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Aetiology and Risk Factors for Mortality in an Adult Community-Acquired Pneumonia Cohort in Malawi.

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AT A GLANCE COMMENTARY:

Scientific Knowledge on the Subject:

In the antiretroviral therapy era, community-acquired pneumonia (CAP) remains the commonest cause of adult hospitalisation and a major cause of mortality in many sub-Saharan Africa HIV-affected countries. With the exception of cohorts from South Africa, contemporary studies describing CAP aetiology and outcome from the region are either small, retrospective or only use limited investigations to define aetiology. Current CAP management protocols applied in sub-Saharan Africa are therefore inadequately informed by contemporary data.

What This Study Adds to the Field:

In a large prospective cohort of hospitalised adults in Malawi we show that the major burden of hospitalised acute CAP remains in young, HIV-infected patients and that *Streptococcus pneumoniae*, tuberculosis and influenza predominate as the major causes. CAP mortality is high compared to populations from well-resourced settings with similar age profiles, and is associated with potentially modifiable risk factors including hypoxaemia. Death from CAP is poorly predicted by commonly used CAP severity-assessment tools such as CURB65.

This article has an online data supplement, which is accessible from this issue's table of content online at www.atsjournals.org

ABSTRACT

Rationale: In the context of rapid antiretroviral therapy (ART) rollout and an increasing burden of non-communicable diseases, there are few contemporary data describing the aetiology and outcome of community-acquired pneumonia (CAP) in sub-Saharan Africa.

Objectives: To describe the current aetiology of CAP in Malawi and identify risk factors for mortality.

Methods: We conducted a prospective observational study of adults hospitalised with CAP to a teaching hospital in Blantyre, Malawi. Aetiology was defined by blood culture, *Streptococcus pneumoniae* urinary antigen detection, sputum mycobacterial culture and Xpert MTB/RIF, and nasopharyngeal aspirate multiplex PCR.

Measurements and Main Results: In 459 patients (285 [62.1%] males; median age 34.7 [IQR: 29.4-41.9] years), 30-day mortality was 14.6% (64/439) and associated with male sex (adjusted odds ratio 2.60 [95% CI: 1.17-5.78]), symptom duration >7 days (2.78 [1.40-5.54]), tachycardia (2.99 [1.48-6.06]), hypoxaemia (4.40 [2.03-9.51]) and inability to stand (3.59 [1.72-7.50]). HIV was common (355/453; 78.4%), frequently newly diagnosed (124/355; 34.9%), but not associated with mortality. *S. pneumoniae* (98/458 [21.4%]) and *Mycobacterium tuberculosis* (75/326 [23.0%]) were the most frequently identified pathogens. Viral infection occurred in 32.6% (148/454) with influenza (40/454 [8.8%]) most common. Bacterial-viral co-infection occurred in 9.1% (28/307). Detection of *M. tuberculosis* was associated with mortality (aOR 2.44 [1.19-5.01]).

Conclusions: In the ART era, CAP in Malawi remains predominantly HIV-associated with a

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large proportion attributable to potentially vaccine-preventable pathogens. Strategies to increase early detection and treatment of tuberculosis and improve supportive care, in particular the correction of hypoxaemia, should be evaluated in clinical trials to address CAP-associated mortality.

Abstract word count: 250

Keywords: community-acquired pneumonia; HIV; Africa South of the Sahara; *Streptococcus pneumoniae*; pulmonary tuberculosis

INTRODUCTION

Globally, pneumonia is the commonest infectious cause of death and the second leading cause of overall life years lost (1). In sub-Saharan Africa alone, lower respiratory tract infections account for 390,000 deaths in older children and adults each year (2). Whilst the aetiology and outcome of community-acquired pneumonia (CAP) has been thoroughly described in large cohorts of adults in well-resourced settings in Europe and North America (3, 4) and more recently in young children (<5 years) from sub-Saharan Africa (5), contemporary data on acute CAP in adults from sub-Saharan Africa are limited. With the exception of cohorts from South Africa (6, 7), recent studies are either small (8, 9), retrospective (10) or only use a restricted panel of investigations to define aetiology (11).

In Malawi – a very low-income country in Southern Africa – pneumonia is the commonest cause of adult hospitalisation (12). There is a generalised HIV epidemic (adult prevalence 10.6% (13)) and high tuberculosis (TB) incidence (159 cases per 100,000 population (14)). These factors create a backdrop distinct from most well-resourced settings and common to many countries in the region, that is likely to have a substantial bearing on the epidemiology and aetiology of CAP; more comprehensive data are therefore crucial to develop appropriate context-specific management guidelines (15). Given the continued rollout of antiretroviral therapy (ART) (16), recent introduction of infant pneumococcal conjugate vaccination (PCV) (17) and the broader context of rapidly increasing life expectancy and emergence of chronic non-communicable diseases (18), contemporaneous data are vital. We therefore conducted a prospective study of adults hospitalised with CAP to the largest central hospital in Malawi to describe aetiology and to identify risk factors for mortality to inform the development of local guidelines for antibiotic choice and severity assessment. Some of the results of this study have been previously reported in the form of abstracts (19, 20).

