 5 (1%) patients, hence excluded from multivariable analysis. Neither age nor any underlying comorbid illness, including HIV status, was found to be significantly associated with 30-day mortality.

162 (35.3%) patients were recruited from the medical wards on the day following admission (see section 4.5.2.4). Baseline observations in this subgroup were obtained by the AETC triage staff rather than the dedicated study team and the median respiratory rate was lower (27 *vs.* 30; *P* <0.0001) (see section 4.5.2.4). Delayed recruitment was not associated with mortality (26/159 (16.4%) vs. 38/280 (13.6%); OR 1.24; 95% CI: 0.72-2.14). Adjustment for delayed recruitment in the multivariable analysis did not affect the variables retained in the final model or their effect size.

5.5.2.2 Radiographic pneumonia

Of the 305 patients with radiographic pneumonia followed to 30 days, 31 (10.2%) died. After controlling for age, sex and HIV status, radiographic pneumonia was associated with a reduced risk of 30-day mortality (aOR 0.47; 95% CI: 0.24-0.92). In this subgroup, elevated heart rate (aOR 1.03 per beat/minute rise; 95% CI: 1.00-105), inability to stand (aOR 2.81; 95% CI: 1.08-7.30) and reduced white cell count (aOR 0.87 per 10^9/L rise; 95% CI: 0.78-0.98) were associated with 30-day mortality (Table 5.3). Multilobar consolidation (OR 4.21; 95% CI: 1.73-10.24), but not pleural effusion or cavitation was associated with mortality. There was no association of oxygen saturations with mortality in this subgroup. There was an unexpected association of reduced respiratory rate and mortality (aOR 0.94 per breath/minute rise; 95% CI: 0.89-1.00), but the absolute difference in respiratory rate was small and clinically insignificant (30 (IQR: 26-33) *vs*. 30 (26-34)).

5.5.2.3 HIV-infected patients

Of the 342 patients with HIV-infection followed to 30 days, 54 (15.8%) died. With the exception of haemoglobin, the independent associations with mortality in this subgroup were the same as the cohort overall (Table 5.4): male sex (aOR 2.48; 95% CI: 1.03-5.99); symptom duration (aOR 1.17 per day increase; 95% CI: 1.06-1.29); heart rate (OR 1.02 per beat/minute rise; 95% CI: 1.00-1.04); oxygen saturations (OR 0.96 per % rise; 95% CI: 0.92-0.99); inability to stand (OR 5.7; 95% CI: 2.45-13.40); white cell count (OR 0.83 per 10^9/L rise; 95% CI: 0.74-0.93). Median CD4 cells were overall lower in patients that died (54 (IQR: 25-137) *vs.* 102 (49-193); *P*=0.03), but were not

associated with increased of mortality in multivariable analysis.

The ability of reported HIV status to stratify patients into risk groups was explored. 310 patients reported a previous HIV test, of whom, 231 (74.5%) were positive and 222 followed to 30-days. Of the 77 patients whose last reported HIV test was negative, 31 (40.3%) were subsequently diagnosed HIV-positive. 30-day mortality amongst known HIV-positive patients was significantly higher compared to all other patients (40/222 (18.0%) vs. 24/217 (11.1%); $P = 0.04$). In this group, ART use did not associate with 30-day mortality (33/180 (18.3) *vs.* 6/38 (15.8%); $P = 0.82$). There was a non-significant trend towards reduced 30-day mortality in patients using co-trimoxazole preventative treatment (CPT), although numbers were small and there was considerable missing data in this analysis (21/147 (14.3) *vs.* 9/36 (25.0%); P 0.13). In the 222 known HIV-positive patients, the independent associations with mortality were: male sex (aOR 5.19; 95% CI: 1.53-17.56); symptom duration (aOR 1.16 per day increase; 95% CI: 1.03-1.32); oxygen saturations (aOR 0.96 per % rise; 95% CI: 0.92-1.00); inability to stand (aOR 8.96; 95% CI: 3.15-25.52); white cell count (aOR 0.83; 95% CI: 0.73-0.95).

5.5.2.4 Treatment related factors

The association of initial treatment components with 30-day mortality was explored (table 5.5). Oxygen use on admission was strongly associated with increase mortality in univariable analysis in the cohort overall (crude OR 3.85; 95% CI: 2.03-7.29), but stratified analyses indicated this was due to confounding with hypoxaemia. Intravenous fluid use was not associated with mortality. Although, information on both oxygen provision and intravenous fluid use was limited to binary variables alone with no data available on concentrations use or volume administered, respectively. Antimicrobial selection – classified as ceftriaxone based regimen or other – was not associated with mortality. Use of agents with atypical bacterial cover was very infrequent and insufficient for stratified analysis to explore differences in outcome.

Table 5.2 Association of candidate clinical and laboratory risk factors with 30-day mortality. Categorical variables shown as number and proportion; denominator varies with available data. Continuous variables (in *italics*) shown as median and interquartile range. Univariable and multivariable analyses by logistic regression. For continuous variables, odds ratio indicates change in risk of mortality with unit increase in variable.

Characteristic	Day 30 survivors (n=375)	Day 30 mortality (n=64)	Outcome unknown (n=20)	Univariable analysis		Multivariable analysis	
				OR (95% CI)	*P*	aOR (95% CI)	*P*
Male sex	224/375 (59.7)	52/64 (81.3)	9/20 (45.0)	2.92 (1.51-5.66)	0.001	2.30 (1.09-4.86)	0.03
Age (yrs)	*34 (29-42)*	*36 (32-42)*	*34 (27-43)*	1.00 (0.98-1.03)	0.73	1.02 (0.99-1.05)	0.24
Current smoker	41/373 (11.0)	7/64 (10.9)	2/20 (2.0)	0.99 (0.43-2.33)	0.99	-	-
Regular alcohol use	92/373 (24.7)	23/63 (36.5)	7/20 (35)	1.76 (1.00-3.09)	0.05	-	-
Unemployed	109/357 (30.5)	13/61 (21.3)	7/20 (35)	0.62 (0.32-1.18)	0.15	-	-
HIV-positive	288/370 (77.8)	54/64 (84.4)	13/19 (68.4)	1.53 (0.75-3.15)	0.24	0.86 (0.34-2.16)	0.75
Chronic lung disease	11/371 (3.0)	3/61 (4.9)	1/20 (5.0)	0.98 (0.53-1.82)	0.94	-[a]	-
Chronic heart disease	2/371 (0.5)	1/61 (1.6)	0/20 0	0.91 (0.39-2.12)	0.83	-[a]	-
Renal disease	0/371 (0)	1/61 (1.6)	0/20 0	0.95 (0.46-1.98)	0.90	-[a]	-
Symptom duration (days)	*7 (5-12)*	*10 (7-14)*	*7 (3.5-9.5)*	1.09 (1.02-1.17)	0.008	1.10 (1.02-1.20)	0.03
Travel time ≥1 hour	278/373 (74.5)	51/62 (82.3)	12/20 (80.0)	1.58 (0.79-3.16)	0.19	-	-
Previous review	231/375 (61.6)	42/63 (66.7)	10/20 (50)	1.25 (0.71-2.19)	0.44	-	-
Temperature (°C)	*38.2 (37.2-38.9)*	*37.9 (36.9-38.9)*	*37.7 (37.1-38.8)*	0.90 (0.72-1.13)	0.37	-[d]	-
Systolic BP (mmHg)	*107 (94-121)*	*99 (88-110)*	*116 (97-129)*	0.98 (0.97-0.99)	0.002	-	-
Diastolic BP (mmHg)	*68 (60-78)*	*63 (55-74)*	*79 (67-90)*	0.98 (0.96-0.99)	0.008	-[c]	-
Mean arterial BP (mmHg)	*81 (71-91)*	*76 (66-86)*	*92 (80-98)*	0.97 (0.96-0.99)	0.003	-[c]	-
Heart rate (/min)	*116 (100-131)*	*127 (113-137)*	*109 (90-123)*	1.02 (1.01-1.03)	0.003	1.02 (1.01-1.04)	0.01
Respiratory rate (/min)	*29 (26-34)*	*30 (26-34)*	*26 (23-32)*	1.00 (0.97-1.04)	0.85	-	-
Oxygen saturations (%)	*96 (92-98)*	*91 (82-96)*	*96 (94-98)*	0.93 (0.90-0.96)	<0.0001	0.95 (0.92-0.99)	0.007

Characteristic	Day 30 survivors (n=375)	Day 30 mortality (n=64)	Outcome unknown (n=20)	Univariable analysis		Multivariable analysis	
				OR (95% CI)	*P*	aOR (95% CI)	*P*
BMI (kg/m²)	*19.9 (18.2-21.7)*	*19.8 (17.6-21.8)*	*20.7 (19.0-21.9)*	*0.98 (0.89-1.08)*	0.65	-[c]	-
MUAC (mm)	*250 (220-260)*	*250 (230-260)*	*260 (240-270)*	1.00 (0.99-1.01)	0.83	-	-
Confusion	2/374 (0.5)	3/64 (4.7)	0/20 (0)	9.15 (1.50-55.87)	0.02	-[a]	-
Inability to stand	57/375 (15.2)	30/64 (46.9)	0/20 (0)	4.92 (2.79-8.67)	<0.0001	3.99 (1.97-8.08)	<0.0001
Pallor	20/375 (5.3)	6/64 (9.4)	1/19 (5.3)	1.84 (0.71-4.77)	0.21	-	-
Oedema	7/372 (1.9)	5/64 (7.8)	2/20 (10)	4.42 (1.36-14.38)	0.01	-[a]	-
Haemoglobin (g/dL)	*11.2 (9.2-13)*	*9.5 (7.8-11.7)*	*11.5 (10.7-12.6)*	0.84 (0.76-0.93)	0.001	0.89 (0.79-1.00)	0.06
White cell count (x 10^9/L)	*7.8 (5.1-11.9)*	*6.1 (4.0-9.1)*	*9.5 (6.2-13.9)*	0.91 (0.86-0.97)	0.006	0.92 (0.84-1.00)	0.04
Platelets (x 10^9/L)	*208 (132-310)*	*161 (109-234)*	*229 (113-291)*	1.00 (0.99-1.00)	0.01	-	-
Urea (mmol/L)	*4.7 (3.2-7.7)*	*6.2 (4.2-10.6)*	*4.2 (2.9-5.7)*	1.03 (1.00-1.06)	0.08	-	-
Creatinine (µmol/L)	*75 (59-99)*	*77 (60-121)*	*78 (61-115)*	1.00 (1.00-1.00)	0.10	-[c]	-
Glucose (mmol/L)	*5.6 (4.9-6.4)*	*5.4 (4.7-6.4)*	*5.4 (5.0-6.1)*	0.86 (0.69-1.08)	0.20	-[b]	-

BP – blood pressure; BMI – body mass index; CI- confidence interval; MUAC – mid-upper arm circumference; OR – odds ratio.

[a] Excluded from multivariable analysis because of prevalence ≤5%.

[b] Excluded from multivariable analysis because data were missing for >5% of patients.

[c] Excluded *a priori* from multivariable analysis because of assumed collinearity with other variables.

[d] Temperature excluded because of observed multicollinearity in multivariable model derivation.

Table 5.3 Association of clinical and laboratory risk factors with 30-day mortality in patients with radiographic pneumonia. Categorical variables shown as number and proportion; denominator varies with available data. Continuous variables (in *italics*) shown as median and interquartile range. Univariable and multivariable analyses by logistic regression. For continuous variables, odds ratio indicates change in risk with unit increase.

Characteristic	Day 30 survivors (n=274)	Day 30 mortality (n=31)	Outcome unknown (n=12)	Univariable analysis		Multivariable analysis	
				OR (95% CI)	*P*	aOR (95% CI)	*P*
Male sex	179/274 (65.3)	24/31 (77.4)	7/12 (58.3)	1.82 (0.76-4.38)	0.18	1.45 (0.56-3.80)	0.45
Age (yrs)	*35 (30-42)*	*37 (32-44)*	*38 (28-54)*	1.01 (0.98-1.03)	0.70	1.02 (0.99-1.06)	0.20
Current smoker	28/272 (10.3)	3/31 (9.7)	1/12 (8.3)	0.93 (0.27-3.27)	0.92	-	-
HIV-positive	216/271 (79.7)	25/31 (80.7)	6/11 (54.5)	1.06 (0.41-2.71)	0.90	0.81 (0.26-2.51)	0.71
Symptom duration (days)	*7 (5-13)*	*10 (7-14)*	*7 (4-12)*	1.13 (1.03-1.24)	0.01	-	-
Temperature (°C)	*38.0 (37.1-38.8)*	*37.5 (36.5-38.4)*	*38.1 (37.4-38.8)*	0.79 (0.57-1.08)	0.14	-[a]	-
Systolic BP (mmHg)	*81 (71-91)*	*81 (67-95)*	*92 (76-108)*	1.00 (0.98-1.01)	0.72	-	-
Heart rate (/min)	*117 (101-132)*	*127 (120-137)*	*110 (90-125)*	1.02 (1.00-1.04)	0.03	1.03 (1.00-1.05)	0.03
Respiratory rate (/min)	*30 (26-34)*	*30 (26-33)*	*27 (22-32)*	0.98 (0.93-1.03)	0.37	0.94 (0.89-1.00)	0.05
Oxygen saturations (%)	*95 (92-98)*	*93 (85-97)*	*96 (93-98)*	0.96 (0.92-1.00)	0.07	-	-
MUAC (mm)	*250 (220-270)*	*250 (230-270)*	*250 (230-260)*	1.01 (0.99-1.02)	0.29	-	-
Inability to stand	41/274 (15.0)	10/31 (32.3)	0/12 (0)	2.71 (1.18-6.16)	0.02	2.81 (1.08-7.30)	0.03
Haemoglobin (g/dL)	*11.1 (9.3-12.7)*	*9.7 (8.4-11.7)*	*11.5 (10.5-12.5)*	0.89 (0.78-1.03)	0.11	-	-
White cell count (x 10^9/L)	*8.4 (5.6-12.1)*	*7 (4.8-9.3)*	*10.1 (6.7-13.9)*	0.91 (0.83-0.99)	0.04	0.87 (0.78-0.98)	0.02
Platelets (x 10^9/L)	*213 (137-340)*	*209 (143-328)*	*201 (113-338)*	1.00 (1.00-1.00)	0.45	-	-
Urea (mmol/L)	*4.8 (3.2-7.9)*	*5.8 (3.8-10.7)*	*4.1 (3.2-6.2)*	1.01 (0.96-1.06)	0.75	-	-
Multilobar consolidation	56/267 (21.0)	14/30 (46.7)	3/12 (25)	3.30 (1.52-7.16)	0.003	4.21 (1.73-10.24)	0.002
Cavitation	18/274 (6.6)	2/31 (6.5)	0/12 (0)	0.98 (0.22-4.44)	0.98	-	-
Pleural effusion	99/272 (36.4)	16/31 (51.6)	3/12 (25)	1.86 (0.88-3.93)	0.10	-	-

BP – blood pressure; BMI – body mass index; CI- confidence interval; MUAC – mid-upper arm circumference; OR – odds ratio. [a] Excluded due to multicollinearity.

Table 5.4 Association of candidate clinical and laboratory risk factors with 30-day mortality in patients with HIV. Categorical variables shown as number and proportion; denominator varies with available data. Continuous variables (in *italics*) shown as median and interquartile range. Univariable and multivariable analyses by logistic regression. For continuous variables, odds ratio indicates change in risk with unit increase in variable.

Characteristic	Day 30 survivors (n=288)	Day 30 mortality (n=54)	Outcome unknown (n=13)	Univariable analysis		Multivariable analysis	
				OR (95% CI)	*P*	aOR (95% CI)	*P*
Male sex	170/288 (59.0)	45/54 (83.3)	5/13 (38.5)	3.47 (1.63-7.37)	0.001	2.48 (1.03-5.99)	0.04
Age (yrs)	*34 (30-41)*	*36 (32-41)*	*33 (27-39)*	1.01 (0.98-1.03)	0.72	1.01 (0.97-1.05)	0.61
Current smoker	23/286 (8.0)	3/54 (5.6)	1/13 (7.7)	0.67 (0.19-2.32)	0.53	-	-
Symptom duration (days)	*7 (5-12)*	*10 (7-14)*	*7 (3-9)*	1.12 (1.04-1.21)	0.002	1.17 (1.06-1.29)	0.002
Temperature (°C)	*38.0 (37.2-39.0)*	*37.9 (37.0-39.0)*	*37.6 (37.0-38.6)*	0.93 (0.72-1.20)	0.58	-[a]	-
Systolic BP (mmHg)	*104 (92-121)*	*98 (88-110)*	*103 (91-119)*	0.98 (0.96-0.99)	0.004	-	-
Heart rate (/min)	*119 (103-134)*	*127 (112-138)*	*113 (87-121)*	1.02 (1.00-1.03)	0.03	1.02 (1.00-1.04)	0.02
Respiratory rate (/min)	*29 (26-34)*	*30 (26-34)*	*26 (24-31)*	1.01 (0.97-1.04)	0.79	-	-
Oxygen saturations (%)	*95 (92-98)*	*91 (82-95)*	*97 (95-98)*	0.92 (0.89-0.96)	<0.0001	0.96 (0.92-0.99)	0.02
MUAC (mm)	*250 (220-260)*	*250 (230-260)*	*260 (230-275)*	1.00 (0.99-1.01)	0.89	-	-
Inability to stand	47/288 (16.3)	26/54 (48.2)	0/13 (0)	4.76 (2.57-8.84)	<0.0001	5.73 (2.45-13.40)	<0.0001
Haemoglobin (g/dL)	*10.7 (8.7-12.3)*	*9.4 (7.6-11.3)*	*11.4 (10.7-12.6)*	0.84 (0.74-0.94)	0.003	-	-
White cell count (x 10^9/L)	*7.5 (5.0-11.1)*	*5.7 (3.9-8.4)*	*9.5 (5.8-14.8)*	0.88 (0.81-0.95)	0.002	0.83 (0.74-0.93)	0.002
Platelets (x 10^9/L)	*208 (131-308)*	*161 (109-267)*	*262 (136-285)*	1.00 (0.99-1.00)	0.04	-	-
Urea (mmol/L)	*4.9 (3.3-8.7)*	*6.0 (4.3-10.3)*	*4.4 (3.3-5.9)*	1.01 (0.98-1.05)	0.45	-	-
CD4 cell count (x 10^3/mL)	*102 (49-193)*	*54 (25-137)*	*123 (91-488)*	1.00 (0.99-1.00)	0.03	1.00 (0.99-1.00)	0.46

BP – blood pressure; BMI – body mass index; CI- confidence interval; MUAC – mid-upper arm circumference; OR – odds ratio.

[a] Temperature excluded because of observed multicollinearity in multivariable model derivation

Table 5.5 Association of initial antimicrobial and supportive treatment with 30-day mortality. Categorical variables shown as number and proportion; denominator varies with available data. Univariable and multivariable analyses by logistic regression.

Characteristic	Day 30 survivors (n=375)	Day 30 mortality (n=64)	Outcome unknown (n=20)	Univariable analysis		Multivariable analysis[a]	
				OR (95% CI)	*P*	aOR (95% CI)	*P*
Oxygen administration	36/357 (10.1)	19/63 (30.2)	1/19 (5.3)	3.85 (2.03-7.29)	<0.0001	1.52 (0.55-4.23)	0.42
Oxygen saturations <90%	25/42 (59.5)	17/27 (63.0)	1/1 (100)	1.16 (0.43-3.13)	0.78	-	-
Oxygen saturations ≥90%	10/308 (3.3)	2/35 (5.7)	0/17 (0)	1.81 (0.38-8.60)	0.46	-	-
IV fluids administration	226/361 (62.6)	47/63 (74.6)	5/19 (26.3)	1.75 (0.96-3.22)	0.07	0.89 (0.43-1.86)	0.76
Systolic BP ≥90 mmHg and heart rate <125 /min	124/166 (74.7)	33/41 (80.5)	1/5 (20.0)	1.40 (0.60-3.26)	0.44	-	-
Systolic BP <90 mmHg and/or heart rate ≥125 /min	101/192 (52.6)	13/21 (61.9)	4/14 (28.6)	1.46 (0.58-3.69)	0.42	-	-
Antimicrobial treatment						0.83 (0.41-1.69)	0.61
Ceftriaxone-based therapy	260/353 (73.7)	45/63 (71.4)	11/19 (57.9)	0.89 (0.49-1.62)	0.71	-	-
Other antimicrobial therapy	93/353 (26.4)	18/63 (28.6)	8/19 (42.1)	1		-	-

BP – blood pressure; CI- confidence interval; OR – odds ratio.

[a] Multivariable model also adjusted for age, sex, HIV status, symptom duration, heart rate, oxygen saturations, inability to stand, white cell count and haemoglobin concentration.

5.5.3 Treatment failure

Treatment failure occurred in 109 (24.0%) patients, including 16 who died within the first 72 hours following hospitalization (Table 5.1). Amongst patients surviving to day 3, persistent hypotension (60/456; 13.2%) was the commonest factor indicating treatment failure. The relationship of treatment failure to 30-day outcome is illustrated in figure 5.3. Non-death treatment failure (i.e. persistent hypotension, hypoxia or fever at 72 hours) was associated with mortality at day 30 (OR 3.45; 95% CI: 1.81-6.58); the sensitivity and specificity for predicting 30-day mortality were 45.5 (30.4-61.2%) and 80.5% (76.2-84.4%), respectively.

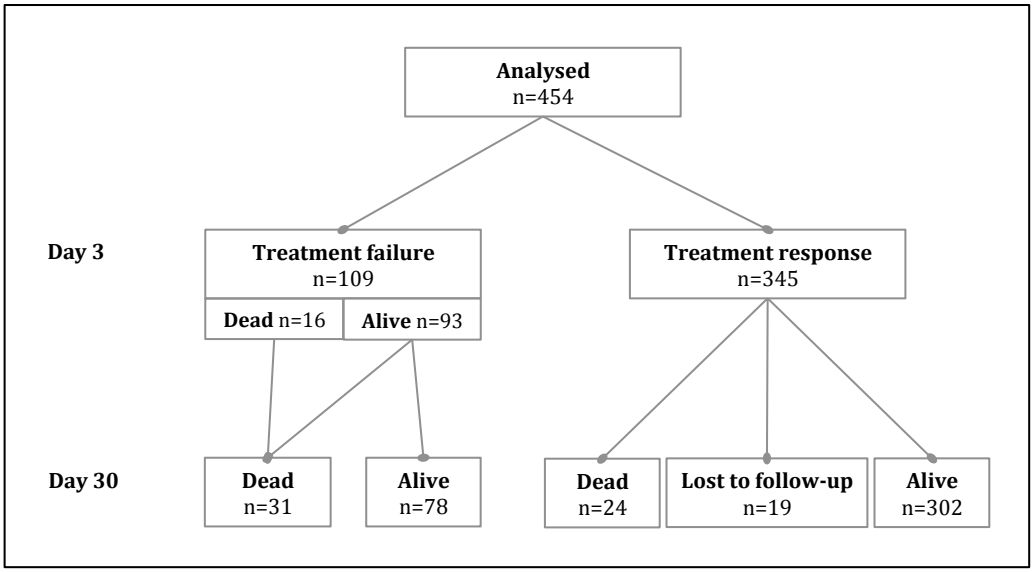

Figure 5.2 30-day mortality stratified by treatment response at day.

The association of the candidate risk factors with treatment failure is shown in table 5.5. Despite efforts to identify potentially collinear variables, the final multivariable had large standard errors suggestive of multicollinearity. Four variables predictive of treatment failure were retained in the final model: HIV infection (aOR 2.74; 95% CI: 1.28-5.87); oxygen saturations (aOR 0.93 per % rise; 95% CI: 0.89-0.96); inability to stand (aOR 2.34; 95% CI: 1.31-4.21); body mass index (aOR 0.86 per kg/m^2 rise; 95% CI: 0.78-0.94). In contrast to the analysis for 30-day mortality, male sex was not significantly associated with treatment failure (aOR 1.20; 95% CI: 0.71-2.05). After controlling for clinical and demographic features, no laboratory parameter was found to be independently associated with treatment failure.

Delayed recruitment was not associated with treatment failure (45/161 (28.0%) vs. 63/293 (21.5%); OR 1.42; 95% CI: 0.91-2.21). Adjustment for delayed recruitment in the multivariable analysis did not affect the variables retained in the final model or their effect size.

Treated failure was identified in 72 (22.9%) of 314 patients with radiographic pneumonia. There was no overall association between the presence of radiographic pneumonia and the risk of treatment failure (aOR 1.02; 95% CI: 0.58-1.80). Amongst the subset of patients with radiographic pneumonia, HIV infection (aOR 2.58; 95% CI: 1.05-6.35), reduced oxygen saturations (aOR 0.92 per % rise; 95% CI: 0.88-0.96) and reduced body mass index (aOR 0.79 per kg/m^2 rise; 95% CI: 0.69-0.91) predicted treatment failure (Table 5.6). There was no association between the presence of specific radiological features (i.e. multilobar involvement, pleural effusion, cavitation) and the risk of treatment failure.

Treatment failure occurred in 96 (27.3%) of the subgroup of 352 patients with HIV-infection. As for the overall cohort, reduced oxygen saturations (aOR 0.91 per % rise; 95% CI: 0.87-0.95), reduced body mass index (aOR 0.85 per kg/m^2 rise; 95% CI: 0.76-0.96) and inability to stand (aOR 2.45; 95% CI: 1.23-4.87) predicted treatment failure (Table 5.7). There was no significant association between CD4 cell count and the risk of treatment failure.

Table 5.6 Association of candidate clinical and laboratory risk factors with treatment failure. Categorical variables shown as number and proportion; denominator varies with available data. Continuous variables (in *italics*) shown as median and interquartile range. Analyses columns show risk ratios with 95% confidence intervals. Univariable and multivariable analyses by logistic regression. For continuous variables odds ratio (OR) indicates change in risk of mortality with unit increase in variable.

Characteristic	Treatment responders (n=345)	Treatment failure (n=109)	Outcome unknown (n=5)	Univariable analysis		Multivariable analysis	
				OR (95% CI)	*P*	aOR (95% CI)	*P*
Male sex	207/345 (60.0)	74/109 (67.9)	4/5 (80)	1.41 (0.89-2.22)	0.14	1.20 (0.71-2.05)	0.50
Age (yrs)	*34 (29-41)*	*36 (31-42)*	*35 (28-39)*	1.01 (1.00-1.03)	0.14	1.01 (0.98-1.03)	0.63
Current smoker	39/343 (11.4)	9/109 (8.3)	2/5 (40)	0.70 (0.33-1.50)	0.36	-	-
Alcohol use	92/342 (26.9)	29/109 (26.6)	1/5 (20)	0.99 (0.61-1.60)	0.95	-	-
HIV-positive	256/340 (75.3)	96/108 (88.9)	3/5 (60)	2.63 (1.37-5.02)	0.004	2.74 (1.28-5.87)	0.01
Chronic lung disease	11/340 (3.2)	4/107 (3.7)	0/5 (0)	1.50 (0.77-2.87)	0.23	-[a]	-
Chronic heart disease	0/340 (0)	3/107 (2.8)	0/5 (0)	-	-	-[a]	-
Renal disease	0/340 (0)	1/107 (0.9)	0/5 (0)	-	-	-[a]	-
Symptom duration (days)	*7 (5-12)*	*7 (6-14)*	*14 (7-14)*	1.05 (1.00-1.11)	0.07	-	-
Travel time ≥1 hour	255/344 (74.1)	82/106 (77.4)	4/5 (80.0)	1.19 (0.71-2.00)	0.50	-	-
Previous review	220/345 (63.8)	60/108 (55.6)	3/5 (60)	0.71 (0.46-1.10)	0.13	-	-
Temperature (°C)	*37.9 (37.1-38.9)*	*38.0 (37.1-38.9)*	*37.0 (36.7-37.9)*	1.03 (0.86-1.24)	0.72	-	-
Systolic BP (mmHg)	*108 (94-121)*	*100 (88-115)*	*123 (114-128)*	0.99 (0.98-1.00)	0.05	-	-
Diastolic BP (mmHg)	*70 (60-79)*	*62 (55-74)*	*81 (70-88)*	0.98 (0.96-0.99)	0.001	-[c]	-
Mean arterial BP (mmHg)	*82 (72-92)*	*75 (66-86)*	*95 (84-100)*	0.98 (0.97-0.99)	0.004	-[c]	-
Heart rate (/min)	*117 (101-132)*	*122 (103-132)*	*113 (68-118)*	1.01 (1.00-1.02)	0.27	-[c]	-
Respiratory rate (/min)	*29 (26-34)*	*30 (26-36)*	*32 (26-36)*	1.01 (0.98-1.04)	0.39	-	-
Oxygen saturations (%)	*96 (92-98)*	*92 (85-96)*	*91 (86-96)*	0.92 (0.88-0.95)	<0.0001	0.93 (0.89-0.96)	<0.0001

Characteristic	Treatment responders (n=345)		Treatment failure (n=109)		Outcome unknown (n=5)		Univariable analysis		Multivariable analysis	
							OR (95% CI)	*P*	aOR (95% CI)	*P*
BMI (kg/m²)	*20.2*	*(18.4-22.0)*	*18.9*	*(17.4-20.7)*	*22.0*	*(21.9-22.6)*	0.85 (0.77-0.93)	<0.0001	0.86 (0.77-0.94)	0.002
MUAC (mm)	*250*	*(220-260)*	*240*	*(222-260)*	*270*	*(250-280)*	1.00 (1.00-1.01)	0.68	-[c]	-
Confusion	2/345	(0.6)	3/108	(2.8)	0/5	(0)	4.9 (0.81-26.72)	0.08	-[a]	-
Inability to stand	47/345	(13.6)	40/109	(36.7)	0/5	(0)	3.68 (2.24-6.04)	<0.0001	2.34 (1.31-4.21)	0.004
Pallor	16/344	(4.7)	11/109	(10.1)	0/5	(0)	2.30 (1.03-5.12)	0.04	-	-
Oedema	10/342	(2.9)	4/109	(3.7)	0/5	(0)	1.26 (0.39-4.12)	0.70	-[a]	-
Haemoglobin (g/dL)	*11.2*	*(9.2-13)*	*10.2*	*(8.3-11.8)*	*12.8*	*(12.4-13.2)*	0.89 (0.82-0.96)	0.003	-	-
White cell count (x 10^9/L)	*8.0*	*(5.0-11.9)*	*6.5*	*(4.6-9.4)*	*8.6*	*(5.3-10)*	0.97 (0.93-1.01)	0.18	-	-
Platelets (x 10^9/L)	*206*	*(134-303)*	*185*	*(100-314)*	*179*	*(169-285)*	1.00 (1.00-1.00)	0.11	-	-
Urea (mmol/L)	*4.5*	*(3.2-7.1)*	*6.5*	*(3.9-10.7)*	*3.8*	*(3.5-7.5)*	1.04 (1.01-1.07)	0.02	-	-
Creatinine (µmol/L)	*74*	*(60-98)*	*79*	*(58-132)*	*78*	*(63-79)*	1.00 (1.00-1.00)	0.06	-[c]	-
Glucose (mmol/L)	*5.6*	*(4.9-6.3)*	*5.7*	*(4.8-6.5)*	*5.7*	*(5.0-5.8)*	0.98 (0.84-1.16)	0.85	-[b]	-

BP – blood pressure; BMI – body mass index; CI- confidence interval; MUAC – mid-upper arm circumference; OR – odds ratio.

[a] Excluded from multivariable analysis because of prevalence ≤5%.

[b] Excluded from multivariable analysis because data were missing for >5% of patients.

[c] Excluded *a priori* from multivariable analysis because of assumed collinearity with other variables.

Table 5.7 Association of candidate clinical and laboratory risk factors with treatment failure in patients with radiographic pneumonia.
Categorical variables shown as number and proportion; denominator varies with available data. Continuous variables (in *italics*) shown as median and interquartile range. Univariable and multivariable analyses by logistic regression. For continuous variables, odds ratio indicates change in risk with unit increase. Treatment failure outcome missing in 3 patients.

Characteristic	Treatment response (n=242)	Treatment failure (n=72)	Univariable analysis		Multivariable analysis	
			OR (95% CI)	*P*	aOR (95% CI)	*P*
Male sex	159/242 (65.7)	49/72 (68.1)	1.11 (0.63-1.95)	0.71	1.14 (0.58-2.22)	0.71
Age (yrs)	*35 (29-42)*	*38 (32-43)*	1.02 (1.00-1.04)	0.09	1.01 (0.99-1.04)	0.42
Current smoker	26/240 (10.8)	5/72 (6.9)	0.61 (0.23-1.66)	0.34	-	-
HIV-positive	183/239 (76.6)	62/71 (87.3)	2.11 (0.99-4.51)	0.06	2.58 (1.05-6.35)	0.04
Symptom duration (days)	*7 (5-13)*	*7 (6-14)*	1.03 (0.97-1.10)	0.36	-	-
Temperature (°C)	*37.8 (37.0-38.8)*	*38.1 (37.2-39.0)*	1.10 (0.88-1.38)	0.40	-	-
Systolic BP (mmHg)	*108 (94-122)*	*102 (88-122)*	1.00 (0.99-1.01)	0.79	-	-
Heart rate (/min)	*117 (99-132)*	*124 (105-134)*	1.01 (1.00-1.02)	0.15	-	-
Respiratory rate (/min)	*29 (26-34)*	*30 (26-36)*	1.01 (0.98-1.05)	0.39	-	-
Oxygen saturations (%)	*96 (92-98)*	*92 (87-96)*	0.92 (0.88-0.96)	<0.0001	0.92 (0.88-0.96)	<0.0001
BMI (kg/m^2)	*19.9 (18.4-21.5)*	*18.9 (14.7-20.8)*	0.84 (0.75-0.95)	0.005	0.79 (0.69-0.91)	0.001
Inability to stand	32/242 (13.2)	19/72 (26.4)	2.35 (1.24-4.47)	0.009	-	-
Haemoglobin (g/dL)	*11.1 (9.3-12.7)*	*10.4 (9.0-12.5)*	0.93 (0.84-1.03)	0.15	-	-
White cell count (x 10^9/L)	*8.7 (5.4-12.2)*	*7.4 (5.7-10.4)*	0.99 (0.95-1.04)	0.76	-	-
Platelets (x 10^9/L)	*212 (141-330)*	*210 (135-340)*	1.00 (1.00-1.00)	0.33	-	-
Urea (mmol/L)	*4.5 (3.2-7.4)*	*6.0 (3.5-11.2)*	1.04 (1.00-1.08)	0.04	-	-
Multilobar consolidation	50/237 (21.1)	22/69 (31.9)	1.75 (0.97-3.17)	0.07	-	-
Cavitation	14/242 (5.8)	6/72 (8.3)	1.48 (0.55-4.00)	0.44	-	-
Pleural effusion	87/240 (36.3)	28/72 (38.9)	1.12 (0.65-1.92)	0.68	-	-

Table 5.8 Association of selected candidate clinical and laboratory risk factors with treatment failure in patients with HIV. Categorical variables shown as number and proportion; denominator varies with available data. Continuous variables (in *italics*) shown as median and interquartile range. Univariable and multivariable analyses by logistic regression. For continuous variables, odds ratio indicates change in risk with unit increase. Treatment failure outcome missing in 3.

Characteristic	Treatment response (n=256)	Treatment failure (n=96)	Univariable analysis		Multivariable analysis	
			OR (95% CI)	*P*	aOR (95% CI)	*P*
Male sex	151/256 (59.0)	67/96 (69.8)	1.60 (0.97-2.65)	0.06	1.10 (0.59-2.04)	0.77
Age (yrs)	*34 (29-41)*	*36 (31-41)*	1.01 (0.99-1.04)	0.2	1.00 (0.97-1.02)	0.74
Current smoker	20/254 (7.9)	6/96 (6.3)	0.78 (0.30-2.01)	0.61	-	-
Symptom duration (days)	*7 (5-11)*	*7 (7-14)*	1.07 (1.01-1.14)	0.03	-	-
Temperature (°C)	*38.0 (37.2-39.0)*	*38.1 (37.2-39.0)*	0.88 (0.83-1.25)	0.58	-	-
Systolic BP (mmHg)	*105 (92-120)*	*98 (87-115)*	0.99 (0.98-1.00)	0.24	-	-
Heart rate (/min)	*120 (103-134)*	*122 (104-134)*	1.01 (0.99-1.02)	0.34	-	-
Respiratory rate (/min)	*29 (25-34)*	*29 (26-36)*	1.02 (0.99-1.05)	0.33	-	-
Oxygen saturations (%)	*96 (92-98)*	*92 (85-96)*	0.90 (0.86-0.93)	<0.0001	0.91 (0.87-0.95)	<0.0001
BMI (kg/m^2)	*20.2 (18.4-21.9)*	*18.8 (17.4-20.7)*	0.86 (0.78-0.94)	0.002	0.85 (0.76-0.96)	0.006
Inability to stand	38/256 (14.8)	35/96 (36.5)	3.29 (1.92-5.65)	<0.0001	2.45 (1.23-4.87)	0.01
Haemoglobin (g/dL)	*10.8 (8.7-12.3)*	*9.8 (7.8-11.7)*	0.91 (0.83-0.99)	0.03	-	-
White cell count (x 10^9/L)	*7.8 (5.0-11.5)*	*6.1 (4.3-8.7)*	0.96 (0.91-1.00)	0.06	-	-
Platelets (x 10^9/L)	*208 (135-302)*	*186 (105-311)*	1.00 (1.00-1.00)	0.22	-	-
Urea (mmol/L)	*4.7 (3.3-7.8)*	*6.7 (4.2-10.5)*	1.03 (1.00-1.06)	0.06	-	-
CD4 cell count (x 10^3/mL)	*106 (54-197)*	*68 (25-158)*	1.00 (0.99-1.00)	0.09	1.00 (1.00-1.00)	0.91

5.5.4 Death within 24 hours

The association of candidate clinical and laboratory risk factors to death within 24 hours of admission is shown in table 5.8. In univariable analyses death within 24 hours was associated with: systolic blood pressure (OR 0.95 per mmHg rise; 95% CI: 0.92-0.98); oxygen saturations (OR 0.90 per % rise; 95% CI: 0.87-0.94); inability to stand (OR 32.32; 95% CI: 7.14-146.25); haemoglobin (OR 0.78 per g/dL rise; 95% CI: 0.64-0.95); platelets (OR 0.99 per 10^9/L rise; 95% CI: 0.98-1.00). The relatively small number of very early deaths precluded stable multivariable analysis. The association of radiographic pneumonia with early could not be examined adequately since only 3 of the 15 patients who died had a chest radiograph prior to death.

Table 5.9 Association of candidate clinical and laboratory risk factors with death within 24 hours. Categorical variables shown as number and proportion; denominator varies with available data. Continuous variables (in *italics*) shown as median and interquartile range. Univariable analysis by logistic regression. For continuous variables, odds ratio indicates change in risk with unit increase in variable. Two patients with unknown hospital discharge outcome are excluded.

Characteristic	Day 1 survivors (n=442)	Day 1 mortality (n=15)	Univariable analysis	
			OR (95% CI)	*P*
Male sex	270/442 (61.1)	13/15 (86.7)	4.14 (0.92-18.57)	0.06
Age (yrs)	*35 (29-43)*	*37 (30-41)*	1.00 (0.96-1.05)	0.86
Current smoker	47/440 (10.1)	2/15 (13.3)	1.29 (0.28-5.88)	0.76
HIV-positive	340/436 (78.0)	14/15 (93.3)	3.95 (0.51-30.44)	0.19
Symptom duration (days)	*7 (5-12)*	*8 (7-10)*	1.02 (0.89-1.16)	0.81
Temperature (°C)	*37.9 (37.1-38.9)*	*37.8 (36.8-39.0)*	1.03 (0.66-1.61)	0.88
Systolic BP (mmHg)	*106 (94-121)*	*90 (77-104)*	0.95 (0.92-0.98)	<0.0001
Heart rate (/min)	*118 (102-132)*	*122 (104-132)*	1.02 (0.99-1.04)	0.23
Respiratory rate (/min)	*29 (26-34)*	*32 (28-36)*	1.05 (0.99-1.11)	0.09
Oxygen saturations (%)	*95 (92-98)*	*82 (71-91)*	0.90 (0.87-0.94)	<0.0001
MUAC (mm)	*250 (220-260)*	*240 (240-250)*	1.00 (0.99-1.02)	0.71
Inability to stand	74/442 (16.7)	13/15 (86.7)	32.32 (7.14-146.25)	<0.0001
Haemoglobin (g/dL)	*11.1 (9.1-12.9)*	*8.7 (7.6-10.3)*	0.78 (0.64-0.95)	0.013
White cell count (x 10^9/L)	*7.7 (5.1-11.5)*	*4.4 (3.5-9.8)*	0.95 (0.85-1.07)	0.43
Platelets (x 10^9/L)	*205 (131-308)*	*109 (55-159)*	0.99 (0.98-1.00)	0.01
Urea (mmol/L)	*4.8 (3.3-7.9)*	*7.8 (5.6-12.0)*	1.03 (0.96-1.09)	0.43

BP – blood pressure; CI- confidence interval; MUAC – mid-upper arm circumference; OR – odds ratio.

5.5.5 Clinical Stability

Of the 451 patients in which data were available, 254 (56.3%) attained clinical stability criteria on at least one day during hospital admission. 242 (95.7%) of these patients were subsequently discharged alive. Failure to attain clinical stability during hospitalisation was associated with an increased risk of inpatient mortality (40/197 (20.3%) *vs*. 11/253 (4.4%); OR 5.61; 95% CI: 2.71-12.44) and, in those surviving to discharge, an increased risk of death by day 30 (11/152 (7.2%) *vs.* 2/230 (0.9%); OR 8.89; 95% CI: 1.89-83.29). Amongst the 399 patients surviving to hospital discharge with available data, 242 (60.7%) had attained clinical stability. The median time to clinical stability in the cohort overall was 4 days. Owing to an initial systematic error in data collection (up to June 2014), day 1 observations were missing in 79 (55.6%) of the 142 patients who were recruited on the day following admission who survived to discharge. An apparent association of delayed recruitment with delayed time to clinical stability was not evident when analysis was restricted to those patients with day 1 data available. Amongst the 319 patients with day 1 observations available, the median time to clinical stability was 4 days (IQR: 2-12)

In univariable analyses using the Kaplan-Meier method (restricted to patients with day 1 observations available), delayed attainment of clinical stability was associated with (Table 5.8): current smoking (P=0.047); low systolic blood pressure (P =0.01)*;* elevated heart rate (P = 0.0007); elevated respiratory rate (P = 0.02); low oxygen saturations (P = 0.0001); low haemoglobin (P = 0.02). In the subgroup of patients with radiographic pneumonia, both multilobar consolidation (P = 0.002) and pleural effusion (P = 0.0002) were associated delayed time to clinical stability.

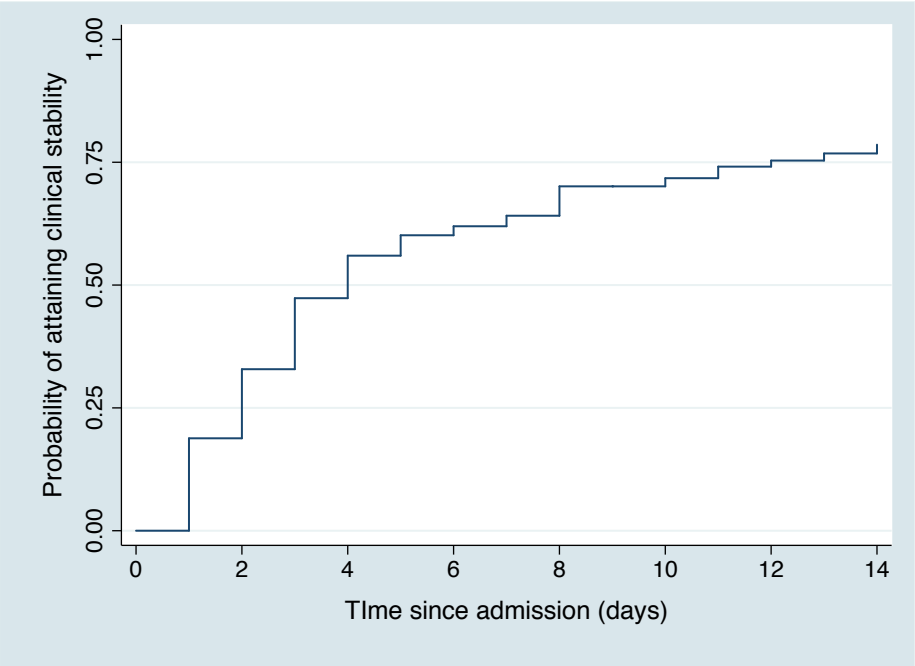

Figure 5.3 Kaplan-Meir failure function curve of first attainment of clinical stability amongst patients surviving to hospital discharge. Analysis restricted to 319 patients with available data for day 1 observations.