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CAP in Malawian adults

METHODS

Study setting and design

We conducted a prospective observational study of adults hospitalised with CAP at Queen Elizabeth Central Hospital - a 1200 bed teaching hospital that provides free healthcare to the 1.3 million residents of Blantyre district in Southern Malawi. Ethical approval was provided by the Research Ethics Committees of University of Malawi College of Medicine (P.11/12/1309) and Liverpool School of Tropical Medicine (13.02). Some patients participated in linked case-control studies describing the impact of HIV on influenza severity (21) and the association of indoor air pollution exposure with pneumonia (22).

Study procedures

We recruited adults (≥18 years) hospitalised with clinically-diagnosed CAP defined as: reported or recorded fever (≥38°C); at least one relevant symptom (cough, chest pain, breathlessness, haemoptysis); and at least one focal chest sign (crepitations, pleural rub, bronchial breathing, percussive dullness or diminished breath sounds (adapted from (23)). Patients with symptoms for more than 14 days, current anti-tuberculous treatment or prior admission within the last month were excluded. Further details of the eligibility criteria are provided in the online data supplement. Written informed consent was provided by the patient, or in the case of incapacity, by their accompanying guardian.

Patients underwent a standardised clinical assessment on admission, were reviewed daily during hospitalisation and then followed at 30-days and 90-days post admission to determine vital status. Blood, urine, sputum and nasopharyngeal aspirate (NPA) were collected at enrolment. Diagnostic pleural aspiration was performed in patients with radiologically confirmed pleural effusion. Clinical care was provided in accordance with local

guidelines and directed by the patients' clinical team.

Radiographic assessment

Chest radiographs were performed as early as possible after admission and independently reported by two radiologists and a study clinician using a standardised form. A consensus report of the three assessors was used for analysis. Radiographic pneumonia was defined as the presence of consolidation or other parenchymal abnormality (including reticulonodular change, cavitation or miliary appearance) or pleural effusion (4). Additional details are provided in the online data supplement.

Laboratory testing

Haematological and biochemical analyses were performed by standard methods. HIV status was established by sequential rapid tests (Alere Determine™, Japan, and Uni-Gold™, Trinity Biotech, Ireland)(24) and CD4 cell count was performed on FACSCount™ flow cytometer (Becton Dickinson, California, USA). Blood cultures were performed using aerobic bottles in the BacT/ALERT 3D automated system (bioMérieux, Marcy-L'Etoile, France) and isolates identified using standard procedures (25). Urine antigen testing was performed for the detection of *Streptococcus pneumoniae* (BinaxNOW; Alere, Massachusetts, USA) and, in a subset of patients, *Legionella pneumophila* (BinaxNOW; Alere, Massachusetts, USA). A PCR assay was performed on NPA specimens for the detection of: adenovirus; bocavirus*;* *Chlamydia pneumoniae*; coronaviruses 229E, HKU1, OC43 and NL63; enterovirus; human metapneumovirus; influenza A and B viruses; *Mycoplasma pneumoniae*; parainfluenza virus types 1 - 4; parechovirus; respiratory syncytial viruses and rhinovirus. Xpert MTB/RIF assay (Cepheid; California, USA) and mycobacterial microscopy and culture (BACTEC MGIT 960 Mycobacterial Detection System; Becton Dickinson, Maryland, USA) were performed on

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non-induced sputum specimens. When obtained, pleural fluid samples were sent for Gram-stain, aerobic culture, mycobacterial microscopy and culture, and pneumococcal antigen testing. Further details of laboratory methods are provided in the online supplement.

Statistical analysis

Statistical analyses were performed with Stata version 12.1 (StataCorp; Texas, US). We tested for differences in continuous variables using Wilcoxon rank-sum test, and categorical variables by χ^2 test or Fisher's exact test as appropriate. Differences in microbial aetiology by radiographic status controlling for the effect of HIV were examined using the Mantel-Haenszel method.