Table 5.10 Univariable analysis of time to attain clinical stability amongst patients surviving to discharge. Left side of table shows the median time to first attainment of clinical stability criteria and the right side shows probability of attainment by day 4. Kaplan-Meier survival curves compared by log-rank test.

Characteristic	Median time to clinical stability (days)		Probability of clinical stability by day 4		
	Characteristic present	Characteristic absent	Characteristic present	Characteristic absent	*P*
Male sex	4 (2-11)	3 (2-	0.54	0.59	0.94
Age ≥50 yrs	3 (2-5)	4 (2-13)	0.74	0.53	0.05
Current smoker	3 (1-6)	4 (2-14)	0.67	0.55	0.047
HIV-positive	4 (2-13)	3 (2-8)	0.54	0.64	0.16
Systolic BP <90 (mmHg)	5 (3-)	4 (2-11)	0.46	0.58	0.01
Heart rate ≥125 (/min)	6 (3-)	3 (2-8)	0.40	0.65	0.0007
Respiratory rate ≥30 (/min)	5 (2-13)	3 (2-11)	0.49	0.64	0.02
Oxygen saturations <90 (%)	12 (4-)	3 (2-10)	0.26	0.60	0.0001
BMI <18.5 (kg/m^2)	4 (2-11)	3 (2-14)	0.52	0.59	0.44
Inability to stand	6 (2-10)	4 (2-14)	0.45	0.58	0.61
Haemoglobin <8 (g/dL)	8 (3-14)	3 (2-12)	0.37	0.59	0.02
WBC count <4 (x 10^9/L)	6 (2-)	4 (2-12)	0.37	0.59	0.12
Urea >7 (mmol/L)	4 (2-)	4 (2-11)	0.53	0.58	0.28
Pleural effusion[a]	8 (3-)	3 (2-10)	0.37	0.63	0.0002
Multilobar consolidation[a]	11 (3-13)	4 (2-14)	0.35	0.56	0.002

[a] For patients with radiographic pneumonia only (n=225).

Table 5.11 Association of disease aetiology with clinical outcomes. Number and proportion of patients with 30-day mortality, treatment failure and delayed attainment of clinical stability shown for three most commonly identified organisms: *S. pneumonia*e, *M. tuberculosis* and influenza. Delayed clinical stability endpoint indicates patients surviving to discharge who had not attained clinical stability within 3 days of admission. Odds ratios adjusted for age, sex and HIV status and calculated by logistic regression.

Organism	30-day mortality			Treatment failure			Days to clinical stability	
	No. (%)	aOR (95% CI)	*P*	No. (%)	aOR (95% CI)	*P*	Median (IQR)	*P*
S. pneumoniae								
Yes	7/94 (7.5)	0.40 (0.17-0.91)	0.03	24/98 (24.5)	1.10 (0.64-1.88)	0.73	3 (2-7)	0.04
No	57/344 (16.6)			85/355 (23.9)			4 (2-14)	
M. tuberculosis								
Yes	17/74 (23.0)	2.44 (1.19-5.01)	0.02	30/74 (40.5)	3.77 (2.04-6.94)	<0.0001	8 (3-)	0.003
No	22/241 (9.1)			40/249 (16.1)			3 (2-8)	
Influenza								
Yes	2/39 (5.1)	0.39 (0.09-1.67)	0.20	7/40 (17.5)	0.75 (0.32-1.80)	0.52	4 (2-14)	0.81
No	61/396 (15.4)			100/409 (24.5)			4 (2-11)	

5.5.6 Relationship of aetiology to clinical outcome

For the three most common identified pathogens –*S. pneumoniae*, *M. tuberculosis* and influenza – the relationship of disease aetiology with clinical outcome was investigated (Table 5.9). After adjusting for patient age, sex and HIV status, the presence of *M. tuberculosis* was associated with an increased risk of 30-day mortality (aOR 2.44; 95% CI: 1.19-5.01) and treatment failure at 72 hours (aOR 3.77; 95% CI: 2.04-6.94). Pneumococcal aetiology was associated with a reduced risk of 30-day mortality (aOR 0.40; 95% CI: 0.17-0.91) and a reduced time to clinical stability (3 days *vs.* 4 days; P = 0.04). In univariable analyses by the Kaplan-Meier method, detection of *M. tuberculosis* was associated with delayed clinical stability (P = 0.003).

5.5.7 Derivation of mortality-risk prediction tool

The multivariable analysis of features associated with 30-day mortality was adapted to derive a severity assessment tool that estimated 30-day mortality. As described above, the intermediate multivariable model of clinical features associated with mortality included: male sex, pre-presentation symptom duration, systolic blood pressure, heart rate, oxygen saturations and inability to stand (see section 5.4.2).

Exploratory analyses showed that pre-presentation symptom duration was not smoothly distributed with reported durations clustering around 3, 7 and 14 days, suggesting concerns about the accuracy and consistency of reporting. As such the variable was excluded from the risk-predication tool.

To develop a tool that could be calculated rapidly in a clinical setting, the continuous variables were dichotomized at standard thresholds (i.e. systolic blood pressure <90mmHg; heart rate ≥125 beats/min; oxygen saturations <90%) before the multivariable analysis was repeated (Table 5.10). As a categorical variable, systolic blood pressure was not significantly associated with 30-day mortality. The final model included male sex, hypoxaemia, inability to stand and tachycardia. Hypoxaemia (aOR 4.14; 95% CI: 2.14-8.01) and inability to stand (aOR 4.15; 95% CI: 2.21-7.80) were regarded as major criteria and assigned 2 points, whilst male sex (aOR 2.91; 95% CI: 1.43-5.94) and tachycardia (aOR 2.77; 95% CI: 1.50-5.09) were minor criteria and each assigned 1 point. The resulting score was termed the MOST score (Male sex, Oxygen saturations, inability to Stand, Tachycardia).

An increasing MOST score was associated with an increasing rate of mortality (Table 5.11). A score of ≥2 identified 82.5% of patients who died. At this threshold, the negative predictive value was 95.2% (95% CI: 91.6-97.6) and negative likelihood ratio

was 0.29 (95% CI: 0.17-0.51) indicating the potential of the tool to identify patients at low risk of death. The overall discriminative capability of the MOST score for the prediction of 30-day mortality as assessed by area under the receiver-operating curve was 0.79; 95% CI: 0.73-0.85.

In HIV-positive patients, the performance of the MOST score was similar to that in the overall cohort with an AUROC 0.78 (95% CI: 0.72-0.85). Amongst the subgroup of patients known to be HIV-positive on admission, AUROC was 0.81 (95% CI: 0.75-0.88). At the threshold value of >=2, its performance was: sensitivity 85.0% (70.2-94.3); specificity 60.9% (53.33-68.1); positive predictive value 32.7% (23.8-42.6); negative predictive value 94.8% (89.0-98.1). The overall discriminative capability of the MOST score did not vary between patients recruited directly on admission and those recruited on the following day (AUROC: 0.81 (95% CI: 0.74-0.89) *vs.* 0.75 (95% CI: 0.66-0.85); $P = 0.31$).

The effect of altering the thresholds values for dichotomizing the physiological variables included in the severity assessment tool was investigated. The threshold values that maximized Youden's index for predicting 30-day mortality were: systolic blood pressure <115mmHg; heart rate ≥120 beats/min; oxygen saturations <92%; and respiratory rate ≥30 breaths/min (Table 5.14). At this threshold, respiratory rate continued to show no significant association with 30-day mortality. Systolic blood pressure (aOR 2.05; 95% CI: 0.97-4.32) was retained in the final multivariable model (Table 5.15), in addition to male sex (aOR 2.68; 95% CI: 1.31-5.50), oxygen saturations (aOR: 3.00; 95% CI: 1.62-5.56), inability to stand (aOR 4.45; 95% CI: 2.36-8.39) and heart rate (aOR: 3.49; 95% CI: 1.82-6.70). The discriminative capability of an alternative severity assessment tool based on these five parameters was not significantly different to that of the MOST score (AUROC 0.80 (95% CI: 0.74-0.85) *vs.* 0.79 (95% CI: 0.73-0.85); $P = 0.60$). Using a threshold value of ≥3, the alternative score had a sensitivity and specificity for predicting 30-day mortality of 91.9% (95% CI: 82.2-97.3) and 46.8% (95% CI: 41.6-52.1), respectively.

5.5.8 Accuracy of existing CAP-severity assessment tools

The prognostic performance of MOST was compared against that of existing CAP-severity assessment tools (Table 5.12). At recommended thresholds for identifying severe disease, CURB65 (14.0%; 95% CI: 6.3-25.8) and the related CRB65 tool (27.9; 95% CI: 17.1-40.8) both had poor sensitivity for identifying individuals at risk of 30-day mortality. The SMRT-CO score - that was originally derived to predict need for mechanical ventilation or inotropic support - performed well with a sensitivity of

89.7% (95% CI: 72.6-97.8). The SWAT-Bp tool derived in a previous cohort of adults with LRTI in Malawi also included male sex and non-ambulatory status as predictors of outcome, but at the recommended threshold of 3 had poor sensitivity (54.1; 95% CI: 40.8-66.9) for predicting 30-day mortality. The overall discriminative capability of the MOST score for the prediction of 30-day mortality as assessed by AUROC compared favourably with the existing tools.

Table 5.12 Multivariable analysis of features associated with 30-day mortality and weighting given in risk prediction tool. Categorical variables shown as number and proportion; denominator varies with available data. Multivariable analysis by logistic regression.

Characteristic	Day 30 survivors (n=375)	Day 30 mortality (n=64)	Multivariable		% bootstrap replications	β coefficient	Points assigned
			aOR (95% CI)	*P*			
Male sex	224/375 (59.7)	52/64 (81.3)	2.91 (1.43-5.94)	0.003	92	1.068	1
Systolic BP <90 (mmHg)	66/371 (17.8)	17/63 (27.0)	-	-	18	-	
Heart rate ≥125 (/min)	135/374 (36.1)	37/64 (57.8)	2.77 (1.50-5.09)	0.001	95	1.017	1
Oxygen saturations <90 (%)	45/368 (12.2)	27/63 (42.9)	4.14 (2.14-8.01)	<0.0001	99	1.421	2
Inability to stand	57/375 (15.2)	30/64 (46.9)	4.15 (2.21-7.80)	<0.0001	99	1.424	2

aOR – adjusted odds ratio; BP – blood pressure; CI – confidence interval.

Table 5.13 Observed 30-day mortality and performance characteristics of MOST score.

Score	No. (%) died	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	Positive LR (95% CI)	Negative LR (95% CI)
0	0/67 (0)	100 (94.3-100)	-	14.6 (11.5-18.4)	-	-	-
≥1	11/162 (6.8)	100 (94.3-100)	18.2 (14.4-22.5)	17.3 (13.6-21.6)	100 (94.6-100)	1.22 (1.17-1.28)	-
≥2	14/96 (14.6)	82.5 (70.9-90.9)	59.2 (54.0-64.3)	25.7 (19.9-32.3)	95.2 (91.6-97.6)	2.02 (1.71-2.39)	0.29 (0.17-0.51)
≥3	14/55 (25.4)	60.3 (47.2-72.4)	81.5 (77.2-85.4)	35.8 (26.8-45.7)	92.3 (88.9-95.0)	3.26 (2.43-4.38)	0.49 (0.36-0.66)
≥4	8/27 (29.6)	38.1 (26.1-51.2)	92.7 (89.5-95.1)	47.1 (32.9-61.5)	89.7 (86.2-92.6)	5.19 (3.21-8.40)	0.67 (0.55-0.81)
≥5	7/13 (53.8)	25.4 (15.3-37.9)	97.8 (95.8-99.1)	66.7 (44.7-84.4)	88.5 (84.9-91.4)	11.68 (5.22-26.14)	0.76 (0.66-0.88)
6	9/11 (81.8)	14.3 (6.7-25.4)	99.5 (98.1-99.9)	81.8 (48.2-97.7)	87.4 (83.6-90.2)	26.29 (5.81-118.83)	0.86 (0.78-0.95)

CI – confidence interval; LR – likelihood ratio; MOST – severity assessment tool based on male sex, oxygenation, inability to stand and tachycardia; NPV – negative predictive value; PPV – positive predictive value.

Table 5.14 Univariable analysis of physiological parameters with 30-day mortality at varying threshold values. Categorical variables shown as number and proportion; denominator varies with available data. Analysis by logistic regression.

	No. (%) died	Sensitivity % (95% CI)	Specificity % (95% CI)	OR (95% CI)
Respiratory rate (/min)				
≥20	62/417 (14.9)	100 (94.2-100)	2.5 (1.1-4.6)	-
≥25	52/334 (15.6)	83.9 (72.3-92.0)	22.5 (18.3-27.2)	1.51 (0.74-3.11)
≥30	33/205 (16.1)	53.2 (40.1-66.0)	52.7 (47.5-58.0)	1.27 (0.74-2.18)
≥35	15/95 (15.8)	24.2 (14.2-36.7)	78.0 (73.4-82.2)	1.13 (0.60-2.13)
≥40	5/40 (12.5)	8.1 (2.7-17.8)	90.4 (86.9-93.2)	0.82 (0.31-2.19)
≥45	1/20 (5.0)	1.6 (0-8.7)	94.8 (92.0-96.8)	0.30 (0.04-2.26)
Heart rate (/min)				
≥80	62/416 (14.9)	96.9 (89.2-99.6)	5.3 (3.3-8.1)	1.75 (0.40-7.68)
≥90	59/383 (15.4)	92.2 (82.7-97.4)	13.4 (10.1-17.2)	1.82 (0.70-4.75)
≥100	58/346 (16.8)	90.6 (80.7-96.5)	23.0 (18.8-27.6)	2.38 (1.20-6.92)
≥110	49/285 (17.2)	76.6 (64.3-86.2)	36.9 (32.0-42.0)	1.91 (1.03-3.53)
≥120	45/213 (21.1)	70.3 (56.6-81.1)	55.1 (49.9-60.2)	2.90 (1.64-5.15)
≥125	37/172 (21.5)	57.8 (44.8-70.1)	63.9 (58.8-68.8)	2.43 (1.42-4.16)
≥130	26/131 (19.9)	40.6 (28.5-53.6)	71.9 (67.1-76.4)	1.75 (1.01-3.03)
≥140	12/54 (22.2)	18.8 (10.1-30.5)	88.8 (85.1-91.8)	1.82 (0.90-3.69)
Systolic blood pressure (mmHg)				
<115	51/290 (17.6)	81.0 (69.1-89.8)	35.6 (30.7-40.7)	2.34 (1.21-4.56)
<110	45/255 (17.7)	71.4 (58.7-82.1)	43.4 (38.3-8.1)	1.92 (1.07-3.44)
<105	39/211 (18.5)	61.9 (48.8-73.9)	53.6 (48.4-58.8)	1.88 (1.09-3.25)
<100	32/166 (19.3)	50.8 (37.9-63.6)	63.9 (58.8-68.8)	1.83 (1.07-3.12)
<95	23/121 (19.0)	36.5 (24.7-49.6)	73.6 (68.8-78.0)	1.60 (0.91-2.81)
<90	17/83 (20.5)	27.0 (16.6-39.7)	82.2 (77.9-86.0)	1.71 (0.92-3.16)
<85	11/54 (20.4)	17.5 (9.1-29.1)	88.4 (84.7-91.5)	1.61 (0.78-3.33)
<80	7/23 (30.4)	11.1 (4.6-21.6)	95.7 (93.1-97.5)	2.77 (1.09-7.04)
Oxygen saturations (%)				
<98	52/314 (16.6)	82.5 (70.9-90.9)	28.8 (24.2-33.7)	1.91 (0.96-3.81)
<96	46/227 (20.3)	73.0 (60.3-83.4)	50.8 (45.6-56.0)	2.80 (1.55-5.06)
<94	38/165 (23.0)	60.3 (47.2-72.4)	65.5 (60.4-70.3)	2.88 (1.67-4.99)
<92	33/110 (30.0)	52.4 (39.4-65.1)	79.1 (74.6-83.1)	4.16 (2.39-7.24)
<90	27/72 (37.5)	42.9 (30.5-56.0)	87.8 (84.0-90.9)	5.38 (2.99-9.70)
<88	20/59 (33.9)	31.7 (20.6-44.7)	89.4 (85.8-92.4)	3.92 (2.10-7.34)

BP – blood pressure; CI – confidence interval; OR – adjusted odds ratio.

Table 5.15 Multivariable analysis of features associated with 30-day mortality using alternative threshold values of physiological observations. Categorical variables shown as number and proportion; denominator varies with available data. Multivariable analysis by logistic regression.

Characteristic	Day 30 survivors (n=375)	Day 30 mortality (n=64)	Multivariable		% bootstrap replications	β coefficient	Points assigned
			aOR (95% CI)	*P*			
Male sex	224/375 (59.7)	52/64 (81.3)	2.68 (1.31-5.50)	0.007	86	0.988	1
Systolic BP <115 (mmHg)	239/371 (64.4)	51/63 (81.0)	2.05 (0.97-4.32)	0.06	62	0.717	1
Heart rate ≥120 (/min)	168/374 (44.9)	45/64 (70.3)	3.49 (1.82-6.70)	<0.0001	99	1.251	2
Oxygen saturations <92 (%)	77/368 (20.9)	33/63 (52.4)	3.00 (1.62-5.56)	<0.0001	96	1.099	1
Inability to stand	57/375 (15.2)	30/64 (46.9)	4.45 (2.36-8.39)	<0.0001	99	1.492	2

aOR – adjusted odds ratio; BP – blood pressure; CI – confidence interval.

Table 5.16 Comparison of the accuracy of pneumonia severity assessment tools for predicting 30-day mortality.

Score group	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	Positive LR (95% CI)	Negative LR (95% CI)	AUROC (95% CI)
MOST ≥2	82.5 (70.9-90.9)	59.2 (54.0-64.3)	25.7 (19.9-32.3)	95.2 (91.6-97.6)	2.02 (1.71-2.39)	0.29 (0.17-0.51)	0.79 (0.73-0.85)
CURB65 ≥3	14.0 (6.3-25.8)	91.6 (88.2-94.2)	21.1 (9.6-37.3)	86.9 (83.1-90.1)	1.66 (0.80-3.44)	0.94 (0.84-1.05	0.60 (0.52-0.67)
CRB65 ≥2	27.9 (17.1-40.8)	81.9 (77.6-85.8)	20.7 (12.6-31.1)	87.0 (83.0-90.4)	1.54 (0.97-2.44)	0.88 (0.75-1.04)	0.57 (0.50-0.65)
SMRT-CO ≥2	89.7 (72.6-97.8)	36.5 (30.6-42.8)	14.0 (9.3-19.8)	96.8 (91.0-99.3)	1.41 (1.21-1.65)	0.28 (0.10-0.84)	0.66 (0.57-0.75)
IDSA/ATS 2007 ≥3	48.3 (29.4-67.5)	71.7 (65.6-77.3)	16.9 (9.5-26.7)	92.1 (87.3-95.5)	1.71 (1.11-2.62)	0.72 (0.50-1.03)	0.65 (0.56-0.75)
SWAT-Bp ≥3	54.1 (40.8-66.9)	68.3 (63.3-73.0)	22.1 (15.8-29.7)	89.9 (85.8-93.2)	1.71 (1.30-2.25)	0.67 (0.51-0.89)	0.65 (0.57-0.72)

AUROC – area under receiver-operating characteristic curve; CURB65 – tool based on confusion, urea, respiratory rate, blood pressure and age ≥65; CRB65 – as per CURB65 with exclusion of urea; NPV – negative predictive value; PPV – positive predictive value; SMRT-CO – tool based on systolic blood pressure, multilobar consolidation, respiratory rate, tachycardia, confusion and oxygenation; SWAT-Bp – tool based on male sex, wasting, non-ambulatory, temperature and blood pressure

5.5.9 Population attributable fractions for mortality

As a potentially modifiable risk factor, the population attributable fraction (PAF) of hypoxameia for 30-day mortality was calculated. The estimated proportion of mortality attributable to hypoxaemia (i.e. oxygen saturations <90%) was 24.5% (95% CI: 10.8-36.1). PAFs were not estimated for the other variables included in the final model since they are not directly modifiable.

5.6 Discussion

5.6.1 Mortality

The observed overall 30-day CAP mortality rate of 14.6% is similar to that described in previous cohorts from Malawi (Birkhamshaw *et al.*, 2013; Hartung *et al.*, 2011), Nigeria (Mbata *et al.*, 2013), Ethiopia (Aderaye, 1994b), Kenya (Scott *et al.*, 2000) and South Africa(Nyamande *et al.*, 2007a). The overall mortality rate must be considered in the context of the age profile of the patient population. Whilst comparisons between settings are often problematic, studies from well-resourced settings that have focused on young CAP patients have reported much lower mortality rates: 1.5% in patients under 50 years (Chalmers *et al.*, 2008; Ewig *et al.*, 2009); 5.2% in those under 65 years (Chen *et al.*, 2010). There are likely to be multiple factors related to the patient population, prevailing pathogens and healthcare delivery that contribute to this elevated mortality rate. Whilst within this cohort, no independent impact of HIV infection on mortality was demonstrated, the high prevalence of advanced immunosuppresion coupled with other factors such as under-nutrition, are likely to in part account for differences in outcome between this and well-resourced setting CAP cohorts. Altered healthcare seeking behaviour resulting in a delayed presentation to hospital may also contribute. The association of increased symptom duration with increased mortality was evident in this cohort despite restricting recruitment to patients with symptoms of 14 days or less. Delays to presentation may be further compounded by delays to receipt of appropriate therapy (Gattarello *et al.*, 2015). In keeping with previous sub-Saharan Africa cohorts, TB was very common and associated with adverse outcome (Feasey *et al.*, 2013; Jacob *et al.*, 2013b). Data on the timing of initiation of anti-TB treatment are unavailable, but given the challenges with diagnosis, therapy is commonly delayed. Whilst the data available on supportive management (i.e. oxygen, intravenous fluid use) in this study are limited, they are sufficient to highlight important inadequacies. Only 61% of patients with oxygen saturations of less than 90% received oxygen on admission. Further shortcomings in care owing to resource limitations such as missed medications doses and limited

availability of appropriately trained staff to monitor clinical response are unaccounted for in this analysis and may also contribute to high mortality (see section 5.6.5).

Most previous studies of CAP outcome in sub-Saharan Africa have described inpatient mortality only (see chapter 2). With more detailed and extended follow-up, the current study offers additional insights: whilst approximately 50% of deaths occurred within the first week following admission, 20% of 30-day mortality occurred following discharge from hospital; amongst patients surviving to day 30, a further 6.5% die prior to day 90. Early deaths following a diagnosis of CAP are typically directly related to pneumonia, occurring as a result of respiratory failure and/or sepsis. Studies from well-resourced settings highlight the importance of underlying comorbid diseases in contributing to later deaths following CAP (Mortensen *et al.*, 2002). The current study was not designed to define causes of death, but 30-day mortality was related to treatment failure and lack of attainment of clinical stability, perhaps indicating the predominant role of inadequately treated primary infection or failure to recognise or respond to a complication as a contributor to death.

In Western cohorts, survivors of CAP have excess mortality compared to hospitalised controls for at least one year (Koivula *et al.*, 1999; Waterer *et al.*, 2004). In the absence of a control group, it is not possible to quantify the numerical significance of the deaths occurring beyond day 30. Whether these deaths represent decompensation of underlying comorbid illness, in particular cardiovascular disease (Musher *et al.*, 2007), as is common in well-resourced settings or are due to other factors (e.g. recurrent infection, tuberculosis, related to antiretroviral treatment) warrants further study.

5.6.2 Early clinical endpoints

Most patients with CAP do not die (Welte *et al.*, 2012). Clinical endpoints such as requirement for intensive care support, treatment failure or time to clinical stability provide a more comprehensive description of CAP disease course and severity (Wiemken *et al.*, 2013). In low-resource settings where investigations to define microbiology or identify complications may be lacking, clinical response to treatment is the major factor in guiding therapeutic decisions (World Health Organization, 2011c). However, the optimal criteria to define adequate clinical response are unclear.

Treatment failure as defined by early death or persistent hypotension, hypoxaemia or fever at 72 hours occurred in 24%. Using a similar definition, treatment failure has been reported in 13-48% of hospitalised CAP patients (Hoogewerf *et al.*, 2006; Martin-Loeches *et al.*, 2014; Menendez *et al.*, 2004b). Treatment failure was associated with an increased risk of 30-day mortality, as previously described (Hoogewerf *et al.*, 2006;

Menendez *et al.*, 2004b; Roson *et al.*, 2004). However, fewer than half of patients that died between day 3 and day 30 met treatment failure criteria. If absence of treatment failure (i.e. resolution of hypotension, hypoxaemia and fever) is alone used as the marker of adequate treatment response, there is a danger that clinicians might be falsely reassured about the likely prognosis of patients and inappropriately de-escalate treatment.

Attainment of clinical stability is an alternative marker of treatment response and may be used to guide timing of switch from intravenous to oral antibiotics and timing of discharge from hospital (Akram *et al.*, 2013; Mandell *et al.*, 2007; Niederman *et al.*, 2001). In keeping with previous studies, failure to attain clinical stability was associated with increased risk of death in the current cohort (Aliberti *et al.*, 2011; Halm *et al.*, 2002). However, inpatient mortality following attainment of stability was 4.4% compared to less than 1% in previous studies (Akram *et al.*, 2013; Halm *et al.*, 1998) and only 60% of patients overall actually met criteria for clinical stability prior to discharge.

The criteria used to define treatment response and clinical stability criteria need to be refined and locally adapted before they can be used as a reliable basis for making therapeutic decisions in Malawi or similar settings. In addition, defining robust clinical endpoints is an important prelude to designing appropriate clinical trials of new interventions. The use of additional clinical parameters such as adequate oral intake and ambulation might improve the accuracy of assessment (Aliberti *et al.*, 2013). Whilst there was substantial missing data for physiological observations taken on the first day following admission, this had little overall impact on the estimate of the median time to clinical stability. Tuberculosis was associated with both treatment failure and delayed clinical stability. Further studies are needed to better define the causes of inadequate treatment response and to suggest the appropriate panel of investigations or broadened empirical treatment.

5.6.3 Risk factors for adverse outcome

Hypoxaemia– as measured by pulse oximetry – was strongly associated with both mortality and treatment failure. This expected finding is consistent with previous studies (Charles *et al.*, 2008b; Fine *et al.*, 1997a). The extent to which hypoxaemia is a potentially remediable factor, the correction of which might improve outcome, rather than a marker of disease severity alone, merits consideration in this resourced-limited context where the number of hypoxaemic patients exceeds the capacity of supplemental oxygen delivery systems several times over (Evans *et al.*, 2012).

Programmes to improve the detection and correction of hypoxaemia in paediatric pneumonia in resource-limited settings have resulted in reductions in mortality of up to 35% (Duke *et al.*, 2010c; Duke *et al.*, 2008; La Vincente *et al.*, 2011). The extent to which these achievements can be replicated in adult pneumonia is uncertain.

Tachypnoea, although strongly correlated with oxygen saturations, was not predictive of adverse outcome, in contrast to many previous studies in diverse populations (Charles *et al.*, 2008b; Fine *et al.*, 1997a; Fine *et al.*, 1996; Lim *et al.*, 2000; Ortqvist, 1990; Scott *et al.*, 2000). A lack of association between respiratory rate and mortality has been observed in other cohorts from low-resource settings (Birkhamshaw *et al.*, 2013; Hartung *et al.*, 2011; Rylance *et al.*, 2009). It is possible that in these predominantly young adult populations with presumably improved physiological reserve increased respiratory rate alone does not indicate imminent respiratory failure. Although inaccuracy in respiratory rate estimation is well-recognised, the lack of association with mortality at even very elevated respiratory rates suggests that this is not relevant (Lovett *et al.*, 2005). The lack of association of elevated respiratory rate with adverse outcome underlines the importance of pulse oximetry as a vital component of pneumonia disease severity assessment. Whilst there are innovations and initiatives to make pulse oximeters more affordable, reliable and robust (Dubowitz *et al.*, 2013), availability in many low-resourced settings is still inadequate (World Health Organization, 2011a).

Inability to stand unaided was associated with both 30-day mortality and treatment failure. This simple observation is not commonly reported in studies of hospitalised patients from most well-resourced settings, but is attractive for use in low-resource settings because it is rapidly ascertainable with no equipment and limited training. In a cohort of acutely hospitalised adults in Tanzania, the inability to walk unaided predicted death with a sensitivity of 86% and a specificity of 52% (Rylance *et al.*, 2009). Further validation work is required to determine the inter-observer variability in recording this feature.

Male sex was independently associated with increased mortality. Several previous CAP studies have identified male sex as risk factor both for incident pneumonia and adverse outcome (Ewig *et al.*, 2009; Fine *et al.*, 1996; Kaplan *et al.*, 2002; Ortqvist, 1990; Welte, 2012). Whilst sex-related variations in the immunological response to sepsis may in part account for the observed differences in outcome (Angele *et al.*, 2014), differences in health-seeking behaviour and clinical management are also likely to be relevant (Arnold *et al.*, 2013).

In contrast to previous CAP studies, no association with age and mortality was demonstrated (Fine *et al.*, 1997a; Kothe *et al.*, 2008; Lim *et al.*, 2000). In studies from developed settings, the increase in mortality with advancing age becomes apparent in patients above the age of 40 (Ewig *et al.*, 2009; Fine *et al.*, 1997a). The median age of the current cohort is 35 with 31% age 40 years or older and 13% aged 50 years or older. This comparatively young average means that the study is relatively underpowered to detect age-related differences in mortality that only become notable beyond 40 years. Residual confounding due to factors related to pre-morbid condition and healthcare utilisation may also pertain.

HIV was not associated with an increased risk of mortality at 30 days, but was associated with an increased risk of treatment failure. The explanation for and relevance of this discrepant result is uncertain. Controlling for CD4 cell count and ART use did not influence these findings. Most studies from the ART era have shown that the mortality of acute, presumed bacterial CAP does not alter with HIV status (Albrich *et al.*, 2014a; Birkhamshaw *et al.*, 2013; Christensen *et al.*, 2005; Malinis *et al.*, 2010; Mwachari *et al.*, 2006; Nyamande *et al.*, 2007a; Scott *et al.*, 2000). Whilst a small effect obscured by residual confounding is possible, it is clear that predominant impact of HIV on CAP is on the rate of acquisition of disease rather than its outcome. For individual episodes of pneumonia, the assessment of disease severity and estimation of prognosis, should not be influenced by HIV status.

Reduced haemoglobin concentration was weakly associated with 30-day mortality risk. Although correlated with haemoglobin, clinically assessed pallor did not predict mortality. Anaemia has previously been associated with both early mortality and, in survivors to hospital discharge, continued excess mortality risk up to 90 days (Fine *et al.*, 1997a; Hartung *et al.*, 2011; Reade *et al.*, 2010; Waterer *et al.*, 2004). Further analysis is needed to determine whether the association is directly causal (i.e. due to impaired tissue oxygen transport compromised) or a marker of underlying disease. The extent to which correction of anaemia may improve outcome is uncertain. In severe sepsis, a restrictive transfusion strategy (i.e. haemoglobin transfusion threshold of 7g/dL) is non-inferior to more liberal use (i.e. threshold of 9g/dL)(Holst *et al.*, 2014).

In keeping with previous studies, leucopenia was also associated with increased mortality (Fine *et al.*, 1996; Scott *et al.*, 2000). The IDSA/ATS criteria for predicting intensive care requirement also include leucopenia (Mandell *et al.*, 2007), but recent re-analyses indicate its non-contributory to prognostic accuracy (Li *et al.*, 2015; Salih *et al.*, 2014). Attempts to manipulate white cell number, function and differentiation using

granulocyte colony stimulating factor (G-CSF) do not improve outcome in pneumonia or sepsis (Bo *et al.*, 2011; Cheng *et al.*, 2007).

5.6.4 CAP severity assessment tools

The clinical course of CAP is variable and difficult to predict. Severity assessment tools support early management by providing an objective assessment of prognosis. The MOST score proposed in the current study is a simple tool based solely on clinical parameters evident at presentation. Using a threshold of 2, it had sensitivity of 82.5% and negative predictive value of 95.2% for 30-day mortality. If these findings are replicated in validation studies, a MOST score of less than 2 might be used to identify those patients at low risk of mortality potentially suitable for outpatient treatment or early hospital discharge. In particular, those lacking any features of severe disease (i.e. MOST score 0) had a minimal risk of mortality (less than 1%). Given the patients with MOST scores of 0 and 1 accounted for 17% and 38% of the cohort, respectively, the potential for admission avoidance and reducing demand on already overstretched inpatient services is considerable.

The mortality rate of patients with a MOST score of 3 was 25% and rose rapidly with increasing score. Comparable rates of predicted mortality would prompt consideration of high-dependency care in CAP patients in well-resourced settings (Lim *et al.*, 2003). Whilst high-dependency care provision is minimal in many sub-Saharan African settings (Adhikari *et al.*, 2010), this group of patients could be targeted for closer monitoring including simple measures such as regular nursing observations, repeated assessment of oxygenation and fluid balance, early review of treatment response. Similarly, the MOST score, if validated, could be used to target or stratify interventions in future clinical trials of severe pneumonia.

Existing CAP-severity assessment tools performed poorly in the current cohort. CURB65 had an area under receive-operating curve of 0.60 for 30-day mortality, indicating poor or moderate discriminatory capability. At the standard threshold for defining severe pneumonia, CURB65 had sensitivity of only 14%. Its poor performance likely reflects that two of its component parameters – age greater than 65 and confusion – were uncommon, each occurring in fewer than 5% of patients. Similarly, SMRT-CO and the IDSA/ATS minor criteria were considerably less accurate than has been observed in validation studies in well-resourced settings (Chalmers *et al.*, 2011c). CURB65, SMRT-CO and IDSA/ATS minor criteria were all derived in CAP populations in well-resourced settings where the demographic distribution and comorbidity profile is markedly different to that seen in Malawi (see chapter 4). The derivation studies also

specifically excluded patients with immunocompromise, TB or non-radiographic pneumonia (Charles *et al.*, 2008b; Lim *et al.*, 2003; Mandell *et al.*, 2007), all of which were common in the current cohort. These findings underline the necessity of using locally derived or recalibrated tools to guide CAP clinical management (Schuetz *et al.*, 2008).

The SWAT-Bp score was designed to predict the mortality risk of in hospitalised adults with clinical lower-respiratory tract infection (Birkhamshaw *et al.*, 2013). In the original derivation cohort in Malawi, it showed excellent discriminative capability for the prediction of inpatient (area under ROC curve 0.867). In this cohort, despite containing variables shown to be predictive of mortality (i.e. male sex and non-ambulatory state), it only showed moderate prognostic performance (area under ROC curve 0.65). This disparity may reflect important differences between the current cohort and the SWAT-Bp derivation cohort: firstly, the diagnosis of LRTI/pneumonia was not prospectively standardised against a case-definition; secondly, patients with chronic or long-standing symptoms were not systematically excluded.

The risk of identifying spurious associations of candidate risk factors with outcome (type 1 error) or failing to detect true risk factors (type 2 errors) is inherent in prognostics research. The inappropriate retention of variables in a multivariable model - termed 'over-fitting' (i.e. type 1 error) – compromises its prognostic performance in independent datasets. The risk of over-fitting increases with the number of predictor variables examined and a minimum events per variable ratio (EPV) of 10 has been recommended (Peduzzi *et al.*, 1996), although this may be excessively conservative and EPV of 5 may be sufficient in many scenarios (Vittinghoff *et al.*, 2007). In the current analysis, 31 candidate predictor variables for mortality were initially considered; 12 were excluded on the basis of low prevalence, incomplete datasets or assumed collinearity (e.g. systolic blood pressure and diastolic blood pressure). For the remaining 19 variables, two separate intermediate multivariable models for clinical and laboratory parameters (both adjusted for age, sex and HIV status) were derived. Only those 11 variables with a *P* value >0.2 (plus age and HIV status) were included in the final multivariable analysis. This approach was considered superior to variable selection on the basis of preliminary univariable analyses that is frequently used but increases the risk of over-fitting. Whilst the risk of over-fitting remains given the relatively low EPV ratio, the identified risk factors for mortality are all plausible and consistent with previous studies. Regardless of the apparent robustness of the multivariable analyses, however, external validation in an independent cohort is essential (Altman *et al.*, 2009).

5.6.5 Strengths and limitations

The MARISO study is one of the largest prospective observational studies of acute CAP in hospitalised adults ever conducted in sub-Saharan Africa. Whilst most previous studies have described CAP outcome solely in terms of short-term mortality, this study gives a comprehensive description of early clinical outcomes and treatment response. The clinical case definition used is reflective of that routinely used in clinical practice in low resource settings. Data on prognostic factors was prospectively collected using consistent methods and the completeness of follow-up was good.

There are several important limitations. The study population is restricted to hospitalised patients, hence the clinical characteristics and outcome of those deemed well enough to be treated at home is unknown. The setting of the study in a referral hospital also potentially limits the applicability of the findings to community level settings where patients are initially assessed. Study recruitment was restricted to working hours: patients presenting with severe pneumonia that deteriorated and died rapidly would not have been included in this cohort. The risk of type 1 errors has been discussed above. The impact of treatment related factors such as antimicrobial choice and speed of administration, adequacy of fluid resuscitation and oxygen delivery is not fully accounted for in this study. Whilst similar criticisms could be made of analogous studies from well-resourced settings, the potential for variability in clinical management is greater in Malawi given inconsistencies in drug supply, inadequate oxygen provision and variation in experience of medical staff. Inadequate nursing staff levels on the medical wards may also compromise timeliness and completeness of drug administration and supportive therapy. Patient guardians play a vital role in maintaining patient nutrition and hydration throughout hospitalisation and highlighting deteriorations in condition to medical and nursing staff. The current analyses do not adequately account for these treatment and care delivery factors.

5.6.6 Future research

This study has described all-cause mortality up to 90 days. Studies from well-resourced settings have highlighted that CAP is associated with continued excess mortality for many months after apparent resolution and that a many deaths result from destabilisation of comorbid illness (Koivula *et al.*, 1999; Musher *et al.*, 2007; Waterer *et al.*, 2004). Further studies are needed from sub-Saharan African settings to broadly define the causes of death and to understand the long-term impacts on health outcomes.

The MOST score is a simple prognostic tool that could potentially be used to provide a rapid assessment of disease in low-resource settings by minimally trained staff. However, to demonstrate its value, a prognostic tool must show that it performs well in groups other than the population in which it was derived (Altman *et al.*, 2009; Moons *et al.*, 2015). The size of the MARISO study cohort was insufficient to develop an adequate prognostic model using a split dataset ("training" and "test" set) approach. Whilst commonly used, this form of internal validation does not remove the requirement for external validation in a separately recruited cohort (Steyerberg *et al.*, 2013). The performance of the MOST score should be evaluated in a CAP cohort from another sub-Saharan African setting. Impact studies are then required to demonstrate that the MOST score (or an optimised derivative) meaningfully influences clinical management decisions to improve patient outcomes.

For physiological parameters, the MOST score used dichotomised variables with threshold values based on those widely used in the CAP literature. The relevance of these thresholds to CAP populations in Malawi or other sub-Saharan African settings that are dominated by young adults is unclear. The impact on prognostic accuracy of altered thresholds to define significant abnormality in physiological parameters should be explored.

Hypoxaemia is a potentially modifiable risk factor for mortality. Supplemental oxygen provision in many low-resource settings is poor and relies mainly on oxygen concentrators (Evans *et al.*, 2012; World Health Organization, 2011a). Whether these devices generate oxygen at sufficient concentration and rates of flow to correct hypoxaemia in adults with acute pneumonia has not been established.

5.7 Conclusions

CAP in adults in Malawi is associated with substantial mortality, almost half of which occurs within 7 days of hospitalisation. Of the identified risk factors for mortality, hypoxaemia is one of the strongest and also most amenable to correction. The MOST score is a simple, 4-variable tool based solely on clinical parameters that appears to estimate the risk of 30-day mortality with reasonable precision. If proved accurate in validation studies, the ability of the MOST score to safely stratify care in CAP patients in Malawi and comparable settings should be assessed in clinical trials.

6 Addressing hypoxaemia in adult pneumonia in Malawi: A pilot study of the effectiveness of supplemental oxygen delivery by oxygen concentrators

6.1 Introduction

Hypoxaemia is common feature of critical illness generally and severe respiratory infection in particular. Pneumonia management guidelines universally recommend that supplemental oxygen be administered to correct hypoxaemia (Lim *et al.*, 2009; Mandell *et al.*, 2007). In adults with pneumonia the presence of hypoxaemia is an indicator of severe disease and is consistently associated with poor outcome (Bowton *et al.*, 1994; Fine *et al.*, 1996; Lim *et al.*, 2003). In the Malawian Adult Lower Respiratory Tract Infection Severity, Aetiology and Outcome (MARISO) Study described in the preceding chapters, hypoxaemia at presentation was independently associated with mortality.

In well-resourced settings the availability of adequate supplies of supplemental oxygen is largely taken for granted. In acute hospital settings, piped wall oxygen is typically available at each bed-space and additional means of respiratory support such as high-flow oxygen, continuous positive airways pressure (CPAP), non-invasive ventilation (NIV) and invasive ventilation are available for deteriorating patients. This is in marked contrast to low-resource settings where the availability of supplemental oxygen provision is woefully inadequate (Duke *et al.*, 2010a; Hill *et al.*, 2009).

In the absence of piped oxygen infrastructure, the World Health Organization (WHO) recommends that oxygen in hospitals is provided using oxygen concentrators (Duke *et al.*, 2008; La Vincente *et al.*, 2011). Oxygen concentrators are the main source of oxygen provision in Queen Elizabeth Central Hospital, Blantyre, Malawi (Evans *et al.*, 2012).

Oxygen concentrators were initially developed in the 1970s for domiciliary oxygen provision for patients with chronic lung disease rather than for acutely unwell patients in a hospitalised setting. They use an oscillating plate to force ambient air across a filter bed to extract nitrogen and produce oxygen-enriched gas. There is now wide-range of oxygen concentrators available that vary considerably in performance characteristics (e.g. maximum flow rate, maximum oxygen concentration), power requirements, and tolerances (i.e. for temperature and humidity). Most devices produce up to 5 L/min of approximately 95% oxygen. Higher flow-rate concentrators that produce up to 10 L/min of 85% oxygen are also available but typically cost 75% more and have higher power requirements.

There is no empiric evidence describing the adequacy of oxygen concentrators in terms of their ability to deliver oxygen at sufficient concentrations and/or flow-rates to correct hypoxaemia. Amongst adults with pneumonia who are hypoxaemic, the proportion that attain normoxaemia with oxygen delivered by concentrator at 5 L/min (i.e. the maximum flow rate of standard concentrators) is not known. The effectiveness of oxygen delivery by oxygen concentrator to induce normoxaemia amongst adults with pneumonia who are hypoxaemic at presentation is unknown. In particular to what extent high flow-rate devices that produce 10 L/min are more effective than standard flow-rate devices has not been described.

6.2 Objectives

6.2.1 Broad

The broad objective of this study was to assess the effectiveness of supplemental oxygen provided by oxygen concentrator to correct hypoxaemia in adults with suspected pneumonia. Hypoxaemia is defined as oxygen saturations (SpO_2) less than 92% measured by pulse oximetry and normoxaemia (or corrected hypoxaemia) is defined as SpO_2 greater than or equal to 92%.

6.2.2 Specific

i. To determine the proportion of adults hospitalised with pneumonia that are hypoxaemic at presentation that attain normoxaemia with supplemental oxygen delivered by concentrator at a standard flow-rate of 5 L/min.

ii. To determine what proportion of those who fail to attain normoxaemia at a rate of 5 L/min, attain normoxaemia at a high flow-rate of 10 L/min.