Candidate risk factors for 30-day mortality were selected *a priori* based on literature review (26-29). Continuous variables, with the exception of age, were dichotomised at standard cut-off points (29-32). Univariable analyses were performed using logistic regression to explore associations with 30-day mortality. Multivariable models were generated using age, sex, HIV status and all variables with a *P* values <0.2 on univariable analysis, prevalence of at least 5% and for which data were available in more than 95% of patients, and then rationalised by stepwise backwards elimination with removal of variables with a *P* value >0.05. The number of covariates in the multivariable model were limited to maintain at least 10 events per variable (33). Subgroup analyses of HIV-infected patients and those with radiographic pneumonia were performed. The association of aetiology with mortality was also assessed (see online supplement). All available case information was used in each univariable analysis. In multivariable models, we excluded patients with missing data for included variables.

The prognostic performance of several CAP severity-assessment tools - CURB65 (29), CRB65 (29), SMRT-CO (simplified version of the SMART-COP tool (34)), modified IDSA/ATS 2007

minor criteria (35) and SWAT-Bp (28) - for predicting 30-day mortality was described 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 (CI). Details of how scores were calculated for each severity-assessment tool are provided in the online supplement (see Table 4).

RESULTS

Baseline characteristics

Between 15th May 2013 and 31st January 2015 we screened 1711 adult patients, of whom 489 fulfilled the eligibility criteria, 472 were enrolled and 459 included in the analysis (Figure 1). The median age was 34.7 years (interquartile range (IQR): 29.4-41.9) and 285 (62.1%) were male (Table 1; see Table E1 in the Online Supplement). HIV infection was common (355/453; 78.4%; HIV status missing in 6 individuals) and often newly diagnosed (124/355; 34.9%) whilst other comorbid illnesses were reported infrequently (31/451; 6.9%). 83.3% (189/227) of those known to be HIV-infected reported current ART use. Prior pneumonia was common (108/457; 23.6%) and associated with HIV (odds ratio (OR) 2.91; 95% CI: 1.46-6.30). The median length of admission was 7 days (IQR: 4-10).

Radiographic pneumonia was identified by consensus report in 317 (76.0%) of 417 patients with available interpretable chest radiographs with moderate inter-observer agreement (Kappa 0.75; 95% CI: 0.69-0.81; Table 1; see Table E2). Pleural effusion was identified in 118/416 (28.4%), being the sole basis of defining radiographic pneumonia in 38/315 (12.1%). The proportion of patients with radiographic pneumonia did not vary with HIV status (HIV-

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infected 247/320 (77.2%) *vs.* HIV-uninfected 66/91 (72.5%); *P*=0.36) or with CD4 count (CD4 <200 cells/mm^3 176/222 (79.3%) *vs.* CD4 ≥ 200 cells/mm^3 49/64 (76.6%), *P*=0.64; CD4 count available in 315/355 (88.7%) HIV-infected patients).

Aetiology

Blood for aerobic culture was obtained from 450 of the 459 (98.0%) of the participants, NPA from 455/459 (99.1%) and urine specimen for *Streptococcus pneumoniae* antigen detection from 433/459 (94.3%) with stored specimens available for *Legionella* antigen testing in 193 (see Table E5). At least one sputum specimen for a mycobacterial diagnostic test was obtained from 322/459 (70.2%) participants: smear microscopy, mycobacterial culture and Xpert MTB/RIF assay were completed in 305/459 (66.4%), 273/459 (59.5%) and 308/459 (67.1%), respectively. A pleural fluid specimen was obtained in 35/459 (7.6%) patients: aerobic bacterial culture, *Streptococcus pneumoniae* antigen detection, mycobacterial smear microscopy and culture were completed in 31, 31 and 35 patients respectively.

Overall at least one potential pathogen was identified in 278/459 (60.6%) patients including at least one bacteria in 125/452 (27.7%) and at least one virus in 148/459 (32.6%; Table 2). *Streptococcus pneumoniae* was the most commonly identified organism, present in 98 (21.4%) of 458 for whom results of blood culture and/or urinary antigen assay were available, of whom 92 (93.9%) were identified by detection of urinary antigen alone (see Table E5). Pneumococcal aetiology was more common in HIV-uninfected patients (30/97 (30.9%) *vs.* 68/355 (19.2%); *P*=0.01) and those with radiographic pneumonia (83/316 (26.3%) *vs*. 8/100 (8.0%); *P*<0.001; see Table E6), in particular confluent consolidation (OR 2.51; 95% CI: 1.26-4.98; see Table E7). Overall, 26 (5.8%) of 450 patients for whom blood was sent for culture were bacteraemic: *Salmonella* Typhi (n=9), nontyphoidal *Salmonella* (NTS; n=7) and

S. pneumoniae (n=5) were most commonly isolated. *S.* Typhi was identified more frequently in HIV-uninfected patients (5/94 (5%) *vs.* 3/350 (1%); *P*=0.02), whilst all cases of NTS infection occurred in HIV-infected patients, and both were more common amongst patients lacking radiographic pneumonia (see Table E6). Infection with *Mycoplasma pneumoniae* (6/455; 1.3%) and *Chlamydia pneumoniae* (2/455; 0.4%) were uncommon. None of the 193 patients tested had a positive *Legionella* urinary antigen assay result.