6.3 Contributors to the AHIP Study

I conceived the study and devised the protocol, wrote all study documents, designed and developed the CRFs and study database. In addition to my supervisors, Dr Jamie Rylance (Liverpool School of Tropical Medicine, UK), Dr Mulinda Nyirenda (QECH) and Dr Aylwin Chick (formerly QECH) provided useful comments in the development of the study protocol. All study clinical procedures were performed by a study clinical officer and two research nurses overseen by the study coordinator, Dr Jacqueline Huwa. Dr Huwa also completed the routine data management activities including CRF scanning and data verification. I completed the reading and grading of the radiographs. Clinical specimens were processed in the MLW Clinical Diagnostic Laboratory under the

supervisions of the laboratory managers, Brigitte Denis and George Selemani. I developed the statistical analysis plan and undertook all analyses myself.

6.4 Methods

6.4.1 Study design

Prospective, open-label, single-arm clinical study

6.4.2 Setting

The study was conducted at Queen Elizabeth Central Hospital (QECH), Blantyre, Malawi as described in detail in section 1.11.2. Enrolment commenced on 25th November 2014 and continued until 17th July 2015. Participant follow-up was completed on 29th August 2015. The study team were based in the Adult Emergency and Trauma Centre (AETC) and study procedures were conducted in the Resuscitation area. Prior to the inception of this study, the only available oxygen delivery capacity was within the resuscitation area where there were 4 or 5 oxygen concentrators, each with a maximum output capacity of 5 L/min. The functionality of the concentrators was not specifically tested. Previous operational research at QECH has found that approximately 10% of medical inpatients require oxygen (as defined by saturations of <90%) but only one-third of patients receive it. Poor functionality of oxygen concentrators is common with many delivering suboptimal flow rates and inadequate concentrations of oxygen (Evans *et al.*, 2012).

6.4.3 Study participants

Hypoxaemic adults with suspected pneumonia.

6.4.3.1 Inclusion criteria

- Adults (aged 18 years or over)
- At least **TWO** of the following: temperature ≥38°C or ≤35°C, fever/rigors/sweats, new or worsened cough, new or worsened dyspnoea, chest pain.
- At least ONE of the following on clinical examination: crepitations, bronchial breathing or pleural rub (This criterion was removed from 1st June in an amendment to the study protocol made in view of slow study recruitment).
- Oxygen saturations in room air of <92%

6.4.3.2 Exclusion criteria

- Illness duration of greater than 21 days.

- Pre-admission diagnosis of terminal illness (e.g. metastatic malignancy, terminal AIDS).
- Patients at high risk of hypercapnic respiratory failure:
    - COPD: known diagnosis or suspected on basis of smoking history of ≥30 pack-years, chronic breathlessness on minor exertion and no other known cause, hyper-expanded chest, signs of cor pulmonale.
    - Bronchiectasis: known diagnosis or suspected on basis of chronic (≥6 months) productive cough with frequent exacerbations.
    - Morbid obesity (clinically assessed)
    - Severe chest wall or spinal deformity (e.g. kyphoscoliosis)
    - Suspected chronic neuromuscular disorder (e.g. motor neurone disease)

6.4.4 Intervention

Monitored response to supplemental oxygen generated by an oxygen concentrator administered to all patients at an initial flow rate of 5 L/min and increased to up to 10 L/min to those in whom hypoxaemia persists.

6.4.5 Outcomes

6.4.5.1 Primary endpoints

i) Proportion of patients that attain SpO_2 ≥92% following 60 minutes of supplemental oxygen at a flow rate of up to 5 L/min.

ii) Proportion of patients who fail to attain SpO_2 ≥92% on 5 L/min that do so with supplemental oxygen at a flow rate of up to 10 L/min for up to 4 hours.

6.4.5.2 Secondary endpoints

i) Change in SpO_2 from baseline levels with supplemental oxygen at 5 L/min and 10 L/min.

ii) Survival to hospital discharge.

6.4.6 Ethical approval

The study protocol was independently reviewed and approved by the Research Ethics Committee of both College of Medicine University of Malawi (Protocol No. P.07/14/1599) and Liverpool School of Tropical Medicine (Protocol No. 14.032).

6.4.7 Study procedures

6.4.7.1 Recruitment

Recruitment took place in the AETC at QECH between 8am and 5pm daily. Patients identified at triage with features of respiratory infection and/or SpO_2 of <92% were assessed for inclusion by the study clinician (clinical officer or medically-qualified investigator) according to the eligibility criteria above. The period of recruitment overlapped with that of the Malawian Adult Lower Respiratory Tract Infection Severity, Aetiology and Outcome (MARISO) Study (described in chapters 3, 4 and 5) for approximately 2 months. During this period, patients with features of respiratory infection were initially screened for inclusion in the MARISO study and then only if ineligible screened for this study. Co-recruitment to both studies was not permitted.

6.4.7.2 Consent

A two-stage consent process was used whereby verbal assent for participation was sought from the patient or their accompanying guardian following a brief description of the proposed study. Emergency management and monitoring was instituted and following stabilisation, written informed consent for continued participation was sought from the patient or, in the case of continued incapacity or deterioration, from the guardian (Maitland *et al.*, 2011b). Initially the ethics committee required that an assenting accompanying guardian was present for all patients recruited. This condition was removed on request following the observation that a substantial number of patients presented to hospital unaccompanied. This two-stage or deferred consent process has previously been used in studies of acute interventions in critically unwell patients, including in low-resource African settings (Food and Drug Administration, 1996; Kortgen *et al.*, 2006; Maitland *et al.*, 2011a; Shapiro *et al.*, 2006).

At QECH the demand for supplemental oxygen outstrips supply; not all patients that require supplemental oxygen actually receive it. To avoid any coercion to participate, the study concentrators were used to provide oxygen for hypoxaemic patients who wished to receive it even if they declined to participate in the study if there were no other concentrators available.

6.4.7.3 Baseline assessment

Recruited participants underwent a thorough, standardised clinical assessment. The medical history included details of the present illness, past medical and drug history and demographic details. Information was obtained via direct questioning of the study participant (or accompanying guardian) and by reference to medical notes and health

passport. Physical examination consisted of cardiovascular, upper and lower respiratory tract and abdominal examinations. Level of consciousness was assessed using the AVPU scale (Kelly *et al.*, 2004). Using this simplified tool patients are assessed as "Alert", "Responsive to voice", "Responsive to pain" or "Unresponsive." In lieu of a validated cognitive assessment tool that is not available in Malawi, the presence of confusion was determined using three standardised questions assessing orientation in time, place and person.

Physiological observations were measured immediately prior to the commencement of oxygen and repeatedly during the monitoring period in accordance with detailed standardised operating procedures and using study-specific equipment (temperature (Welch Allyn SureTemp Plus thermometer using an oral probe; Welch Allyn, Buckinghamshire, UK); blood pressure (A&D UA767 Digital Blood Pressure Monitor; A&D Instruments, Abingdon, UK); oxygen saturations (Nonin 2500 PalmSAT® Pulse Oximeter; Nonin Medical, Inc., Minnesota, USA)).

A 3ml venous blood specimen was obtained for full blood count and HIV test. A chest radiograph was requested for all patients.

6.4.7.4 Oxygen delivery and monitoring

Following baseline observations, supplemental oxygen generated by an oxygen concentrator (NewLife Intensity 10 Oxygen Concentrator; AirSep, New York, USA) was immediately administered to all patients at an initial flow rate of 5 L/min via a Hudson facemask or, if not tolerated, nasal cannulae. SpO_2 was monitored continuously and recorded automatically every five minutes (see figure 6.1). Respiratory rate, heart rate and blood pressure was recorded every 15 minutes. At 60 minutes, if SpO_2 was ≥92%, the patient was classified as having responded adequately to the standard flow-rate and the study intervention considered complete. If SpO_2 at 60 minutes was between 90 and 94%, an average of 3 readings taken over the following 3 minutes was used.[10] If SpO_2 was <92%, the response to standard flow-rate oxygen was classified as inadequate and the oxygen flow rate increased to 10 L/min and the mask changed to a Hudson mask with reservoir bag. Oxygen flow-rate was immediately increased to 10 L/min if at any point during the first 60 minutes of monitoring the SpO_2 fell consistently below 85%. Patients were monitored for up to a further 4 hours on the high-flow rate of oxygen. Those that attained sustained increases in SpO_2 to ≥92% (i.e. on two readings separated by at least 5 minutes) were classified as responding to high

[10] If SpO_2 at 60 minutes was between 90 and 94%, an average of 3 readings taken over the following 3 minutes was used.

flow-rate oxygen, otherwise patients were classified as non-responders to oxygen therapy. If SpO_2 were consistently >98% during the monitoring period, the flow-rate of oxygen was reduced incrementally by 1 L/min every 5 minutes until the target range of 92-98% was achieved.

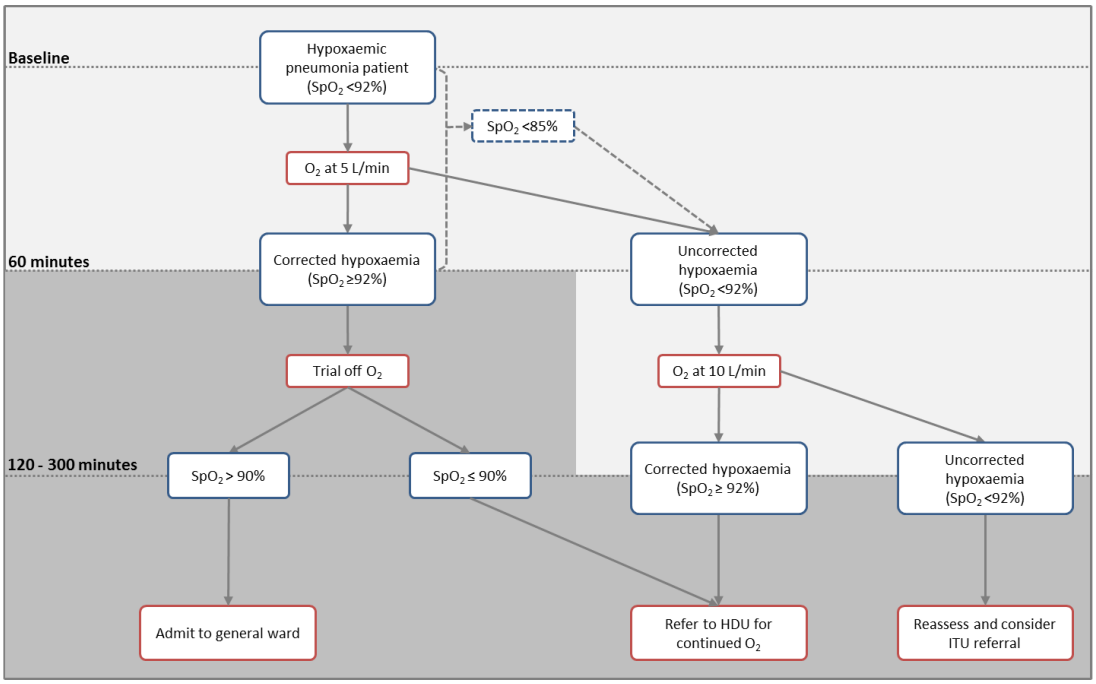

Figure 6.1 Overview of AHIP study oxygen delivery procedures. Light shaded areas indicate study monitoring period; darker areas indicate post-intervention management. SpO_2 – oxygen saturation

6.4.7.5 Ancillary management

Study participants were managed in accordance with local guidelines for severe pneumonia as resources permitted. Antibiotics were administered promptly following recruitment: either once daily intravenous ceftriaxone 2g or alternatively penicillin 2 megaunits intravenously and chloramphenicol 500mg intravenously four times daily. If there was evidence of shock (systolic blood pressure <90 mmHg, heart rate >100 beats/minute, capillary refill time >2 seconds) 1 litre of intravenous crystalloid fluid (Ringers lactate or 0.9% saline) was given over 30-60 minutes. Additional fluids were given at the discretion of the treating clinician.

6.4.7.6 Continued inpatient care and follow-up

After the acute response to supplemental oxygen was determined, patients were referred to the clinical teams for subsequent care. Local guidelines at QECH use a SpO_2 threshold of <90% for continued oxygen provision on the medical high-dependency units (HDUs). Previous operational research at QECH has shown that the demand for

supplemental oxygen considerably exceeds supply (Evans *et al.*, 2012). Patients who had responded to standard flow-rate oxygen who had SpO_2 ≥92% on 5 L/min or less were trialled off oxygen for up to 60 minutes (see figure 6.1). If SpO_2 fell to below 90%, oxygen was re-commenced and the patients referred to HDU for continued oxygen therapy. Patients with SpO_2 ≥90% were admitted to the general medical wards. To improve the availability of supplemental oxygen, the study provided one high flow oxygen concentrator for each of the two medical HDUs. Patients were followed to determine hospital discharge date and outcome.

6.4.7.7 Concentrator assessment and maintenance

The oxygen concentrators were maintained in accordance to the manufacturer's instructions. External cleaning was performed and the gross particulate filter was cleaned and replaced at weekly intervals. The flow-rate, oxygen concentration and outlet pressure of the gas delivered was also checked using a flowmeter and oxygen analyser (Invacare Check O_2 Plus Oxygen Analyzer; Invacare, Ohio, USA). If any measurements were outside of manufacturer's recommended tolerances, the concentrators were withdrawn from service and sent for maintenance.

6.4.7.8 Clinical specimen processing

All specimen processing and investigations were performed at MLW Clinical Diagnostic and Molecular Laboratories. Clinical diagnostic tests were performed in the MLW quality assured laboratories. HIV testing was performed on whole blood specimens using rapid diagnostic test kits in a serial testing pathway in accordance with WHO guidelines (World Health Organization, 2004). Initial screening was performed using the Alere Determine HIV-1/2 Ag/Ab Combo assay (Alere, Massachusetts, USA); negative results were reported and positive results prompted confirmatory testing using the Uni-Gold Recombinogen HIV-1/2 test (Trinity Biotech, Co Wicklow, Ireland). If results were discrepant a second confirmatory test was performed using a different assay (Bioline HIV-1/2 3.0; Standard Diagnostics, Gyeonggi-do, Republic of Korea).

6.4.7.9 Chest radiograph photography

Plain chest radiograph films were photographed on a light-box using a standard light-reflex digital camera mounted on a tripod in a darkened room. Several high-resolution photographs at a range of exposure settings were taken of each radiograph to compensate for some of the variability in penetration of the original radiograph. All study radiograph reports were generated by review of the set of digital images rather than the original radiograph. Chest radiographs were reported by myself to define the presence of consolidation, multilobar involvement, cavitation and pleural effusion.

Radiographic pneumonia was defined as the presence of a parenchymal abnormality (consolidation or other infiltrate) or pleural effusion (Jain *et al.*, 2015).

6.4.8 Data management

Study participants were assigned a unique study number at the time of recruitment, under which all data were captured. The clinical data were collected in paper-based CRFs and subsequently converted to electronic form using Intelligent Character Recognition scanning software (TeleForm; Cardiff Software Developers, Cardiff, UK). Following verification the data were initially exported to a Microsoft Access database (Microsoft Corporation, Redmond, Washington, USA) and subsequently to Stata 12 (StataCorp LP, College Station, Texas, USA) for cleaning and analysis.

Prior to scanning the CRFs were checked by the clinical team and again by Dr Jacqueline Huwa. Discrepancies were queried and addressed. The TeleForm software automatically scans each CRF twice; any discrepant values or values outwith a range pre-specified by the user are highlighted for manual review. Further certain essential fields containing, for example, identifiers or key outcome variables were set for mandatory manual review.

The study database was hosted on the secure MLW server; access was restricted to Dr Jacqueline Huwa, the MLW data management and myself. The corresponding paper records were held securely at MLW in a locked office. These records were pseudo-anonymised, identifiable by study number and initials only.

6.4.9 Analysis

6.4.9.1 Sample size considerations

The proportion of patients that attain normoxaemia with 5 L/min of supplemental oxygen is unknown. As there was no preliminary or background data on which to base calculations, the study constituted a pilot. The initial target study population was 150 patients. This sample size was selected to enable the true population proportion of patients that respond to standard flow-rate oxygen to be estimated with a precision of ±8% and 95% confidence, assuming that a treatment response rate of approximately 50%. An estimated 75 patients would therefore receive high-flow oxygen; the proportion that respond to treatment would be estimated with a precision of ±12% and 95% confidence, again assuming a treatment response rate of approximately 50%.

6.4.9.2 Statistical methods

The proportion of patients (with 95% confidence intervals) that attain normoxaemia with standard flow-rate and high flow-rate oxygen was calculated. The primary analysis included the entire cohort of patients with suspected pneumonia. Subgroup analyses of patients with SpO_2 <90% and radiographically confirmed pneumonia were performed. The demographic, comorbid and radiological characteristics of patients that attain and failure to attain normoxaemia was compared Mann Whitney U test and Chi-squared test for continuous and categorical variables, respectively. The association between response to oxygen therapy and hospital outcome was described by risk ratio (with 95% confidence intervals) and assessed using the Chi-squared test. *P* values less than 0.05 were regarded as significant.

6.5 Results

6.5.1 Recruitment and follow-up

Patients were recruited between 25th November 2014 and 17th July 2015 (Figure 6.2). 142 patients were assessed for inclusion in the study. Recruitment to the MARISO study closed on 31st January 2015; during this period of overlap, 6 patients were screened and 2 recruited to the current study. The commonest reasons for non-inclusion were illness duration of greater than 21 days, lack of focal chest signs and lack of accompanying patient guardian. The eligibility criteria for the study were re-evaluated in the light of a slow recruitment rate. The requirement for the presence of focal clinical signs was removed from 1st June. This is relevant to the last 40 patients screened and the last 20 patients recruited. However only 2 patients lacking focal signs were in fact recruited. Following a review by the ethics committee, the requirement for an accompanying guardian to be available to give proxy consent for the patient to be recruited was removed. 60 patients were recruited, but one was excluded from analysis because SpO_2 immediately prior to starting oxygen was >92%.

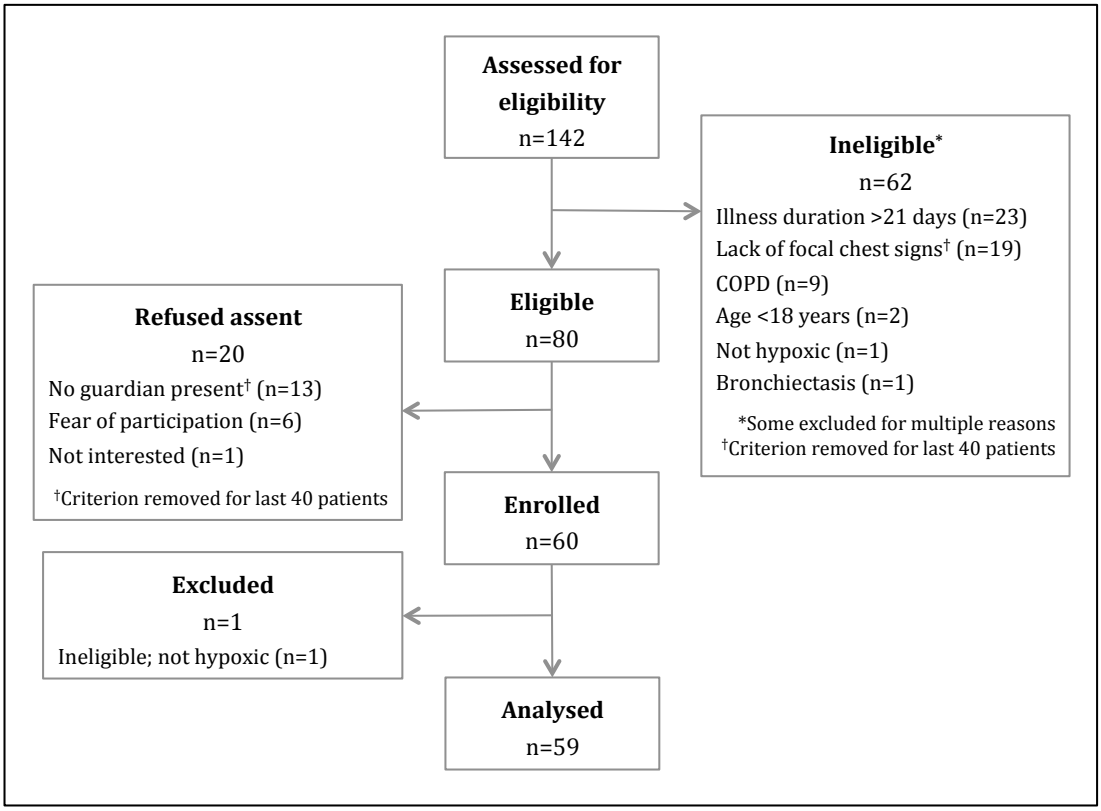

Figure 6.2 CONSORT diagram of patient screening, recruitment and follow-up in AHIP study.

6.5.2 Baseline characteristics

The median age of the 59 patients recruited was 38 (IQR: 31-59) and there was a preponderance of males (39/59; 66.1%) (Table 6.1). 37 (64.9%) were HIV-infected, of whom 27% were newly diagnosed. There was a high rate of both antiretroviral therapy (25/27; 92.6%) and co-trimoxazole prophylactic therapy use (23/27; 85.2%) amongst known HIV-infected patients. 11 patients (18.6%) were active smokers, but no patients had a prior diagnosis of chronic lung or heart disease. A quarter of patients (15/59; 25.4%) reported prior treatment for tuberculosis.

Table 6.1 Baseline characteristics of AHIP patient cohort. Data presented as number and proportion of total episodes or in *italics* as median and interquartile range are shown. Denominator is 59 unless specified.

Characteristic	No. (%) of episodes
Demographics	
Male sex	39 (66.1)
Age	*38 (31-59)*
Current smoker	11 (18.6)
Comorbidities	
HIV positive	37/57 (64.9)
Newly diagnosed[a]	10/37 (27.0)
ART use[a]	25/37 (67.6)
CPT use[a]	23/37 (62.2)
Chronic lung disease[b]	0 (0)
Chronic heart disease[c]	0 (0)
Hypertension	2 (3.4)
Diabetes	0 (0)
Cancer	2 (3.4)
Chronic kidney disease	0 (0)
Liver disease	0 (0)
Stroke	1 (1.7)
Epilepsy	0 (0)
Dementia	1 (1.7)
Previous tuberculosis[d]	15 (25.4)
Previous pneumonia in last 5 years[e]	18 (30.5)

ART – antiretroviral therapy; CPT – co-trimoxazole preventative therapy

[a] Only applies to HIV-positive patients

[a] Chronic lung disease includes asthma, COPD and bronchiectasis.

[b] Chronic heart disease includes heart failure, cor pulmonale, dilated cardiomyopathy and ischaemic heart disease.

[c] Any previous episode of treated tuberculosis regardless of site and confirmation.

[d] Any prior episode within the last 5 years of a syndrome compatible with lower respiratory tract infection reviewed in a healthcare facility and treated with antibiotics.

Characteristic	No. (%) of episodes *Median (IQR)*
Pneumonia-related characteristics	
Pre-admission symptom duration	*14 (7-21)*
Prior antibiotics	40 (67.8)
Inability to stand	27 (45.8)
Confusion	0 (0)
Temperature (°C)	*37.8 (37.0-39.0)*
<35 or ≥40	2 (3.4)
Systolic blood pressure (mmHg)	*103 (88-120)*
<90	18 (30.5)
Diastolic blood pressure (mmHg)	*66 (55-82)*
≤60	24 (40.7)
Heart rate (beats/min)	*120 (110-135)*
≥125	28 (47.5)
Respiratory rate (breaths/min)	*40 (36-47)*
≥30	55 (93.2)
Oxygen saturations (%)	*87 (81-89)*
<90	52 (88.1)
Haemoglobin (g/dL)	*10.4 (7.8-11.8)*
<8	15/57 (26.3)
WBC count (x 10^9 cells/L)	*7.1 (5.0-9.5)*
<4 or >15	15/56 (26.8)
Platelets (x 10^9 cells/L)	*215 (126-337)*
<100	9/57 (15.8)
Radiographic pneumonia	44/48 (91.7)
Multilobar consolidation	26/48 (54.2)
Cavitation	5/48 (10.4)
Effusion	16/48 (33.3)
MOST ≥2	55/59 (93.2)
CRB65 ≥2	30/58 (53.4)
SMRT-CO ≥2	46/58 (96.6)

CRB65 – tool based on confusion, urea, blood pressure and age ≥65; MOST – tool based on male sex, oxygen saturations, inability to stand and tachycardia; SMRT-CO – tool based on systolic blood pressure, multilobar consolidation, respiratory rate, tachycardia, confusion and oxygenation; WBC – white blood cell;

The median duration of symptoms prior to presentation was 14 days (IQR: 7-21) and 40 patients (67.8%) had received prior antibiotics. Interpretable chest radiographs were available in 48 patients (81.4%), of whom 44 (91.7%) had radiographic evidence of pneumonia, with multilobar consolidation present in just over half (26/48; 54.2%).

Median oxygen saturation in room air just prior to the commencement of supplemental oxygen was 87% (IQR: 81-89%). Tachypnoea was common and marked; 55 patients (93.2%) had a respiratory rate of 30 breaths per minute or greater. Using the validated severity assessment tools SMRT-CO and CRB65 at standard thresholds, 46 (96.6%) and 30 (53.4%) patients, respectively, were classified as having severe pneumonia.

6.5.3 Response to supplemental oxygen

51 patients (86.4%; 95% CI: 75.0%-94.0%) attained SpO_2 ≥92% within the first 60 minutes of supplemental oxygen at standard flow-rate (up to 5 litres per minute) (Table 6.2). In one patient, the study intervention was interrupted by an electrical power-cut. The patient was classified as responding to standard flow-rate oxygen on the basis of rapid and sustained correction of SpO_2 from the point of oxygen delivery to 50 minutes. Over the course of 60 minutes of standard flow-rate supplemental oxygen the average change in SpO_2 was 10.3% (SD ±5.6%); the mean maximal change was 12.1% (SD ±5.3%). Amongst the 52 patients that had baseline SpO_2 <90%, 44 (84.6%; 95% CI: 71.9-93.1) attained normoxaemia with standard flow-rate oxygen. 48 patients (81.4%; 95% CI: 69.1.0%-90.3%) attained SpO_2 ≥94% (an alternative more stringent definition of normoxaemia) at 60 minutes.

The 8 patients failing to attain SpO_2 ≥92% on standard flow-rate oxygen received high flow-rate oxygen (up to 10 L/min). 7 patients (87.5%: 95%CI: 47.3%-99.7%) attained stable normoxaemia during the four-hour observation period, including 4 patients (50%; 95%CI: 15.7%-84.2%) within the first hour.

Of the 44 patients with radiographic pneumonia, 41 (93.2%; 95% CI: 85.4%-100%) attained SpO_2 ≥92% within 60 minutes of standard flow-rate oxygen. The remaining 3 patients all attained normoxaemia with high flow-rate oxygen.

52 patients used oxygen delivered by facemask throughout the standard-flow rate intervention period. 2 patients used nasal cannulae throughout the first hour, a further 2 for at least 45 minutes and a further 3 for between 5 and 15 minutes. All of these patients attained normoxaemia with standard flow-rate oxygen. Average change in SpO_2 at 60 minutes did not differ between patients using facemasks and nasal cannuale

(11.2% *vs.* 9.6%; $P = 0.96$). All patients who failed standard flow-rate oxygen were switched to high flow-rate oxygen via facemask.

Inability to stand (RR 8.30; 95% CI 1.09-63.28) and lower SpO_2 at presentation ($P < 0.001$) were associated with lack of response to standard flow-rate oxygen (Table 6.3). The small size of the cohort precludes multivariable analysis to further examine the correlates of oxygen response.

Table 6.2 Response to supplemental oxygen. All patients received standard flow-rate oxygen (≤5 L/min); only patients not attaining oxygen saturations (SpO_2) ≥92% received high flow-rate oxygen (≤10 L/min). Patients observed at standard flow-rate for up to 60 minutes and high flow rate for up to 4 hours.

Standard flow-rate (≤5 L/min	**(All patients; n=59)**
Baseline SpO_2 (median(IQR))	87 (81-89)
SpO_2 ≥92% at 60 mins (n(%))	51 (86.4)
Average Δ SpO_2 (mean±SD)	10.3 ±5.6
Max Δ SpO_2 (mean±SD)	12.1 ±5.3
High flow-rate (≤10 L/min)	**SpO_2 ≥92% after standard flow-rate; n=8)**
Baseline SpO_2 (median(IQR))	82 (80-91)
SpO_2 ≥92% at 60 mins (n(%))	4 (50)
Final SpO_2 ≥92% (n(%))	7 (87.5)
Average Δ SpO_2 (mean±SD)	5.7 ±3.9
Max Δ SpO_2 (mean±SD)	10.8 ±6.6

Δ – change in; IQR – interquartile range; SD – standard deviation; SpO_2 – oxygen saturations

Table 6.3 Univariable analysis of features associated with attainment of normoxaemia with standard flow-rate supplemental oxygen. Categorical variables shown as number and proportion; continuous variables (in *italics*) shown as median and interquartile range. Denominators as per columns heads unless otherwise specified. Univariable analysis by Chi-squared test with risk ratios and 95% confidence intervals for categorical variables and Mann Whitney U test for continuous variables.

Characteristic	Attained normoxaemia (n=51)	Normoxaemia not attained (n=8)	Univariable analysis	
			RR (95% CI)	*P*
Male sex	33 (64.7)	6 (75)	1.54 (0.34-6.94)	0.57
Age (yrs)	*38 (30-59)*	*41 (33-66)*	-	*0.61*
Current smoker	10 (19.6)	1 (12.5)	0.62 (0.09-4.56)	0.63
HIV-positive	32/49 (65.3)	5 (62.5)	0.90 (0.24-3.39)	0.88
Inability to stand	20 (39.2)	7 (87.5)	8.30 (1.09-63.28)	0.01
Symptom duration (days)	*14 (7-21)*	*11 (3-18)*	-	*0.26*
Systolic BP (mmHg)	*103 (89-120)*	*93 (78-113)*	-	*0.21*
Diastolic BP (mmHg)	*67 (54-82)*	*66 (60-84)*	-	*0.74*
Heart rate (/min)	*119 (109-132)*	*133 (143-141)*	-	*0.32*
Respiratory rate (/min)	*40 (36-47)*	*40 (34-53)*	-	*1.00*
Oxygen saturations (%)	*88 (84-89)*	*78 (76-82)*	-	*<0.001*
Haemoglobin (g/dL)	*10.7 (8.2-12)*	*9.6 (5.9-12.2)*	-	*0.62*
Multilobar consolidation	24/44 (54.6)	2/4 (50)	0.85 (0.13-5.52)	0.86

BP – blood pressure

6.5.4 Mortality

All patients were successfully followed to determine hospital discharge outcome. The overall in-hospital mortality rate was 17.0% (10/59). The acute response to supplemental oxygen was associated with in-hospital mortality. Failure to attain normoxaemia with standard flow-rate oxygen therapy was associated with a more than four-fold increase in the risk of death (4/8 (50%) *vs.* 6/51 (11.8%); RR 4.25; 95% CI: 1.53-11.81).

The simple four-parameter MOST score (based on male sex (1 point), oxygen saturations <90% (2 points), inability to stand (2 points) and heart rate ≥125 /min (1 point)) derived in the MARISO score was calculated for all patients. In-patient mortality rate increased with MOST score (MOST 0: 0/1 (0%); 1: 0/3 (0%); 2: 0/6 (0%); 3: 1/17 (5.9%); 4: 3/10 (30%); 5: 4/13 (30.8%); 6: 2/9 (22.2%)). The overall discriminative capability of the MOST score for the prediction of in-hospital mortality as assessed by area under the receiver-operating curve (AUROC) was 0.71 (95% CI: 0.57-0.85). Using a MOST score of 2 or more (present in 52 (93.2%) patients) to predict in-hospital mortality had the following characteristics: sensitivity 100% (95% CI: 69.2-100), specificity 8.2% (95% CI: 2.3-19.6), positive predictive value 18.2% (95% CI: 9.1-30.9), negative predictive value 100% (95% CI: 39.8-100).

6.5.5 Oxygen concentrator performance

A single oxygen concentrator was used for the study. Oxygen concentration always exceeded manufacturer's minimum specifications; minimum concentration at 5 L/min was 94.8% (specification: 92% +3.5%/-3%) and 10 L/min was 95.1% (specification: 90% +3.5%/-3%). Flow-rate was consistently accurate to within ±10%. Outlet pressure was always within ±15% of 20 PSI.

6.6 Discussion

6.6.1 Main findings

In this study of adults with clinically-suspected pneumonia in Malawi, hypoxaemia is correctable in a large majority of patients using supplemental oxygen delivered by oxygen concentrator at flow-rates of up to 5 L/min. Attainment of normoxaemia is associated with a markedly reduced risk of mortality.

Whilst previous research on supplemental oxygen provision in low-resource settings has largely focused on programmatic aspects such as assessing the capacities and relative costs of different oxygen delivery systems (Hill *et al.*, 2009; Howie *et al.*, 2009;

2011a), this study provides individual patient-level data to demonstrate the effectiveness of supplemental oxygen provision at flow-rates and concentrations achievable by oxygen concentrator to correct hypoxaemia in adults with pneumonia.

6.6.2 Hypoxaemic respiratory failure in pneumonia

Pneumonia is characterised by the presence of intra-alveolar consolidation that impairs ventilation to affected lung areas resulting in a ventilation-perfusion mismatch and reduced gas exchange across the alveolar surface. In lung areas with dense consolidation and focal collapse, there is no effective ventilation and the extreme ventilation-perfusion mismatch is termed an intra-pulmonary shunt. Supplemental oxygen increases intra-alveolar oxygen concentration in ventilated areas of the lung, resulting in a steeper gradient for diffusion, increased gas transfer and arterial oxygen content (Gea *et al.*, 1991). However, since blood oxygen content is largely haemoglobin bound, increased oxygen transfer in ventilated lung units cannot fully compensate for non-ventilated areas. In the presence of a large intra-pulmonary shunt, hypoxaemia is not correctable with supplemental oxygen alone; improved oxygenation requires re-recruitment of non-ventilated areas of lung using, for example, positive pressure ventilation (Cosentini *et al.*, 2010; Ferrer *et al.*, 2012; Gea *et al.*, 1991; O'Driscoll *et al.*, 2008; Wijesinghe *et al.*, 2012).

In the current study, 86% of hypoxaemic pneumonia patients attained SpO_2 ≥92% with modest rates of supplemental oxygen. Few studies from sub-Saharan Africa have consistently reported and recorded SpO_2. In a cohort of patients with suspected pneumonia admitted to a high-dependency unit in Malawi, Hartung described mean SpO_2 of 76% but did not describe the response to oxygen therapy (Hartung *et al.*, 2011). In Ugandan suspected pneumonia cohort, 16.4% of patients had SpO_2 <90% at presentation and were at 2-fold increased risk of death, but again acute response to oxygen was not described (Koss *et al.*, 2015).

Data from well-resourced settings on oxygen response are also sparse. In settings where piped oxygen infrastructure is standard in acute hospitals and supplemental oxygen at high flow-rates is routinely available, there is no necessity to describe effectiveness of supplemental oxygen delivered at the modest flow-rates achievable by oxygen concentrator. In recent cohorts of hospitalised community-acquired pneumonia (CAP) patients, the rates of acute hypoxaemic respiratory failure vary with the definition used, but typically range from 25-40% (Chalmers *et al.*, 2011a; Charles *et al.*, 2008b; Fine *et al.*, 1997a; Lim *et al.*, 2000). Taking mechanical ventilation as a conservative indication of failure of response, between 14 and 60% of CAP patients

with acute hypoxaemic respiratory failure require an intervention beyond supplemental oxygen alone (Brambilla *et al.*, 2014; Confalonieri *et al.*, 1999; Kohno *et al.*, 2013).

Variations in the definitions of respiratory failure and the endpoints used to indicate lack of improvement make direct comparisons across cohorts difficult. Nonetheless, the rate of responsiveness to supplemental oxygen at modest flow rates observed in the current study is relatively high. The SpO_2 threshold of <92% used to define entry to the current study is a less stringent definition of respiratory failure compared to other studies (Brambilla *et al.*, 2014; Confalonieri *et al.*, 1999; Kohno *et al.*, 2013). However, a similar rate of response to standard flow-rate oxygen was seen in the subgroup of patients with SpO_2 <90% at presentation. Other studies also have used a higher threshold of SpO_2 ≥94% to define normoxaemia. More than 80% of patients attained this higher threshold with standard flow-rate oxygen.

6.6.3 Strategies for oxygen delivery in low-resource settings

In the absence of onsite oxygen generation and a piped oxygen infrastructure, the options for the delivery of supplemental oxygen in low-resource setting are oxygen cylinders and oxygen concentrators (Hill *et al.*, 2009; Howie *et al.*, 2009; 2011a). Whilst oxygen cylinders may be better suited to low-volume users (e.g. local health centres), particularly in settings where the electrical supply is inconsistent, the costs and logistical challenges of continually replenishing a large stock of cylinders make them less suitable for district and central hospitals (Hill *et al.*, 2009; Schneider, 2001). In hospital settings where the electrical power supply is consistent, oxygen concentrators provide the cheapest and most consistent source of oxygen (Duke *et al.*, 2010a; Duke *et al.*, 2010b; Duke *et al.*, 2010c; La Vincente *et al.*, 2011; Matai *et al.*, 2008).

Oxygen concentrators vary considerably in performance characteristics (e.g. maximum flow rate, maximum oxygen concentration) and tolerances (i.e. for temperature and humidity). The current study used AirSep NewLife Intensity 10 concentrators based on their ability to operate adequately at temperatures of up to 40°C and relative humidity of up to 95%. In rigorous independent testing, the predecessor concentrator produced by the same manufacturer (AirSep Elite) was judged most suitable for use in low-resource tropical settings (Peel *et al.*, 2013). Experience with the AirSep NewLife Intensity 10 over the course of the study would support its suitability for use in Malawi and comparable settings. The study concentrators performed consistently within the manufacturers specifications for oxygen concentration production, gas flow-rate and outlet pressure. Regular maintenance, simply consisting of replacement of the external

particulate filter and external cleaning, was performed readily by the study team after minimal training.

The AirSep NewLife Intensity 10 concentrator was also selected because of its ability to produce greater than 90% oxygen at flow-rates of up to 10 L/min. Most other concentrators have a maximum output of 5 L/min. Due to the small size of the study and the greater than anticipated rate of response to standard flow-rate oxygen, no conclusions can be made regarding any additional benefit of high-flow concentrators in this setting for adults with pneumonia and whether their additional cost over standard flow-rate devices is justified.

6.6.4 Will correction of hypoxaemia improve outcome?

In adults with pneumonia the presence of hypoxaemia is an indicator of severe disease and is consistently associated with poor outcome (Bowton *et al.*, 1994; Fine *et al.*, 1996; Lim *et al.*, 2003). The results of the MARISO cohort that prompted the instigation of the current study clearly identified hypoxaemia as independently predictive of 30-day mortality amongst Malawian adults with pneumonia. The results of the current study demonstrate that hypoxaemia is correctable using an intervention that is a feasible in low-resource settings. The extent to which this may alter clinical outcome needs to be determined.

Whilst the administration of oxygen to acutely hypoxaemic patients is an established component of emergency care (Duke *et al.*, 2010a), there is little empirical data available that directly defines the indications for and therapeutic benefit of supplemental oxygen (O'Driscoll *et al.*, 2008). For example, there are no randomised trials that define the risks and benefits of oxygen therapy in pneumonia (Wijesinghe *et al.*, 2012). The optimal target range for normoxaemia is not firmly established. WHO advocates using SpO_2 <90% as the definition of hypoxaemia and the trigger to prompt use of oxygen since there is no known risk of hypoxic tissue injury above this level (Bowton *et al.*, 1994; Fulmer *et al.*, 1984; O'Driscoll *et al.*, 2008; World Health Organization, 2011a). British guidelines suggest that oxygen be administered to maintain SpO_2 in a target range of 94-98% to give a wide margin of safety above the 90% threshold.

The potential adverse effects of supplemental oxygen are increasingly being appreciated. In vulnerable patients such as those with advanced COPD or chest wall deformities excessive supplemental oxygen may lead to hypercapnic respiratory failure. Excessive supplemental oxygen has been associated with increased peripheral vascular resistance, coronary artery vasoconstriction, and reduced coronary blood flow

and worsened outcome following myocardial infarction and stroke (Martin *et al.*, 2013; O'Driscoll *et al.*, 2008; Ronning *et al.*, 1999; Wijesinghe *et al.*, 2009). In mechanically ventilated patients, excessive supplemental oxygen may worsen lung injury and ARDS through the production of reactive-oxygen species. These findings underline the need for further clinical trials to define the optimal target ranges for oxygenation in acutely unwell patients (O'Driscoll *et al.*, 2008).

6.6.5 Strengths and limitations

This study is the first to provide individual patient-level data on the effectiveness of oxygen delivery by concentrator in adults with pneumonia in a low-resource setting. It demonstrates that hypoxaemia is correctable in most adults with pneumonia using the relatively modest rates of flow deliverable by an oxygen concentrator. The successful installation, use and maintenance of the oxygen concentrators following minimal staff training supports the feasibility of programmes to improve supplemental oxygen availability based on the use of oxygen concentrators.

The definition of hypoxaemia and assessment of response to supplemental oxygen therapy was based entirely on the measurement of arterial oxygen saturation by pulse oximetry (i.e. SpO_2). In low-resource settings, pulse oximetry is strongly advocated as a robust, affordable and non-invasive means of rapidly assessing oxygenation (Duke *et al.*, 2010a). However, the accuracy of pulse oximetry may be considerably reduced when peripheral perfusion is poor as in hypotension or hypovolaemia (O'Driscoll *et al.*, 2008). In patients with marked anaemia – which was common in the study cohort – SpO_2 may give a misleadingly high estimate of blood arterial content. Whilst arterial blood gas analysis would have provided a more accurate estimation of blood oxygen content, it is expensive, invasive and not widely available in low-resource settings (Duke *et al.*, 2009; Weber *et al.*, 1998; World Health Organization, 2011a).

In isolation, attainment of SpO_2 above a threshold values is not necessarily an informative endpoint about the clinical effectiveness of oxygen therapy. Recent studies from well-resourced settings looking at the benefit of techniques of non-invasive ventilation in hypoxaemic respiratory failure have used mechanical ventilation or composite criteria of requirement for mechanical ventilation as endpoints that are more readily translatable into clinical practice (Brambilla *et al.*, 2014; Confalonieri *et al.*, 1999). Although in resource-limited contexts with minimal intensive care unit capacity, a mechanical ventilation endpoint is unlikely to be relevant. Ultimately, studies capable of detecting a survival benefit of different oxygen use strategies are needed.

6.6.6 Future research

The results of the current study indicate the potential benefit of improved oxygen delivery infrastructure based on oxygen concentrators in adult pneumonia. Randomised clinical trials powered to detect a reduction in mortality are required to confirm this finding. Since the correction of hypoxaemia is generally considered a fundamental component of clinical care in pneumonia, a cluster-randomised or step-wedge trial would be the most robust and ethically appropriate study design.

The beneficial effect of correcting hypoxaemia is presumed to relate to improved tissue oxygen delivery. Since pneumonia is frequently complicated by systemic sepsis in which tissue perfusion is impaired, the effect of improved oxygen provision would need to be assessed in parallel with strategies to optimise fluid resuscitation (Aliberti *et al.*, 2014a; Ferrer *et al.*, 2012).

6.7 Conclusions

Hypoxaemia in pneumonia is correctable in the majority of patients using simple oxygen delivery equipment that can be readily installed with minimal infrastructural change. Response to oxygen therapy predicts hospital discharge outcome; failure to attain normoxaemia with an oxygen flow-rate of 5 L/min or less is strongly associated with mortality. As a potentially reversible risk factor for mortality, improved correction of hypoxaemia is an important potential strategy to improve outcomes in adults with pneumonia in Malawi and similar low-resource settings. Large-scale clinical trials are required to determine the clinical benefit of increased oxygen provision and to inform the expansion of oxygen delivery systems.

7 Overall discussion: Improving outcomes of community-acquired pneumonia in Malawi

7.1 Introduction

Community-acquired pneumonia (CAP) is a leading cause of adult hospitalisation and death throughout the world (Lopez *et al.*, 2006; Lozano *et al.*, 2012). CAP may be caused by a broad range of pathogens and varies in severity from a mild, short-lived illness to an acute, fulminant disease complicated by respiratory failure and sepsis (Welte *et al.*, 2012). Effective management of CAP consists of an accurate assessment of disease severity followed by prompt initiation of appropriate empirical antimicrobials (National Clinical Guideline Centre, 2014). These components, in turn, depend upon an awareness of the key prognostic factors that predict adverse outcome and knowledge of the prevailing causal pathogens based on local epidemiology. In sub-Saharan Africa, as in the rest of the world, CAP is a major cause of morbidity and mortality with an estimated 4 million episodes each year, resulting in 200,000 deaths (Scott *et al.*, 2012). However, the key determinants of poor outcome and the aetiology of disease in the region are both poorly described and as such the evidence required to support appropriate local management guidelines is lacking (World Health Organization, 2011c; Zijlstra, 2006).