Overall, *M. tuberculosis* was identified in 75 (23.0%) of 326 patients who submitted a sputum and/or pleural fluid specimen (Table 2). TB was confirmed by culture in 65/75 (86.7%) and diagnosed on the basis of Xpert MTB/RIF alone, sputum microscopy alone or pleural fluid microscopy alone in 8/75 (10.7%), 1/75 (1.3%) and 1/75 (1.3%) patients, respectively (see Table E5). Non-tuberculous mycobacteria were isolated in 8/273 (2.9%) for whom sputum for culture was obtained of whom 1 was smear positive. The frequency of TB did not differ significantly between the groups with and without radiographic pneumonia (58/232 (25%) *vs.* 13/68 (19.1%); see Table E6), although in the latter, TB displaced *S. pneumoniae* as the most commonly identified pathogen, with all cases occurring in HIV-infected patients.

Influenza (40/454; 8.8%), adenovirus (35/455; 7.7%) and coronavirus (31/455; 6.8%) were the most commonly detected viruses. Detection of these respiratory viruses was not associated with HIV status or the presence of radiographic pneumonia (see Tables 2 and E6).

Co-infection relationships were investigated in 307 patients (66.9% of cohort) for whom results for blood culture, pneumococcal urine antigen, sputum mycobacterial culture and/or Xpert MTB/RIF, NPA PCR were available. At least one organism was detected in 206/307 (67.1%) and co-infection with 2 or more organisms was present in 67/307 (21.8%; Figure 2);

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the combination of bacterial-viral co-infection was most frequent (28/307; 9.1%). *S. pneumoniae* was co-detected in one-fifth of patients with influenza (6/31; 19.4%). *M. tuberculosis* was isolated in 9.6% (7/73) of those with *S. pneumoniae* (see Table E8). Detection of multiple organisms did not vary with HIV status (54/243 (22.2%) *vs.* 12/62 (19.4%)).

Mortality

439 of 459 (95.6%) patients were successfully followed to 30 days of whom 64 (14.6%) had died, including 15 and 31 within the first 3 and 7 days following admission, respectively (Table 1). 418 were followed to 90 days of whom an additional 23 had died. Male sex (aOR 2.60; 95% CI: 1.17-5.78), pre-presentation symptom duration >7 days (aOR 2.78; 95% CI: 1.40-5.54), heart rate ≥125 per minute (aOR 2.99; 95% CI: 1.48-6.06), oxygen saturations <90% (aOR 4.40; 95% CI: 2.03-9.51) and inability to stand (aOR 3.59; 95% CI: 1.72-7.50) were independently associated with 30-day mortality (Table 3). Neither age nor any underlying comorbid illness, including HIV, or initial antimicrobial treatment was found to be significantly associated with 30-day mortality. Detection of *S. pneumoniae* was associated with reduced mortality (aOR 0.40; 95% CI: 0.17-0.91; see Table E9), whilst TB was associated with increased mortality (aOR 2.44; 95% CI: 1.19-5.01). Mortality did not vary with detection of multiple organisms compared to a single organism (5/65 (7.7%) *vs*. 13/135 (9.6%); *P*=0.80).

In a subgroup analysis of the 342 HIV-infected patients followed to day 30, symptom duration >7 days (aOR 3.56; 95% CI: 1.60-7.93), heart rate ≥125 per minute (aOR 3.06; 95% CI: 1.40-6.71), oxygen saturations <90% (aOR 2.97; 95% CI: 1.28-6.88), inability to stand (aOR 4.25; 95% CI: 1.84-9.79) and CD4 count <50 cells/mm^3 (aOR 2.30; 95% CI: 1.07-4.92) were

associated with mortality in multivariable analysis (see Table E10). CD4 count <200 cells/mm^3 was not associated with mortality (OR 1.63; 95% CI: 0.69-3.83). In the subgroup of 305 patients with radiographic pneumonia followed to day 30, symptom duration >7 days (aOR 3.30; 95% CI: 1.37-7.96), heart rate ≥125 per minute (aOR 2.66; 95% CI: 1.08-6.57) and multilobar consolidation (aOR 2.75; 95% CI: 1.17-6.47) were significantly associated with mortality, with a trend towards an association for inability to stand (aOR 2.63; 95% CI: 1.00-6.89; see Table E11). 30-day mortality was however significantly higher in the small group of patients for whom a chest radiograph was unavailable (17/36 (47.2%) *vs.* 47/403 (11.7%); *P*<0.0001; see Table E3).