The focus of the work presented in this thesis concerns the assessment and management of CAP in adults in Malawi where it is a leading cause of hospitalisation and death (SanJoaquin *et al.*, 2013). In this final chapter I discuss how the results of the studies presented in this thesis may be applied to improve the outcome of CAP in Malawi and comparable resource-limited, HIV-prevalent settings. Firstly, I briefly summarise and evaluate the results of the three component studies: the systematic review of CAP aetiology and outcome in sub-Saharan Africa; the Malawian Adult Lower Respiratory Tract Infection Severity, Aetiology and Outcome (MARISO) study; the Addressing Hypoxaemia in Adult Pneumonia in Malawi (AHIP) Study. I then discuss the relevance of the results with respect to CAP prevention, severity assessment, antimicrobial treatment and supportive management before suggesting key priorities for future research.

7.2 Main results

The systematic review included data from 47 studies conducted in 15 sub-Saharan African countries between 1968 and 2014. The major reported burden of CAP was in young (mean age 38; 95% CI: 36-40) and HIV-positive (52%; 95% CI: 41-63) patients.

Other comorbid illness was poorly described but relatively infrequent: chronic lung disease present, 9%; heart disease, 3%. The overall mortality rate for hospitalised patients was 9.5% (95% CI: 6.3-11.6%). Data describing risk factors for mortality, particularly from studies with a low risk of bias, were limited and meta-analysis restricted to a small number of studies. Hypotension (OR 4.55; 95% CI: 2.40-8.66) and multilobar consolidation (OR 3.54; 95% CI: 1.61-7.41) were associated with mortality. No significant association HIV with mortality was found (OR 1.43; 95% CI: 0.92-2.22). Aetiological data were mainly based on sputum microscopy and blood and sputum culture with limited use of invasively obtained lower respiratory tract specimens or modern molecular diagnostics. *Streptococcus pneumoniae* (27%) and *M. tuberculosis* (19%) were the most commonly identified causes. *Pneumocystis jirovecii* was identified in 2-27% of patients in studies performing suitable investigations. Data on viral or atypical bacterial causes of CAP were limited.

The systematic review highlighted the need for large prospective studies of CAP in sub-Saharan Africa to better describe its epidemiology and aetiology and to define the risk factors for adverse outcome. The MARISO study was a prospective observational study of adult hospitalised with clinically diagnosed CAP conducted in Blantyre, Malawi and is amongst the largest studies of acute CAP in sub-Saharan Africa ever conducted. Of the 459 patients recruited, 439 (95.6%) and 418 (91.1%) were successfully followed to determine outcome at 30-days and 90-days, respectively. In keeping with findings of the systematic review, the MARISO cohort was predominantly young (median age 34.6; IQR 29.6-41.9) and HIV positive (78.4%), with limited chronic cardiovascular (0.7%) and pulmonary comorbidity (3.3%). HIV was typically advanced (median CD4 count 99; IQR 44-193) and often undiagnosed (34.9% new diagnosis) at presentation.

Using a combination of blood culture, pneumococcal urinary antigen testing, multiplex PCR on nasopharyngeal aspirate and TB diagnostic tests on sputum and pleural fluid, a potentially causal organism was identified in 61% of patients. *S. pneumoniae* was found in 21%. A sputum specimen for TB diagnostics was obtained in 71% with a positive result in 23%. Viral infection was common, with influenza (9%), adenovirus (8%) and coronavirus (7%) most frequently identified. *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* together were found in fewer than 2%. Co-infection with multiple organisms was identified in 22% with the combination of a bacterial viral co-infection most frequently observed (9%).

Radiographic pneumonia was identified in 76% and was positively associated with the detection of *S. pneumoniae* (OR 3.93; 95% CI: 1.86-8.29) and negatively associated with *Salmonella typhi* (OR 0.09; 95% CI: 0.02-0.48) and nontyphoidal *Salmonella* (OR 0.06;

95% CI: 0.01-0.53). The relative abundance of all other aetiologies did not vary significantly with the presence of radiological change. *M. tuberculosis* (19%) and influenza (11%) were the most frequently identified pathogens in the subgroup lacking radiographic pneumonia. Radiographic characteristics did not vary significantly with HIV status.

The 30-day mortality rate in the MARISO cohort was 14.6% with 25% of deaths occurring within the first three days following admission and 48.4% within the first week. Amongst patients surviving to day 30, a further 6.5% died by day 90. Treatment failure at three days defined as death or persistent hypoxaemia, hypotension or fever occurred in 24%. Treatment failure excluding death (i.e. persistent hypotension, hypoxia or fever) was predictive of subsequent mortality (OR 3.45; 95% CI: 1.81-6.58). In multivariable analysis, 30-day mortality was associated with: male sex (aOR 2.57; 95% CI: 1.23-5.39); pre-presentation symptom duration (aOR 1.11 per day increase; 95% CI 1.02-1.20); inability to stand (aOR 4.28; 95% CI: 2.14-8.57); heart rate (aOR 1.02 per beat/minute rise; 95% CI: 1.00-1.04); oxygen saturations (aOR 0.95 per % rise; 95% CI: 0.92-0.98); white cell count (aOR 0.91 per 10^9/L rise; 95% CI: 0.84-0.98); haemoglobin (aOR 0.90 per g/dL rise; 95% CI: 0.80-1.01).

A CAP severity assessment tool based on clinical indices evident at presentation was derived. The simple four parameter MOST score (based on male sex (1 point), oxygen saturations <90% (2 points), inability to stand (2 points) and heart rate ≥125 /min (1 point)) predicted 30-day mortality with reasonable discriminative capability (area under the receiver-operating curve (AUROC) 0.79; 95% CI: 0.73-0.85) and compared favourably with existing tools (CURB65: AUROC 0.60; 95% CI: 0.52-0.67; SMRT-CO: AUROC 0.66; 95% CI: 0.57-0.75). Using a threshold score of <2, the MOST score had a negative predictive value of 95.2% (91.6-97.6) for 30-day mortality. A suggested CAP management algorithm based on MOST score is shown in figure 7.1.

Having identified the prognostic importance of hypoxaemia in preliminary analyses of the MARISO study, the AHIP study was conducted to determine if supplemental oxygen delivery by oxygen concentrator was sufficient to correct hypoxaemia in adults with suspected pneumonia. In this small pilot study of 59 patients, 86.4% attained oxygen saturations (SpO_2) ≥92% with supplemental oxygen at standard flow-rate of 5 litres/minute. Failure to attain normoxaemia with standard flow-rate oxygen therapy was associated with a more than four-fold increase in the risk of death (RR 4.25; 95% CI: 1.53-11.81).

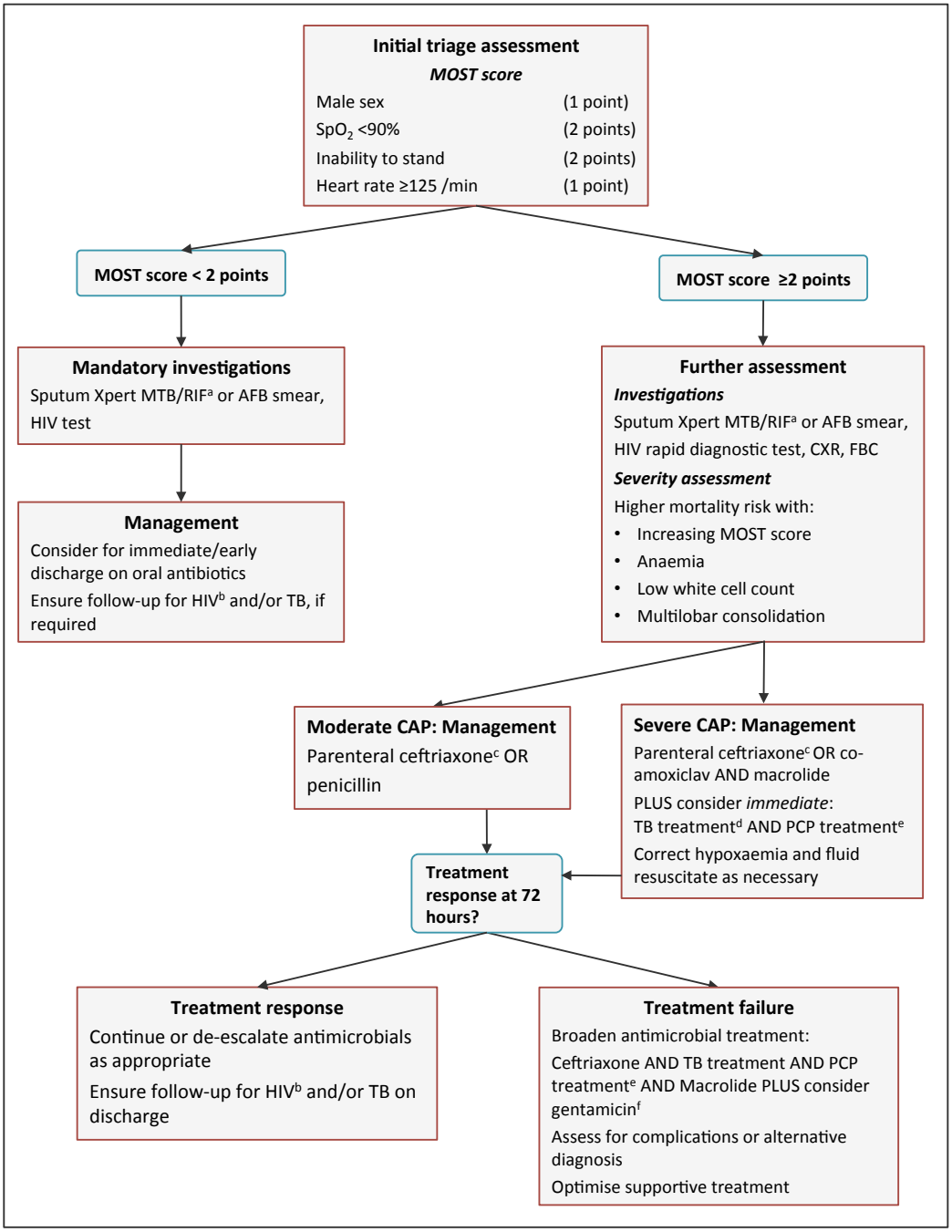

Figure 7.1 Suggested management algorithm for CAP in low-resource, sub-Saharan African setting.

[a] Xpert MTB/RIF preferred when available.
[b] All HIV-positive patients should be started on co-trimoxazole prophylactic treatment and referred to ART clinic on discharge.
[c] Consider risk of invasive nontyphoidal Salmonella in HIV-positive patients.
[d] Risk of TB increased with HIV infection, multilobar consolidation, reticulonodular appearance and mediastinal lymphadenopathy
[e] If HIV-positive
[f] Consider aminoglycoside based on local prevalence of drug resistant Gram-negative pathogens, in particular *Klebsiella pneumoniae.*

7.3 Overall strengths and limitations

The systematic review provides a detailed and comprehensive overview of the published literature describing the aetiology and outcome of CAP in sub-Saharan Africa and sets the MARISO and AHIP studies in a broader context. In contrast to many previous CAP studies from the region, the MARISO study is both large and prospective. Patients were recruited according to a standard clinical case definition reflective of that used in clinical practice in low-resource settings; the demographic and comorbidity profile of the study population was comparable to that described in other sub-Saharan African cohorts indicating that the findings are likely to be generalisable across the region. The panel of microbiological investigations was broad and with the exception of sputum specimens for mycobacterial investigations, specimen collection was reasonably complete. The clinical outcome data is more detailed than previous studies, describing both early endpoints (i.e. treatment failure, clinical stability) and mortality up to 90 days with good follow-up retention. The analysis of risk factors for adverse outcome focuses on clinical parameters measurable with minimal equipment and training that could form the basis of CAP triage assessment in resource-limited settings. The AHIP study is the first to provide individual patient-level data on the effectiveness of oxygen delivery by concentrator to correct hypoxaemia in adults with pneumonia.

There are several important limitations of the MARISO study that are common both to other African CAP cohorts and studies from well-resourced settings. Patients were recruited from a single, urban teaching hospital and as such may not be reflective of the broader CAP population. Certain groups, for example older adults, may be under-represented because of differences in health seeking behaviour or access to care. Recruitment in a secondary care setting also means that the study population is pre-selected in terms of the expected risk of adverse outcome; prognostic factors identified in this setting may not accurately predict individuals at risk of death or deterioration in an unselected, community population. The study does also not provide information on the likely cause of death, particularly for those patients dying after hospital discharge. This information would usefully guide future interventions to target factors associated with preventable mortality. The MARISO study relied on blood, urine, upper respiratory tract and spontaneously expectorated sputum specimens to determine CAP aetiology. As such the burden of TB might be underestimated and the contribution of opportunistic pathogens, in particular PCP, to acute CAP has not been established.

7.4 What strategies can be used to prevent pneumonia in Malawi?

The major burden of CAP in Malawi occurs in patients with potentially reversible immunocompromise and is due to pathogens for which there are either effective vaccines or preventative treatments. Preventative strategies to reduce the impact of CAP are therefore of key importance.

Antiretroviral therapy (ART) markedly reduces the risk of pneumonia and early initiation improves survival (Dworkin *et al.*, 2001; Kohli *et al.*, 2006; Sullivan *et al.*, 2000). The rapid roll-out of ART in sub-Saharan Africa has been a huge public health success with more than 9.1 million started on treatment (World Health Organization, 2014b). In Malawi, the scale up of ART has been associated with a marked decline in both the incidence of bacteraemia overall and invasive pneumococcal disease (IPD) (Everett *et al.*, 2011; Feasey *et al.*, 2014). However, the experience of the MARISO cohort highlights the continued challenges of timely diagnosis and prompt initiation of ART. Mortality is particularly high among adults being assessed for ART initiation, with the majority of deaths occurring in individuals that do not actually start treatment (van Lettow *et al.*, 2012). Across sub-Saharan African, average CD4 cell counts at presentation and ART initiation remain low at 251 and 152 cells/mm^3, respectively (Siedner *et al.*, 2015; World Health Organization, 2015b). The recent shift of WHO policy to recommending universal ART for all HIV-infected patients regardless of CD4 count may be beneficial (World Health Organization, 2015b).

Co-trimoxazole preventative therapy (CPT) continues to reduce the risk of hospitalisation and pneumonia after ART initiation (Suthar *et al.*, 2015). In the MARISO cohort, 20% of known HIV-positive patients did not use CPT. Isoniazid preventative therapy (IPT) also provides an additive benefit over ART, reducing incident TB cases by as much as 43% in high burden settings (Danel *et al.*, 2015; Rangaka *et al.*, 2014; Samandari *et al.*, 2015; Samandari *et al.*, 2011), but to date has been widely underutilised in sub-Saharan Africa. A single fixed-dose pill combining both co-trimoxazole and isoniazid is currently in development (Harries *et al.*, 2015).

In the MARISO cohort, 21% of CAP was attributable to *S. pneumoniae*. Other studies from the region using additional pneumococcal diagnostic tests (e.g. lung aspirate culture (Scott *et al.*, 2000), quantitative nasopharyngeal colonisation density (Albrich *et al.*, 2012)) have identified higher rates. The 13-valent pneumococcal conjugate vaccine (PCV) has proven effectiveness to protect against IPD in HIV-infected patients (French *et al.*, 2010) and pneumococcal pneumonia in elderly adults (Bonten *et al.*, 2015). However, the need for direct vaccination of susceptible adults is unclear. Introduction

of PCV into the routine childhood immunisation schedule in the UK and US, led to large falls in the rates of vaccine-serotype IPD and pneumococcal CAP in adults as a result of indirect protection (i.e. reduced pneumococcal carriage in vaccine recipients leads to reduced pneumococcal transmission to contacts) (Griffin *et al.*, 2013; Waight *et al.*, 2015). Similarly in South Africa, in the three years following the introduction of PCV7 into the routine infant immunization programme, the incidence of vaccine-serotype IPD fell by 57% (HIV-positive, 59%; HIV-negative, 52%) in adults aged 25 to 44 years. The reduction in older adults was less marked or non-significant (von Gottberg *et al.*, 2014). Universal infant pneumococcal vaccination using PCV13 was introduced in Malawi in November 2011 (Bar-Zeev *et al.*, 2015). The extent of indirect effects, particularly in HIV-infected adults, needs careful study to determine whether the burden of residual disease warrants additional targeted vaccination programmes. Preliminary results indicate that HIV-infected adults remain an important reservoir for carriage of both vaccine and non-vaccine serotype pneumococci even amongst those established on ART for several years with apparent immune reconstitution (Heinsbroek *et al.*, 2015; Mwalukomo *et al.*, 2016; Swarthout *et al.*, 2016 [Abstract ID - 367]). Studies from well-resourced settings using recently developed serotype-specific pneumococcal urinary antigen tests that allow the serotype of non-bacteraemic pneumococcal CAP to be defined have shown that the serotype distribution of non-invasive pneumococcal pneumonia may differ from that of IPD and that even several years after PCV introduction, a substantial proportion of adult CAP remains attributable to vaccine serotypes (Bewick *et al.*, 2012; Huijts *et al.*, 2013; Pride *et al.*, 2012; Sheppard *et al.*, 2011; Sherwin *et al.*, 2013). Similar efforts should be made to determine the serotype distribution of pneumococcal CAP in sub-Saharan Africa.

7.5 Optimising severity assessment to stratify CAP management

In the MARISO cohort, male sex, hypoxaemia, inability to stand and tachycardia were independently associated with 30-day mortality. These variables were combined into a severity assessment tool called the MOST score that predicted 30-day mortality with reasonable accuracy as described above. Assuming adequate performance in an external validation pneumonia cohort, the MOST score could be readily used at emergency triage in Malawi to stratify patients into risk groups to guide care.

In well-resourced settings, use of the pneumonia severity index (PSI) to stratify care allows the proportion of patients treated in the community to be safely increased (Aujesky *et al.*, 2008). A similar application would be potentially highly valuable in Malawi both to the patient (e.g. avoidance of nosocomial infection including tuberculosis, reduced lost income for patient guardians) and the healthcare system (e.g.

reduced bed-occupancy and costs). A MOST score of less than 2 had negative predictive value of >95% for 30-day mortality indicating its potential use for identifying low risk patients. Assuming adequate performance in external validation, the clinical impact of the use of the MOST tool to guide early discharge should be assessed in a pragmatic clinical trial in Malawi. A suggested CAP management algorithm based on MOST score is shown in figure 7.1.

Severity assessment tools may alternatively be used to identify the sickest patients most at risk of death or early deterioration. In well-resourced settings, these tools are typically used to guide ICU admission. In a resource-limited context such as Malawi where ICU resources are largely unavailable, the practical use of severity assessment is to identify the group of patients most likely to benefit from early aggressive therapy. The IDSA/ATS 2007 minor criteria have been successfully used in this way. In Singapore, Lim *et al* showed both reduced mortality and ICU admission following introduction of a scheme of targeted early aggressive fluid resuscitation based on IDSA/ATS 2007 minor criteria (Lim *et al.*, 2014).

7.6 Optimal antimicrobial therapy

7.6.1 Antibacterial therapy

Current antimicrobial guidelines for the treatment of severe CAP in Malawi recommend an initial regimen of ceftriaxone or a combination of penicillin plus chloramphenicol, with additional agents added for patients failing to improve at 48 hours (Zijlstra, 2006). The lack of initial combination treatment with a macrolide or fluoroquinolone is at odds with most other international CAP treatment guidelines (Feldman *et al.*, 2007a; Lim *et al.*, 2009; Mandell *et al.*, 2007). In the MARISO cohort, 60% received ceftriaxone and 40% penicillin plus chloramphenicol. No patients received a macrolide from the outset and less than 5% of patients at any point in the admission.

The requirement for atypical bacterial coverage for hospitalised CAP in adults in this setting prior to this study was unclear. The systematic review estimated rates of *Mycoplasma* and *Chlamydophila* of 8% and 2%, respectively, but data were limited. In the MARISO cohort *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* were each present in less than 1% of patients. Based on studies from South African and Kenya, the systematic review estimated the frequency of Legionella at 2%, which is comparable to that described in Europe and North America (Maartens *et al.*, 1994; Mpe *et al.*, 2001; Odera *et al.*, 2009). In the MARISO cohort however, *Legionella* spp. were detected by PCR in 18.5% of nasopharyngeal aspirates. Whilst some geographical variation in the frequency of *Legionella* is described, this result is implausibly high. Environmental

contamination of laboratory water sources leading to false positive *Legionella* PCR results has previously been described and is a possible explanation here (Avni *et al.*, 2016; Pancer *et al.*, 2012). *Legionella* urinary antigen testing on stored specimens is planned to clarify this result before recommendations on the requirement for atypical bacterial coverage are made.

The benefits of dual antimicrobial therapy in severe CAP, particularly β-lactam-macrolide combination, are not limited to those patients with atypical bacterial infection. There is observational data from well-resourced settings that the inclusion of macrolides in initial treatment reduces mortality in severe disease due to all aetiologies (Gattarello *et al.*, 2015; Martin-Loeches *et al.*, 2010; Restrepo *et al.*, 2009; Sligl *et al.*, 2014), particularly pneumococcal pneumonia (Baddour *et al.*, 2004; Gattarello *et al.*, 2014; Waterer *et al.*, 2001b). Potential concerns over the widespread use of macrolides include the emergence of antimicrobial resistance (Wolter *et al.*, 2008) and the risk of cardiac arrhythmias (Ray *et al.*, 2012; Wong *et al.*, 2016). In the context of severe CAP in Malawi with limited access to diagnostic tests to define aetiology, there is equipoise for a clinical trial to determine the benefit of universal or deferred macrolide treatment (Restrepo *et al.*, 2016).

7.6.2 Tuberculosis diagnostics and treatment

The MARISO cohort highlights the huge burden of tuberculosis amongst patients presenting with acute CAP, particularly amongst HIV-infected patients. Tuberculosis was identified in 23% of patients (HIV-positive 25%; HIV-negative 16%) and was independently associated with 30-day mortality and treatment failure. Recent studies from South Africa, Zambia and Malawi similarly estimate that up to one-third of all HIV-positive acute medical inpatients have TB (Bates *et al.*, 2012; Gupta *et al.*, 2015; Lawn *et al.*, 2015). Disseminated, bacteraemic disease is common, occurring in between 6 and 23% of febrile inpatients, (Crump *et al.*, 2012; Feasey *et al.*, 2013; Jacob *et al.*, 2013b; Lewis *et al.*, 2002) and has a mortality rate in excess of 50% with most deaths occurring within the first week of admission (Feasey *et al.*, 2013; Jacob *et al.*, 2013b). Even amongst ambulatory HIV-infected patients seen in outpatient settings, TB remains very common (up to 25%) and is associated with six-month mortality of up to 44% if treatment is delayed (Bedell *et al.*, 2012; van Lettow *et al.*, 2012).

The current approach advocated by the WHO for acutely hospitalised HIV-infected adults with respiratory infection, negative sputum smears and danger signs (i.e. high temperature, tachycardia, tachypnoea, inability to walk unaided) is to first trial broad spectrum antibacterials and if no improvement after 3-5 days start TB treatment

(World Health Organization, 2006). This approach misses 20% of patients with culture positive TB and risks delaying treatment in a group of patients with a high risk of early death (Theron *et al.*, 2014).

Recent advances in TB diagnostics may help facilitate early, accurate treatment. The Xpert MTB/RIF system offers real-world improved sensitivity compared to smear microscopy, resulting in more early treatment initiation and a higher proportion of smear positive patients on treatment, but to date has not had a demonstrable effect on TB-related morbidity (Lawn *et al.*, 2013c; Theron *et al.*, 2014). The Alere Determine TB LAM Ag is a point-of-care test assay that detects the mycobacterial cell wall glycopeptide lipoarabinomannan (LAM) in urine (Lawn, 2012; Talbot *et al.*, 2012). It provides an incremental increase in sensitivity over sputum smear microscopy alone of approximately 19% (Shah *et al.*, 2016), particularly in the most highly immunocompromised patients and those with features of severe disease (e.g. anaemia, elevated CRP) at greatest risk of death (Gupta-Wright *et al.*, 2016; Lawn *et al.*, 2012; Minion *et al.*, 2011). A recent multicentre clinical trial demonstrated that Determine TB LAM Ag test guided initiation of anti-tuberculous was associated with a 17% relative reduction in mortality compared to standard diagnostic strategy (Peter *et al.*, 2016). The clinical benefit of different TB diagnostic strategies in acute CAP, particularly amongst sputum-sparse patients requires further assessment in clinical trials.

Even with the best available diagnostics, however, post-mortem studies highlight that TB frequently goes unrecognised particularly in patients with concurrent pyogenic pneumonia (Bates *et al.*, 2015). Empirical TB treatment in which all patients within a groups at high risk of TB and high risk of early mortality may be warranted (Munseri *et al.*, 2011). Whilst two randomised trials of empirical TB treatment in community-settings amongst patients initiating ART have failed to show benefit (Fielding *et al.*, 2015; Grant *et al.*, 2016; Hosseinipour *et al.*, 2016), it has not yet been studied in hospitalised patients who are more likely to have severe or bacteraemic disease where very early treatment may be beneficial (Jacob *et al.*, 2013b). The MARISO data support a randomised controlled trial of universal empirical TB treatment versus current practice of deferred treatment for non-responders in HIV-infected patients with pneumonia and risk factors for early mortality.

7.7 Optimising supportive care

Severe CAP is frequently complicated by respiratory failure and severe sepsis (Aliberti *et al.*, 2014a; Mayr *et al.*, 2014). In the MARISO cohort, 16% of patients were hypoxaemia and 43% had severe sepsis (using criteria proposed by Andrews et al. for

use in low-resource settings) (Andrews *et al.*, 2014; Singer *et al.*, 2016; Vincent *et al.*, 1996). Effective management of sepsis requires adequate intravenous fluid resuscitation and supplemental oxygen use to correct tissue hypoperfusion and optimise tissue oxygen delivery (Dellinger *et al.*, 2013). The limited data available on sepsis in sub-Saharan Africa indicate that it is frequently under-recognised, fluid resuscitation often inadequate and antimicrobial therapy delayed with an inadequate spectrum (Becker *et al.*, 2009; Jacob *et al.*, 2013a; Jacob *et al.*, 2009). Simplified adaptations of sepsis guidelines for the use in low-resource settings have been developed, but have largely been bases on extrapolations of evidence and experience accumulated in high-resource settings (Becker *et al.*, 2009; Dunser *et al.*, 2012; Jacob *et al.*, 2013a). Locally derived and validated strategies for oxygen delivery and fluid resuscitation are required.

7.7.1 Oxygen delivery

Prior data on the burden of hypoxaemia in adults in sub-Saharan African settings are limited. The MARISO and AHIP studies demonstrate that hypoxaemia in adults with pneumonia is prevalent, prognostically important and correctable in the majority of patients using standard flow-rate oxygen concentrators. Large clinical trials are required to determine the clinical benefit of expanded oxygen provision. Further studies are also needed to define the utility of additional respiratory support techniques (e.g. non-invasive ventilation).

Expanding the availability of oxygen delivery provision represents a key opportunity to improving pneumonia outcomes in sub-Saharan Africa. At present, fewer than half of health care facilities in sub-Saharan Africa have uninterrupted access to an oxygen source and one-quarter have no access at all (Belle *et al.*, 2010). A recent cross-sectional study at Queen Elizabeth Central Hospital in Blantyre found that 10% of adults admitted to medical wards were hypoxaemic, but fewer than a third were receiving supplemental oxygen (Evans *et al.*, 2012). Developing a sustainable, efficient and cost-effective oxygen infrastructure within a low-resource setting is challenging. Over the last decade there has been concerted effort and considerable progress in achieving this in paediatric care settings (Duke *et al.*, 2010a; Duke *et al.*, 2008). The experience highlights several key areas that need to be considered to successfully expand oxygen provision. Firstly, expansion of oxygen delivery infrastructure is largely redundant without improved systems for the detection hypoxaemia. Interventions to improve the quality of emergency triage and to expand the use of pulse-oximetry are needed (Dubowitz *et al.*, 2013; Duke *et al.*, 2009). Secondly, the dynamics of oxygen need at a facility level must be understood to ensure demand is adequately met without

excess redundant capacity. Single point assessments of oxygen demand fail to capture the day-to-day and seasonal variability and may substantially underestimate the required oxygen delivery (Bradley *et al.*, 2014). Thirdly, oxygen concentrators must be carefully selected to ensure suitability in terms of performance (e.g. oxygen concentration, flow-rates), physical tolerances (e.g. temperature, humidity, power fluctuations) and maintenance requirements (e.g. cost, required technical expertise) (Duke *et al.*, 2010b). Standardisation of equipment facilitates sustainable systems for equipment maintenance and procurement of replacement components (Enarson *et al.*, 2008). Finally, the installation of new systems should be allied to a programme of staff training and public engagement to avoid inappropriate or underutilisation (Enarson *et al.*, 2008).

7.7.2 Fluid resuscitation

In severe sepsis, fluid resuscitation is required to correct tissue hypoperfusion and optimise tissue oxygen delivery. The optimal approach to fluid resuscitation has been extensively studied in well-resourced settings and international guidelines developed defining the volume of fluid administration and haemodynamic targets (Dellinger *et al.*, 2013; Survivng Sepsis Campaign, 2015). Some authors have attempted to adapt international sepsis guidelines for use in low-resource settings (Becker *et al.*, 2009; Dunser *et al.*, 2012; World Health Organization, 2011c), but recommendations are largely based on application of physiological principles, extrapolated from experience in high-resource settings (Jacob *et al.*, 2013a). The generalisability of recommendations to sub-Saharan Africa where sepsis differs both in terms of causal pathogen (e.g. TB, NTS, malaria) and host (e.g. immunosuppression, nutritional status, comorbidities) is uncertain (Jacob *et al.*, 2013a). A recent clinical trial of paediatric fluid resuscitation strategies in children with severe febrile illness conducted in Uganda, Kenya and Tanzania that unexpectedly showed increased mortality with bolus fluid administration in children with impaired perfusion highlights the importance of generating context-relevant data (Maitland *et al.*, 2011a).

Specific data on fluid resuscitation strategies in adult sepsis in sub-Saharan Africa are limited to two recent clinical trials that yielded conflicting results. A before-after comparison study in Uganda showed reduced mortality with increased early fluid resuscitation and prompt antibacterial therapy (Jacob *et al.*, 2012). A similar study in Zambia in which up to 4000ml of intravenous fluid was administered in the first 6 hours guided by jugular venous pressure assessment was stopped early because of futility and possibly increased mortality amongst patients with hypoxaemic respiratory failure (Andrews *et al.*, 2014).

The optimal approach to fluid resuscitation in severe sepsis remains unclear. In the absence of invasive monitoring, fluid resuscitation is usually guided by simple physiological markers that may lack specificity. Tachycardia, for example, may reflect sepsis-related hypoperfusion and an indication for further fluid resuscitation, but equally may reflect hypoxaemia or anaemia where further fluid may be deleterious (Andrews *et al.*, 2014). Alternative robust surrogate markers of intra-vascular filling to guide fluid resuscitation are needed (Jacob *et al.*, 2013a). The safety of aggressive fluid resuscitation in the absence of mechanical ventilatory support needs to be investigated, particularly for patients with presumed respiratory infection and hypoxaemia. More fundamentally, research is needed to define whether an approach to management based on rapid correction of deranged physiology is appropriate for all aetiologies of sepsis encountered in sub-Saharan Africa given that a large proportion may be secondary to mycobacterial infection and sub-acute in evolution (Andrews *et al.*, 2014).

7.8 Future research

7.8.1 Access to care

Male sex and prolonged pre-presentation symptom duration were independently associated with mortality. Community-based studies including qualitative work are needed to better understand the care pathway from the time of symptom onset to identify barriers to accessing appropriate care.

7.8.2 Aetiology

The contribution of PCP to acute CAP in this setting is the key aetiological question that has not been addressed by the MARISO study. Data from well-resourced settings and children in South Africa support the use of quantitative real-time PCR on expectorated sputum or upper respiratory tract specimens for PCP diagnosis (Samuel *et al.*, 2011; To *et al.*, 2013). Serum 1-3-β-D-glucan is also a promising option (Karageorgopoulos *et al.*, 2013). These diagnostics should be evaluated against the current reference standard of detection of *Pneumocystis* in BAL in African centres that can safely support bronchoscopy in patients with acute CAP.

The burden of *Legionella* is another issue that has a direct bearing on antimicrobial treatment. As mentioned above, there are plans to address this by *Legionella* urinary antigen testing on stored specimens from the MARISO cohort.

7.8.3 Severity assessment

The MOST score is a useful starting point to develop a CAP severity assessment tool for use in low-resource settings in sub-Saharan Africa. External validation in observational CAP cohorts in both inpatient and community settings, preferably in other sub-Saharan African countries, is necessary to demonstrate its accuracy. In the current analysis, to avoid over-fitting of data to the derivation population, standard thresholds were used to define abnormal observations (e.g. respiratory rate ≥30 /min, systolic blood pressure <90 mmHg). Given the differences in age and comorbidity profile in sub-Saharan African cohorts compared to well-resourced settings, the use of alternative thresholds should be analysed during validation studies (e.g. age-adjusted respiratory rate thresholds (Charles *et al.*, 2008b)).

The value of a severity assessment tool is ultimately determined by incorporating it into a clinical pathway and its impact on clinical decisions and patient outcomes measured (Aujesky *et al.*, 2008). Assuming adequate performance in validation cohorts, the impact on patient safety, antimicrobial use and cost-effectiveness of a care pathway that recommended individuals with a MOST score of 0 or 1 be managed as outpatients should be evaluated.

7.8.4 Monitoring treatment response

The MARISO study is unique amongst sub-Saharan African CAP studies in providing to data on early non-mortality clinical endpoints. Non-death treatment failure (i.e. persistent hypotension, hypoxia or fever at 72 hours) was strongly associated with 30-day mortality, but lacked sensitivity. Lack of attainment of clinical stability criteria by day 3 had improved sensitivity but was non-specific. Exploratory analyses of the MARISO physiological data may be useful to derive locally adapted endpoints of treatment failure and response that could serve as prompts for further investigation and escalation of treatment or de-escalation and discharge, respectively.

Serum specimens were collected at recruitment and day 3 for procalcitonin measurement as part of the MARISO study protocol. Planned analyses include examining the use of procalcitonin to improve the accuracy of severity assessment on admission and correlating changes in procalcitonin with treatment failure, attainment of clinical stability and subsequent mortality.

7.8.5 Antimicrobial treatment

In many sub-Saharan African settings, a “step-up” approach to antimicrobial therapy in severe CAP is taken by default, whereby clinical non-response on broad-spectrum

antibacterials results in sequential addition of TB and PCP treatment. This limits the use of expensive and complex treatment, but may miss the opportunity for early gains from aggressive therapy. In patients with severe CAP at high risk of death (as determined by a locally validated clinical assessment tool) a randomised clinical trial of immediate extended empirical antimicrobial therapy including a broad spectrum antibacterial and TB treatment, and possibly also a macrolide and PCP treatment, is warranted.

7.8.6 Supportive treatment

The results of the AHIP study support the expansion of oxygen delivery infrastructure based on the use of oxygen concentrators. A step-wedge trial of provision of oxygen concentrators to healthcare centres and hospitals that currently have insufficient oxygen capacity is necessary to define the clinical and health-economic impacts.

Correction of hypoxaemia in CAP occurs within the broader context of supportive therapy. Further studies examining the effects of different fluid resuscitations strategies on detailed measurement of intravascular volume status are planned in Malawi to help define the clinical correlates of adequate fluid resuscitation.

7.8.7 Long-term follow-up

The numerical significance of the mortality beyond 30-days observed in the MARISO cohort should to be compared against HIV-matched control populations including adults hospitalised for other indications, and its relationship to ART initiation, subsequent TB diagnosis and recurrent episodes of CAP explored. Longer-term follow-up should be undertaken to determine if the increased rates of adverse cardiovascular outcomes seen in Western CAP cohorts are also applicable, particularly given the higher rates of cardiovascular disease in HIV (Corrales-Medina *et al.*, 2013; Palella *et al.*, 2011).

7.8.8 Research priorities

Of the possible future areas for research discussed above, the following issues should be prioritised since they offer potential immediate patient benefit or are necessary intermediate steps to inform larger clinical trials:

a) Define the contribution of *Legionella* to CAP in Malawi: Current use of antibiotics with activity against *Legionella* in initial treatment regimens is negligible even though appropriate agents are widely available. If a substantial burden of legionellosis is demonstrated through repeat molecular assays of the

nasopharyngeal aspirates, urinary *Legionella pneumophila* antigen testing and/or serological tests, a change to the CAP empirical antimicrobial treatment regimen could be rapidly implemented.

b) Validation of a locally adapted severity assessment tool: In well-resourced settings CAP severity assessment tools are used both to guide key aspects of clinical management (e.g. site of care, extent of microbiological investigations, initial empirical antimicrobial selection) and to inform the design of research studies (e.g. define patient eligibility). To determine whether a similar severity-stratified approach can be safely employed in low-resource sub-Saharan African settings a locally validated severity assessment tool is needed.

c) Define the burden of PCP in CAP in Malawi: This is the key aetiological question that the MARISO study failed to address. Whilst a previous study in HDU patients, indicated a high burden of PCP in Malawi (Hartung *et al.*, 2011), the prevalence in acute CAP patients across the spectrum of disease severity is unknown. With the facilities available to undertake bronchoscopy at QECH, the diagnostic accuracy of quantitative real-time PCR on non-invasively obtained specimens (e.g. expectorated sputum, nasopharyngeal aspirate, oral wash) could be evaluated against a gold-standard test (i.e. bronchoalveolar lavage) in carefully selected pneumonia patients.

Coupled with current and planned work from other investigators in Malawi on point of care diagnostics for TB and optimal approaches to fluid resuscitation, these studies would provide the key data necessary to inform the design of a trial of severity-stratified expanded empirical antimicrobial therapy in HIV-positive adults with acute CAP.

7.9 Conclusions

The assessment and management of CAP needs to be adapted to local circumstances. Extrapolating CAP assessment and treatment algorithms to Malawi from settings where the epidemiology and aetiology of disease is very different is flawed. Severity assessment tools derived in well-resourced settings fail to accurately identify either those patients with mild disease that might be safely managed in the community or those with severe disease that might benefit from intensive early treatment. The MOST score derived in the MARISO cohort is a simple clinical assessment tool that could be readily applied in emergency departments in low-resource settings and form a rational basis for stratified management. Antimicrobial recommendations also need to be adapted to the local epidemiology of disease. Given the high prevalence of tuberculosis and its association with early mortality in Malawi, empirical anti-tuberculous treatment strategies in patients at high risk of early deterioration should be evaluated

in clinical trials. Strategies to improve supportive care, in particular the correction of hypoxaemia, hold considerable promise for improving CAP outcomes and should also be evaluated in clinical trials.

Appendix A: Supplementary materials for systematic review of community-acquired pneumonia in sub-Saharan Africa

1. **Study eligibility assessment form**

2. **Data extraction form**

3. **Risk of bias and quality assessment tool**

4. **Summary of search strategies**

Study Eligibility Assessment Form

First author		Publication Year	
Article title			
Journal title			

Inclusion criteria

Study design (Any one of the following acceptable)	Randomised clinical trial	
	Cohort study	
	Case-control study	
	Case series reporting 25 or more cases	
Exposure (Any acceptable)	Describes population with radiographic pneumonia (Defined as: Acute illness with radiographic evidence of pulmonary consolidation/infiltrate)	
	Describes population with clinical pneumonia (Defined as: Symptoms of acute lower respiratory tract infection (any one of cough, shortness of breath, chest pain) with systemic features of infection (any of fever, shivers, aches and pains, temperature of 38°C or more) and new focal chest signs on examination	
	Author reported pneumonia (Not otherwise specified or not meeting above criteria)	
Participants (Both must apply)	Residents of any sub-Saharan African country	
	Adults aged 15 years or older	

Additional inclusion criteria for specific analyses

1. Mortality	
Either deaths in-hospital or by day 30 following admission/enrolment reported	
2. Risk factors for mortality	
In-hospital or 30-day mortality rates reported separately for patient groups with and without putative risk factor (Indicate below all risk factor groups reported)	
Demographic (age, sex, smoking status)	
Comorbid illness (HIV, chronic lung, heart, renal or liver disease, neurological disease)	
Clinical features at presentation (confusion, raised respiratory rate, hypoxia, hypotension, hypothermia/pyrexia)	
Radiological features (cavitation, multilobar involvement)	
Laboratory parameters (raised urea, anaemia, high or low white cell count, low CD4 cell count, blood culture positivity)	
Severity score indices (CURB65, CRB65, Pneumonia severity index)	
Other	
3. Aetiology *(Both of the following must apply)*	
Recruitment not restricted to specific causative organism	
Microbiological methods for defining aetiology are adequately described	

Exclusion criteria

Multicentre study in which data for African patients not presented separately	
Pneumonia data not presented separately in pathogen-defined cohort	
SARI or other RTI population not meeting above definitions for pneumonia	
Hospital-acquired/nosocomial pneumonia study population	
Recruitment restricted to confirmed/suspected Pneumocystis jirovecii pneumonia	
Recruitment restricted to confirmed/suspected tuberculosis	
Non-acute presentation	
Other reason – *Specify:*	

Data Extraction Form

Study No.		Reviewer		Date	

First author		Publication Year	
Journal title			

Study population and setting

Country and region	
Recruitment period/study duration	
Study design	Single centre ☐ Multicentre ☐
	Prospective ☐ Retrospective ☐
	Observational ☐ Interventional ☐
	Clinical trial ☐ Cohort ☐ Case-control ☐ Case series ☐
Setting (i.e. community, hospital, ICU)	
Study population (Specify any restrictions by age, sex, occupation, aetiology, comorbidity, occupation)	
	Patients screened/excluded if +ve AFB smear/culture ☐ **Other exclusions:**
Pneumonia case-definition	
Mortality endpoint? Assessed when?	
Other comments	

Confirmation of eligibility/Included analyses

Criteria		**Included analyses**	
Study design	☐	Mortality	☐
Pneumonia	☐	Risk factors	☐
Participants	☐	Aetiology	☐
Other exclusions	☐		

Results

Total number of participants in study	
Sex	
Age (average, range, distribution as presented)	
Comorbid illnesses	

1. MORTALITY	
Number (%) for whom outcome determined and included in analysis	
Number (%) died	

2. RISK FACTORS FOR MORTALITY					
For categorical variables, record number and proportion of patients with and without characteristic by outcome status. For continuous variables, record average (median/mean) and appropriate range; if presented as ordinal variables, record cut-off(s) and number and proportion in each group. Where necessary record how risk factor defined. 'Missing' refers to number of patients for whom data is lacking for that specific risk factor. Leave row blank if data on factor not reported.					
	Definition / Other comments	Deaths with factor **OR** No.(%) with factor dying ***(delete as appropriate)***	Deaths w/o factor **OR** No.(%) with factor surviving ***(delete as appropriate)***	**Missing**	**Effect size**
Sex					
Age					
Smoking status					
HIV positive					
Chronic lung disease					
Chronic heart disease					
Chronic renal failure					
Neurological disease					
Confusion					
Heart rate					
Respiratory rate					
Hypoxia					
Hypotension					
Pyrexia and/or pyrexia					
Cavitation					
Multilobar involvement					
Urea					
Haemoglobin					
White cell count					
CD4 cell count					
Blood culture positivity					
CURB65 ≥3					
CRB65 ≥3					
PSI ≥4					
PSI ≥5					
Other:					
Comments:					

3. AETIOLOGY			
Indicate all clinical specimen type collected for microbiological testing and list each microbiological technique used.			
Clinical specimen		**Test**	**No. done**
Blood	☐		
Spontaneous sputum	☐		
Induced sputum	☐		
Bronchoalveolar lavage	☐		
Transbronchial aspirate	☐		
Transthoracic needle aspirate	☐		
Pleural fluid	☐		
Nasopharyngeal swab/aspirate	☐		
Urine	☐		
Other, specify:	☐		
Comments: e.g. adequacy of description of techniques; quality control procedures			

For each organism identified, record the number and proportion of patients affected. If organism identified by multiple tests, record the total number identified by all methods combined.	
Organism	Number (proportion) patients/episodes **(delete as appropriate)**
Unknown aetiology	

* Not reported

Risk of Bias and Quality Assessment Tool

Key Quality Indicator Domains

1. Pneumonia case definition				
Participants prospectively identified and recruited using a standardised case definition				
Radiological confirmation of pneumonia				
*If any of the above **NOT** present, assign high risk of bias.*	**Low risk**		**High risk**	
2. Generalisability				
Recruitment restricted on the basis of a specific factor likely to influence outcome: (NB. This does not refer to clinical setting (e.g. ICU vs ward patients) since these groups will be analysed separately:				
Age				
HIV status				
Disease aetiology				
Other, specify:				
*If any of the above **PRESENT**, assign high risk of bias.*	**Low risk**		**High risk**	
3. Assessment of outcome[1]				
Loss to follow is less than 10% of total cohort				
*If any of the above **NOT** present, assign high risk of bias.*	**Low risk**		**High risk**	
4. Assessment of exposure[2]				
Data on potential prognostic factors collected prospectively using standardised methods				
Data on prognostic factors analysed are available in greater than 90% patients				
*If any of the above **NOT** present, assign high risk of bias.*	**Low risk**		**High risk**	
5. Completeness of outcome data[2]				
Considering the reported event rate, the extent of missing exposure/outcome data is insufficient to have clinically relevant impact on result.				
Missing outcome data are balanced between exposure groups and reasons for missing are similar				
*If any of the above **NOT** present, assign high risk of bias.*	**Low risk**		**High risk**	
6. Analysis[2]				
Association of potential prognostic factor with mortality reported with adjustment for important confounding variables				
Analysis completed according to pre-specified methods and all outcomes have been reported				
*If any of the above **NOT** present, assign high risk of bias.*	**Low risk**		**High risk**	
7. Assessment of microbiological work-up[3]				
Systematic collection of clinical specimens with minimal missingness				
Clear description of laboratory techniques with appropriate quality control measures				
*If any of the above **NOT** present, assign high risk of bias.*	**Low risk**		**High risk**	
8. Other				
There is another source of significant bias				
Describe:				
*If **PRESENT**, assign high risk of bias.*	**Low-risk**		**High risk**	

[1]Only for studies included in mortality analysis; [2]Only for studies reporting included in risk factor for mortality analysis; [3]Only for studies included in aetiology analysis.

Overall Assessment

Overall risk of bias for each analysis	Low	High	Unclear
Mortality analysis *Assign high/unclear risk if high/unclear risk in one or more of domains 1-3 and 8; otherwise low risk.*	☐	☐	☐
Risk factors for mortality analysis *Assign high/unclear risk if high/unclear risk in one or more of* domains 1-6 and 8; *otherwise low risk.*	☐	☐	☐
Aetiology analysis *Assign high/unclear risk if high/unclear risk in one or more of* domains 1, 2, 7 and 8; *otherwise low risk.*	☐	☐	☐

Databases: Medline (OVID; 1946 to Present) and Embase (OVID; 1947-Present)

1 Pneumonia/
2 limit 1 to humans
3 pneumonia.ab. or pneumonia.ti.
4 limit 3 to humans
5 community-acquired pneumonia.mp.
6 limit 5 to humans
7 Respiratory Tract Infections/
8 limit 7 to humans
9 lower respiratory tract infection*.mp.
10 limit 9 to humans
11 acute respiratory infection*.mp.
12 limit 11 to humans
13 SARI.ab. or SARI.ti.
14 limit 13 to humans
15 Pneumonia, Pneumococcal/
16 Streptococcus pneumoniae/
17 Bronchopneumonia/
18 limit 17 to humans
19 Pleuropneumonia/
20 limit 19 to humans
21 Legionnaires' Disease/
22 limit 21 to humans
23 Legionella pneumophila/
24 ((lung* or pulmonary or pleur*) adj2 (infect* or inflam*)).ab. or ((lung* or pulmonary or pleur*) adj2 (infect* or inflam*)).ti.
25 limit 24 to humans
26 2 or 4 or 6 or 8 or 10 or 12 or 14 or 15 or 16 or 18 or 20 or 22 or 23 or 25
27 sub-saharan Africa.mp. or "Africa South of the Sahara"/
28 (Angola or Benin or Botswana or Burkina Faso or Burundi or Cameroon or Cape Verde or Central African Republic or Chad or Comoros or Congo or Democratic Republic of Congo or DRC or Djibouti or Equatorial Guinea or Eritrea or Ethiopia or Gabon or Gambia or Ghana or Guinea or Bissau or Ivory Coast or (Cote and Ivoire) or Jamahiriya or Kenya or Lesotho or Liberia or Madagascar or Malawi or Mali or Mauritania or Mauritius or Mayote or Mozambique or Mocambique or Namibia or Niger or Nigeria or Principe or Reunion or Rwanda or Sao Tome or Senegal or Seychelles or Sierra Leone or Somalia or South Africa or St Helena or Sudan or Swaziland or Tanzania or Togo or Uganda or Zaire or Zambia or Zimbabwe or Central Africa or Central African or West Africa or West African or Western Africa or Western African or East Africa or East African or Eastern Africa or Eastern African or South African or Southern Africa or Southern African or South Africa).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
29 27 or 28
30 26 and 29
31 (baby or babies or infant* or toddler* or preschool* or pre-school* or neonate* or newborn*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
32 30 and 31
33 30 not 32
34 Guinea Pigs/ or guinea pig*.mp.
35 33 not 34

Databases: Science Citation Index Expanded and Conference Proceedings Citation Index (Web of Science)

TOPIC: (pneumonia) *OR* TOPIC: (respiratory infection*) *OR* TOPIC: (pulmonary infection*) *OR* TOPIC: (legionnaires' AND disease)
Refined by: TOPIC: (Angola or Benin or Botswana or Burkina Faso or Burundi or Cameroon or Cape Verde or Central African Republic or Chad or Comoros or Congo or Democratic Republic of Congo or DRC or Djibouti OR Equatorial Guinea or Eritrea or Ethiopia or Gabon or Gambia or Ghana or Guinea or Bissau or Ivory Coast or (Cote and Ivoire) or Jamahiriya or Kenya or Lesotho or Liberia or Madagascar or Malawi or Mali or Mauritania or Mauritius or Mayote or Mozambique or Mocambique or Namibia or Niger or Nigeria or Principe or Reunion or Rwanda or Sao Tome or Senegal or Seychelles or Sierra Leone or Somalia or South Africa or St Helena or Sudan or Swaziland or Tanzania or Togo or Uganda or Zaire or Zambia or Zimbabwe or Central Africa or Central African or West Africa or West African or Western Africa or Western African or East Africa or East African or Eastern Africa or Eastern African or South African or Southern Africa or Southern African or South Africa or sub-saharan Africa) AND TOPIC: (adult* OR elderly)
Indexes=SCI-EXPANDED, CPCI-S Timespan=All years

Database: CINAHL (EBSCOHost)

1 1 TX pneumonia OR TX pulmonary infection* OR TX respiratory infection*
2 TX legionell*
3 1 OR 2
4 Angola or Benin or Botswana or Burkina Faso or Burundi or Cameroon or Cape Verde or Central African Republic or Chad or Comoros or Congo or Democratic Republic of Congo or DRC or Djibouti OR Equatorial Guinea or Eritrea or Ethiopia or Gabon or Gambia or Ghana or Guinea or Bissau or Ivory Coast or (Cote and Ivoire) or Jamahiriya or Kenya or Lesotho or Liberia or Madagascar or Malawi or Mali or Mauritania or Mauritius or Mayote or Mozambique or Mocambique or Namibia or Niger or Nigeria or Principe or Reunion or Rwanda or Sao Tome or Senegal or Seychelles or Sierra Leone or Somalia or South Africa or St Helena or Sudan or Swaziland or Tanzania or Togo or Uganda or Zaire or Zambia or Zimbabwe or Central Africa or Central African or West Africa or West African or Western Africa or Western African or East Africa or East African or Eastern Africa or Eastern African or South African or Southern Africa or Southern African or South Africa or sub-Saharan Africa
5 4 AND 3

Database: CAB Abstracts® and Global Health® (CABI, Web of Science)

1 TS = pneumonia OR TS =pulmonary infection* OR TS = respiratory infection* OR TS = Legionnaires' disease
2 TOPIC: (Angola or Benin or Botswana or Burkina Faso or Burundi or Cameroon or Cape Verde or Central African Republic or Chad or Comoros or Congo or Democratic Republic of Congo or DRC or Djibouti OR Equatorial Guinea or Eritrea or Ethiopia or Gabon or Gambia or Ghana or Guinea or Bissau or Ivory Coast or (Cote and Ivoire) or Jamahiriya or Kenya or Lesotho or Liberia or Madagascar or Malawi or Mali or Mauritania or Mauritius or Mayote or Mozambique or Mocambique or Namibia or Niger or Nigeria or Principe or Reunion or Rwanda or Sao Tome or Senegal or Seychelles or Sierra Leone or Somalia or South Africa or St Helena or Sudan or Swaziland or Tanzania or Togo or Uganda or Zaire or Zambia or

Zimbabwe or Central Africa or Central African or West Africa or West African or Western Africa or Western African or East Africa or East African or Eastern Africa or Eastern African or South African or Southern Africa or Southern African or South Africa or sub-Saharan Africa)

3 #2 AND #1

4 TOPIC: (adult* OR elderly)

5 #4 AND #3

Database: Scopus

(ABS (africa*) AND ABS (adult*) AND SUBJAREA (mult OR agri OR bioc OR immu OR neur OR phar OR mult OR medi OR nurs OR vete OR dent OR heal)) AND ((TITLE-ABS-KEY (pneumonia) OR TITLE-ABS-KEY (pulmonary infection*) OR TITLE-ABS-KEY (acute respiratory infection*)) AND SUBJAREA (mult OR agri OR bioc OR immu OR neur OR phar OR mult OR medi OR nurs OR vete OR dent OR heal)) AND (LIMIT-TO (SUBJAREA , "MEDI"))

Database: African Index Medicus (World Health Organisation)

pneumonia [Key Word] or pulmonary infection$ [Key Word] or respiratory infection$ [Key Word]

Search results summary

Search No.	Date	Database searched	Total hits
1	31/10/2014	Medline	1198
2	31/10/2014	Embase	2303
3	31/10/2014	Science Citation Index Expanded and Conference Proceedings Citation Index- Science	795
4	31/10/2014	CINAHL	170
5	31/10/2014	CAB Abstracts and Global Health	699
6	02/11/2014	Scopus	401
7	03/11/2014	African Index Medicus	32

Appendix B: Supplementary materials for MARISO study

1. **Patient consent forms**

2. **Chest radiograph reporting proforma and guide**

3. **Other case report forms (see attached CD)**

THE COLLEGE OF MEDICINE
Malawi-Liverpool-Wellcome Trust
Clinical Research Programme

www.mlw.medcol.mw

Study Number

PATIENT CONSENT FORM

BURDEN AND SEVERITY OF HIV-ASSOCIATED INFLUENZA ILLNESS IN MALAWI

MALAWIAN ADULT LOWER RESPIRATORY TRACT INFECTION SEVERITY, AETIOLOGY AND OUTCOME STUDY

H1N1 INFLUENZA SURVEILLANCE

Statement by patient (tick boxes as appropriate):

	Yes	No
I have read/been read the information sheet(s) for the **BASH-FLU study** (Version 3; 16th June 2013), the **MARISO study** (Version 6; 12th March 2014), and the **H1N1 influenza surveillance** (version; June 2013) (delete as appropriate). I have had the opportunity to ask questions about this study and I am satisfied with the answers that I have been given.	☐	☐
I understand that even after agreeing to take part now, I can withdraw at any time, without giving a reason and without this affecting my medical care.	☐	☐
I agree that the information collected about me during this study may be looked at by the study staff and also individuals from regulatory authorities. I give permission for these individuals to have access to my medical records including x-rays.	☐	☐
I agree that samples of my blood, sputum, nasal, saliva and chest fluid and urine may be collected for the purpose of this study. I understand that some of my samples may be stored for analysis later or shipped overseas for tests that cannot be done in Malawi.	☐	☐
I voluntarily agree to take part in the BASH-FLU study.	☐	☐
I voluntarily agree also to take part in the MARISO study.	☐	☐
I voluntarily agree also to take part in the H1N1 influenza surveillance.	☐	☐

Name of participant	Date	Signature/Thumbprint
*Name of witness	Date	Signature/Thumbprint

*Witnessed consent will be adequate in the case of patients unable to sign their own name. Witnesses must be mentally competent adults over 18 years old who have no involvement with the research project.

Burden and Severity of HIV-Associated Influenza Illness in Malawi (BASH-FLU)
Malawian Adult Lower Respiratory Tract Infection Severity, Aetiology and Outcome Study (MARISO)
H1N1 Influenza Surveillance
Patient Consent Form, Version 5a (English); 12th March 2014

☐ **Statement by the researcher taking consent:**

The patient information document(s) for this study has been read by/been read out to the potential study participant. To the best of my ability I have ensured that the participant understands

1. The reasons for the study
2. The sampling and follow-up arrangements for participation
3. Plans for protection of confidential data and dissemination of results

I confirm that the participant was given an opportunity to ask questions about the study, and all questions have been answered correctly and to the best of my ability. I confirm that consent has been given freely and voluntarily.

A copy of the consent form and patient information document has been given to the patient to keep.

Name of Researcher	Date	Signature

52460

BASH-FLU MARISO Study
Form BMBC-CXR: Chest Radiograph Review

BASH-FLU

Y0 *bmbar* — *Place BASH-FLU MARISO ID barcode here*

Y1 *bmstid* BASH-FLU MARISO Study Number ☐☐☐

Tick the box if this page has any corrections ☐

Y101 *cxrqual*	Radiograph quality	(1)☐ Optimal (2)☐ Suboptimal (9)☐ Uninterpretable *If Uninterpretable - Skip to Form Completion*
Y201 *parabn*	Is there any parenchymal abnormality?	(1)☐ Yes (0)☐ No *If No - Skip to Y301*
Y202 *consol*	Consolidation?	(1)☐ Yes (0)☐ No
	If Y202 = Yes, indicate:	
Y203 *qual*	Quality	(1)☐ Confluent (2)☐ Patchy
Y204 *extnt*	Extent	(1)☐ Segmental (2)☐ Lobar (3)☐ Multifocal
Y205 *condis*	Distribution *Tick all that apply*	(1)☐ Upper zone (2)☐ Middle zone (3)☐ Lower zone (4)☐ Diffuse
Y206 *cavtn*	Cavitation?	(1)☐ Yes (0)☐ No
Y207 *retic*	Reticular/reticulonodular/nodular pattern?	(1)☐ Yes (0)☐ No
	If Y207 = Yes, indicate:	
Y208 *retdis*	Distribution *Tick all that apply*	(1)☐ Central (2)☐ Peripheral
Y209 *retsde*	Side	(1)☐ Unilateral (2)☐ Bilateral
Y210 *mil*	Miliary appearance?	(1)☐ Yes (0)☐ No
Y301 *plabn*	Is there any pleural abnormality?	(1)☐ Yes (0)☐ No *If No - Skip to Y401*
Y302 *pleff*	Pleural effusion?	(1)☐ Yes (0)☐ No
	If Y302 = Yes, indicate:	
Y303 *plsde*	Side	(1)☐ Unilateral (2)☐ Bilateral
Y304 *plsze*	Size	(1)☐ Small (2)☐ Large
Y305 *ptx*	Pneumothorax?	(1)☐ Yes (0)☐ No
Y401 *mdabn*	Is there any mediastinal abnormality?	(1)☐ Yes (0)☐ No *If No - Skip to Y501*
Y402 *lymph*	Mediastinal/hilar lymphadenopathy?	(1)☐ Yes (0)☐ No
	If Y402 = Yes, indicate:	
Y403 *lymsde*	Side	(1)☐ Unilateral (2)☐ Bilateral
Y404 *cardio*	Cardiomegaly?	(1)☐ Yes (0)☐ No
Y501 *othabn*	Is there any other abnormality?	(1)☐ Yes (0)☐ No *If No - Skip to Y601*
Y502 *othsp*	Other abnormalities? *Tick all that apply*	(1)☐ Volume loss/collapse (2)☐ Hyperinflation (3)☐ Bronchiectasis (4)☐ Bullae (5)☐ Non-cavitating mass (6)☐ Ground glass opacification
Y601 *infn*	**Are the changes compatible with infection?**	(1)☐ Yes (0)☐ No

FORM COMPLETION

Y2 *stfid* Staff ID ☐

Y3 *date* Date completed ☐☐ ☐☐☐ 2 0 1 ☐

CXR reporting guide

Quality:

Optimal – All of the following are present:

1. The entire thoracic cage is visible
2. Adequate inspiration (5^{th}-7^{th} anterior rib intersects the hemidiaphragm)
3. There is no/minimal rotation (spinous processes are equidistant from the medial ends of the clavicles)
4. Well penetrated (the vertebra are visible behind the heart)

Sub-optimal – Not all of the above are present, but the reporter feels the X-ray quality is adequate.

Uninterpretable – The reporter feels the X-ray quality is insufficient to report.

Consolidation – Homogeneous increase in pulmonary parenchymal attenuation that obscures the margins of vessels and airway walls. An air bronchogram may be present.

If consolidation is present, the reporter should specify the following characteristics.

Consolidation quality – if there are areas of both confluent and patchy consolidation, select confluent only.

Consolidation size – tick the option referring to the largest area seen (segmental<lobar<multi-focal).

Consolidation location – select all that apply.

Diffuse – Upper, middle and lower zones are affected bilaterally.

Reticular/reticulonodular/nodular pattern:

Reticular – Innumerable small linear opacities that, by summation, produce an appearance resembling a net.

Nodular – Innumerable small rounded opacities that are discrete and range in diameter from 2 to 10mm.

Reticulonodular – A combined reticular and nodular pattern.

Miliary pattern – Profuse tiny, discrete, rounded pulmonary opacities (≤3mm in diameter,) that are generally uniform in size and diffusely distributed throughout the lung.

If any of the above are present, the reporter should specify if the changes are central or peripheral, unilateral or bilateral, and if the change is miliary. It is not necessary to distinguish between reticular, nodular or Reticulonodular patterns.

Pleural effusion:

Small - Blunting of the costophrenic angle.

Large - The hemidiaphragm is completely obscured.

Cardiomegaly – Cardiothoracic ratio >50% on PA view.

Hyperinflation – Either the diaphragm is flattened or >7th anterior rib intersects the hemidiaphragm at the mid-clavicular line.

Bullae – Large airspaces, sharply demarcated by a thin wall, usually accompanied by emphysematous changes in the adjacent lung.

Non-cavitating lung mass – Solid opacification that is larger than a nodule.

Ground glass opacification – Hazy opacity within which margins of pulmonary vessels may be indistinct.

Appendix C: Supplementary materials for AHIP study

1. **Patient verbal assent form**

2. **Patient consent form**

3. **Oxygen delivery and monitoring form**

4. **Other case report forms (see attached CD)**

VERBAL ASSENT FORM

Study Number:

ADDRESSING HYPOXAEMIA IN ADULT PNEUMONIA IN MALAWI

Statement by study team member:

_____ (name of participant) or his/her guardian has given verbal indication of his/her willingness for his/her preliminary enrolment in the clinical study 'Addressing hypoxaemia in adult pneumonia in Malawi.'

I have explained the purpose of the study and the main risks and benefits of taking part. I have specifically stated the following:

- We would like patients to participate in this research study for us to learn the best way of providing oxygen for adults with pneumonia with low oxygen levels.
- The study involves giving participants extra oxygen to breathe and carefully monitoring their oxygen levels.
- We will also record some details from the medical history and take a small amount of blood for laboratory tests.
- All participants will also receive the standard treatment for pneumonia provided by this hospital.
- This research has been checked and approved by an independent committee to make sure that the potential benefits out weight the risks.
- The risks of being in the study are expected to be low, and all participants are being monitored carefully for any harm.
- All participation in research is voluntary so patients can refuse to take part and will still get the treatment for pneumonia recommended in this hospital.

Name of participant	Date	Signature/Thumbprint
Name of guardian	Date	Signature/Thumbprint
*Name of witness	Date	Signature
Name of researcher	Date	Signature

*A witness will be used for patients/guardians unable to sign their own name. Witnesses must be mentally competent adults over 18 years old who have no involvement with the research project.

Addressing hypoxaemia in adult pneumonia in Malawi.
Verbal Assent Form, Version 3 (English); 9th March 2015

PATIENT CONSENT FORM

Study Number:

ADDRESSING HYPOXAEMIA IN ADULT PNEUMONIA IN MALAWI

Statement by patient:

	Tick boxes as appropriate
I have read/been read and understood the information sheet for the study (Version 4; 9th March 2015). I have had the opportunity to ask questions about this study and I am satisfied with the answers that I have been given.	☐
I understand that information about me is to be used for the purposes indicated in the information sheet and I have been informed of all types of information that will be collected.	☐
I have been informed of the risks and benefits of participation in this study.	☐
I understand that even after agreeing to take part now, I can withdraw at any time, without giving a reason and without this affecting my medical care.	☐
I agree that the information collected about me during this study may be looked at by the study staff, researchers at MLW, Liverpool School of Tropical Medicine and also individuals from regulatory authorities.	☐
I agree that samples of my blood may be taken for the purposes indicated in the information sheet.	☐
I understand that if I come to harm as a participant in this study I can claim appropriate compensation from the study team without this affecting my clinical care	☐
I voluntarily agree to take part in the study.	☐
I do not wish to continue to take part in this study and request that all information collected about me to date is destroyed.	☐

Name of participant	Date	Signature/Thumbprint
*Name of witness	Date	Signature/Thumbprint

*A witness will be used for patients/guardians unable to sign their own name. Witnesses must be mentally competent adults over 18 years old who have no involvement with the research project

Statement by the researcher taking consent:

The patient information document(s) for this study has been read by/been read out to the potential study participant. To the best of my ability I have ensured that the participant understands

1. The reasons for the study
2. The sampling and follow-up arrangements for participation
3. Plans for protection of confidential data and dissemination of results

I confirm that the participant was given an opportunity to ask questions about the study, and all questions have been answered correctly and to the best of my ability. I confirm that consent has been given freely and voluntarily.

A copy of the consent form and patient information document has been given to the patient to keep.

Name of Researcher	Date	Signature

Addressing Hypoxaemia in Adult Pneumonia
Form AHIP-OXYGEN: Oxygen Delivery and Monitoring

D0 *dbar* | *AHIP barcode* | D1 *init* Initials

Tick the box if this page has any corrections ☐

SECTION 1: STANDARD FLOW OXYGEN THERAPY

Time-point	Baseline	5	10	15	20	25	30	35	40	45	50	55	60
Time D101 *time*	☐☐ ☐☐												☐☐ ☐☐
Flow-rate D102 *flow*		☐☐	☐☐	☐☐	☐☐	☐☐	☐☐	☐☐	☐☐	☐☐	☐☐	☐☐	☐☐
Device D103 *dev*		☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
O2 satn D104 *sat*	☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐☐☐ *
Resp. rate D105 *rr*	☐☐			☐☐			☐☐			☐☐			☐☐
Sys. BP D106 *sbp*	☐☐☐			☐☐☐			☐☐☐			☐☐☐			☐☐☐
Dia. BP D107 *dbp*	☐☐☐			☐☐☐			☐☐☐			☐☐☐			☐☐☐
Heart rate D108 *hr*	☐☐☐			☐☐☐			☐☐☐			☐☐☐			☐☐☐

Device codes: **1 - Hudson facemask** **2 - Nasal cannulae** **3 - Facemask with reservoir bag**

Notes:

(Include time for all notes)

D104a *satchk*

Reading 1 ☐☐☐
Reading 2 ☐☐☐
Reading 3 ☐☐☐
Average ☐☐☐

Record baseline saturations (SpO2) immediately before starting oxygen. Use a Hudson facemask initially; if not tolerated, use nasal cannulae. If SpO2 are <85% at two consecutive recordings, proceed directly to Section 2: High Flow Oxygen Therapy. If SpO2 are >98% at two consecutive recordings, reduce oxygen flow rate by 1 L/min.
If SpO2 at 60 minutes are <92%, then proceed to Section 2. If SpO2 at 60 mins are >=92% then go to Section 3: Post-intervention management.
**Note: If SpO2 at 60 minutes are 90-94%, use average of three readings taken at 1 min. intervals to determine progression.*

22903

SECTION 2: HIGH FLOW OXYGEN THERAPY

Attempt to obtain arterial blood sample for arterial blood gas analysis; record specimen collection and results on Form AHIP-SPEC: Specimen Collection and Results. Record baseline observations just prior to switching to facemask with reservoir bag and increasing flow-rate to 10 L/min.

Time-point	Baseline	5	10	15	20	25	30	35	40	45	50	55	60
Time D201 *time*	☐☐ ☐☐												☐☐ ☐☐
Flow-rate D202 *flow*	☐☐	☐☐	☐☐	☐☐	☐☐	☐☐	☐☐	☐☐	☐☐	☐☐	☐☐	☐☐	☐☐
Device D203 *dev*	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
O2 satn D204 *sat*	☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐☐☐ *
Resp. rate D205 *rr*	☐☐			☐☐			☐☐			☐☐			☐☐
Sys. BP D206 *sbp*	☐☐☐			☐☐☐			☐☐☐			☐☐☐			☐☐☐
Dia. BP D207 *dbp*	☐☐☐			☐☐☐			☐☐☐			☐☐☐			☐☐☐
Heart rate D208 *hr*	☐☐☐			☐☐☐			☐☐☐			☐☐☐			☐☐☐

Device codes: **1 - Hudson facemask** **2 - Nasal cannulae** **3 - Facemask with reservoir bag**

Notes:

(Include time for all notes)

D204a *satchk*

Reading 1 ☐☐☐

Reading 2 ☐☐☐

Reading 3 ☐☐☐

Average ☐☐☐

22903

If SpO2 are >98% at two consecutive recordings, switch to Hudson facemask and reduce oxygen flow rate by 1 L/min. If SpO2 at 60 mins are >=92% then go to Section 3: Post-intervention management. If SpO2 at 60 minutes are <92%, continue with high flow oxygen.
**Note: If SpO2 at 60 minutes are 90-94%, use average of three readings taken at 1 min. intervals to determine progression.*

SECTION 2: HIGH FLOW OXYGEN THERAPY (CONTINUED)

Time-point	75	90	105	120	135	150	165	180	195	210	225	240
Time D201 *time*												
Flow-rate D202 *flow*												
Device D203 *dev*												
O2 satn D204 *sat*												
Resp. rate D205 *rr*												
Sys. BP D206 *sbp*												
Dia. BP D207 *dbp*												
Heart rate D208 *hr*												

Device codes: **1 - Hudson facemask** **2 - Nasal cannulae** **3 - Facemask with reservoir bag**

D209 *intend* If patient reponds to oxygen, record time of end of intervention period.

Notes:

(Include time for all notes)

22903

If SpO2 are >=92% at two consecutive recordings, then complete question D209 and go to Section 3: Post-intervention management.
If SpO2 at remain <92%, continue with high flow oxygen upto 240 mintues and discuss with Medical Registrar.

Addressing Hypoxaemia in Adult Pneumonia
Form AHIP-OXYGEN: Oxygen Delivery and Monitoring

D6 *dbar* AHIP barcode

D7 Initials *init*

Tick the box if this page has any corrections ☐

SECTION 3: POST-INTERVENTION MANAGEMENT

D301 *intout* Indicate outcome of intervention period:
(1) ☐ Responded to standard flow oxygen
(2) ☐ Responded to high-flow oxygen
(3) ☐ Did not respond

If responded to standard flow (i.e. SpO2 are >=92% and oxygen flow-rate is =<5 L/min), then go to Section 3a for trial withdrawal of oxygen. Otherwise go to Section 3b.

Section 3a: Trial withdrawal of oxygen

Time-point	Baseline		1	2	5	10	15	30	45	60
Time D302 *time*	☐☐ ☐☐	REMOVE OXYGEN								☐☐ ☐☐
Flow-rate D303 *flow*	☐☐		☐☐	☐☐	☐☐	☐☐	☐☐	☐☐	☐☐	☐☐
Device D304 *dev*	☐		☐	☐	☐	☐	☐	☐	☐	☐
O2 satn D305 *sat*	☐☐☐		☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐☐☐	☐☐☐
Resp. rate D306 *rr*	☐☐				☐☐		☐☐			☐☐
Sys. BP D307 *sbp*	☐☐☐		*If SpO2 drop below 90% during trial then restart oxygen and refer to HDU. If at 60 minutes off oxygen, SpO2 are >=90% and patient stable then refer to main ward. If continued oxygen is thought necessary outside these criteria, indicate reasons below.*							☐☐☐
Dia. BP D308 *dbp*	☐☐☐									☐☐☐
Heart rate D309 *hr*	☐☐☐		D310 *restart* If applicapble, record time oxygen was restarted? ☐☐ ☐☐							☐☐☐

Section 3b: Onward referral from AETC

D311 *ref* What is the planned route of referral?
(1) ☐ Main ward (3) ☐ ICU
(2) ☐ HDU (4) ☐ Discharge

D312 *trans* What is the actual transfer destination?
(1) ☐ Main ward (4) ☐ Discharged home
(2) ☐ HDU (5) ☐ Death in AETC
(3) ☐ ICU

D313 *date* D314 *time* What is the date and time of transfer, discharge or death?
☐☐ ☐☐☐ 2 0 1 ☐ ☐☐ ☐☐

Device codes: **1 - Hudson facemask** **2 - Nasal cannulae** **3 - Facemask with reservoir bag**

Notes: *(Include time for all notes)*

22903

FORM COMPLETION

D7 Staff ID *stfid* ☐

D8 Date completed *date* ☐☐ (d d) ☐☐☐ (m o n) 2 0 1 ☐ (y y y y)

References

Aberdein, J., Cole, J., Bewley, M., & Dockrell, D. H. (2013). Alveolar macrophages in pulmonary host defence- the unrecognised role of apoptosis as a mechanism of intracellular bacterial killing. *Clinical and Experimental Immunology*.

Abouya, Y. L., Beaumel, A., Lucas, S., Dago-Akribi, A., Coulibaly, G., N'Dhatz, M., . . . De Cock, K. M. (1992). Pneumocystis carinii pneumonia. An uncommon cause of death in African patients with acquired immunodeficiency syndrome. *American Review of Respiratory Disease, 145*(3), 617-620.

Adegbola, R. A., Obaro, S. K., Biney, E., & Greenwood, B. M. (2001). Evaluation of Binax now Streptococcus pneumoniae urinary antigen test in children in a community with a high carriage rate of pneumococcus. *Pediatric Infectious Disease Journal, 20*(7), 718-719.

Aderaye, G. (1994a). Community acquired pneumonia in adults in Addis Ababa: etiologic agents and the impact of HIV infection. *Tubercle and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease, 75*(4), 308-312.

Aderaye, G. (1994b). The etiology of community acquired pneumonia in adults in Addis Ababa. *West African Journal of Medicine, 13*(3), 142-145.

Aderaye, G., Bruchfeld, J., Aseffa, G., Nigussie, Y., Melaku, K., Woldeamanuel, Y., . . . Lindquist, L. (2007). Pneumocystis jiroveci pneumonia and other pulmonary infections in TB smear-negative HIV-positive patients with atypical chest X-ray in Ethiopia. *Scandinavian Journal of Infectious Diseases, 39*(11-12), 1045-1053.

Adhikari, N. K., Fowler, R. A., Bhagwanjee, S., & Rubenfeld, G. D. (2010). Critical care and the global burden of critical illness in adults. *Lancet, 376*(9749), 1339-1346.

Ahmedtaha, O. M., Yami, A., & Mohammed, M. A. (2014). Treatment and Outcomes of Community-Acquired Pneumonia in Hospitalized Patients: The Case of Jimma University Specialized Hospital. *Therapeutic Innovation and Regulatory Science, 48 (2)*, 220-225.

Akram, A. R., Chalmers, J. D., Taylor, J. K., Rutherford, J., Singanayagam, A., & Hill, A. T. (2013). An evaluation of clinical stability criteria to predict hospital course in community-acquired pneumonia. *Clinical Microbiology and Infection, 19*(12), 1174-1180.

Albaum, M. N., Hill, L. C., Murphy, M., Li, Y. H., Fuhrman, C. R., Britton, C. A., . . . Fine, M. J. (1996). Interobserver reliability of the chest radiograph in community-acquired pneumonia. PORT Investigators. *Chest, 110*(2), 343-350.

Albrich, W. C., Madhi, S. A., Adrian, P. V., van Niekerk, N., Mareletsi, T., Cutland, C., . . . Klugman, K. P. (2012). Use of a rapid test of pneumococcal colonization density to diagnose pneumococcal pneumonia. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America, 54*(5), 601-609.

Albrich, W. C., Madhi, S. A., Adrian, P. V., Van Niekerk, N., Telles, J. N., Ebrahim, N., . . . Klugman, K. P. (2014a). Pneumococcal colonisation density: A new marker for disease severity in HIV-infected adults with pneumonia. *BMJ Open, 4 (8)*(e005953).

Albrich, W. C., Telles, J. N., Adrian, P. V., Messaoudi, M., Van Niekerk, N., Paranhos-Baccala, G., . . . Klugman, K. (2014b). Aetiology of community-acquired pneumonia in HIV-infected South African adults. *International Journal of Infectious Diseases, Conference: 16th International Congress on Infectious Diseases, ICID 2014 Cape Town South Africa. Conference Start: 20140402 Conference End: 20140405. Conference Publication: (var.pagings). 21*, 339-340.

Alere. (2015). BinaxNOW Streptococcus pneumoniae Antigen Card Package Insert. Maine, USA: Alere.

Aliberti, S., Amir, A., Peyrani, P., Mirsaeidi, M., Allen, M., Moffett, B. K., . . . Ramirez, J. A. (2008). Incidence, etiology, timing, and risk factors for clinical failure in hospitalized patients with community-acquired pneumonia. *Chest, 134*(5), 955-962.

Aliberti, S., Brambilla, A. M., Chalmers, J. D., Cilloniz, C., Ramirez, J., Bignamini, A., . . . Cosentini, R. (2014a). Phenotyping community-acquired pneumonia according to the presence of acute respiratory failure and severe sepsis. *Respiratory Research, 15*, 27.

Aliberti, S., & Faverio, P. (2014b). Early oucomes in CAP: clinical stability, clinical failure and nonresolving pneumonia. In J. D. Chalmers, M. W. Pletz, & S. Aliberti (Eds.), *Community-acquired pneumonia* (Vol. 63, pp. 205-218): European Respiratory Society.

Aliberti, S., Peyrani, P., Filardo, G., Mirsaeidi, M., Amir, A., Blasi, F., & Ramirez, J. A. (2011). Association between time to clinical stability and outcomes after discharge in hospitalized patients with community-acquired pneumonia. *Chest, 140*(2), 482-488.

Aliberti, S., Zanaboni, A. M., Wiemken, T., Nahas, A., Uppatla, S., Morlacchi, L. C., . . . Ramirez, J. (2013). Criteria for clinical stability in hospitalised patients with community-acquired pneumonia. *European Respiratory Journal, 42*(3), 742-749.

Allen, S. C. (1984). Lobar pneumonia in Northern Zambia: clinical study of 502 adult patients. *Thorax, 39*(8), 612-616.

Almeida, A., Almeida, A. R., Branco, S. C., Vesza, Z., & Pereira, R. (2015). CURB-65 and other markers of illness severity in community-acquired pneumonia among HIV-positive patients. *International Journal of STD and AIDS*.

Almirall, J., Bolibar, I., Serra-Prat, M., Roig, J., Hospital, I., Carandell, E., . . . Community-Acquired Pneumonia in Catalan Countries Study, G. (2008). New evidence of risk factors for community-acquired pneumonia: a population-based study. *European Respiratory Journal, 31*(6), 1274-1284.

Almirall, J., Gonzalez, C. A., Balanzo, X., & Bolibar, I. (1999). Proportion of community-acquired pneumonia cases attributable to tobacco smoking. *Chest, 116*(2), 375-379.

Altman, D. G., & Royston, P. (2000). What do we mean by validating a prognostic model? *Statistics in Medicine, 19*(4), 453-473.

Altman, D. G., Vergouwe, Y., Royston, P., & Moons, K. G. (2009). Prognosis and prognostic research: validating a prognostic model. *BMJ, 338*, b605.

American Thoracic Society. (2005). Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *American Journal of Respiratory and Critical Care Medicine, 171*(4), 388-416.

An, M. M., Zou, Z., Shen, H., Gao, P. H., Cao, Y. B., & Jiang, Y. Y. (2010). Moxifloxacin monotherapy versus beta-lactam-based standard therapy for community-acquired pneumonia: a meta-analysis of randomised controlled trials. *International Journal of Antimicrobial Agents, 36*(1), 58-65.

Andrews, B., Muchemwa, L., Kelly, P., Lakhi, S., Heimburger, D. C., & Bernard, G. R. (2014). Simplified severe sepsis protocol: a randomized controlled trial of modified early goal-directed therapy in Zambia. *Critical Care Medicine, 42*(11), 2315-2324.

Angele, M. K., Pratschke, S., Hubbard, W. J., & Chaudry, I. H. (2014). Gender differences in sepsis: cardiovascular and immunological aspects. *Virulence, 5*(1), 12-19.

Antonelli, M., Conti, G., Bufi, M., Costa, M. G., Lappa, A., Rocco, M., . . . Meduri, G. U. (2000). Noninvasive ventilation for treatment of acute respiratory failure in patients undergoing solid organ transplantation: a randomized trial. *JAMA, 283*(2), 235-241.

Arancibia, F., Ewig, S., Martinez, J. A., Ruiz, M., Bauer, T., Marcos, M. A., . . . Torres, A. (2000). Antimicrobial treatment failures in patients with community-acquired pneumonia: causes and prognostic implications. *American Journal of Respiratory and Critical Care Medicine, 162*(1), 154-160.

Arnold, F. W., Brock, G. N., Peyrani, P., Rodriguez, E. L., Diaz, A. A., Rossi, P., & Ramirez, J. A. (2010). Predictive accuracy of the pneumonia severity index vs CRB-65 for time to

clinical stability: results from the Community-Acquired Pneumonia Organization (CAPO) International Cohort Study. *Respiratory Medicine, 104*(11), 1736-1743.

Arnold, F. W., Wiemken, T. L., Peyrani, P., Mirsaeidi, M., Ramirez, J. A., & Community Acquired Pneumonia Organization Study, G. (2013). Outcomes in females hospitalised with community-acquired pneumonia are worse than in males. *European Respiratory Journal, 41*(5), 1135-1140.

Arnold, R. R., Brewer, M., & Gauthier, J. J. (1980). Bactericidal activity of human lactoferrin: sensitivity of a variety of microorganisms. *Infection and Immunity, 28*(3), 893-898.

Asadi, L., Sligl, W. I., Eurich, D. T., Colmers, I. N., Tjosvold, L., Marrie, T. J., & Majumdar, S. R. (2012). Macrolide-Based Regimens and Mortality in Hospitalized Patients with Community-Acquired Pneumonia: A Systematic Review and Meta-Analysis. *Clinical Infectious Diseases*.

Assefa, G., Nigussie, Y., Aderaye, G., Worku, A., & Lindquist, L. (2011). Chest X-ray evaluation of pneumonia-like syndromes in smear negative HIV-positive patients with atypical chest x-ray. Findings in Ethiopian setting. *Ethiopian Medical Journal, 49*(1), 35-42.

Aston, S. J. (2014). The role of rapid diagnostic tests in managing adults with pneumonia in low-resource settings. *Pneumonia, 5*, 8-17.

Atzori, C., Bruno, A., Chichino, G., Gatti, S., & Scaglia, M. (1993). Pneumocystis carinii pneumonia and tuberculosis in Tanzanian patients infected with HIV. *Transactions of the Royal Society of Tropical Medicine and Hygiene, 87*(1), 55-56.

Aujesky, D., & Fine, M. J. (2008). The pneumonia severity index: a decade after the initial derivation and validation. *Clinical Infectious Diseases, 47 Suppl 3*, S133-139.

Austin, P. C., & Tu, J. V. (2004). Bootstrap methods for developing predictive models. *The American Statistician, 58*(2), 131-137.

Avni, T., Bieber, A., Green, H., Steinmetz, T., Leibovici, L., & Paul, M. (2016). Diagnostic Accuracy of PCR Alone and Compared to Urinary Antigen Testing for Detection of Legionella spp.: a Systematic Review. *Journal of Clinical Microbiology, 54*(2), 401-411.

Awunor-Renner, C. (1979). Length of antibiotic therapy in in-patients with primary pneumonias. *Annals of Tropical Medicine and Parasitology, 73*(3), 235-240.

Baddour, L. M., Yu, V. L., Klugman, K. P., Feldman, C., Ortqvist, A., Rello, J., . . . International Pneumococcal Study, G. (2004). Combination antibiotic therapy lowers mortality among severely ill patients with pneumococcal bacteremia. *American Journal of Respiratory and Critical Care Medicine, 170*(4), 440-444.

Bar-Zeev, N., Mtunthama, N., Gordon, S. B., Mwafulirwa, G., & French, N. (2015). Minimum incidence of adult invasive pneumococcal disease in Blantyre, Malawi an urban african setting: a hospital based prospective cohort study. *PloS One, 10*(6), e0128738.

Barlow, G. D., Lamping, D. L., Davey, P. G., & Nathwani, D. (2003). Evaluation of outcomes in community-acquired pneumonia: a guide for patients, physicians, and policy-makers. *Lancet Infectious Diseases, 3*(8), 476-488.

Barrow, G. I., & Feltham, R. K. A. (1993). *Cowan and Steel's Manual for the Identification of Medical Bacteria*. Cambridge: Cambridge University Press, UK.

Bartlett, J. G. (2011). Diagnostic tests for agents of community-acquired pneumonia. *Clinical Infectious Diseases, 52 Suppl 4*, S296-304.

Basi, S. K., Marrie, T. J., Huang, J. Q., & Majumdar, S. R. (2004). Patients admitted to hospital with suspected pneumonia and normal chest radiographs: epidemiology, microbiology, and outcomes. *American Journal of Medicine, 117*(5), 305-311.

Bates, M., Mudenda, V., Mwaba, P., & Zumla, A. (2013). Deaths due to respiratory tract infections in Africa: a review of autopsy studies. *Current Opinion in Pulmonary Medicine, 19*(3), 229-237.

Bates, M., Mudenda, V., Shibemba, A., Kaluwaji, J., Tembo, J., Kabwe, M., . . . Zumla, A. (2015). Burden of tuberculosis at post mortem in inpatients at a tertiary referral centre in sub-Saharan Africa: a prospective descriptive autopsy study. *Lancet Infectious Diseases, 15*(5), 544-551.

Bates, M., O'Grady, J., Mwaba, P., Chilukutu, L., Mzyece, J., Cheelo, B., . . . Zumla, A. (2012). Evaluation of the burden of unsuspected pulmonary tuberculosis and co-morbidity with non-communicable diseases in sputum producing adult inpatients. *PloS One, 7*(7), e40774.

Batungwanayo, J., Taelman, H., Lucas, S., Bogaerts, J., Alard, D., Kagame, A., . . . Allen, S. (1994). Pulmonary disease associated with the human immunodeficiency virus in Kigali, Rwanda. A fiberoptic bronchoscopic study of 111 cases of undetermined etiology. *American Journal of Respiratory and Critical Care Medicine, 149*(6), 1591-1596.

Bauer, T. T., Welte, T., Strauss, R., Bischoff, H., Richter, K., & Ewig, S. (2013). Why do nonsurvivors from community-acquired pneumonia not receive ventilatory support? *Lung, 191*(4), 417-424.

Becker, J. U., Theodosis, C., Jacob, S. T., Wira, C. R., & Groce, N. E. (2009). Surviving sepsis in low-income and middle-income countries: new directions for care and research. *Lancet Infectious Diseases, 9*(9), 577-582.

Bedell, R. A., Anderson, S. T., van Lettow, M., Akesson, A., Corbett, E. L., Kumwenda, M., . . . Ramsay, A. R. (2012). High prevalence of tuberculosis and serious bloodstream infections in ambulatory individuals presenting for antiretroviral therapy in Malawi. *PloS One, 7*(6), e39347.

Belle, J., Cohen, H., Shindo, N., Lim, M., Velazquez-Berumen, A., Ndihokubwayo, J. B., & Cherian, M. (2010). Influenza preparedness in low-resource settings: a look at oxygen delivery in 12 African countries. *J Infect Dev Ctries, 4*(7), 419-424.