Prognostic performance of severity-assessment tools

Of the CAP severity-assessment tools examined, SMRT-CO had the highest sensitivity (89.7%; 95% CI: 72.6-97.8), negative predictive value (96.8%; CI: 91.0-99.3%) and overall discriminatory capability (AUROC 0.66; 95% CI: 0.57-0.75) for 30-day mortality (Table 4). CURB65 had poor sensitivity and discriminatory capability. Only 38 (8.8%) patients had 'severe CAP' by CURB65 (i.e. score ≥3) and mortality amongst those with 'mild CAP' (i.e. CURB65 ≤1) was 10.8% (29/268). The prognostic performance of each tool was similarly poor in the subgroup with radiographic pneumonia (see Table E12).

DISCUSSION

In this prospective study of acute CAP in adults that is amongst the largest conducted in sub-Saharan Africa, we have shown that: the burden of hospitalised pneumonia in adults predominantly remains in young, HIV-infected patients; tuberculosis and vaccine-preventable pathogens such as *S. pneumoniae* and influenza are common; mortality is

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substantial and associated with potentially modifiable risk factors but poorly predicted by widely-used CAP severity-assessment tools.

Although completed within the era of ART scale-up, 35% of HIV-infected patients were newly diagnosed, 17% of those with known HIV were not receiving ART and more than three-quarters had advanced immunosuppression (i.e. CD4 <200 cells/mm^3). Further substantial reductions in CAP incidence may therefore be achieved by improved HIV testing and linkage to early initiation of ART (36).

At first glance, the overall crude mortality rate of 14.6% is comparable to that seen in well-resourced settings (26, 29, 37). However, a recent UK cohort reported 30-day mortality of 1.5% in patients under 50 (38), suggesting a substantially higher age-adjusted mortality rate in our cohort. The identified associations of TB and uncorrected hypoxaemia with death, may explain some of this apparent large discrepancy in mortality rate. In keeping with other studies of acute CAP (7, 27, 28), we did not find evidence that HIV overall influenced outcome; increased mortality was evident in only the most profoundly immunocompromised with CD4 cell count <50 cells/mL.

Given the observed strong association of hypoxaemia with mortality, expansion of supplemental oxygen provision, which across much of sub-Saharan Africa is currently severely limited (39), represents an obvious strategy to be evaluated in an effort to improve CAP outcomes. Programmatic interventions in children in low-resource settings based on improved oxygen supply using oxygen concentrators have been associated with a 35% reduction in mortality (40). The lack of association between respiratory rate and mortality underlines the importance of expanding the availability of pulse oximetry in tandem. Similarly, the association of pre-presentation symptom duration with mortality suggests that

interventions to improve patient education to alter healthcare-seeking behaviour or referral mechanisms within community healthcare centres should be considered. The continued substantial mortality rate beyond day 30 also warrants further study to devise targeted interventions to enhance care following discharge from hospital.

The use of objective CAP severity assessment tools has been shown to improve both the recognition of patients with severe CAP likely to require intensive care support (41) and those with mild disease who can be safely managed as outpatients (42). Current South African CAP guidelines recommend that CURB65 is used to inform site of care and initial antimicrobial treatment (43). However, we found that CURB65 showed poor prognostic performance in predicting 30-day mortality in this cohort compared to its performance in CAP cohorts from well-resourced settings (44). This variation likely reflects differences in microbial aetiology, demographics and comorbidity profiles between this cohort and the patient populations in which CURB65 was derived (29, 37), and underlines the importance of prospective validation of prognostic tools in relevant settings (29, 44). The similarly poor performance of the SWAT-Bp score that was derived in a LRTI cohort from Malawi (28), however, highlights the challenges of developing a simple and accurate locally-adapted tool. Rather than attempting to derive a single tool capable of accurately predicting mortality across the whole spectrum of disease severity, a tool with high negative predictive performance aimed at identifying those patients with a low risk of adverse outcome suitable for outpatient management may be more feasible and equally useful. In this respect, the SMRT-CO tool performed well with a negative predictive value of 96.8%, but the inclusion of a radiographic parameter (i.e. multilobar involvement (34)) limits its use as a triage tool in settings where chest radiography might not be readily available.