Benito, N., Moreno, A., Miro, J. M., & Torres, A. (2012). Pulmonary infections in HIV-infected patients: an update in the 21st century. *European Respiratory Journal, 39*(3), 730-745.

Berger, P., Papazian, L., Drancourt, M., La Scola, B., Auffray, J. P., & Raoult, D. (2006). Ameba-associated microorganisms and diagnosis of nosocomial pneumonia. *Emerging Infectious Diseases, 12*(2), 248-255.

Bewick, T., Sheppard, C., Greenwood, S., Slack, M., Trotter, C., George, R., & Lim, W. S. (2012). Serotype prevalence in adults hospitalised with pneumococcal non-invasive community-acquired pneumonia. *Thorax, 67*(6), 540-545.

Birkhamshaw, E., Waitt, C. J., Innes, M., & Waitt, P. I. (2013). Severity assessment of lower respiratory tract infection in Malawi: derivation of a novel index (SWAT-Bp) which outperforms CRB-65. *PloS One, 8*(12), e82178.

Bo, L., Wang, F., Zhu, J., Li, J., & Deng, X. (2011). Granulocyte-colony stimulating factor (G-CSF) and granulocyte-macrophage colony stimulating factor (GM-CSF) for sepsis: a meta-analysis. *Critical Care (London, England), 15*(1), R58.

Bogaert, D., De Groot, R., & Hermans, P. W. (2004). Streptococcus pneumoniae colonisation: the key to pneumococcal disease. *Lancet Infectious Diseases, 4*(3), 144-154.

Bone, R. C., Balk, R. A., Cerra, F. B., Dellinger, R. P., Fein, A. M., Knaus, W. A., . . . Sibbald, W. J. (1992). Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest, 101*(6), 1644-1655.

Bonten, M. J., Huijts, S. M., Bolkenbaas, M., Webber, C., Patterson, S., Gault, S., . . . Grobbee, D. E. (2015). Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. *New England Journal of Medicine, 372*(12), 1114-1125.

Bordon, J., Aliberti, S., Fernandez-Botran, R., Uriarte, S. M., Rane, M. J., Duvvuri, P., . . . Ramirez, J. A. (2012). Understanding the roles of cytokines and neutrophil activity and neutrophil apoptosis in the protective versus deleterious inflammatory response in pneumonia. *International Journal of Infectious Diseases*.

Bos, J. C., Beishuizen, S. J., Madeira, G. C., Gomonda, E. D. S., Cossa, E. O., Macome, A. C., . . . Prins, J. M. (2014). Antimicrobial susceptibility of Streptococcus pneumoniae in adult patients with pneumococcal pneumonia in an urban hospital in Mozambique. *BMC Research Notes, 7*(1).

Boulware, D. R., Daley, C. L., Merrifield, C., Hopewell, P. C., & Janoff, E. N. (2007). Rapid diagnosis of pneumococcal pneumonia among HIV-infected adults with urine antigen detection. *Journal of Infection, 55*(4), 300-309.

Bowton, D. L., Scuderi, P. E., & Haponik, E. F. (1994). The incidence and effect on outcome of hypoxemia in hospitalized medical patients. *American Journal of Medicine, 97*(1), 38-46.

Bradley, B. D., Howie, S. R., Chan, T. C., & Cheng, Y. L. (2014). Estimating oxygen needs for childhood pneumonia in developing country health systems: a new model for expecting the unexpected. *PloS One, 9*(2), e89872.

Brambilla, A. M., Aliberti, S., Prina, E., Nicoli, F., Del Forno, M., Nava, S., . . . Cosentini, R. (2014). Helmet CPAP vs. oxygen therapy in severe hypoxemic respiratory failure due to pneumonia. *Intensive Care Medicine, 40*(7), 942-949.

Breuninger, M., van Ginneken, B., Philipsen, R. H., Mhimbira, F., Hella, J. J., Lwilla, F., . . . Reither, K. (2014). Diagnostic accuracy of computer-aided detection of pulmonary tuberculosis in chest radiographs: a validation study from sub-Saharan Africa. *PloS One, 9*(9), e106381.

Brown, J. S., Hussell, T., Gilliland, S. M., Holden, D. W., Paton, J. C., Ehrenstein, M. R., . . . Botto, M. (2002). The classical pathway is the dominant complement pathway required for innate immunity to Streptococcus pneumoniae infection in mice. *Proceedings of the National Academy of Sciences of the United States of America, 99*(26), 16969-16974.

Buigut, S., Ettarh, R., & Amendah, D. D. (2015). Catastrophic health expenditure and its determinants in Kenya slum communities. *Int J Equity Health, 14*, 46.

Buising, K. (2008). Severity scores for community-acquired pneumonia. *Expert Review of Respiratory Medicine, 2*(2), 261-271.

Carrillo, A., Gonzalez-Diaz, G., Ferrer, M., Martinez-Quintana, M. E., Lopez-Martinez, A., Llamas, N., . . . Torres, A. (2012). Non-invasive ventilation in community-acquired pneumonia and severe acute respiratory failure. *Intensive Care Medicine, 38*(3), 458-466.

Carrol, E. D., Mankhambo, L. A., Jeffers, G., Parker, D., Guiver, M., Newland, P., . . . Hart, C. A. (2009). The diagnostic and prognostic accuracy of five markers of serious bacterial infection in Malawian children with signs of severe infection. *PloS One, 4*(8), e6621.

Carron, M., Freo, U., Zorzi, M., & Ori, C. (2010). Predictors of failure of noninvasive ventilation in patients with severe community-acquired pneumonia. *Journal of Critical Care, 25*(3), 540.e549-514.

Cepheid. (2015). Xpert MTB/RIF Package Insert. California, USA: Cepheid.

Chalmers, J. D. (2015). Identifying severe community-acquired pneumonia: moving beyond mortality. *Thorax*.

Chalmers, J. D., Mandal, P., Singanayagam, A., Akram, A. R., Choudhury, G., Short, P. M., & Hill, A. T. (2011a). Severity assessment tools to guide ICU admission in community-acquired pneumonia: systematic review and meta-analysis. *Intensive Care Medicine, 37*(9), 1409-1420.

Chalmers, J. D., Singanayagam, A., Akram, A. R., Choudhury, G., Mandal, P., & Hill, A. T. (2011b). Safety and efficacy of CURB65-guided antibiotic therapy in community-acquired pneumonia. *Journal of Antimicrobial Chemotherapy, 66*(2), 416-423.

Chalmers, J. D., Singanayagam, A., Akram, A. R., Mandal, P., Short, P. M., Choudhury, G., . . . Hill, A. T. (2010). Severity assessment tools for predicting mortality in hospitalised patients with community-acquired pneumonia. Systematic review and meta-analysis. *Thorax, 65*(10), 878-883.

Chalmers, J. D., Singanayagam, A., & Hill, A. T. (2008). Predicting the need for mechanical ventilation and/or inotropic support for young adults admitted to the hospital with community-acquired pneumonia. *Clinical Infectious Diseases, 47*(12), 1571-1574.

Chalmers, J. D., Taylor, J. K., Mandal, P., Choudhury, G., Singanayagam, A., Akram, A. R., & Hill, A. T. (2011c). Validation of the Infectious Diseases Society of America/American Thoratic Society minor criteria for intensive care unit admission in community-acquired pneumonia patients without major criteria or contraindications to intensive care unit care. *Clinical Infectious Diseases, 53*(6), 503-511.

Chang, K. C., Leung, C. C., Yew, W. W., Lau, T. Y., Leung, W. M., Tam, C. M., . . . Ma, Y. H. (2010). Newer fluoroquinolones for treating respiratory infection: do they mask tuberculosis? *European Respiratory Journal, 35*(3), 606-613.

Charalambous, S., Day, J. H., Fielding, K., De Cock, K. M., Churchyard, G. J., & Corbett, E. L. (2003). HIV infection and chronic chest disease as risk factors for bacterial pneumonia: a case-control study. *AIDS (London, England), 17*(10), 1531-1537.

Charles, P. G., Whitby, M., Fuller, A. J., Stirling, R., Wright, A. A., Korman, T. M., . . . Grayson, M. L. (2008a). The etiology of community-acquired pneumonia in Australia: why penicillin

plus doxycycline or a macrolide is the most appropriate therapy. *Clinical Infectious Diseases, 46*(10), 1513-1521.

Charles, P. G., Wolfe, R., Whitby, M., Fine, M. J., Fuller, A. J., Stirling, R., . . . Grayson, M. L. (2008b). SMART-COP: a tool for predicting the need for intensive respiratory or vasopressor support in community-acquired pneumonia. *Clinical Infectious Diseases, 47*(3), 375-384.

Chen, J. H., Chang, S. S., Liu, J. J., Chan, R. C., Wu, J. Y., Wang, W. C., . . . Lee, C. C. (2010). Comparison of clinical characteristics and performance of pneumonia severity score and CURB-65 among younger adults, elderly and very old subjects. *Thorax, 65*(11), 971-977.

Chen, T. C., Lu, P. L., Lin, C. Y., Lin, W. R., & Chen, Y. H. (2011). Fluoroquinolones are associated with delayed treatment and resistance in tuberculosis: a systematic review and meta-analysis. *International Journal of Infectious Diseases, 15*(3), e211-216.

Cheng, A. C., Stephens, D. P., & Currie, B. J. (2007). Granulocyte-colony stimulating factor (G-CSF) as an adjunct to antibiotics in the treatment of pneumonia in adults. *Cochrane Database Syst Rev*(2), Cd004400.

Cheng, Y. J., Nie, X. Y., Chen, X. M., Lin, X. X., Tang, K., Zeng, W. T., . . . Wu, S. H. (2015). The Role of Macrolide Antibiotics in Increasing Cardiovascular Risk. *Journal of the American College of Cardiology, 66*(20), 2173-2184.

Chew, K. W., Yen, I. H., Li, J. Z., & Winston, L. G. (2011). Predictors of pneumonia severity in HIV-infected adults admitted to an Urban public hospital. *AIDS Patient Care and STDS, 25*(5), 273-277.

Cho, M. C., Kim, H., An, D., Lee, M., Noh, S. A., Kim, M. N., . . . Woo, J. H. (2012). Comparison of sputum and nasopharyngeal swab specimens for molecular diagnosis of Mycoplasma pneumoniae, Chlamydophila pneumoniae, and Legionella pneumophila. *Annals of Laboratory Medicine, 32*(2), 133-138.

Chon, S. B., Kim, T. S., Oh, W. S., Lee, S. J., Han, S. S., & Kim, W. J. (2013). Pulmonary tuberculosis among patients hospitalised with community-acquired pneumonia in a tuberculosis-prevalent area. *International Journal of Tuberculosis and Lung Disease, 17*(12), 1626-1631.

Choudhury, G., Chalmers, J. D., Mandal, P., Akram, A. R., Murray, M. P., Short, P., . . . Hill, A. T. (2011). Physician judgement is a crucial adjunct to pneumonia severity scores in low-risk patients. *European Respiratory Journal, 38*(3), 643-648.

Christ-Crain, M., Jaccard-Stolz, D., Bingisser, R., Gencay, M. M., Huber, P. R., Tamm, M., & Muller, B. (2004). Effect of procalcitonin-guided treatment on antibiotic use and outcome in

lower respiratory tract infections: cluster-randomised, single-blinded intervention trial. *Lancet, 363*(9409), 600-607.

Christ-Crain, M., Stolz, D., Bingisser, R., Muller, C., Miedinger, D., Huber, P. R., . . . Muller, B. (2006). Procalcitonin guidance of antibiotic therapy in community-acquired pneumonia: a randomized trial. *American Journal of Respiratory and Critical Care Medicine, 174*(1), 84-93.

Christensen, D., Feldman, C., Rossi, P., Marrie, T., Blasi, F., Luna, C., . . . Ramirez, J. (2005). HIV infection does not influence clinical outcomes in hospitalized patients with bacterial community-acquired pneumonia: results from the CAPO international cohort study. *Clinical Infectious Diseases, 41*(4), 554-556.

Chuma, J., & Maina, T. (2012). Catastrophic health care spending and impoverishment in Kenya. *BMC Health Services Research, 12*, 413.

Cilloniz, C., Albert, R. K., Liapikou, A., Gabarrus, A., Rangel, E., Bello, S., . . . Torres, A. (2015). The Effect of Macrolide Resistance on the Presentation and Outcome of Patients Hospitalized for Streptococcus pneumoniae Pneumonia. *American Journal of Respiratory and Critical Care Medicine, 191*(11), 1265-1272.

Cilloniz, C., Torres, A., Polverino, E., Gabarrus, A., Amaro, R., Moreno, E., . . . Miro, J. M. (2014). Community-acquired lung respiratory infections in HIV-infected patients: microbial aetiology and outcome. *European Respiratory Journal, 43*(6), 1698-1708.

Claessens, Y. E., Debray, M. P., Tubach, F., Brun, A. L., Rammaert, B., Hausfater, P., . . . Duval, X. (2015). Early Chest Computed Tomography Scan to Assist Diagnosis and Guide Treatment Decision for Suspected Community-acquired Pneumonia. *American Journal of Respiratory and Critical Care Medicine, 192*(8), 974-982.

Cochrane Collaboration. (2014). Tool to Assess Risk of Bias in Cohort Studies. Retrieved from http://methods.cochrane.org/bias/sites/methods.cochrane.org.bias/files/uploads/Tool to Assess Risk of Bias in Cohort Studies.pdf

Coles, C. L., Mabula, K., Seidman, J. C., Levens, J., Mkocha, H., Munoz, B., . . . West, S. (2013). Mass distribution of azithromycin for trachoma control is associated with increased risk of azithromycin-resistant Streptococcus pneumoniae carriage in young children 6 months after treatment. *Clinical Infectious Diseases, 56*(11), 1519-1526.

Colice, G. L., Morley, M. A., Asche, C., & Birnbaum, H. G. (2004). Treatment costs of community-acquired pneumonia in an employed population. *Chest, 125*(6), 2140-2145.

Collins, G. S., Reitsma, J. B., Altman, D. G., & Moons, K. G. (2015). Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. *BMJ, 350*, g7594.

Confalonieri, M., Potena, A., Carbone, G., Porta, R. D., Tolley, E. A., & Umberto Meduri, G. (1999). Acute respiratory failure in patients with severe community-acquired pneumonia. A prospective randomized evaluation of noninvasive ventilation. *American Journal of Respiratory and Critical Care Medicine, 160*(5 Pt 1), 1585-1591.

Corrales-Medina, V. F., Musher, D. M., Shachkina, S., & Chirinos, J. A. (2013). Acute pneumonia and the cardiovascular system. *Lancet, 381*(9865), 496-505.

Corrales-Medina, V. F., Suh, K. N., Rose, G., Chirinos, J. A., Doucette, S., Cameron, D. W., & Fergusson, D. A. (2011). Cardiac complications in patients with community-acquired pneumonia: a systematic review and meta-analysis of observational studies. *PLoS Medicine, 8*(6), e1001048.

Correa Rde, A., Lundgren, F. L., Pereira-Silva, J. L., Frare e Silva, R. L., Cardoso, A. P., Lemos, A. C., . . . da Rocha, R. T. (2009). Brazilian guidelines for community-acquired pneumonia in immunocompetent adults - 2009. *Jornal Brasileiro de Pneumologia : Publicacao Oficial da Sociedade Brasileira de Pneumologia e Tisilogia, 35*(6), 574-601.

Cortellaro, F., Colombo, S., Coen, D., & Duca, P. G. (2012). Lung ultrasound is an accurate diagnostic tool for the diagnosis of pneumonia in the emergency department. *Emergency Medicine Journal, 29*(1), 19-23.

Cosentini, R., Brambilla, A. M., Aliberti, S., Bignamini, A., Nava, S., Maffei, A., . . . Pelosi, P. (2010). Helmet continuous positive airway pressure vs oxygen therapy to improve oxygenation in community-acquired pneumonia: a randomized, controlled trial. *Chest, 138*(1), 114-120.

Coulibaly, N., Duchassin, M., Darracq, M., Rey, J. L., Lamarque, G., Yapi, A., . . . N'Dri, K. (1986). Etude de la Biclinocilline dans le traitment des penumopathies bacteriennes hospitalieres a Abidjan. *Médecine d'Afrique Noire, 33*(1), 61-65.

Cruciani, M., Marcati, P., Malena, M., Bosco, O., Serpelloni, G., & Mengoli, C. (2002). Meta-analysis of diagnostic procedures for Pneumocystis carinii pneumonia in HIV-1-infected patients. *European Respiratory Journal, 20*(4), 982-989.

Cruciani, M., Scarparo, C., Malena, M., Bosco, O., Serpelloni, G., & Mengoli, C. (2004). Meta-analysis of BACTEC MGIT 960 and BACTEC 460 TB, with or without solid media, for detection of mycobacteria. *Journal of Clinical Microbiology, 42*(5), 2321-2325.

Crump, J. A., Ramadhani, H. O., Morrissey, A. B., Saganda, W., Mwako, M. S., Yang, L. Y., . . . Bartlett, J. A. (2012). Bacteremic disseminated tuberculosis in sub-saharan Africa: a prospective cohort study. *Clinical Infectious Diseases, 55*(2), 242-250.

Curran, A., Falco, V., Crespo, M., Martinez, X., Ribera, E., Villar del Saz, S., . . . Pahissa, A. (2008). Bacterial pneumonia in HIV-infected patients: use of the pneumonia severity index and impact of current management on incidence, aetiology and outcome. *HIV Medicine, 9*(8), 609-615.

Dajani, R., Zhang, Y., Taft, P. J., Travis, S. M., Starner, T. D., Olsen, A., . . . Engelhardt, J. F. (2005). Lysozyme secretion by submucosal glands protects the airway from bacterial infection. *American Journal of Respiratory Cell and Molecular Biology, 32*(6), 548-552.

Danel, C., Moh, R., Gabillard, D., Badje, A., Le Carrou, J., Ouassa, T., . . . Anglaret, X. (2015). A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa. *New England Journal of Medicine, 373*(9), 808-822.

Dawson, R., Masuka, P., Edwards, D. J., Bateman, E. D., Bekker, L. G., Wood, R., & Lawn, S. D. (2010). Chest radiograph reading and recording system: evaluation for tuberculosis screening in patients with advanced HIV. *International Journal of Tuberculosis and Lung Disease, 14*(1), 52-58.

Deeks, J. J., Dinnes, J., D'Amico, R., Sowden, A. J., Sakarovitch, C., Song, F., . . . Altman, D. G. (2003). Evaluating non-randomised intervention studies. *Health Technology Assessment, 7*(27), iii-x, 1-173.

Dellinger, R. P., Levy, M. M., Rhodes, A., Annane, D., Gerlach, H., Opal, S. M., . . . Surviving Sepsis Campaign Guidelines Committee including the Pediatric, S. (2013). Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Critical Care Medicine, 41*(2), 580-637.

Den Boer, J. W., & Yzerman, E. P. (2004). Diagnosis of Legionella infection in Legionnaires' disease. *European Journal of Clinical Microbiology and Infectious Diseases, 23*(12), 871-878.

DeRiemer, K., Kawamura, L. M., Hopewell, P. C., & Daley, C. L. (2007). Quantitative impact of human immunodeficiency virus infection on tuberculosis dynamics. *American Journal of Respiratory and Critical Care Medicine, 176*(9), 936-944.

Dheda, K., Barry, C. E., 3rd, & Maartens, G. (2016). Tuberculosis. *Lancet, 387*(10024), 1211-1226.

Diederen, B. M., & Peeters, M. F. (2006). Evaluation of two new immunochromatographic assays (Rapid U Legionella antigen test and SD Bioline Legionella antigen test) for detection of

Legionella pneumophila serogroup 1 antigen in urine. *Journal of Clinical Microbiology, 44*(8), 2991-2993.

Diez-Padrisa, N., Bassat, Q., Machevo, S., Quinto, L., Morais, L., Nhampossa, T., . . . Roca, A. (2010). Procalcitonin and C-reactive protein for invasive bacterial pneumonia diagnosis among children in Mozambique, a malaria-endemic area. *PloS One, 5*(10), e13226.

Ditommaso, S., Giacomuzzi, M., Gentile, M., & Zotti, C. M. (2008). Antibody detection and cross-reactivity among species and serogroups of Legionella by indirect immunofluorescence test. *Journal of Microbiological Methods, 75*(2), 350-353.

Dockrell, D. H., Marriott, H. M., Prince, L. R., Ridger, V. C., Ince, P. G., Hellewell, P. G., & Whyte, M. K. (2003). Alveolar macrophage apoptosis contributes to pneumococcal clearance in a resolving model of pulmonary infection. *J Immunol., 171*(10), 5380-5388.

Domoua, K., N'dhatz, M., Coulibaly, G., Traore, F., Ouattara, B., Achy, V., . . . Yapi, A. (1993). Pneumopathies aigues bacteriennes au cours de l'infection retrovirale aspects epidemiologiques, cliniques, radiologiques, bacteriologiques et evolutifs. *Médecine Tropicale, 53*(4), 505-509.

Dubowitz, G., Breyer, K., Lipnick, M., Sall, J. W., Feiner, J., Ikeda, K., . . . Bickler, P. E. (2013). Accuracy of the Lifebox pulse oximeter during hypoxia in healthy volunteers. *Anaesthesia, 68*(12), 1220-1223.

Duke, T., Graham, S. M., Cherian, M. N., Ginsburg, A. S., English, M., Howie, S., . . . Union Oxygen Systems Working, G. (2010a). Oxygen is an essential medicine: a call for international action. *International Journal of Tuberculosis and Lung Disease, 14*(11), 1362-1368.

Duke, T., Peel, D., Graham, S., Howie, S., Enarson, P. M., & Jacobson, R. (2010b). Oxygen concentrators: a practical guide for clinicians and technicians in developing countries. *Annals of Tropical Paediatrics, 30*(2), 87-101.

Duke, T., Peel, D., Wandi, F., Subhi, R., Sa'avu, M., & Matai, S. (2010c). Oxygen supplies for hospitals in Papua New Guinea: a comparison of the feasibility and cost-effectiveness of methods for different settings. *Papua New Guinea Medical Journal, 53*(3-4), 126-138.

Duke, T., Subhi, R., Peel, D., & Frey, B. (2009). Pulse oximetry: technology to reduce child mortality in developing countries. *Annals of Tropical Paediatrics, 29*(3), 165-175.

Duke, T., Wandi, F., Jonathan, M., Matai, S., Kaupa, M., Saavu, M., . . . Peel, D. (2008). Improved oxygen systems for childhood pneumonia: a multihospital effectiveness study in Papua New Guinea. *Lancet, 372*(9646), 1328-1333.

Dunser, M. W., Festic, E., Dondorp, A., Kissoon, N., Ganbat, T., Kwizera, A., . . . Schultz, M. J. (2012). Recommendations for sepsis management in resource-limited settings. *Intensive Care Medicine, 38*(4), 557-574.

Durand-Joly, I., Chabe, M., Soula, F., Delhaes, L., Camus, D., & Dei-Cas, E. (2005). Molecular diagnosis of Pneumocystis pneumonia. *FEMS Immunology and Medical Microbiology, 45*(3), 405-410.

Dworkin, M. S., Ward, J. W., Hanson, D. L., Jones, J. L., Kaplan, J. E., Adult, & Adolescent Spectrum of, H. I. V. D. P. (2001). Pneumococcal disease among human immunodeficiency virus-infected persons: incidence, risk factors, and impact of vaccination. *Clinical Infectious Diseases, 32*(5), 794-800.

Eagan, R., Twigg, H. L., 3rd, French, N., Musaya, J., Day, R. B., Zijlstra, E. E., . . . Gordon, S. B. (2007). Lung fluid immunoglobulin from HIV-infected subjects has impaired opsonic function against pneumococci. *Clinical Infectious Diseases, 44*(12), 1632-1638.

El Moussaoui, R., Opmeer, B. C., de Borgie, C. A., Nieuwkerk, P., Bossuyt, P. M., Speelman, P., & Prins, J. M. (2006). Long-term symptom recovery and health-related quality of life in patients with mild-to-moderate-severe community-acquired pneumonia. *Chest, 130*(4), 1165-1172.

El-Amin, A. M. (1978). Bacterial pneumonias in the rural society of Solwezi District of the North-Western Province of Zambia. *Medical Journal of Zambia, 12*(2), 42-45.

Eliakim-Raz, N., Robenshtok, E., Shefet, D., Gafter-Gvili, A., Vidal, L., Paul, M., & Leibovici, L. (2012). Empiric antibiotic coverage of atypical pathogens for community-acquired pneumonia in hospitalized adults. *Cochrane Database Syst Rev, 9*, Cd004418.

Enarson, P., La Vincente, S., Gie, R., Maganga, E., & Chokani, C. (2008). Implementation of an oxygen concentrator system in district hospital paediatric wards throughout Malawi. *Bulletin of the World Health Organization, 86*(5), 344-348.

Erard, V., Lamy, O., Bochud, P. Y., Bille, J., Cometta, A., & Calandra, T. (2004). Full-course oral levofloxacin for treatment of hospitalized patients with community-acquired pneumonia. *European Journal of Clinical Microbiology and Infectious Diseases, 23*(2), 82-88.

Espana, P. P., Capelastegui, A., Gorordo, I., Esteban, C., Oribe, M., Ortega, M., . . . Quintana, J. M. (2006). Development and validation of a clinical prediction rule for severe community-acquired pneumonia. *American Journal of Respiratory and Critical Care Medicine, 174*(11), 1249-1256.

Etyang, A. O., & Scott, J. A. (2013). Medical causes of admissions to hospital among adults in Africa: a systematic review. *Glob Health Action, 6*, 1-14.

Evans, G. E., Murdoch, D. R., Anderson, T. P., Potter, H. C., George, P. M., & Chambers, S. T. (2003). Contamination of Qiagen DNA extraction kits with Legionella DNA. *Journal of Clinical Microbiology, 41*(7), 3452-3453.

Evans, H.-G. T., Mahmood, N., Fullerton, D. G., Rylance, J., Gonani, A., Gordon, S. B., . . . Allain, T. J. (2012). Oxygen saturations of medical inpatients in a Malawian hospital: cross-sectional study of oxygen supply and demand. . *Pneumonia, 1*, 3-6.

Everett, D. B., Mukaka, M., Denis, B., Gordon, S. B., Carrol, E. D., van Oosterhout, J. J., . . . Heyderman, R. S. (2011). Ten years of surveillance for invasive Streptococcus pneumoniae during the era of antiretroviral scale-up and cotrimoxazole prophylaxis in Malawi. *PloS One, 6*(3), e17765.

Ewig, S. (2014). The pneumonia triad. In J. D. Chalmers, M. W. Pletz, & S. Aliberti (Eds.), *Community-acquired pneumonia* (Vol. 63, pp. 13-24): European Respiratory Society.

Ewig, S., Birkner, N., Strauss, R., Schaefer, E., Pauletzki, J., Bischoff, H., . . . Hoeffken, G. (2009). New perspectives on community-acquired pneumonia in 388 406 patients. Results from a nationwide mandatory performance measurement programme in healthcare quality. *Thorax, 64*(12), 1062-1069.

Ezzati, M., & Kammen, D. (2001). Indoor air pollution from biomass combustion and acute respiratory infections in Kenya: an exposure-response study. *Lancet, 358*(9282), 619-624.

Feasey, N. A., Banada, P. P., Howson, W., Sloan, D. J., Mdolo, A., Boehme, C., . . . Alland, D. (2013). Evaluation of Xpert MTB/RIF for detection of tuberculosis from blood samples of HIV-infected adults confirms Mycobacterium tuberculosis bacteremia as an indicator of poor prognosis. *Journal of Clinical Microbiology, 51*(7), 2311-2316.

Feasey, N. A., Dougan, G., Kingsley, R. A., Heyderman, R. S., & Gordon, M. A. (2012). Invasive non-typhoidal salmonella disease: an emerging and neglected tropical disease in Africa. *Lancet, 379*(9835), 2489-2499.

Feasey, N. A., Houston, A., Mukaka, M., Komrower, D., Mwalukomo, T., Tenthani, L., . . . Heyderman, R. S. (2014). A reduction in adult blood stream infection and case fatality at a large African hospital following antiretroviral therapy roll-out. *PloS One, 9*(3), e92226.

Feikin, D. R., Feldman, C., Schuchat, A., & Janoff, E. N. (2004). Global strategies to prevent bacterial pneumonia in adults with HIV disease. *Lancet Infectious Diseases, 4*(7), 445-455.

Feikin, D. R., Njenga, M. K., Bigogo, G., Aura, B., Aol, G., Audi, A., . . . Breiman, R. F. (2012). Etiology and Incidence of viral and bacterial acute respiratory illness among older children and adults in rural western Kenya, 2007-2010. *PloS One, 7*(8), e43656.

Feldman, C., Brink, A. J., Richards, G., Maartens, G., & Bateman, E. (2007a). Management of community-acquired pneumonia. *South African Medical Journal, 97*(12), 1296-1306.

Feldman, C., Glatthaar, M., Morar, R., Mahomed, A. G., Kaka, S., Cassel, M., & Klugman, K. P. (1999). Bacteremic pneumococcal pneumonia in HIV-seropositive and HIV-seronegative adults. *Chest, 116*(1), 107-114.

Feldman, C., Kallenbach, J. M., Levy, H., Reinach, S. G., Hurwitz, M. D., Thorburn, J. R., & Koornhof, H. J. (1989). Community-acquired pneumonia of diverse aetiology: prognostic features in patients admitted to an intensive care unit and a "severity of illness" core. *Intensive Care Medicine, 15*(5), 302-307.

Feldman, C., Kallenbach, J. M., Levy, H., Thorburn, J. R., Hurwitz, M. D., & Koornhof, H. J. (1991). Comparison of bacteraemic community-acquired lobar pneumonia due to Streptococcus pneumoniae and Klebsiella pneumoniae in an intensive care unit. *Respiration; international review of thoracic diseases, 58*(5-6), 265-270.

Feldman, C., Klugman, K. P., Yu, V. L., Ortqvist, A., Choiu, C. C., Chedid, M. B., . . . Wagener, M. (2007b). Bacteraemic pneumococcal pneumonia: impact of HIV on clinical presentation and outcome. *Journal of Infection, 55*(2), 125-135.

Feldman, C., Mahomed, A. G., Mahida, P., Morar, R., Schoeman, A., Mpe, J., . . . Wadee, A. (1996). IgG subclasses in previously healthy adult patients with acute community-acquired pneumonia. *South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde, 86*(5 Suppl), 600-602.

Feldman, C., Ross, S., Mahomed, A. G., Omar, J., & Smith, C. (1995). The aetiology of severe community-acquired pneumonia and its impact on initial, empiric, antimicrobial chemotherapy. *Respiratory Medicine, 89*(3), 187-192.

Fernandez-Sola, J., Junque, A., Estruch, R., Monforte, R., Torres, A., & Urbano-Marquez, A. (1995). High alcohol intake as a risk and prognostic factor for community-acquired pneumonia. *Archives of Internal Medicine, 155*(15), 1649-1654.

Ferrer, M., Cosentini, R., & Nava, S. (2012). The use of non-invasive ventilation during acute respiratory failure due to pneumonia. *European Journal of Internal Medicine, 23*(5), 420-428.

Ferrer, M., & Torres, A. (2015). Noninvasive ventilation for acute respiratory failure. *Current Opinion in Critical Care, 21*(1), 1-6.

Fiberesima, F. P. D., & Onwuchekwa, A. C. (2007). The prevalence of HIV and TB in acute community-acquired pneumonia. *African Journal of Respiratory Medicine, 3*, 23-26.

Fiberesima, F. P. D., & Onwuchekwa, A. C. (2008). Community acquired pneumonia in Port Harcourt Rivers State of Nigeria. *The Central African journal of medicine, 54*(1-4), 1-8.

Fielding, K. L., Charalambous, S., Hoffmann, C. J., Johnson, S., Tlali, M., Dorman, S. E., . . . Grant, A. D. (2015). Evaluation of a point-of-care tuberculosis test-and-treat algorithm on early mortality in people with HIV accessing antiretroviral therapy (TB Fast Track study): study protocol for a cluster randomised controlled trial. *Trials, 16*, 125.

File, T. M., Jr., & Marrie, T. J. (2010). Burden of community-acquired pneumonia in North American adults. *Postgraduate Medicine, 122*(2), 130-141.

File, T. M., Jr., Segreti, J., Dunbar, L., Player, R., Kohler, R., Williams, R. R., . . . Rubin, A. (1997). A multicenter, randomized study comparing the efficacy and safety of intravenous and/or oral levofloxacin versus ceftriaxone and/or cefuroxime axetil in treatment of adults with community-acquired pneumonia. *Antimicrobial Agents and Chemotherapy, 41*(9), 1965-1972.

Fine, M. J., Auble, T. E., Yealy, D. M., Hanusa, B. H., Weissfeld, L. A., Singer, D. E., . . . Kapoor, W. N. (1997a). A prediction rule to identify low-risk patients with community-acquired pneumonia. *New England Journal of Medicine, 336*(4), 243-250.

Fine, M. J., Hough, L. J., Medsger, A. R., Li, Y. H., Ricci, E. M., Singer, D. E., . . . Kapoor, W. N. (1997b). The hospital admission decision for patients with community-acquired pneumonia. Results from the pneumonia Patient Outcomes Research Team cohort study. *Archives of Internal Medicine, 157*(1), 36-44.

Fine, M. J., Smith, M. A., Carson, C. A., Mutha, S. S., Sankey, S. S., Weissfeld, L. A., & Kapoor, W. N. (1996). Prognosis and outcomes of patients with community-acquired pneumonia. A meta-analysis. *JAMA, 275*(2), 134-141.

Fisk, D. T., Meshnick, S., & Kazanjian, P. H. (2003). Pneumocystis carinii pneumonia in patients in the developing world who have acquired immunodeficiency syndrome. *Clinical Infectious Diseases, 36*(1), 70-78.

Food and Drug Administration. (1996). Protection of human subjects; informed consent--FDA. Final rule. *Federal Register, 61*(192), 51498-51533.

French, N., Gordon, S. B., Mwalukomo, T., White, S. A., Mwaiponya, M., Longwe, H., . . . Gilks, C. F. (2010). A trial of a 7-valent pneumococcal conjugate vaccine in HIV-infected adults. . *New England Journal of Medicine, 362*, 812-822.

French, N., Williams, G., Williamson, V., Bhatt, S. M., & Gilks, C. F. (2002). The radiographic appearance of pneumococcal pneumonia in adults is unaltered by HIV-1-infection in hospitalized Kenyans. *AIDS (London, England), 16*(15), 2095-2096.

Froes, F., Diniz, A., Mesquita, M., Serrado, M., & Nunes, B. (2013). Hospital admissions of adults with community-acquired pneumonia in Portugal between 2000 and 2009. *European Respiratory Journal, 41*(5), 1141-1146.

Fry, A. M., Shay, D. K., Holman, R. C., Curns, A. T., & Anderson, L. J. (2005). Trends in hospitalizations for pneumonia among persons aged 65 years or older in the United States, 1988-2002. *JAMA, 294*(21), 2712-2719.

Fullerton, D. G., Semple, S., Kalambo, F., Suseno, A., Malamba, R., Henderson, G., . . . Gordon, S. B. (2009). Biomass fuel use and indoor air pollution in homes in Malawi. *Occupational and Environmental Medicine, 66*(11), 777-783.

Fulmer, J. D., & Snider, G. L. (1984). American College of Chest Physicians/National Heart, Lung, and Blood Institute National Conference on Oxygen Therapy. *Heart and Lung, 13*(5), 550-562.

Furrer, H., Egger, M., Opravil, M., Bernasconi, E., Hirschel, B., Battegay, M., . . . Malinverni, R. (1999). Discontinuation of primary prophylaxis against Pneumocystis carinii pneumonia in HIV-1-infected adults treated with combination antiretroviral therapy. Swiss HIV Cohort Study. *New England Journal of Medicine, 340*(17), 1301-1306.

Garin, N., Genne, D., Carballo, S., Chuard, C., Eich, G., Hugli, O., . . . Perrier, A. (2014). beta-Lactam monotherapy vs beta-lactam-macrolide combination treatment in moderately severe community-acquired pneumonia: a randomized noninferiority trial. *JAMA Intern Med, 174*(12), 1894-1901.

Gattarello, S. (2015). What Is New in Antibiotic Therapy in Community-Acquired Pneumonia? An Evidence-Based Approach Focusing on Combined Therapy. *Current Infectious Disease Reports, 17*(10), 501.

Gattarello, S., Borgatta, B., Sole-Violan, J., Valles, J., Vidaur, L., Zaragoza, R., . . . Community-Acquired Pneumonia en la Unidad de Cuidados Intensivos, I. I. S. I. (2014). Decrease in mortality in severe community-acquired pneumococcal pneumonia: impact of improving antibiotic strategies (2000-2013). *Chest, 146*(1), 22-31.

Gattarello, S., Lagunes, L., Vidaur, L., Sole-Violan, J., Zaragoza, R., Valles, J., . . . Rello, J. (2015). Improvement of antibiotic therapy and ICU survival in severe non-pneumococcal community-acquired pneumonia: a matched case-control study. *Critical Care (London, England), 19*, 335.

Gea, J., Roca, J., Torres, A., Agusti, A. G., Wagner, P. D., & Rodriguez-Roisin, R. (1991). Mechanisms of abnormal gas exchange in patients with pneumonia. *Anesthesiology, 75*(5), 782-789.

Genne, D., Kaiser, L., Kinge, T. N., & Lew, D. (2003). Community-acquired pneumonia: causes of treatment failure in patients enrolled in clinical trials. *Clinical Microbiology and Infection, 9*(9), 949-954.

Genne, D., Sommer, R., Kaiser, L., Saaidia, A., Pasche, A., Unger, P. F., & Lew, D. (2006). Analysis of factors that contribute to treatment failure in patients with community-acquired pneumonia. *European Journal of Clinical Microbiology and Infectious Diseases, 25*(3), 159-166.

Getahun, H., Matteelli, A., Chaisson, R. E., & Raviglione, M. (2015). Latent Mycobacterium tuberculosis infection. *New England Journal of Medicine, 372*(22), 2127-2135.

Giamarellos-Bourboulis, E. J. (2008). Immunomodulatory therapies for sepsis: unexpected effects with macrolides. *International Journal of Antimicrobial Agents, 32 Suppl 1*, S39-43.

Gilks, C. F., Ojoo, S. A., Ojoo, J. C., Brindle, R. J., Paul, J., Batchelor, B. I., . . . et al. (1996). Invasive pneumococcal disease in a cohort of predominantly HIV-1 infected female sex-workers in Nairobi, Kenya. *Lancet, 347*(9003), 718-723.

Ginsburg, A. S., Tinkham, L., Riley, K., Kay, N. A., Klugman, K. P., & Gill, C. J. (2013). Antibiotic non-susceptibility among Streptococcus pneumoniae and Haemophilus influenzae isolates identified in African cohorts: a meta-analysis of three decades of published studies. *International Journal of Antimicrobial Agents, 42*(6), 482-491.

Girardi, E., Sabin, C. A., d'Arminio Monforte, A., Hogg, B., Phillips, A. N., Gill, M. J., . . . Antiretroviral Therapy Cohort, C. (2005). Incidence of Tuberculosis among HIV-infected patients receiving highly active antiretroviral therapy in Europe and North America. *Clinical Infectious Diseases, 41*(12), 1772-1782.

Glennie, S. J., Sepako, E., Mzinza, D., Harawa, V., Miles, D. J., Jambo, K. C., . . . Heyderman, R. S. (2011). Impaired CD4 T cell memory response to Streptococcus pneumoniae precedes CD4 T cell depletion in HIV-infected Malawian adults. *PloS One, 6*(9), e25610.

Gonzales, R., & Sande, M. A. (2000). Uncomplicated acute bronchitis. *Annals of Internal Medicine, 133*(12), 981-991.

Gordon, S. B., Chaponda, M., Walsh, A. L., Whitty, C. J. M., Gordon, M. A., Machili, C. E., . . . Molyneux, M. E. (2002). Pneumococcal disease in HIV-infected Malawian adults: acute mortality and long-term survival. *AIDS (London, England), 16*(10), 1409-1417.

Gordon, S. B., Jarman, E. R., Kanyanda, S., French, N., Pridmore, A. C., Zijlstra, E. E., . . . Read, R. C. (2005). Reduced interleukin-8 response to Streptococcus pneumoniae by alveolar macrophages from adults with HIV/AIDS. *AIDS, 19*(11), 1197-1200.

Government of Malawi. (2014). Global AIDS Response Progress Report: Malawi Progress Report for 2013. Retrieved from http://www.unaids.org/sites/default/files/country/documents/MWI_narrative_report_2014.pdf

Graffelman, A. W., Willemssen, F. E., Zonderland, H. M., Neven, A. K., Kroes, A. C., & van den Broek, P. J. (2008). Limited value of chest radiography in predicting aetiology of lower respiratory tract infection in general practice. *British Journal of General Practice, 58*(547), 93-97.

Grant, A. D., Charalambous, S., Tlali, M., Johnson, S., Dorman, S. E., Hoffman, C., . . . Fielding, K. (2016). *Empirical TB treatment in advanced HIV disease: Results of the TB Fast Track trial*. Paper presented at the Conference on Retorviruses and Opportunistic Infections, Boston, Massachusetts, US.

Griffin, M. R., Zhu, Y., Moore, M. R., Whitney, C. G., & Grijalva, C. G. (2013). U.S. hospitalizations for pneumonia after a decade of pneumococcal vaccination. *New England Journal of Medicine, 369*(2), 155-163.

Guest, J. F., & Morris, A. (1997). Community-acquired pneumonia: the annual cost to the National Health Service in the UK. *European Respiratory Journal, 10*(7), 1530-1534.

Gupta, R. K., Lucas, S. B., Fielding, K. L., & Lawn, S. D. (2015). Prevalence of tuberculosis in post-mortem studies of HIV-infected adults and children in resource-limited settings: a systematic review and meta-analysis. *AIDS, 29*(15), 1987-2002.

Gupta-Wright, A., Peters, J. A., Flach, C., & Lawn, S. D. (2016). Detection of lipoarabinomannan (LAM) in urine is an independent predictor of mortality risk in patients receiving treatment for HIV-associated tuberculosis in sub-Saharan Africa: a systematic review and meta-analysis. *BMC Medicine, 14*(1), 53.

Gutierrez, F., Masia, M., Mirete, C., Soldan, B., Rodriguez, J. C., Padilla, S., . . . Martin-Hidalgo, A. (2006). The influence of age and gender on the population-based incidence of community-acquired pneumonia caused by different microbial pathogens. *Journal of Infection, 53*(3), 166-174.

Hackel, M., Lascols, C., Bouchillon, S., Hilton, B., Morgenstern, D., & Purdy, J. (2013). Serotype prevalence and antibiotic resistance in Streptococcus pneumoniae clinical isolates among global populations. *Vaccine, 31*(42), 4881-4887.

Hagaman, J. T., Rouan, G. W., Shipley, R. T., & Panos, R. J. (2009). Admission chest radiograph lacks sensitivity in the diagnosis of community-acquired pneumonia. *American Journal of the Medical Sciences, 337*(4), 236-240.

Halm, E. A., Fine, M. J., Kapoor, W. N., Singer, D. E., Marrie, T. J., & Siu, A. L. (2002). Instability on hospital discharge and the risk of adverse outcomes in patients with pneumonia. *Archives of Internal Medicine, 162*(11), 1278-1284.

Halm, E. A., Fine, M. J., Marrie, T. J., Coley, C. M., Kapoor, W. N., Obrosky, D. S., & Singer, D. E. (1998). Time to clinical stability in patients hospitalized with community-acquired pneumonia: implications for practice guidelines. *JAMA, 279*(18), 1452-1457.

Han, K., Song, K., & Choi, B. W. (2016). How to Develop, Validate, and Compare Clinical Prediction Models Involving Radiological Parameters: Study Design and Statistical Methods. *Korean J Radiol, 17*(3), 339-350.

Hansell, D. M., Bankier, A. A., MacMahon, H., McLoud, T. C., Muller, N. L., & Remy, J. (2008). Fleischner Society: glossary of terms for thoracic imaging. *Radiology, 246*(3), 697-722.

Hargreaves, N. J., Kadzakumanja, O., Phiri, S., Lee, C. H., Tang, X., Salaniponi, F. M., . . . Squire, S. B. (2001). Pneumocystis carinii pneumonia in patients being registered for smear-negative pulmonary tuberculosis in Malawi. *Transactions of the Royal Society of Tropical Medicine and Hygiene, 95*(4), 402-408.

Harries, A. D., Lawn, S. D., Suthar, A. B., & Granich, R. (2015). Benefits of combined preventive therapy with co-trimoxazole and isoniazid in adults living with HIV: time to consider a fixed-dose, single tablet coformulation. *Lancet Infectious Diseases, 15*(12), 1492-1496.

Harries, A. D., Makombe, S. D., Libamba, E., & Schouten, E. J. (2011). Why did the scale-up of HIV treatment work? A case example from Malawi. *Journal of Acquired Immune Deficiency Syndromes, 57 Suppl 2*, S64-67.

Harries, A. D., Speare, R., & Wirima, J. J. (1988a). A profile of respiratory disease in an African medical ward. *Journal of the Royal College of Physicians of London, 22*(2), 109-113.

Harries, A. D., & Wirima, J. J. (1988b). Pneumonia in adult admissions to Kamuzu Central Hospital, Lilongwe: clinical features and response to treatment. *Medical Quarterly, 5*(2), 39-43.

Hartung, T. K., Chimbayo, D., van Oosterhout, J. J., Chikaonda, T., van Doornum, G. J., Claas, E. C., . . . Zijlstra, E. E. (2011). Etiology of suspected pneumonia in adults admitted to a high-dependency unit in Blantyre, Malawi. *American Journal of Tropical Medicine and Hygiene, 85*(1), 105-112.

Hash, R. B., Stephens, J. L., Laurens, M. B., & Vogel, R. L. (2000). The relationship between volume status, hydration, and radiographic findings in the diagnosis of community-acquired pneumonia. *Journal of Family Practice, 49*(9), 833-837.

Heinsbroek, E., Tafatatha, T., Phiri, A., Ngwira, B., Crampin, A. C., Read, J. M., & French, N. (2015). Persisting high prevalence of pneumococcal carriage among HIV-infected adults receiving antiretroviral therapy in Malawi: a cohort study. *AIDS, 29*(14), 1837-1844.

Helbig, J. H., Uldum, S. A., Luck, P. C., & Harrison, T. G. (2001). Detection of Legionella pneumophila antigen in urine samples by the BinaxNOW immunochromatographic assay and comparison with both Binax Legionella Urinary Enzyme Immunoassay (EIA) and Biotest Legionella Urin Antigen EIA. *Journal of Medical Microbiology, 50*(6), 509-516.

Hilbert, G., Gruson, D., Vargas, F., Valentino, R., Gbikpi-Benissan, G., Dupon, M., . . . Cardinaud, J. P. (2001). Noninvasive ventilation in immunosuppressed patients with pulmonary infiltrates, fever, and acute respiratory failure. *New England Journal of Medicine, 344*(7), 481-487.

Hill, S. E., Njie, O., Sanneh, M., Jallow, M., Peel, D., Njie, M., . . . Howie, S. R. (2009). Oxygen for treatment of severe pneumonia in The Gambia, West Africa: a situational analysis. *International Journal of Tuberculosis and Lung Disease, 13*(5), 587-593.

Hirschtick, R. E., Glassroth, J., Jordan, M. C., Wilcosky, T. C., Wallace, J. M., Kvale, P. A., . . . Hopewell, P. C. (1995). Bacterial pneumonia in persons infected with the human immunodeficiency virus. Pulmonary Complications of HIV Infection Study Group. *New England Journal of Medicine, 333*(13), 845-851.

Hoffken, G., Lorenz, J., Kern, W., Welte, T., Bauer, T., Dalhoff, K., . . . Sitter, H. (2010). Guidelines of the Paul-Ehrlich-Society of Chemotherapy, the German Respiratory Diseases Society, the German Infectious Diseases Society and of the Competence Network CAPNETZ for the Management of Lower Respiratory Tract Infections and Community-acquired Pneumonia. *Pneumologie, 64*(3), 149-154.

Holst, L. B., Haase, N., Wetterslev, J., Wernerman, J., Guttormsen, A. B., Karlsson, S., . . . Scandinavian Critical Care Trials, G. (2014). Lower versus higher hemoglobin threshold for transfusion in septic shock. *New England Journal of Medicine, 371*(15), 1381-1391.

Hoogewerf, M., Oosterheert, J. J., Hak, E., Hoepelman, I. M., & Bonten, M. J. (2006). Prognostic factors for early clinical failure in patients with severe community-acquired pneumonia. *Clinical Microbiology and Infection, 12*(11), 1097-1104.

Hopstaken, R. M., Muris, J. W., Knottnerus, J. A., Kester, A. D., Rinkens, P. E., & Dinant, G. J. (2003). Contributions of symptoms, signs, erythrocyte sedimentation rate, and C-reactive

protein to a diagnosis of pneumonia in acute lower respiratory tract infection. *British Journal of General Practice, 53*(490), 358-364.

Hopstaken, R. M., Witbraad, T., van Engelshoven, J. M., & Dinant, G. J. (2004). Inter-observer variation in the interpretation of chest radiographs for pneumonia in community-acquired lower respiratory tract infections. *Clinical Radiology, 59*(8), 743-752.

Horo, K., Gode, V. C., Ahui, J. M., Kouassi, A. B., Djereke, G. B., Cardenat, M., . . . Aka-Danguy, E. (2009). Pneumoni par le VIH: etude preliminaire prospective. *Revue de Pneumologie Clinique, 65*, 137-142.

Hosseinipour, M. C., Bisson, G. P., Miyahara, S., Sun, X., Moses, A., Riviere, C., . . . Adult, A. C. T. G. A. S. T. (2016). Empirical tuberculosis therapy versus isoniazid in adult outpatients with advanced HIV initiating antiretroviral therapy (REMEMBER): a multicountry open-label randomised controlled trial. *Lancet, 387*(10024), 1198-1209.

Howie, S. R., Hill, S., Ebonyi, A., Krishnan, G., Njie, O., Sanneh, M., . . . Adegbola, R. A. (2009). Meeting oxygen needs in Africa: an options analysis from the Gambia. *Bulletin of the World Health Organization, 87*(10), 763-771.

Hraiech, S., Alingrin, J., Dizier, S., Brunet, J., Forel, J. M., La Scola, B., . . . Pauly, V. (2013). Time to intubation is associated with outcome in patients with community-acquired pneumonia. *PloS One, 8*(9), e74937.

Huijts, S. M., Pride, M. W., Vos, J. M., Jansen, K. U., Webber, C., Gruber, W., . . . Bonten, M. J. (2013). Diagnostic accuracy of a serotype-specific antigen test in community-acquired pneumonia. *Eur Respir J, 42*(5), 1283-1290.

Huson, M. A., Grobusch, M. P., & van der Poll, T. (2015). The effect of HIV infection on the host response to bacterial sepsis. *Lancet Infectious Diseases, 15*(1), 95-108.

Isenman, H. L., Chambers, S. T., Pithie, A. D., MacDonald, S. L., Hegarty, J. M., Fenwick, J. L., . . . Murdoch, D. R. (2016). Legionnaires' disease caused by Legionella longbeachae: Clinical features and outcomes of 107 cases from an endemic area. *Respirology*.

Isturiz, R. E., Luna, C. M., & Ramirez, J. (2010). Clinical and economic burden of pneumonia among adults in Latin America. *International Journal of Infectious Diseases, 14*(10), e852-856.

Jackson, M. L., Nelson, J. C., & Jackson, L. A. (2009). Risk factors for community-acquired pneumonia in immunocompetent seniors. *Journal of the American Geriatrics Society, 57*(5), 882-888.

Jackson, M. L., Neuzil, K. M., Thompson, W. W., Shay, D. K., Yu, O., Hanson, C. A., & Jackson, L. A. (2004). The burden of community-acquired pneumonia in seniors: results of a population-based study. *Clinical Infectious Diseases, 39*(11), 1642-1650.

Jacob, S. T., Banura, P., Baeten, J. M., Moore, C. C., Meya, D., Nakiyingi, L., . . . Scheld, W. M. (2012). The impact of early monitored management on survival in hospitalized adult Ugandan patients with severe sepsis: a prospective intervention study*. *Critical Care Medicine, 40*(7), 2050-2058.

Jacob, S. T., Lim, M., Banura, P., Bhagwanjee, S., Bion, J., Cheng, A. C., . . . West, T. E. (2013a). Integrating sepsis management recommendations into clinical care guidelines for district hospitals in resource-limited settings: the necessity to augment new guidelines with future research. *BMC Medicine, 11*, 107.

Jacob, S. T., Moore, C. C., Banura, P., Pinkerton, R., Meya, D., Opendi, P., . . . Scheld, W. M. (2009). Severe sepsis in two Ugandan hospitals: a prospective observational study of management and outcomes in a predominantly HIV-1 infected population. *PloS One, 4*(11), e7782.

Jacob, S. T., Pavlinac, P. B., Nakiyingi, L., Banura, P., Baeten, J. M., Morgan, K., . . . Scheld, W. M. (2013b). Mycobacterium tuberculosis bacteremia in a cohort of hiv-infected patients hospitalized with severe sepsis in uganda-high frequency, low clinical suspicion [corrected] and derivation of a clinical prediction score. *PloS One, 8*(8), e70305.

Jain, S., Self, W. H., Wunderink, R. G., Fakhran, S., Balk, R., Bramley, A. M., . . . Team, C. E. S. (2015). Community-Acquired Pneumonia Requiring Hospitalization among U.S. Adults. *New England Journal of Medicine, 373*(5), 415-427.

Jambo, K. C., Banda, D. H., Afran, L., Kankwatira, A. M., Malamba, R. D., Allain, T. J., . . . Mwandumba, H. C. (2014a). Asymptomatic HIV-infected individuals on antiretroviral therapy exhibit impaired lung CD4(+) T-cell responses to mycobacteria. *American Journal of Respiratory and Critical Care Medicine, 190*(8), 938-947.

Jambo, K. C., Banda, D. H., Kankwatira, A. M., Sukumar, N., Allain, T. J., Heyderman, R. S., . . . Mwandumba, H. C. (2014b). Small alveolar macrophages are infected preferentially by HIV and exhibit impaired phagocytic function. *Mucosal Immunology, 7*(5), 1116-1126.

Jambo, K. C., Sepako, E., Fullerton, D. G., Mzinza, D., Glennie, S., Wright, A. K., . . . Gordon, S. B. (2011). Bronchoalveolar CD4+ T cell responses to respiratory antigens are impaired in HIV-infected adults. *Thorax, 66*(5), 375-382.

Jary, H., Mallewa, J., Nyirenda, M., Faragher, B., Heyderman, R., Peterson, I., . . . Mortimer, K. (2015). Study protocol: the effects of air pollution exposure and chronic respiratory

disease on pneumonia risk in urban Malawian adults--the Acute Infection of the Respiratory Tract Study (The AIR Study). *BMC Pulmonary Medicine, 15*, 96.

Jasti, H., Mortensen, E. M., Obrosky, D. S., Kapoor, W. N., & Fine, M. J. (2008). Causes and risk factors for rehospitalization of patients hospitalized with community-acquired pneumonia. *Clinical Infectious Diseases, 46*(4), 550-556.

Jenkins, S. G., & Farrell, D. J. (2009). Increase in pneumococcus macrolide resistance, United States. *Emerging Infectious Diseases, 15*(8), 1260-1264.

Jinno, S., & Jacobs, M. R. (2012). Pneumonia Due to Drug-Resistant Streptococcus pneumoniae. *Current Infectious Disease Reports, 14*(3), 292-299.

Johansson, N., Kalin, M., Tiveljung-Lindell, A., Giske, C. G., & Hedlund, J. (2010). Etiology of community-acquired pneumonia: increased microbiological yield with new diagnostic methods. *Clinical Infectious Diseases, 50*(2), 202-209.

Jokinen, J., & Scott, J. A. (2010). Estimating the proportion of pneumonia attributable to pneumococcus in Kenyan adults: latent class analysis. *Epidemiology, 21*(5), 719-725.

Jounai, N., Kobiyama, K., Takeshita, F., & Ishii, K. J. (2012). Recognition of damage-associated molecular patterns related to nucleic acids during inflammation and vaccination. *Front Cell Infect Microbiol, 2*, 168.

Kadioglu, A., De Filippo, K., Bangert, M., Fernandes, V. E., Richards, L., Jones, K., . . . Hogg, N. (2011). The integrins Mac-1 and alpha4beta1 perform crucial roles in neutrophil and T cell recruitment to lungs during Streptococcus pneumoniae infection. *Journal of Immunology, 186*(10), 5907-5915.

Kaplan, V., Angus, D. C., Griffin, M. F., Clermont, G., Scott Watson, R., & Linde-Zwirble, W. T. (2002). Hospitalized community-acquired pneumonia in the elderly: age- and sex-related patterns of care and outcome in the United States. *American Journal of Respiratory and Critical Care Medicine, 165*(6), 766-772.

Kaplan, V., Clermont, G., Griffin, M. F., Kasal, J., Watson, R. S., Linde-Zwirble, W. T., & Angus, D. C. (2003). Pneumonia: still the old man's friend? *Archives of Internal Medicine, 163*(3), 317-323.

Karageorgopoulos, D. E., Qu, J. M., Korbila, I. P., Zhu, Y. G., Vasileiou, V. A., & Falagas, M. E. (2013). Accuracy of beta-D-glucan for the diagnosis of Pneumocystis jirovecii pneumonia: a meta-analysis. *Clinical Microbiology and Infection, 19*(1), 39-49.

Kariuki, S., & Dougan, G. (2014). Antibacterial resistance in sub-Saharan Africa: an underestimated emergency. *Annals of the New York Academy of Sciences, 1323*, 43-55.

Kellum, J. A., Kong, L., Fink, M. P., Weissfeld, L. A., Yealy, D. M., Pinsky, M. R., . . . Gen, I. M. S. I. (2007). Understanding the inflammatory cytokine response in pneumonia and sepsis: results of the Genetic and Inflammatory Markers of Sepsis (GenIMS) Study. *Archives of Internal Medicine, 167*(15), 1655-1663.

Kelly, C. A., Upex, A., & Bateman, D. N. (2004). Comparison of consciousness level assessment in the poisoned patient using the alert/verbal/painful/unresponsive scale and the Glasgow Coma Scale. *Annals of Emergency Medicine, 44*(2), 108-113.

Khalil, A., Kelen, G., & Rothman, R. E. (2007). A simple screening tool for identification of community-acquired pneumonia in an inner city emergency department. *Emergency Medicine Journal, 24*(5), 336-338.

Klare, B., Kubini, R., & Ewig, S. (2002). [Risk factors for pneumonia in patients with cardiovascular diseases]. *Pneumologie, 56*(12), 781-788.

Klesney-Tait, J., Keck, K., Li, X., Gilfillan, S., Otero, K., Baruah, S., . . . Colonna, M. (2013). Transepithelial migration of neutrophils into the lung requires TREM-1. *Journal of Clinical Investigation, 123*(1), 138-149.

Knapp, S., von Aulock, S., Leendertse, M., Haslinger, I., Draing, C., Golenbock, D. T., & van der Poll, T. (2008). Lipoteichoic acid-induced lung inflammation depends on TLR2 and the concerted action of TLR4 and the platelet-activating factor receptor. *Journal of Immunology, 180*(5), 3478-3484.

Ko, W. C., Paterson, D. L., Sagnimeni, A. J., Hansen, D. S., Von Gottberg, A., Mohapatra, S., . . . Yu, V. L. (2002). Community-acquired Klebsiella pneumoniae bacteremia: global differences in clinical patterns. *Emerging Infectious Diseases, 8*(2), 160-166.

Kobashi, Y., Yoshida, K., Miyashita, N., Niki, Y., & Matsushima, T. (2007). Evaluating the use of a Streptococcus pneumoniae urinary antigen detection kit for the management of community-acquired pneumonia in Japan. *Respiration, 74*(4), 387-393.

Koffi, N., Ngom, A., Kouassi, B., Aka-Danguy, E., & Tchamran, M. (1997). Bacterial lung diseases from common bacteria during HIV infection in African adults hospitalized in Abidjan, Cote d'Ivoire. [French]. *Bulletin de la Societe de pathologie exotique (1990), 90 (5)*, 370-372.

Koffi, N., Ngom, A., Kouassi, B., Horo, K., Mansare, L., & Aka-Danguy, E. (2001). Evaluation of the probabilist antibiotherapy in bacterial-like acute pneumonias hospitalised in Africa. *Bulletin de la Société de Pathologie Exotique, 94*(5), 397-400.

Kohli, R., Lo, Y., Homel, P., Flanigan, T. P., Gardner, L. I., Howard, A. A., . . . Schoenbaum, E. E. (2006). Bacterial pneumonia, HIV therapy, and disease progression among HIV-infected

women in the HIV epidemiologic research (HER) study. *Clinical Infectious Diseases, 43*(1), 90-98.

Kohno, S., Seki, M., Takehara, K., Yamada, Y., Kubo, K., Ishizaka, A., & Soma, K. (2013). Prediction of requirement for mechanical ventilation in community-acquired pneumonia with acute respiratory failure: a multicenter prospective study. *Respiration, 85*(1), 27-35.

Koivula, I., Sten, M., & Makela, P. H. (1999). Prognosis after community-acquired pneumonia in the elderly: a population-based 12-year follow-up study. *Archives of Internal Medicine, 159*(14), 1550-1555.

Kolditz, M., Ewig, S., Klapdor, B., Schutte, H., Winning, J., Rupp, J., . . . group, C. s. (2015). Community-acquired pneumonia as medical emergency: predictors of early deterioration. *Thorax*.

Kortgen, A., Niederprum, P., & Bauer, M. (2006). Implementation of an evidence-based "standard operating procedure" and outcome in septic shock. *Critical Care Medicine, 34*(4), 943-949.

Koss, C. A., Jarlsberg, L. G., den Boon, S., Cattamanchi, A., Davis, J. L., Worodria, W., . . . International, H. I. V. a. O. P. S. (2015). A Clinical Predictor Score for 30-Day Mortality among HIV-Infected Adults Hospitalized with Pneumonia in Uganda. *PloS One, 10*(5), e0126591.

Kothe, H., Bauer, T., Marre, R., Suttorp, N., Welte, T., Dalhoff, K., & Competence Network for Community-Acquired Pneumonia study, g. (2008). Outcome of community-acquired pneumonia: influence of age, residence status and antimicrobial treatment. *European Respiratory Journal, 32*(1), 139-146.

Koulla-Shiro, S., Kuaban, C., & Belec, L. (1997). Microbial etiology of acute community-acquired pneumonia in adult hospitalized patients in Yaounde-Cameroon. *Clinical Microbiology and Infection, 3 (2)*, 180-186.

Koulla-Shiro, S., Ondoa, P., Youmbissi, T. J., Monny-Lobe, M., & Auckenthaler, R. (1994). Pneumopathies communautaires de l'aculte dans un milieu hospitalier a Douala: epidemiologies et clinique. *Médecine d'Afrique Noire, 41*(4), 218-222.

Kovaleva, A., Remmelts, H. H., Rijkers, G. T., Hoepelman, A. I., Biesma, D. H., & Oosterheert, J. J. (2012). Immunomodulatory effects of macrolides during community-acquired pneumonia: a literature review. *Journal of Antimicrobial Chemotherapy, 67*(3), 530-540.

La Vincente, S. F., Peel, D., Carai, S., Weber, M. W., Enarson, P., Maganga, E., . . . Duke, T. (2011). The functioning of oxygen concentrators in resource-limited settings: a situation

assessment in two countries. *International Journal of Tuberculosis and Lung Disease, 15*(5), 693-699.

Larsen, H. H., Huang, L., Kovacs, J. A., Crothers, K., Silcott, V. A., Morris, A., . . . Fischer, S. H. (2004). A prospective, blinded study of quantitative touch-down polymerase chain reaction using oral-wash samples for diagnosis of Pneumocystis pneumonia in HIV-infected patients. *Journal of Infectious Diseases, 189*(9), 1679-1683.

Lawn, S. D. (2012). Point-of-care detection of lipoarabinomannan (LAM) in urine for diagnosis of HIV-associated tuberculosis: a state of the art review. *BMC Infectious Diseases, 12*, 103.

Lawn, S. D. (2013). Diagnosis of pulmonary tuberculosis. *Current Opinion in Pulmonary Medicine, 19*(3), 280-288.

Lawn, S. D., Badri, M., & Wood, R. (2005). Tuberculosis among HIV-infected patients receiving HAART: long term incidence and risk factors in a South African cohort. *AIDS, 19*(18), 2109-2116.

Lawn, S. D., Dheda, K., Kerkhoff, A. D., Peter, J. G., Dorman, S., Boehme, C. C., & Nicol, M. P. (2013a). Determine TB-LAM lateral flow urine antigen assay for HIV-associated tuberculosis: recommendations on the design and reporting of clinical studies. *BMC Infectious Diseases, 13*, 407.

Lawn, S. D., Kerkhoff, A. D., Burton, R., Schutz, C., van Wyk, G., Vogt, M., . . . Meintjes, G. (2015). Rapid microbiological screening for tuberculosis in HIV-positive patients on the first day of acute hospital admission by systematic testing of urine samples using Xpert MTB/RIF: a prospective cohort in South Africa. *BMC Medicine, 13*, 192.

Lawn, S. D., Kerkhoff, A. D., Vogt, M., & Wood, R. (2012). Diagnostic accuracy of a low-cost, urine antigen, point-of-care screening assay for HIV-associated pulmonary tuberculosis before antiretroviral therapy: a descriptive study. *Lancet Infectious Diseases, 12*(3), 201-209.

Lawn, S. D., Meintjes, G., McIlleron, H., Harries, A. D., & Wood, R. (2013b). Management of HIV-associated tuberculosis in resource-limited settings: a state-of-the-art review. *BMC Medicine, 11*, 253.

Lawn, S. D., Mwaba, P., Bates, M., Piatek, A., Alexander, H., Marais, B. J., . . . Zumla, A. (2013c). Advances in tuberculosis diagnostics: the Xpert MTB/RIF assay and future prospects for a point-of-care test. *Lancet Infectious Diseases, 13*(4), 349-361.

Lawn, S. D., Myer, L., Edwards, D., Bekker, L. G., & Wood, R. (2009). Short-term and long-term risk of tuberculosis associated with CD4 cell recovery during antiretroviral therapy in South Africa. *AIDS, 23*(13), 1717-1725.

Lee, J. S., Giesler, D. L., Gellad, W. F., & Fine, M. J. (2016). Antibiotic Therapy for Adults Hospitalized With Community-Acquired Pneumonia: A Systematic Review. *JAMA, 315*(6), 593-602.

Lee, M. T., Lee, S. H., Chang, S. S., Chan, Y. L., Pang, L., Hsu, S. M., & Lee, C. C. (2015). Comparative Treatment Failure Rates of Respiratory Fluoroquinolones or beta-Lactam + Macrolide Versus beta-Lactam Alone in the Treatment for Community-Acquired Pneumonia in Adult Outpatients: An Analysis of a Nationally Representative Claims Database. *Medicine (Baltimore), 94*(39), e1662.

Lee, R. W., & Lindstrom, S. T. (2007). A teaching hospital's experience applying the Pneumonia Severity Index and antibiotic guidelines in the management of community-acquired pneumonia. *Respirology, 12*(5), 754-758.

Leopold, S. J., van Leth, F., Tarekegn, H., & Schultsz, C. (2014). Antimicrobial drug resistance among clinically relevant bacterial isolates in sub-Saharan Africa: a systematic review. *Journal of Antimicrobial Chemotherapy, 69*(9), 2337-2353.

Lewis, D. K., Peters, R. P., Schijffelen, M. J., Joaki, G. R., Walsh, A. L., Kublin, J. G., . . . Zijlstra, E. E. (2002). Clinical indicators of mycobacteraemia in adults admitted to hospital in Blantyre, Malawi. *International Journal of Tuberculosis and Lung Disease, 6*(12), 1067-1074.

Li, H. Y., Guo, Q., Song, W. D., Zhou, Y. P., Li, M., Chen, X. K., . . . Jiang, M. (2015). Modified IDSA/ATS Minor Criteria for Severe Community-Acquired Pneumonia Best Predicted Mortality. *Medicine (Baltimore), 94*(36), e1474.

Li, Y., Gierahn, T., Thompson, C. M., Trzcinski, K., Ford, C. B., Croucher, N., . . . Lipsitch, M. (2012). Distinct effects on diversifying selection by two mechanisms of immunity against Streptococcus pneumoniae. *PLoS Pathogens, 8*(11), e1002989.

Liam, C. K., Pang, Y. K., & Poosparajah, S. (2006). Pulmonary tuberculosis presenting as community-acquired pneumonia. *Respirology, 11*(6), 786-792.

Lim, H. F., Phua, J., Mukhopadhyay, A., Ngerng, W. J., Chew, M. Y., Sim, T. B., . . . Lim, T. K. (2014). IDSA/ATS minor criteria aid pre-intensive care unit resuscitation in severe community-acquired pneumonia. *European Respiratory Journal, 43*(3), 852-862.

Lim, W. S., Baudouin, S. V., George, R. C., Hill, A. T., Jamieson, C., Le Jeune, I., . . . Woodhead, M. A. (2009). BTS guidelines for the management of community acquired pneumonia in adults: update 2009. *Thorax, 64 Suppl 3*, iii1-55.

Lim, W. S., Lewis, S., & Macfarlane, J. T. (2000). Severity prediction rules in community acquired pneumonia: a validation study. *Thorax, 55*(3), 219-223.

Lim, W. S., van der Eerden, M. M., Laing, R., Boersma, W. G., Karalus, N., Town, G. I., . . . Macfarlane, J. T. (2003). Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. *Thorax, 58*(5), 377-382.

Lin, Y. T., Jeng, Y. Y., Chen, T. L., & Fung, C. P. (2010). Bacteremic community-acquired pneumonia due to Klebsiella pneumoniae: clinical and microbiological characteristics in Taiwan, 2001-2008. *BMC Infectious Diseases, 10*, 307.

Lopez, A. D., Mathers, C. D., Ezzati, M., Jamison, D. T., & Murray, C. J. (2006). Global and regional burden of disease and risk factors, 2001: systematic analysis of population health data. *Lancet, 367*(9524), 1747-1757.

Lorenzo, M. J., Moret, I., Sarria, B., Cases, E., Cortijo, J., Mendez, R., . . . Menendez, R. (2015). Lung inflammatory pattern and antibiotic treatment in pneumonia. *Respiratory Research, 16*, 15.

Lovett, P. B., Buchwald, J. M., Sturmann, K., & Bijur, P. (2005). The vexatious vital: neither clinical measurements by nurses nor an electronic monitor provides accurate measurements of respiratory rate in triage. *Annals of Emergency Medicine, 45*(1), 68-76.

Low, D. E., Mazzulli, T., & Marrie, T. (2005). Progressive and nonresolving pneumonia. *Current Opinion in Pulmonary Medicine, 11*(3), 247-252.

Lowe, D. M., Rangaka, M. X., Gordon, F., James, C. D., & Miller, R. F. (2013). Pneumocystis jirovecii pneumonia in tropical and low and middle income countries: a systematic review and meta-regression. *PloS One, 8*(8), e69969.

Lozano, R., Naghavi, M., Foreman, K., Lim, S., Shibuya, K., Aboyans, V., . . . Memish, Z. A. (2012). Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet, 380*(9859), 2095-2128.

Maartens, G., Lewis, S. J., Degoveia, C., Bartie, C., Roditi, D., & Klugman, K. P. (1994). 'Atypical' bacteria are a common cause of community-acquired pneumonia in hospitalised adults. *South African Medical Journal, 84*(10), 678-682.

Macfarlane, J. T., Colville, A., Guion, A., Macfarlane, R. M., & Rose, D. H. (1993). Prospective study of aetiology and outcome of adult lower-respiratory-tract infections in the community. *Lancet, 341*(8844), 511-514.

Macfarlane, J. T., Holmes, W., Gard, P., Macfarlane, R., Rose, D., Weston, V., . . . Myint, S. (2001). Prospective study of the incidence, aetiology and outcome of adult lower respiratory tract illness in the community. *Thorax, 56*(2), 109-114.

Madeddu, G., Laura Fiori, M., & Stella Mura, M. (2010). Bacterial community-acquired pneumonia in HIV-infected patients. *Current Opinion in Pulmonary Medicine, 16*(3), 201-207.

Madhi, S. A., Maskew, M., Koen, A., Kuwanda, L., Besselaar, T. G., Naidoo, D., . . . Sanne, I. (2011). Trivalent inactivated influenza vaccine in African adults infected with human immunodeficient virus: double blind, randomized clinical trial of efficacy, immunogenicity, and safety. *Clinical Infectious Diseases, 52*(1), 128-137.

Maitland, K., Babiker, A., Kiguli, S., Molyneux, E., & Group, F. T. (2012). The FEAST trial of fluid bolus in African children with severe infection. *Lancet, 379*(9816), 613; author reply 613-614.

Maitland, K., Kiguli, S., Opoka, R. O., Engoru, C., Olupot-Olupot, P., Akech, S. O., . . . Group, F. T. (2011a). Mortality after fluid bolus in African children with severe infection. *New England Journal of Medicine, 364*(26), 2483-2495.

Maitland, K., Molyneux, S., Boga, M., Kiguli, S., & Lang, T. (2011b). Use of deferred consent for severely ill children in a multi-centre phase III trial. *Trials, 12*, 90.

Malin, A. S., Gwanzura, L. K., Klein, S., Robertson, V. J., Musvaire, P., & Mason, P. R. (1995). Pneumocystis carinii pneumonia in Zimbabwe. *Lancet, 346*(8985), 1258-1261.

Malinis, M., Myers, J., Bordon, J., Peyrani, P., Kapoor, R., Nakamatzu, R., . . . Ramirez, J. (2010). Clinical outcomes of HIV-infected patients hospitalized with bacterial community-acquired pneumonia. *International Journal of Infectious Diseases, 14*(1), e22-27.

Mandell, L. A., Wunderink, R. G., Anzueto, A., Bartlett, J. G., Campbell, G. D., Dean, N. C., . . . Whitney, C. G. (2007). Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clinical Infectious Diseases, 44 Suppl 2*, S27-72.

Marti, C., Garin, N., Grosgurin, O., Poncet, A., Combescure, C., Carballo, S., & Perrier, A. (2012). Prediction of severe community-acquired pneumonia: a systematic review and meta-analysis. *Critical Care (London, England), 16*(4), R141.

Martin, D. S., & Grocott, M. P. (2013). Oxygen therapy in critical illness: precise control of arterial oxygenation and permissive hypoxemia. *Critical Care Medicine, 41*(2), 423-432.

Martin-Loeches, I., Lisboa, T., Rodriguez, A., Putensen, C., Annane, D., Garnacho-Montero, J., . . . Rello, J. (2010). Combination antibiotic therapy with macrolides improves survival in intubated patients with community-acquired pneumonia. *Intensive Care Medicine, 36*(4), 612-620.

Martin-Loeches, I., Valles, X., Menendez, R., Sibila, O., Montull, B., Cilloniz, C., . . . Torres, A. (2014). Predicting treatment failure in patients with community acquired pneumonia: a case-control study. *Respiratory Research, 15*, 75.

Matai, S., Peel, D., Wandi, F., Jonathan, M., Subhi, R., & Duke, T. (2008). Implementing an oxygen programme in hospitals in Papua New Guinea. *Annals of Tropical Paediatrics, 28*(1), 71-78.

Mathers, C. D., & Loncar, D. (2006). Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Medicine, 3*(11), e442.

Mayr, F. B., Yende, S., & Angus, D. C. (2014). Epidemiology of severe sepsis. *Virulence, 5*(1), 4-11.

Mbata, G. C., Chukwuka, C. J., Onyedum, C. C., & Onwubere, B. J. C. (2013). The CURB-65 scoring system in severity assessment of Eastern Nigerian patients with community-acquired pneumonia: a prospective observational study. *Primary care respiratory journal : journal of the General Practice Airways Group, 22*(2), 175-180.

McCubbrey, A. L., & Curtis, J. L. (2013). Efferocytosis and lung disease. *Chest, 143*(6), 1750-1757.

McNeela, E. A., Burke, A., Neill, D. R., Baxter, C., Fernandes, V. E., Ferreira, D., . . . Lavelle, E. C. (2010). Pneumolysin activates the NLRP3 inflammasome and promotes proinflammatory cytokines independently of TLR4. *PLoS Pathogens, 6*(11), e1001191.

McNerney, R., & Daley, P. (2011). Towards a point-of-care test for active tuberculosis: obstacles and opportunities. *Nature Reviews: Microbiology, 9*(3), 204-213.

Melbye, H., Straume, B., Aasebo, U., & Dale, K. (1992). Diagnosis of pneumonia in adults in general practice. Relative importance of typical symptoms and abnormal chest signs evaluated against a radiographic reference standard. *Scandinavian Journal of Primary Health Care, 10*(3), 226-233.

Menendez, R., Cavalcanti, M., Reyes, S., Mensa, J., Martinez, R., Marcos, M. A., . . . Torres, A. (2008). Markers of treatment failure in hospitalised community acquired pneumonia. *Thorax, 63*(5), 447-452.

Menendez, R., Torres, A., Rodriguez de Castro, F., Zalacain, R., Aspa, J., Martin Villasclaras, J. J., . . . Molinos, L. (2004a). Reaching stability in community-acquired pneumonia: the effects of the severity of disease, treatment, and the characteristics of patients. *Clinical Infectious Diseases, 39*(12), 1783-1790.

Menendez, R., Torres, A., Zalacain, R., Aspa, J., Martin Villasclaras, J. J., Borderias, L., . . . Molinos, L. (2004b). Risk factors of treatment failure in community acquired pneumonia: implications for disease outcome. *Thorax, 59*(11), 960-965.

Mercante, J. W., & Winchell, J. M. (2015). Current and emerging Legionella diagnostics for laboratory and outbreak investigations. *Clinical Microbiology Reviews, 28*(1), 95-133.

Metersky, M. L., Ma, A., Houck, P. M., & Bratzler, D. W. (2007). Antibiotics for bacteremic pneumonia: Improved outcomes with macrolides but not fluoroquinolones. *Chest, 131*(2), 466-473.

Metlay, J. P., & Fine, M. J. (2003). Testing strategies in the initial management of patients with community-acquired pneumonia. *Annals of Internal Medicine, 138*(2), 109-118.

Metlay, J. P., Kapoor, W. N., & Fine, M. J. (1997). Does this patient have community-acquired pneumonia? Diagnosing pneumonia by history and physical examination. *JAMA, 278*(17), 1440-1445.

Millett, E. R., Quint, J. K., Smeeth, L., Daniel, R. M., & Thomas, S. L. (2013). Incidence of community-acquired lower respiratory tract infections and pneumonia among older adults in the United Kingdom: a population-based study. *PloS One, 8*(9), e75131.

Minion, J., Leung, E., Talbot, E., Dheda, K., Pai, M., & Menzies, D. (2011). Diagnosing tuberculosis with urine lipoarabinomannan: systematic review and meta-analysis. *European Respiratory Journal, 38*(6), 1398-1405.

Moncada, D. C., Rueda, Z. V., Macias, A., Suarez, T., Ortega, H., & Velez, L. A. (2011). Reading and interpretation of chest X-ray in adults with community-acquired pneumonia. *Brazilian Journal of Infectious Diseases, 15*(6), 540-546.

Moons, K. G., Altman, D. G., Reitsma, J. B., Ioannidis, J. P., Macaskill, P., Steyerberg, E. W., . . . Collins, G. S. (2015). Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): explanation and elaboration. *Annals of Internal Medicine, 162*(1), W1-73.

Moons, K. G., Altman, D. G., Vergouwe, Y., & Royston, P. (2009). Prognosis and prognostic research: application and impact of prognostic models in clinical practice. *BMJ, 338*, b606.

Moore, R. D., & Chaisson, R. E. (1999). Natural history of HIV infection in the era of combination antiretroviral therapy. *AIDS, 13*(14), 1933-1942.

Mortensen, E. M., Coley, C. M., Singer, D. E., Marrie, T. J., Obrosky, D. S., Kapoor, W. N., & Fine, M. J. (2002). Causes of death for patients with community-acquired pneumonia: results from the Pneumonia Patient Outcomes Research Team cohort study. *Archives of Internal Medicine, 162*(9), 1059-1064.

Mouncey, P. R., Osborn, T. M., Power, G. S., Harrison, D. A., Sadique, M. Z., Grieve, R. D., . . . Rowan, K. M. (2015). Trial of early, goal-directed resuscitation for septic shock. *New England Journal of Medicine, 372*(14), 1301-1311.

Mpe, M. J., Jobo, R. D., & Modise, J. P. (2001). The incidence of community-acquired Legionella pneumonia as determined by the urine antigen test. A one-year prospective study in an academic hospital. *South African Journal of Epidemiology and Infection, 16*, 54-56.

Muller, B., Harbarth, S., Stolz, D., Bingisser, R., Mueller, C., Leuppi, J., . . . Christ-Crain, M. (2007). Diagnostic and prognostic accuracy of clinical and laboratory parameters in community-acquired pneumonia. *BMC Infectious Diseases, 7*, 10.

Munoz, A., Schrager, L. K., Bacellar, H., Speizer, I., Vermund, S. H., Detels, R., . . . Phair, J. P. (1993). Trends in the incidence of outcomes defining acquired immunodeficiency syndrome (AIDS) in the Multicenter AIDS Cohort Study: 1985-1991. *American Journal of Epidemiology, 137*(4), 423-438.

Munseri, P. J., Talbot, E. A., Bakari, M., Matee, M., Teixeira, J. P., & von Reyn, C. F. (2011). The bacteraemia of disseminated tuberculosis among HIV-infected patients with prolonged fever in Tanzania. *Scandinavian Journal of Infectious Diseases, 43*(9), 696-701.

Murad, A., Li, P. Z., Dial, S., & Shahin, J. (2015). The role of noninvasive positive pressure ventilation in community-acquired pneumonia. *Journal of Critical Care, 30*(1), 49-54.

Murray, C. J., Vos, T., Lozano, R., Naghavi, M., Flaxman, A. D., Michaud, C., . . . Memish, Z. A. (2012). Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet, 380*(9859), 2197-2223.

Musher, D. M., Rueda, A. M., Kaka, A. S., & Mapara, S. M. (2007). The association between pneumococcal pneumonia and acute cardiac events. *Clinical Infectious Diseases, 45*(2), 158-165.

Mwachari, C. W., Nduba, V. N., Park, D. R., Meier, A. S., Kariuki, J. N., Muyodi, J. A., . . . Cohen, C. R. (2006). Clinical presentation among HIV-infected and non-infected adults with community acquired pneumonia in Nairobi. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease, 10*(5), 516-522.

Mwalukomo, T., Swarthout, T., Everett, D. B., Bar-Zeev, N., Kamn'gona, A., Mwansambo, C., . . . Heyderman, R. S. (2016). *Effect of long duration of ART on pneumococcal carriage in HIV-infected adults following PCV13 introduction into the infant schedule in Malawi*. Paper presented at the 10th International Symposium on Pneumococci and Pneumococcal Diseases, Glasgow, United Kingdom.

National Clinical Guideline Centre. (2014). *Pneumonia: Diagnosis and management of community-acquired and hospital-acquired pneumonia in adults*. Retrieved from London: http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0071334/pdf/PubMedHealth_PMH0071334.pdf

National Statistical Office of Malawi. (2008). *Population and Housing Census, 2008*. Retrieved from Zomba, Malawi: http://www.nsomalawi.mw/2008-population-and-housing-census/107-2008-population-and-housing-census-results.html

Neill, A. M., Martin, I. R., Weir, R., Anderson, R., Chereshsky, A., Epton, M. J., . . . Town, G. I. (1996). Community acquired pneumonia: aetiology and usefulness of severity criteria on admission. *Thorax, 51*(10), 1010-1016.

Nicolini, A., Ferraioli, G., Ferrari-Bravo, M., Barlascini, C., Santo, M., & Ferrera, L. (2016). Early non-invasive ventilation treatment for respiratory failure due to severe community-acquired pneumonia. *Clinical Respiratory Journal, 10*(1), 98-103.

Nie, W., Li, B., & Xiu, Q. (2014). beta-Lactam/macrolide dual therapy versus beta-lactam monotherapy for the treatment of community-acquired pneumonia in adults: a systematic review and meta-analysis. *Journal of Antimicrobial Chemotherapy, 69*(6), 1441-1446.

Niederman, M. S., Mandell, L. A., Anzueto, A., Bass, J. B., Broughton, W. A., Campbell, G. D., . . . Yu, V. L. (2001). Guidelines for the management of adults with community-acquired pneumonia. Diagnosis, assessment of severity, antimicrobial therapy, and prevention. *American Journal of Respiratory and Critical Care Medicine, 163*(7), 1730-1754.

Nolt, B. R., Gonzales, R., Maselli, J., Aagaard, E., Camargo, C. A., Jr., & Metlay, J. P. (2007). Vital-sign abnormalities as predictors of pneumonia in adults with acute cough illness. *American Journal of Emergency Medicine, 25*(6), 631-636.

Nyamande, K., & Lalloo, U. G. (2006). Serum procalcitonin distinguishes CAP due to bacteria, Mycobacterium tuberculosis and PJP. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease, 10*(5), 510-515.

Nyamande, K., Lalloo, U. G., & John, M. (2007a). TB presenting as community-acquired pneumonia in a setting of high TB incidence and high HIV prevalence. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease, 11*(12), 1308-1313.

Nyamande, K., Lalloo, U. G., & Vawda, F. (2007b). Comparison of plain chest radiography and high-resolution CT in human immunodeficiency virus infected patients with

community-acquired pneumonia: a sub-Saharan Africa study. *British Journal of Radiology, 80*(953), 302-306.

O'Brien, W. T., Sr., Rohweder, D. A., Lattin, G. E., Jr., Thornton, J. A., Dutton, J. P., Ebert-Long, D. L., & Duncan, M. D. (2006). Clinical indicators of radiographic findings in patients with suspected community-acquired pneumonia: who needs a chest x-ray? *J Am Coll Radiol, 3*(9), 703-706.

O'Driscoll, B. R., Howard, L. S., Davison, A. G., & British Thoracic, S. (2008). BTS guideline for emergency oxygen use in adult patients. *Thorax, 63 Suppl 6*, vi1-68.

Odera, A. S., & Anzala, O. (2009). Survey of Legionella pneumophila among pneumonia patients at Kenyatta National Hospital. *East African Medical Journal, 86*(12), 565-571.

Okwera, A., Bwanga, F., Najjingo, I., Mulumba, Y., Mafigiri, D. K., Whalen, C. C., & Joloba, M. L. (2013). Aetiology of pulmonary symptoms in HIV-infected smear negative recurrent PTB suspects in Kampala, Uganda: A cross-sectional study. *PloS One, 8 (12)*(e82257).

Onyedum, C. C., & Chukwuka, J. C. (2011). Admission profile and management of community acquired pneumonia in Nigeria--5 year experience in a tertiary hospital. *Respiratory Medicine, 105*(2), 298-302.

Ortqvist, A. (1990). Prognosis in community-acquired pneumonia requiring treatment in hospital. Importance of predisposing and complicating factors, and of diagnostic procedures. *Scandinavian Journal of Infectious Diseases. Supplementum, 65*, 1-62.

Ott, S. R., Hauptmeier, B. M., Ernen, C., Lepper, P. M., Nuesch, E., Pletz, M. W., . . . Bauer, T. T. (2012). Treatment failure in pneumonia: impact of antibiotic treatment and cost analysis. *European Respiratory Journal, 39*(3), 611-618.

Ouedraogo, S. M., Toloba, Y., Badoum, G., Ouedraogo, G., Boncoungou, K., Bambara, M., . . . Ouedraogo, M. (2010). [Epidemio-clinical aspects of adult acute bacterial pneumonia at Yalgado Ouedraogo University Health Center]. [French]. *Le Mali Medical, 25 (3)*, 15-18.

Oxford Institute of Population Ageing. (2015). Global & regional population pyramids. Retrieved from http://www.ageing.ox.ac.uk/population-horizons/data/gpt/

Palella, F. J., Jr., & Phair, J. P. (2011). Cardiovascular disease in HIV infection. *Current Opinion in HIV and AIDS, 6*(4), 266-271.

Pancer, K., Jahnz-Rozyk, K., Kucharczyk, A., Gut, W., Kucharczyk, P., Elverdal, P. L., & Litwinska, B. (2012). Sequence based typing and pre-absorption test in retrospective analysis of a pseudo-outbreak of Legionella infections differentiates true cases of legionellosis. *Annals of Agricultural and Environmental Medicine, 19*(3), 437-443.