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Recent CAP studies corroborate our observation that *S. pneumoniae* remains the commonest identified cause of adult CAP in sub-Saharan Africa (6, 10, 27). Universal infant vaccination with PCV was introduced in Malawi in 2011, approximately 2.5 years before the start of recruitment. Following the introduction of PCV in the US and South Africa, rates of adult pneumococcal disease – including pneumonia hospitalisations – fell rapidly as a result of indirect protection due to reduced pneumococcal transmission from vaccine recipients (45, 46). Further studies are needed to describe the serotype distribution of pneumococcal pneumonia in Malawi, to determine whether targeted vaccination programmes of at risk groups may be beneficial to tackle the persistent burden of adult disease. Recently developed urinary assays that can detect serotype-specific antigens in non-invasive pneumococcal pneumonia may provide a more comprehensive description (47).

When adequate diagnostic tests are performed, TB is identified in a substantial proportion of patients presenting with acute CAP in sub-Saharan Africa with the major burden of disease and associated mortality occurring in HIV-infected individuals (7-9, 27). At 23% of those tested and 16% of the overall cohort, the frequency of TB is similar to that previously reported (7-9, 27), but probably underestimates the true burden given the reliance on spontaneously expectorated sputum specimens and a single specimen submitted for culture. In most sub-Saharan African settings, laboratory diagnosis of TB has until recently relied on sputum smear microscopy that has poor sensitivity, particularly for HIV-associated TB. The WHO has advocated an empirical “step-up” approach, whereby anti-tuberculous treatment is initiated for HIV-infected adults with features of severe respiratory infection and negative sputum smears who fail to improve after 3-5 days of antibacterial treatment (48). Whilst this approach may limit inappropriate anti-tuberculous treatment, it may miss up to 20% of patients with culture positive TB and risks delaying treatment in a group of patients with a

very high risk of early death (49). The increasingly available Xpert MTB/RIF assay used in this study offers much improved sensitivity and is now recommended as the first-line diagnostic for HIV-associated TB (50). Rapid urine-based diagnostics (e.g. urine Xpert MTB/RIF, mycobacterial glycopeptide lipoarabinomannan assay) may have a complementary role to guide initiation of anti-tuberculous treatment, particularly for acutely ill patients from whom sputum is frequently unobtainable (51, 52).

In keeping with recent CAP studies from well-resourced settings that have utilised molecular diagnostics (4, 53), we identified high rates of co-infection with multiple organisms, most commonly bacterial-viral co-isolation. Defining the clinical significance of each organism detected is challenging, particularly amongst immunocompromised individuals. Whilst co-isolation may reflect genuine co-pathogenicity or simply detection of bystander colonising organisms, more complex relationships in which one organism facilitates the acquisition or pathogenesis of another (e.g. influenza and *S. pneumoniae* (54)) are possible. Bacterial-viral coinfection has been associated with altered levels of innate immune factors (e.g. CRP, IP10 (55)) and more severe clinical course (56). Further work is needed to define the implications for CAP therapy and prevention.

Radiographic facilities are limited in most healthcare facilities in sub-Saharan Africa where the majority of CAP patients are initially managed. Whilst the clinical case definition used in this study may have missed some patients with radiographic pneumonia who lacked focal signs at the time of recruitment it nonetheless reflects routine clinical practice and usefully provides data to show how the aetiological spectrum of disease varies with chest radiograph findings (57). The association of radiographic changes compatible with infection with *S. pneumoniae* is unsurprising. Although still relatively uncommon, the greater prevalence of

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invasive *Salmonella* infection amongst those lacking radiographic pneumonia has important implications for antimicrobial management. Whilst specific radiological features were statistically associated with certain pathogens, the marked inter-observer variability in interpretation of these features suggests that the clinical utility of this approach is limited.

In recruiting patients exclusively from a single referral hospital, this study shares the limitations common to many CAP observational cohorts. Most patients were seen at another facility prior to attendance; how they were selected for referral and correspondingly, the characteristics and outcome of those treated at home is unknown. Hence, the applicability of the findings to community level settings is potentially limited. Extrapolation of these findings to other countries in sub-Saharan Africa must also be done cautiously because of the potential impact that variations in factors such as TB incidence, HIV-prevalence and climate may have on CAP epidemiology and aetiology. Given limitations of the healthcare infrastructure in Malawi, chronic comorbid illnesses may be underdiagnosed. Inconsistencies in drug supply, equipment provision and staff experience may result in variations in CAP treatment that may impact patient outcome but are not fully accounted for in analyses. The description of CAP aetiology was limited by the lack of sputum microscopy and culture which may have increased the detection of bacterial pathogens such as *Haemophilus influenzae* as has been described in previous studies from the region (27, 58). Similarly, we were unable to support invasive respiratory sampling for diagnostic testing for *Pneumocystis jirovecii* (PCP) and other HIV-associated opportunistic pathogens. The low rate of bacteraemia observed may relate to both pre-hospital antibiotic use and antibiotic initiation prior to blood couture collection in hospital which occurred in up to one-third of patients. Interpretation of the significance of respiratory pathogen multiplex PCR results, particularly for respiratory viruses, is hampered by the lack of data from an appropriate control population. The relative

contribution of pathogens with seasonal transmission patterns (e.g. influenza) may also have been skewed by a recruitment period that spanned two incomplete years.

In conclusion, more than a decade after the introduction of ART, the major burden of CAP in Malawi remains in young, HIV patients rather than the elderly patients with chronic non-communicable comorbidities that predominate in well-resourced settings. Accordingly, context-specific approaches to severity assessment and defining empirical antimicrobial treatment are needed. The predominance of *S. pneumoniae* and influenza suggest significant opportunities for CAP prevention through targeted vaccination programmes. Strategies to encourage prompt patient presentation, to increase early detection and treatment of TB and to improve supportive care, in particular the correction of hypoxaemia, should be evaluated in clinical trials to address the high burden of CAP-related mortality.

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CAP in Malawian adults

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Figure 1. Recruitment and follow-up of a cohort of Malawian adults hospitalised community-acquired pneumonia. *Some patients excluded for multiple reasons hence totals exceed total number excluded.

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Figure 2. Bacterial, viral and mycobacterial infection in isolation and combination in Malawian adults hospitalised with community-acquired pneumonia. Aetiology defined by blood culture, *Streptococcus pneumoniae* urinary antigen detection, sputum mycobacterial culture and Xpert MTB/RIF, and nasopharyngeal aspirate respiratory pathogen multiplex PCR. Analysis restricted to 307 patients with results available for all tests.

Table 1. Demographic, clinical and radiographic characteristics of 459 Malawian adults hospitalised with community-acquired pneumonia.

Characteristic	No. (%) of episodes
Demographics	
Male sex	285/459 (62.1)
Age*	34.7 (29.4-41.9)
HIV status	
HIV positive†	355/453 (78.4)
Newly diagnosed	124/355 (34.9)
CD4 cell count (cells/mm^3)†	
All HIV-positive	99 (44-193)
Newly diagnosed HIV-positive	93 (43-179)
ART use in known HIV-positive†	189/227 (83.3)
Medical history	
Any other comorbid condition	31/451 (6.9)
Chronic lung disease‡	15/452 (3.3)
Chronic heart disease§	3/452 (0.7)
Hypertension	8/452 (1.8)
Previous tuberculosis‖	84/458 (18.3)
Previous pneumonia in last 5 years**	108/457 (23.6)
Pregnancy	2/174 (1.2)
Current smoker	50/457 (10.9)
Pre-hospital/clinic attendance & treatment	
Attended another health facility††	283/458 (61.8)
Antibiotics within 2 weeks‡‡	280/455 (61.5)
Antimalarials within 2 weeks	79/457 (17.3)
Traditional remedies within 2 weeks	40/456 (8.8)
Baseline observations	
Temperature (°C)*	37.9 (37.1-38.9)
<35 or ≥40	14/459 (3.1)
Systolic BP (mmHg)*	106 (93-121)
<90	86/454 (18.9)
Diastolic BP (mmHg)*	68 (59-78)
≤60	143/454 (31.5)
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	73/450 (16.2)
Body mass index (kg/m^2)*	19.9 (18.2-21.8)
<18.5	132/444 (29.7)

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Characteristic	No. (%) of episodes
Baseline 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	67/448 (15.0)
≥15	x63/448 (14.1)
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)
Radiological features§§	
Radiographic pneumonia	317/417 (76.0)
Consolidation	251/313 (80.2)
Multilobar involvement	73/247 (29.6)
Cavitation	20/317 (6.3)
Pleural effusion	118/315 (37.5)
OutcomeIIII	
Inpatient mortality	51/457 (11.2)
Day 30 mortality	64/439 (14.6)
Day 90 mortality	87/418 (20.8)

Definition of abbreviations: ART = antiretroviral therapy; BP = blood pressure; IQR = interquartile range

Data are n/N (%)unless indicated by * where median and interquartile range are shown. Variation in denominator reflecting missing data unless further specified.

†HIV status missing in 6 patients; CD4 count missing in 40 of all with HIV; ART usage missing in 4 with known HIV.

‡Chronic lung disease includes asthma, COPD and bronchiectasis.

§Chronic heart disease includes congestive cardiac failure, cor pulmonale and dilated cardiomyopathy.

‖Any previous episode of treated tuberculosis regardless of site and confirmation.

**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.

††Included attendance to other hospital, health centre, private clinic, traditional healer or pharmacy.