Peake, S. L., Delaney, A., Bailey, M., Bellomo, R., Cameron, P. A., Cooper, D. J., . . . Williams, P. (2014). Goal-directed resuscitation for patients with early septic shock. *New England Journal of Medicine, 371*(16), 1496-1506.

Peduzzi, P., Concato, J., Kemper, E., Holford, T. R., & Feinstein, A. R. (1996). A simulation study of the number of events per variable in logistic regression analysis. *Journal of Clinical Epidemiology, 49*(12), 1373-1379.

Peel, D., Neighbour, R., & Eltringham, R. J. (2013). Evaluation of oxygen concentrators for use in countries with limited resources. *Anaesthesia, 68*(7), 706-712.

Penner, J., Meier, A. S., Mwachari, C., Ayuka, F., Muchina, B., Odhiambo, J., & Cohen, C. R. (2003). Risk factors for pneumonia in urban-dwelling HIV-infected women: a case-control study in Nairobi, Kenya. *Journal of Acquired Immune Deficiency Syndromes, 32*(2), 223-228.

Perlman, D. C., el-Sadr, W. M., Nelson, E. T., Matts, J. P., Telzak, E. E., Salomon, N., . . . Hafner, R. (1997). Variation of chest radiographic patterns in pulmonary tuberculosis by degree of human immunodeficiency virus-related immunosuppression. The Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA). The AIDS Clinical Trials Group (ACTG). *Clinical Infectious Diseases, 25*(2), 242-246.

Peter, J. G., Theron, G., Muchinga, T. E., Govender, U., & Dheda, K. (2012). The diagnostic accuracy of urine-based Xpert MTB/RIF in HIV-infected hospitalized patients who are smear-negative or sputum scarce. *PloS One, 7*(7), e39966.

Peter, J. G., Zijenah, L. S., Chanda, D., Clowes, P., Lesosky, M., Gina, P., . . . Dheda, K. (2016). Effect on mortality of point-of-care, urine-based lipoarabinomannan testing to guide tuberculosis treatment initiation in HIV-positive hospital inpatients: a pragmatic, parallel-group, multicountry, open-label, randomised controlled trial. *Lancet, 387*(10024), 1187-1197.

Peterson, J., Yektashenas, B., & Fisher, A. C. (2009). Levofloxacin for the treatment of pneumonia caused by Streptococcus pneumoniae including multidrug-resistant strains: pooled analysis. *Current Medical Research and Opinion, 25*(3), 559-568.

Peto, L., Nadjm, B., Horby, P., Ngan, T. T., van Doorn, R., Van Kinh, N., & Wertheim, H. F. (2014). The bacterial aetiology of adult community-acquired pneumonia in Asia: a systematic review. *Transactions of the Royal Society of Tropical Medicine and Hygiene, 108*(6), 326-337.

Pfister, R., Kochanek, M., Leygeber, T., Brun-Buisson, C., Cuquemelle, E., Machado, M. B., . . . Michels, G. (2014). Procalcitonin for diagnosis of bacterial pneumonia in critically ill patients during 2009 H1N1 influenza pandemic: a prospective cohort study, systematic

review and individual patient data meta-analysis. *Critical Care (London, England), 18*(2), R44.

Phares, C. R., Wangroongsarb, P., Chantra, S., Paveenkitiporn, W., Tondella, M. L., Benson, R. F., . . . Olsen, S. J. (2007). Epidemiology of severe pneumonia caused by Legionella longbeachae, Mycoplasma pneumoniae, and Chlamydia pneumoniae: 1-year, population-based surveillance for severe pneumonia in Thailand. *Clinical Infectious Diseases, 45*(12), e147-155.

Pinto, L. M., Dheda, K., Theron, G., Allwood, B., Calligaro, G., van Zyl-Smit, R., . . . Dawson, R. (2013). Development of a simple reliable radiographic scoring system to aid the diagnosis of pulmonary tuberculosis. *PloS One, 8*(1), e54235.

Pletz, M. W., van der Linden, M., von Baum, H., Duesberg, C. B., Klugman, K. P., & Welte, T. (2011). Low prevalence of fluoroquinolone resistant strains and resistance precursor strains in Streptococcus pneumoniae from patients with community-acquired pneumonia despite high fluoroquinolone usage. *International Journal of Medical Microbiology, 301*(1), 53-57.

Postma, D. F., van Werkhoven, C. H., van Elden, L. J., Thijsen, S. F., Hoepelman, A. I., Kluytmans, J. A., . . . Bonten, M. J. (2015). Antibiotic treatment strategies for community-acquired pneumonia in adults. *New England Journal of Medicine, 372*(14), 1312-1323.

Potgieter, P. D., & Hammond, J. M. (1992). Etiology and diagnosis of pneumonia requiring ICU admission. *Chest, 101*(1), 199-203.

Pretorius, M. A., Madhi, S. A., Cohen, C., Naidoo, D., Groome, M., Moyes, J., . . . Venter, M. (2012). Respiratory viral coinfections identified by a 10-plex real-time reverse-transcription polymerase chain reaction assay in patients hospitalized with severe acute respiratory illness--South Africa, 2009-2010. *Journal of Infectious Diseases, 206 Suppl 1*, S159-165.

Pride, M. W., Huijts, S. M., Wu, K., Souza, V., Passador, S., Tinder, C., . . . Jansen, K. U. (2012). Validation of an immunodiagnostic assay for detection of 13 Streptococcus pneumoniae serotype-specific polysaccharides in human urine. *Clinical and Vaccine Immunology, 19*(8), 1131-1141.

Principi, N., & Esposito, S. (2013). Macrolide-resistant Mycoplasma pneumoniae: its role in respiratory infection. *Journal of Antimicrobial Chemotherapy, 68*(3), 506-511.

Prout, S., Potgieter, P. D., Forder, A. A., Moodie, J. W., & Matthews, J. (1983). Acute community-acquired pneumonias. *South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde, 64*(12), 443-446.

Querol-Ribelles, J. M., Tenias, J. M., Querol-Borras, J. M., Labrador, T., Nieto, A., Gonzalez-Granda, D., & Martinez, I. (2005). Levofloxacin versus ceftriaxone plus clarithromycin in the treatment of adults with community-acquired pneumonia requiring hospitalization. *International Journal of Antimicrobial Agents, 25*(1), 75-83.

Rakotoson, J. L., Rakotomizao, J. R., & Andrianarisoa, A. C. F. (2010). Acute community acquired pneumonia: 96 Cases in Madagascar. [French]. *Médecine Tropicale, 70 (1)*, 62-64.

Ramirez, J. A., Srinath, L., Ahkee, S., Huang, A., & Raff, M. J. (1995). Early switch from intravenous to oral cephalosporins in the treatment of hospitalized patients with community-acquired pneumonia. *Archives of Internal Medicine, 155*(12), 1273-1276.

Rangaka, M. X., Wilkinson, R. J., Boulle, A., Glynn, J. R., Fielding, K., van Cutsem, G., . . . Maartens, G. (2014). Isoniazid plus antiretroviral therapy to prevent tuberculosis: a randomised double-blind, placebo-controlled trial. *Lancet, 384*(9944), 682-690.

Ray, W. A., Murray, K. T., Hall, K., Arbogast, P. G., & Stein, C. M. (2012). Azithromycin and the risk of cardiovascular death. *New England Journal of Medicine, 366*(20), 1881-1890.

Raz-Pasteur, A., Shasha, D., & Paul, M. (2015). Fluoroquinolones or macrolides alone versus combined with beta-lactams for adults with community-acquired pneumonia: Systematic review and meta-analysis. *International Journal of Antimicrobial Agents, 46*(3), 242-248.

Reade, M. C., Weissfeld, L., Angus, D. C., Kellum, J. A., & Milbrandt, E. B. (2010). The prevalence of anemia and its association with 90-day mortality in hospitalized community-acquired pneumonia. *BMC Pulmonary Medicine, 10*, 15.

Reddy, E. A., Shaw, A. V., & Crump, J. A. (2010). Community-acquired bloodstream infections in Africa: a systematic review and meta-analysis. *Lancet Infectious Diseases, 10*(6), 417-432.

Reissig, A., Copetti, R., Mathis, G., Mempel, C., Schuler, A., Zechner, P., . . . Hoyer, H. (2012). Lung ultrasound in the diagnosis and follow-up of community-acquired pneumonia: a prospective, multicenter, diagnostic accuracy study. *Chest, 142*(4), 965-972.

Restrepo, M. I., Faverio, P., & Anzueto, A. (2013). Long-term prognosis in community-acquired pneumonia. *Current Opinion in Infectious Diseases*.

Restrepo, M. I., Mortensen, E. M., Waterer, G. W., Wunderink, R. G., Coalson, J. J., & Anzueto, A. (2009). Impact of macrolide therapy on mortality for patients with severe sepsis due to pneumonia. *European Respiratory Journal, 33*(1), 153-159.

Restrepo, M. I., Sole-Violan, J., & Martin-Loeches, I. (2016). Macrolide therapy of pneumonia: is it necessary, and how does it help? *Current Opinion in Infectious Diseases, 29*(2), 212-217.

Richards, P. J., Riddell, L., Reznek, R. H., Armstrong, P., Pinching, A. J., & Parkin, J. M. (1996). High resolution computed tomography in HIV patients with suspected Pneumocystis carinii pneumonia and a normal chest radiograph. *Clinical Radiology, 51*(10), 689-693.

Rivers, E., Nguyen, B., Havstad, S., Ressler, J., Muzzin, A., Knoblich, B., . . . Tomlanovich, M. (2001). Early goal-directed therapy in the treatment of severe sepsis and septic shock. *New England Journal of Medicine, 345*(19), 1368-1377.

Robins-Browne, K. L., Cheng, A. C., Thomas, K. A., Palmer, D. J., Currie, B. J., & Davis, J. S. (2012). The SMART-COP score performs well for pneumonia risk stratification in Australia's Tropical Northern Territory: a prospective cohort study. *Tropical Medicine and International Health, 17*(7), 914-919.

Roe, P. F. (1968). Lobar and segmental pneumonia in Busoga. *East African Medical Journal, 45*(9), 619-624.

Ronning, O. M., & Guldvog, B. (1999). Should stroke victims routinely receive supplemental oxygen? A quasi-randomized controlled trial. *Stroke, 30*(10), 2033-2037.

Roson, B., Carratala, J., Fernandez-Sabe, N., Tubau, F., Manresa, F., & Gudiol, F. (2004). Causes and factors associated with early failure in hospitalized patients with community-acquired pneumonia. *Archives of Internal Medicine, 164*(5), 502-508.

Royston, P., Moons, K. G., Altman, D. G., & Vergouwe, Y. (2009). Prognosis and prognostic research: Developing a prognostic model. *BMJ, 338*, b604.

Rylance, J., Baker, T., Mushi, E., & Mashaga, D. (2009). Use of an early warning score and ability to walk predicts mortality in medical patients admitted to hospitals in Tanzania. *Transactions of the Royal Society of Tropical Medicine and Hygiene, 103*(8), 790-794.

Said, M. A., Johnson, H. L., Nonyane, B. A., Deloria-Knoll, M., O'Brien, K. L., Team, A. A. P. B. S., . . . Watt, J. P. (2013). Estimating the burden of pneumococcal pneumonia among adults: a systematic review and meta-analysis of diagnostic techniques. *PloS One, 8*(4), e60273.

Saindou, M., Chidiac, C., Miailhes, P., Voirin, N., Baratin, D., Amiri, M., . . . Vanhems, P. (2008). Pneumococcal pneumonia in HIV-infected patients by antiretroviral therapy periods. *HIV Medicine, 9*(4), 203-207.

Sakurada, S., Hang, N. T., Ishizuka, N., Toyota, E., Hung le, D., Chuc, P. T., . . . Kobayashi, N. (2012). Inter-rater agreement in the assessment of abnormal chest X-ray findings for tuberculosis between two Asian countries. *BMC Infectious Diseases, 12*, 31.

Salih, W., Schembri, S., & Chalmers, J. D. (2014). Simplification of the IDSA/ATS criteria for severe CAP using meta-analysis and observational data. *European Respiratory Journal, 43*(3), 842-851.

Samandari, T., Agizew, T. B., Nyirenda, S., Tedla, Z., Sibanda, T., Mosimaneotsile, B., . . . Shepherd, J. (2015). Tuberculosis incidence after 36 months' isoniazid prophylaxis in HIV-infected adults in Botswana: a posttrial observational analysis. *AIDS, 29*(3), 351-359.

Samandari, T., Agizew, T. B., Nyirenda, S., Tedla, Z., Sibanda, T., Shang, N., . . . Wells, C. D. (2011). 6-month versus 36-month isoniazid preventive treatment for tuberculosis in adults with HIV infection in Botswana: a randomised, double-blind, placebo-controlled trial. *Lancet, 377*(9777), 1588-1598.

Samuel, C. M., Whitelaw, A., Corcoran, C., Morrow, B., Hsiao, N. Y., Zampoli, M., & Zar, H. J. (2011). Improved detection of Pneumocystis jirovecii in upper and lower respiratory tract specimens from children with suspected pneumocystis pneumonia using real-time PCR: a prospective study. *BMC Infectious Diseases, 11*, 329.

SanJoaquin, M. A., Allain, T. J., Molyneux, M. E., Benjamin, L., Everett, D. B., Gadabu, O., . . . Heyderman, R. S. (2013). Surveillance Programme of IN-patients and Epidemiology (SPINE): implementation of an electronic data collection tool within a large hospital in Malawi. *PLoS Medicine, 10*(3), e1001400.

Sanz, F., Restrepo, M. I., Fernandez, E., Mortensen, E. M., Aguar, M. C., Cervera, A., . . . Neumonia Adquirida en la Comunidad de la Comunidad Valenciana Study, G. (2011). Hypoxemia adds to the CURB-65 pneumonia severity score in hospitalized patients with mild pneumonia. *Respiratory Care, 56*(5), 612-618.

Scarborough, M., Gordon, S. B., Whitty, C. J., French, N., Njalale, Y., Chitani, A., . . . Zijlstra, E. E. (2007). Corticosteroids for bacterial meningitis in adults in sub-Saharan Africa. *New England Journal of Medicine, 357*(24), 2441-2450.

Schleicher, G. K., Herbert, V., Brink, A., Martin, S., Maraj, R., Galpin, J. S., & Feldman, C. (2005). Procalcitonin and C-reactive protein levels in HIV-positive subjects with tuberculosis and pneumonia. *European Respiratory Journal, 25*(4), 688-692.

Schneider, G. (2001). Oxygen supply in rural africa: a personal experience. *International Journal of Tuberculosis and Lung Disease, 5*(6), 524-526.

Schuetz, P., Christ-Crain, M., Thomann, R., Falconnier, C., Wolbers, M., Widmer, I., . . . Pro, H. S. G. (2009). Effect of procalcitonin-based guidelines vs standard guidelines on antibiotic use in lower respiratory tract infections: the ProHOSP randomized controlled trial. *JAMA, 302*(10), 1059-1066.

Schuetz, P., Koller, M., Christ-Crain, M., Steyerberg, E., Stolz, D., Muller, C., . . . Muller, B. (2008). Predicting mortality with pneumonia severity scores: importance of model recalibration to local settings. *Epidemiology and Infection, 136*(12), 1628-1637.

Scott, G., Scott, H., Turley, M., & Baker, M. (2004). Economic cost of community-acquired pneumonia in New Zealand adults. *New Zealand Medical Journal, 117*(1196), U933.

Scott, J. A., Adegbola, R., & Gordon, S. B. (2012). Pneumonia in adults. *Principles of Medicine in Africa, 4th Edition*, 264-276.

Scott, J. A., Hall, A. J., Muyodi, C., Lowe, B., Ross, M., Chohan, B., . . . Marsh, K. (2000). Aetiology, outcome, and risk factors for mortality among adults with acute pneumonia in Kenya. *Lancet, 355*(9211), 1225-1230.

Segal, L. N., Methe, B. A., Nolan, A., Hoshino, Y., Rom, W. N., Dawson, R., . . . Weiden, M. D. (2011). HIV-1 and bacterial pneumonia in the era of antiretroviral therapy. *Proceedings of the American Thoracic Society, 8*(3), 282-287.

Sepako, E., Glennie, S. J., Jambo, K. C., Mzinza, D., Iwajomo, O. H., Banda, D., . . . Heyderman, R. S. (2014). Incomplete recovery of pneumococcal CD4 T cell immunity after initiation of antiretroviral therapy in HIV-infected malawian adults. *PloS One, 9*(6), e100640.

Serraino, D., Puro, V., Boumis, E., Angeletti, C., Girardi, E., Petrosillo, N., & Ippolito, G. (2003). Epidemiological aspects of major opportunistic infections of the respiratory tract in persons with AIDS: Europe, 1993-2000. *AIDS, 17*(14), 2109-2116.

Shah, M., Hanrahan, C., Wang, Z. Y., Dendukuri, N., Lawn, S. D., Denkinger, C. M., & Steingart, K. R. (2016). Lateral flow urine lipoarabinomannan assay for detecting active tuberculosis in HIV-positive adults. *Cochrane Database Syst Rev*(5), CD011420.

Shapiro, N. I., Howell, M. D., Talmor, D., Lahey, D., Ngo, L., Buras, J., . . . Lisbon, A. (2006). Implementation and outcomes of the Multiple Urgent Sepsis Therapies (MUST) protocol. *Critical Care Medicine, 34*(4), 1025-1032.

Sheppard, C. L., Harrison, T. G., Smith, M. D., & George, R. C. (2011). Development of a sensitive, multiplexed immunoassay using xMAP beads for detection of serotype-specific streptococcus pneumoniae antigen in urine samples. *Journal of Medical Microbiology, 60*(Pt 1), 49-55.

Sherwin, R. L., Gray, S., Alexander, R., McGovern, P. C., Graepel, J., Pride, M. W., . . . File, T. M., Jr. (2013). Distribution of 13-valent pneumococcal conjugate vaccine Streptococcus pneumoniae serotypes in US adults aged >/=50 years with community-acquired pneumonia. *Journal of Infectious Diseases, 208*(11), 1813-1820.

Siedner, M. J., Ng, C. K., Bassett, I. V., Katz, I. T., Bangsberg, D. R., & Tsai, A. C. (2015). Trends in CD4 count at presentation to care and treatment initiation in sub-Saharan Africa, 2002-2013: a meta-analysis. *Clinical Infectious Diseases, 60*(7), 1120-1127.

Sinclair, A., Xie, X., Teltscher, M., & Dendukuri, N. (2013). Systematic review and meta-analysis of a urine-based pneumococcal antigen test for diagnosis of community-acquired pneumonia caused by Streptococcus pneumoniae. *Journal of Clinical Microbiology, 51*(7), 2303-2310.

Singanayagam, A., Chalmers, J. D., & Welte, T. (2014). Epidemiology of CAP in Europe. *Eur Respir Monogr, 63*, 1-12.

Singer, M., Deutschman, C. S., Seymour, C. W., Shankar-Hari, M., Annane, D., Bauer, M., . . . Angus, D. C. (2016). The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA, 315*(8), 801-810.

Sintes, H., Sibila, O., Waterer, G. W., & Chalmers, J. D. (2014). Severity assessment tools in CAP. In J. D. Chalmers, M. W. Pletz, & S. Aliberti (Eds.), *Community-acquired pneumonia* (Vol. 63, pp. 88-104). Sheffield, United Kingdom: European Respiratory Society.

Sire, J. M., Sow, P. S., Chartier, L., Ndiaye, B., Ndaye, M., Sarr, F. D., . . . Diop, B. (2010). Aetiology of AFB negative pneumonias in hospitalized HIV patients in Dakar. [French]. *Revue des Maladies Respiratoires, 27 (9)*, 1015-1021.

Slack, R. C., Stewart, J. D., Lewis, C. L., Cameron, D. I., Carvalho, G. R., Mangalji, Z., . . . Wanjala, S. (1976). Acute pneumonias in adults in Nairobi. *East African Medical Journal, 53*(8), 480-483.

Sligl, W. I., Asadi, L., Eurich, D. T., Tjosvold, L., Marrie, T. J., & Majumdar, S. R. (2014). Macrolides and mortality in critically ill patients with community-acquired pneumonia: a systematic review and meta-analysis. *Critical Care Medicine, 42*(2), 420-432.

Smith, S. M., Fahey, T., Smucny, J., & Becker, L. A. (2014). Antibiotics for acute bronchitis. *Cochrane Database Syst Rev, 3*, CD000245.

Sofowora, E. O., & Onadeko, B. O. (1973). Complications and prognostic factors in pneumonia among Nigerians. *Nigerian medical journal : journal of the Nigeria Medical Association, 3*(3), 144-145.

Song, J. H., Thamlikitkul, V., & Hsueh, P. R. (2011). Clinical and economic burden of community-acquired pneumonia amongst adults in the Asia-Pacific region. *International Journal of Antimicrobial Agents, 38*(2), 108-117.

Sonnenberg, P., Glynn, J. R., Fielding, K., Murray, J., Godfrey-Faussett, P., & Shearer, S. (2005). How soon after infection with HIV does the risk of tuberculosis start to increase? A retrospective cohort study in South African gold miners. *Journal of Infectious Diseases, 191*(2), 150-158.

Sousa, D., Justo, I., Dominguez, A., Manzur, A., Izquierdo, C., Ruiz, L., . . . Carratala, J. (2013). Community-acquired pneumonia in immunocompromised older patients: incidence, causative organisms and outcome. *Clinical Microbiology and Infection, 19*(2), 187-192.

Sow, O., Frechet, M., Diallo, A. A., Soumah, S., Conde, M. K., Diot, P., . . . Lemarie, E. (1996). Community acquired pneumonia in adults: a study comparing clinical features and outcome in Africa (Republic of Guinea) and Europe (France). *Thorax, 51*(4), 385-388.

Spindler, C., Stralin, K., Eriksson, L., Hjerdt-Goscinski, G., Holmberg, H., Lidman, C., . . . Hedlund, J. (2012). Swedish guidelines on the management of community-acquired pneumonia in immunocompetent adults--Swedish Society of Infectious Diseases 2012. *Scandinavian Journal of Infectious Diseases, 44*(12), 885-902.

Stearns-Kurosawa, D. J., Osuchowski, M. F., Valentine, C., Kurosawa, S., & Remick, D. G. (2011). The pathogenesis of sepsis. *Annual Review of Pathology, 6*, 19-48.

Steingart, K. R., Ng, V., Henry, M., Hopewell, P. C., Ramsay, A., Cunningham, J., . . . Pai, M. (2006). Sputum processing methods to improve the sensitivity of smear microscopy for tuberculosis: a systematic review. *Lancet Infectious Diseases, 6*(10), 664-674.

Steingart, K. R., Sohn, H., Schiller, I., Kloda, L. A., Boehme, C. C., Pai, M., & Dendukuri, N. (2013). Xpert(R) MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. *Cochrane Database Syst Rev, 1*, CD009593.

Steyerberg, E. W., Moons, K. G., van der Windt, D. A., Hayden, J. A., Perel, P., Schroter, S., . . . Altman, D. G. (2013). Prognosis Research Strategy (PROGRESS) 3: prognostic model research. *PLoS Medicine, 10*(2), e1001381.

Steyerberg, E. W., Vickers, A. J., Cook, N. R., Gerds, T., Gonen, M., Obuchowski, N., . . . Kattan, M. W. (2010). Assessing the performance of prediction models: a framework for traditional and novel measures. *Epidemiology, 21*(1), 128-138.

Stroup, D. F., Berlin, J. A., Morton, S. C., Olkin, I., Williamson, G. D., Rennie, D., . . . Thacker, S. B. (2000). Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA, 283*(15), 2008-2012.

Sullivan, J. H., Moore, R. D., Keruly, J. C., & Chaisson, R. E. (2000). Effect of antiretroviral therapy on the incidence of bacterial pneumonia in patients with advanced HIV infection. *American Journal of Respiratory and Critical Care Medicine, 162*(1), 64-67.

Survivng Sepsis Campaign. (2015). Updated bundles in response to new evidence. Retrieved from http://www.survivingsepsis.org/SiteCollectionDocuments/SSC_Bundle.pdf

Suthar, A. B., Vitoria, M. A., Nagata, J. M., Anglaret, X., Mbori-Ngacha, D., Sued, O., . . . Doherty, M. C. (2015). Co-trimoxazole prophylaxis in adults, including pregnant women, with HIV: a systematic review and meta-analysis. *Lancet HIV, 2*(4), e137-150.

Swarthout, T., Mwalukomo, T., Everett, D. B., Bar-Zeev, N., Kamn'gona, A., Chipasula, T., . . . Heyderman, R. S. (2016 [Abstract ID - 367]). *Persistent vaccine type carriage of Streptococcus pneumoniae four years after introducing 13-valent pneumococcal conjugate vaccine in a 3+0 schedule in Malawi.* Paper presented at the 10th International Symposium on Pneumococci and Pneumococcal Diseases, Glasgow, United Kingdom.

Syrjala, H., Broas, M., Suramo, I., Ojala, A., & Lahde, S. (1998). High-resolution computed tomography for the diagnosis of community-acquired pneumonia. *Clinical Infectious Diseases, 27*(2), 358-363.

Takahashi, K., Suzuki, M., Minh le, N., Anh, N. H., Huong, L. T., Son, T. V., . . . Yoshida, L. M. (2013). The incidence and aetiology of hospitalised community-acquired pneumonia among Vietnamese adults: a prospective surveillance in Central Vietnam. *BMC Infectious Diseases, 13*, 296.

Talbot, E., Munseri, P., Teixeira, P., Matee, M., Bakari, M., Lahey, T., & von Reyn, F. (2012). Test characteristics of urinary lipoarabinomannan and predictors of mortality among hospitalized HIV-infected tuberculosis suspects in Tanzania. *PloS One, 7*(3), e32876.

Tang, A. M., Dong, K., Deitchler, M., Chung, M., Maalouf-Manasseh, Z., Tumilowicz, A., & Wanke, C. (2013). *Use of cut-offs for mid-upper arm circumference (MUAC) as an indicator or predictor of nutritional or health-related outcomes in adolescents and adults: A systematic review*. Retrieved from Washington, DC: http://www.cmamforum.org/Pool/Resources/MUACcutoffs-for-adols-adults-Systematic-Review-FANTA-2013.pdf

Tang, C. M., & Macfarlane, J. T. (1993). Early management of younger adults dying of community acquired pneumonia. *Respiratory Medicine, 87*(4), 289-294.

Tecle, T., Tripathi, S., & Hartshorn, K. L. (2010). Review: Defensins and cathelicidins in lung immunity. *Innate Immunity, 16*(3), 151-159.

Theron, G., Zijenah, L., Chanda, D., Clowes, P., Rachow, A., Lesosky, M., . . . Dheda, K. (2014). Feasibility, accuracy, and clinical effect of point-of-care Xpert MTB/RIF testing for tuberculosis in primary-care settings in Africa: a multicentre, randomised, controlled trial. *Lancet, 383*(9915), 424-435.

Thomas, C. P., Ryan, M., Chapman, J. D., Stason, W. B., Tompkins, C. P., Suaya, J. A., . . . Shepard, D. S. (2012). Incidence and cost of pneumonia in medicare beneficiaries. *Chest, 142*(4), 973-981.

Tichopad, A., Roberts, C., Gembula, I., Hajek, P., Skoczynska, A., Hryniewicz, W., . . . Kolek, V. (2013). Clinical and economic burden of community-acquired pneumonia among adults in the Czech Republic, Hungary, Poland and Slovakia. *PloS One, 8*(8), e71375.

To, K. K., Wong, S. C., Xu, T., Poon, R. W., Mok, K. Y., Chan, J. F., . . . Yuen, K. Y. (2013). Use of nasopharyngeal aspirate for diagnosis of pneumocystis pneumonia. *Journal of Clinical Microbiology, 51*(5), 1570-1574.

Torres, A., Blasi, F., Peetermans, W. E., Viegi, G., & Welte, T. (2014). The aetiology and antibiotic management of community-acquired pneumonia in adults in Europe: a literature review. *European Journal of Clinical Microbiology and Infectious Diseases, 33*(7), 1065-1079.

Torres, A., Peetermans, W. E., Viegi, G., & Blasi, F. (2013). Risk factors for community-acquired pneumonia in adults in Europe: a literature review. *Thorax, 68*(11), 1057-1065.

Torres, A., Sibila, O., Ferrer, M., Polverino, E., Menendez, R., Mensa, J., . . . Agusti, C. (2015). Effect of corticosteroids on treatment failure among hospitalized patients with severe community-acquired pneumonia and high inflammatory response: a randomized clinical trial. *JAMA, 313*(7), 677-686.

Tortoli, E., Cichero, P., Piersimoni, C., Simonetti, M. T., Gesu, G., & Nista, D. (1999). Use of BACTEC MGIT 960 for recovery of mycobacteria from clinical specimens: multicenter study. *Journal of Clinical Microbiology, 37*(11), 3578-3582.

Tristram, S., Jacobs, M. R., & Appelbaum, P. C. (2007). Antimicrobial resistance in Haemophilus influenzae. *Clinical Microbiology Reviews, 20*(2), 368-389.

Trotter, C. L., Stuart, J. M., George, R., & Miller, E. (2008). Increasing hospital admissions for pneumonia, England. *Emerging Infectious Diseases, 14*(5), 727-733.

Turner, P., Turner, C., Kaewcharernnet, N., Mon, N. Y., Goldblatt, D., & Nosten, F. (2011). A prospective study of urinary pneumococcal antigen detection in healthy Karen mothers with high rates of pneumococcal nasopharyngeal carriage. *BMC Infectious Diseases, 11*, 108.

United Nations Development Programme. (2014). Human Development Report 2014. Retrieved from http://hdr.undp.org/en/2014-report/download

United Nations Statistics Division. (2014). World Statistics Pocketbook; Country Profile: Malawi. Retrieved from http://data.un.org/CountryProfile.aspx?crName=malawi

Valdivia, L., Nix, D., Wright, M., Lindberg, E., Fagan, T., Lieberman, D., . . . Galgiani, J. N. (2006). Coccidioidomycosis as a common cause of community-acquired pneumonia. *Emerging Infectious Diseases, 12*(6), 958-962.

van der Poll, T., & Opal, S. M. (2009). Pathogenesis, treatment, and prevention of pneumococcal pneumonia. *Lancet, 374*(9700), 1543-1556.

van der Zee, A., Peeters, M., de Jong, C., Verbakel, H., Crielaard, J. W., Claas, E. C., & Templeton, K. E. (2002). Qiagen DNA extraction kits for sample preparation for legionella PCR are not suitable for diagnostic purposes. *Journal of Clinical Microbiology, 40*(3), 1126.

van Lettow, M., Akesson, A., Martiniuk, A. L., Ramsay, A., Chan, A. K., Anderson, S. T., . . . Bedell, R. A. (2012). Six-month mortality among HIV-infected adults presenting for antiretroviral therapy with unexplained weight loss, chronic fever or chronic diarrhea in Malawi. *PloS One, 7*(11), e48856.

van Vugt, S. F., Verheij, T. J., de Jong, P. A., Butler, C. C., Hood, K., Coenen, S., . . . Group, G. P. (2013). Diagnosing pneumonia in patients with acute cough: clinical judgment compared to chest radiography. *European Respiratory Journal, 42*(4), 1076-1082.

Vardakas, K. Z., Siempos, II, Grammatikos, A., Athanassa, Z., Korbila, I. P., & Falagas, M. E. (2008). Respiratory fluoroquinolones for the treatment of community-acquired pneumonia: a meta-analysis of randomized controlled trials. *CMAJ: Canadian Medical Association Journal, 179*(12), 1269-1277.

Vincent, J. L., Moreno, R., Takala, J., Willatts, S., De Mendonca, A., Bruining, H., . . . Thijs, L. G. (1996). The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Medicine, 22*(7), 707-710.

Vittinghoff, E., & McCulloch, C. E. (2007). Relaxing the rule of ten events per variable in logistic and Cox regression. *American Journal of Epidemiology, 165*(6), 710-718.

von Gottberg, A., de Gouveia, L., Tempia, S., Quan, V., Meiring, S., von Mollendorf, C., . . . Investigators, G.-S. (2014). Effects of vaccination on invasive pneumococcal disease in South Africa. *New England Journal of Medicine, 371*(20), 1889-1899.

Vray, M., Germani, Y., Chan, S., Duc, N. H., Sar, B., Sarr, F. D., . . . Mayaud, C. (2008). Clinical features and etiology of pneumonia in acid-fast bacillus sputum smear-negative HIV-infected patients hospitalized in Asia and Africa. *AIDS, 22 (11)*, 1323-1332.

Waight, P. A., Andrews, N. J., Ladhani, N. J., Sheppard, C. L., Slack, M. P., & Miller, E. (2015). Effect of the 13-valent pneumococcal conjugate vaccine on invasive pneumococcal disease in England and Wales 4 years after its introduction: an observational cohort study. *Lancet Infectious Diseases, 15*(6), 629.

Waitt, P. I., Mukaka, M., Goodson, P., SimuKonda, F. D., Waitt, C. J., Feasey, N., . . . Heyderman, R. S. (2015). Sepsis carries a high mortality among hospitalised adults in Malawi in the era of

antiretroviral therapy scale-up: a longitudinal cohort study. *Journal of Infection, 70*(1), 11-19.

Wan, X., Wang, W., Liu, J., & Tong, T. (2014). Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Medical Research Methodology, 14*, 135.

Wasserman, S., Engel, M. E., & Mendelson, M. (2013). Burden of pneumocystis pneumonia in HIV-infected adults in sub-Saharan Africa: protocol for a systematic review. *Syst Rev, 2*, 112.

Waterer, G. W., Baselski, V. S., & Wunderink, R. G. (2001a). Legionella and community-acquired pneumonia: a review of current diagnostic tests from a clinician's viewpoint. *American Journal of Medicine, 110*(1), 41-48.

Waterer, G. W., Kessler, L. A., & Wunderink, R. G. (2004). Medium-term survival after hospitalization with community-acquired pneumonia. *American Journal of Respiratory and Critical Care Medicine, 169*(8), 910-914.

Waterer, G. W., Somes, G. W., & Wunderink, R. G. (2001b). Monotherapy may be suboptimal for severe bacteremic pneumococcal pneumonia. *Archives of Internal Medicine, 161*(15), 1837-1842.

Waterer, G. W., & Wunderink, R. G. (2001c). The influence of the severity of community-acquired pneumonia on the usefulness of blood cultures. *Respiratory Medicine, 95*(1), 78-82.

Weber, M. W., & Mulholland, E. K. (1998). Pulse oximetry in developing countries. *Lancet, 351*(9115), 1589.

Wells, G. A., Shea, B., O'Connell, D., Peterson, J., Welxh, V., Losos, M., & Tugwell, P. (2014). The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Retrieved from http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

Welte, T. (2012). Risk factors and severity scores in hospitalized patients with community-acquired pneumonia: prediction of severity and mortality. *European Journal of Clinical Microbiology and Infectious Diseases, 31*(1), 33-47.

Welte, T., Torres, A., & Nathwani, D. (2012). Clinical and economic burden of community-acquired pneumonia among adults in Europe. *Thorax, 67*(1), 71-79.

Wenzel, R. P., & Fowler, A. A., 3rd. (2006). Clinical practice. Acute bronchitis. *New England Journal of Medicine, 355*(20), 2125-2130.

Wheeler, I., Price, C., Sitch, A., Banda, P., Kellett, J., Nyirenda, M., & Rylance, J. (2013). Early warning scores generated in developed healthcare settings are not sufficient at predicting early mortality in Blantyre, Malawi: a prospective cohort study. *PloS One, 8*(3), e59830.

Wiemken, T., Kelley, R. R., & Ramirez, J. (2013). Clinical scoring tools: Whici is best to predict clinical response and long-term outcomes? In T. File (Ed.), *Community-acquired pneumonia: Controversies and questions* (Vol. 27, pp. 33-48). Philadephlia, Pennsylvania: Elsevier.

Wijesinghe, M., Perrin, K., Healy, B., Weatherall, M., & Beasley, R. (2012). Randomized controlled trial of high concentration oxygen in suspected community-acquired pneumonia. *Journal of the Royal Society of Medicine, 105*(5), 208-216.

Wijesinghe, M., Perrin, K., Ranchord, A., Simmonds, M., Weatherall, M., & Beasley, R. (2009). Routine use of oxygen in the treatment of myocardial infarction: systematic review. *Heart, 95*(3), 198-202.

Wipf, J. E., Lipsky, B. A., Hirschmann, J. V., Boyko, E. J., Takasugi, J., Peugeot, R. L., & Davis, C. L. (1999). Diagnosing pneumonia by physical examination: relevant or relic? *Archives of Internal Medicine, 159*(10), 1082-1087.

Wolter, N., von Gottberg, A., du Plessis, M., de Gouveia, L., Klugman, K. P., Group for Enteric, R., & Meningeal Disease Surveillance in South, A. (2008). Molecular basis and clonal nature of increasing pneumococcal macrolide resistance in South Africa, 2000-2005. *International Journal of Antimicrobial Agents, 32*(1), 62-67.

Wong, A. Y., Root, A., Douglas, I. J., Chui, C. S., Chan, E. W., Ghebremichael-Weldeselassie, Y., . . . Wong, I. C. (2016). Cardiovascular outcomes associated with use of clarithromycin: population based study. *BMJ, 352*, h6926.

Woodhead, M. A., Blasi, F., Ewig, S., Garau, J., Huchon, G., Ieven, M., . . . Verheij, T. J. (2011). Guidelines for the management of adult lower respiratory tract infections--full version. *Clinical Microbiology and Infection, 17 Suppl 6*, E1-59.

Woodhead, M. A., Macfarlane, J. T., McCracken, J. S., Rose, D. H., & Finch, R. G. (1987). Prospective study of the aetiology and outcome of pneumonia in the community. *Lancet, 1*(8534), 671-674.

Wootton, D. G., Aston, S. J., & Gordon, S. B. (2014). The pathophysiology of pneumococcal pneumonia. In J. D. Chalmers, M. W. Pletz, & S. Aliberti (Eds.), *Community-acuired pneumonia* (Vol. 63, pp. 1-24). Sheffield, United Kingdom: European Respiratory Society.

World Bank. (2015). World Development Indicators database. Retrieved from http://databank.worldbank.org/data/views/reports/tableview.aspx

World Health Organization. (1995). *Physical status: The use and interpretation of anthropometry - Report of WHO Expert Committee*. Geneva, Swizerland: World Health Organization.

World Health Organization. (2004). *Rapid HIV tests: Guidelines for use in HIV testing and counselling services in resource-constrained settings*. Geneva, Switzerland: World Health Organization.

World Health Organization. (2006). *Improving the diagnosis and treatment of smear-negative pulmonary and extrapulmonary tuberculosis among adults and adolescents: Recommendations for HIV-prevalent and resource-constrained settings*. Retrieved from Geneva, Switzerland:

World Health Organization. (2009). *Integrated Management of Adolescent and Adult Illness: Acute Care*. Geneva, Switzerland: World Health Organization.

World Health Organization. (2011a). *The clinical use of oxygen in hospitals with limited resources: guidelines for health-care workers, hospital engineers and managers.*

World Health Organization. (2011b). *Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity.* Retrieved from Geneva, Switzerland: http://www.who.int/vmnis/indicators/haemoglobin.pdf

World Health Organization. (2011c). *Integrated Management of Adolescent and Adult Illness (IMAI), District Clinician Manual Volume 1: Hospital care for adolescents and adults*. Geneva, Switzerland: World Health Organization.

World Health Organization. (2013a). *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: Recommendations for a public health approach*. Geneva, Switzerland: World Health Organization.

World Health Organization. (2013b). *Global epidemiological surveillance standards for influenza*. Geneva, Switzerland: World Health Organization.

World Health Organization. (2013c). *Systematic screeening for active tuberculosis: principles and recommendations*. Geneva, Switzerland: World Health Organization.

World Health Organization. (2014a). *Global status report on non-communicable diseases 2014*. Geneva, Switzerland: World Health Organization.

World Health Organization. (2014b). *Global update on the health sector response to HIV, 2014*. Geneva, Switzerland: World Health Organization.

World Health Organization. (2014c). *Xpert MTB/RIF implementation manual. Technical and operational 'how to': practical considerations*. Geneva, Switzerland: World Health Organization.

World Health Organization. (2015a). *Global tuberculosis report*. Geneva, Switzerland: World Health Organization.

World Health Organization. (2015b). *Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV*. Geneva, Switzerland: World Health Organization.

Worodria, W., Okot-Nwang, M., Yoo, S. D., & Aisu, T. (2003). Causes of lower respiratory infection in HIV-infected Ugandan adults who are sputum AFB smear-negative. *International Journal of Tuberculosis and Lung Disease, 7*(2), 117-123.

Wunderink, R. G. (2015). CAP death: what goes wrong when everything is right? *Lancet Infectious Diseases, 15*(9), 995-996.

Xaba, S. N., Greeff, O., & Becker, P. (2014). Determinants, outcomes and costs of ceftriaxone v. amoxicillin-clavulanate in the treatment of community-acquired pneumonia at Witbank Hospital. *SAMJ - South African Medical Journal, 104*(3), 187-191.

Yealy, D. M., Kellum, J. A., Huang, D. T., Barnato, A. E., Weissfeld, L. A., Pike, F., . . . Angus, D. C. (2014). A randomized trial of protocol-based care for early septic shock. *New England Journal of Medicine, 370*(18), 1683-1693.

Yende, S., Alvarez, K., Loehr, L., Folsom, A. R., Newman, A. B., Weissfeld, L. A., . . . Angus, D. C. (2013). Epidemiology and long-term clinical and biologic risk factors for pneumonia in community-dwelling older Americans: analysis of three cohorts. *Chest, 144*(3), 1008-1017.

Yone, E. W. P., Balkissou, A. D., Kengne, A. P., & Kuaban, C. (2012). Influence of HIV infection on the clinical presentation and outcome of adults with community-acquired pneumonia in Yaounde, Cameroon: a retrospective hospital-based study. *BMC Pulmonary Medicine, 12*, 46-54.

Yoshimine, H., Oishi, K., Mubiru, F., Nalwoga, H., Takahashi, H., Amano, H., . . . Nagatake, T. (2001). Community-acquired pneumonia in Ugandan adults: short-term parenteral ampicillin therapy for bacterial pneumonia. *The American journal of tropical medicine and hygiene, 64*(3-4), 172-177.

Yu, H., Rubin, J., Dunning, S., Li, S., & Sato, R. (2012). Clinical and economic burden of community-acquired pneumonia in the Medicare fee-for-service population. *Journal of the American Geriatrics Society, 60*(11), 2137-2143.

Yu, V. L., Hansen, D. S., Ko, W. C., Sagnimeni, A., Klugman, K. P., von Gottberg, A., . . . International Klebseilla Study, G. (2007). Virulence characteristics of Klebsiella and clinical manifestations of K. pneumoniae bloodstream infections. *Emerging Infectious Diseases, 13*(7), 986-993.

Yuan, X., Liang, B. B., Wang, R., Liu, Y. N., Sun, C. G., Cai, Y., . . . Chen, L. A. (2012). Treatment of community-acquired pneumonia with moxifloxacin: a meta-analysis of randomized controlled trials. *Journal of Chemotherapy, 24*(5), 257-267.

Yuste, J., Sen, A., Truedsson, L., Jonsson, G., Tay, L. S., Hyams, C., . . . Brown, J. S. (2008). Impaired opsonization with C3b and phagocytosis of Streptococcus pneumoniae in sera from subjects with defects in the classical complement pathway. *Infection and Immunity, 76*(8), 3761-3770.

Zar, H. J., Madhi, S. A., Aston, S. J., & Gordon, S. B. (2013). Pneumonia in low and middle income countries: progress and challenges. *Thorax, 68*(11), 1052-1056.

Zhang, Z., Clarke, T. B., & Weiser, J. N. (2009). Cellular effectors mediating Th17-dependent clearance of pneumococcal colonization in mice. *Journal of Clinical Investigation, 119*(7), 1899-1909.

Zijlstra, E. E. (2006). *The Clinical Book* (E. E. Zijlstra Ed.). Blantyre, Malawi: College of Medicine, University of Malawi.

Zoubga, A. Z., Ouedraogo, M., Boncoungou, K., Ki, C., Ouedraogo, S. M., Ouedraogo, G., . . . Drabo, Y. J. (2000). Aspects epidemilogiques, cliniques, therapeutics des pneumopathies aigues bacteriennes dans le service de pneumologie du centre hospitalier national sanou souro de Bobo-Dioulasso. *Médecine d'Afrique Noire, 47*(11), 470-472.