‡‡Excluded co-trimoxazole prophylaxis in HIV-infected individuals.

§§Chest radiographs available in 421 patients; reports based on consensus grading of assessors and denominator may vary when consensus not obtained.

‖‖Status at hospital discharge, day 30 and day 90 missing in 2, 20 and 41, respectively.

Table 2. Aetiology of community-acquired pneumonia in Malawian adults stratified by HIV status.

Organism	All* (n=459)	HIV-positive (n=355)	HIV-negative (n=98)	*P* for difference†
Streptococcus pneumoniae	98/458 (21.4)	68/355 (19.2)	30/97 (30.9)	0.01
Salmonella Typhi	10/450 (2.2)	4/350 (1.1)	5/94 (5.3)	0.02‡
Nontyphoidal *Salmonella*§	7/450 (1.6)	7/350 (2)	0/94 (0)	0.35‡
Other GNEB‖	3/450 (0.7)	3/350 (0.9)	0/94 (0)	1.00‡
Staphylococcus aureus	2/450 (0.4)	1/350 (0.3)	1/94 (1.1)	0.38‡
Mycoplasma pneumoniae	6/455 (1.3)	6/355 (1.7)	0/98 (0)	0.35‡
Chlamydia pneumoniae	2/455 (0.4)	0/355 (0)	2/98 (2.0)	0.05‡
Legionella pneumophila	0/193 (0)	0/154 (0)	0/38 (0)	-
Mycobacterium tuberculosis	75/326 (23.0)	64/257 (24.9)	10/64 (15.6)	0.12
Nontuberculous mycobacteria	8/273 (2.9)	5/217 (2.3)	3/52 (5.8)	0.19‡
Influenza viruses	40/454 (8.8)	30/354 (8.5)	9/98 (9.2)	0.83
Adenovirus	35/455 (7.7)	30/355 (8.5)	5/98 (5.1)	0.39‡
Coronaviruses	31/455 (6.8)	28/355 (7.9)	3/98 (3.1)	0.11‡
Parainfluenza viruses	17/455 (3.7)	15/355 (4.2)	1/98 (1)	0.21‡
Rhinovirus	17/455 (3.7)	15/355 (4.2)	2/98 (2)	0.55‡
Bocavirus	13/455 (2.9)	13/355 (3.6)	0/98 (0)	0.08‡
Metapneumovirus	9/455 (2.0)	8/355 (2.3)	1/98 (1)	0.69‡
RSV	8/455 (1.8)	4/355 (1.1)	3/98 (3.1)	0.18‡
Enterovirus	5/455 (1.1)	5/355 (1.4)	0/98 (0)	0.59‡
Parechovirus	5/455 (1.1)	5/355 (1.4)	0/98 (0)	0.59‡
No pathogen detected	181/459 (39.4)	137/355 (38.6)	42/98 (42.9)	0.44

Definition of abbreviations: GNEB = Gram-negative enteric bacilli; OR = odds ratio; RSV = respiratory syncytial virus. Data are n/N (%). Denominators indicate number of patients with at least one relevant test available. *S. pneumoniae* diagnosis based on combination of blood and pleural fluid culture and antigen assay of urine and pleural fluid. *M. tuberculosis* based on combination of sputum microscopy, culture and Xpert MTB/RIF and pleural fluid culture. Other organisms based on single test. Column totals exceed number of patients since multiple organisms detected in some.

*Includes 6 patients with missing HIV status in whom the following organisms were identified: *Salmonella* Typhi, 1; *Mycobacterium tuberculosis*, 1; Influenza, 1; Parainfluenza, 1; RSV, 1; No pathogen detected, 2.

†χ^2 test unless otherwise stated.

‡Fisher's exact test.

§S. Enteritidis and S. Typhimurium combined.

‖*Escherichia coli* and *Enterobacter cloacae* combined.

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Table 3. Association of candidate clinical and laboratory risk factors with 30-day mortality in Malawian adults hospitalised with community-acquired pneumonia.

Characteristic	Day 30 survivors (n=375)	Day 30 mortality (n=64)	Univariable analysis		Multivariable analysis	
			OR (95% CI)	*P*	aOR (95% CI)	*P*
Male sex	224/375 (59.7)	52/64 (81.3)	2.92 (1.51-5.66)	0.001	2.60 (1.17-5.78)	0.02
Age (yrs)	*34 (29-42)*	*36 (32-42)*	1.00 (0.98-1.03)	0.73	1.00 (0.97-1.03)	0.93
Current smoker	41/373 (11.0)	7/64 (10.9)	0.99 (0.43-2.33)	0.99	-	-
Regular alcohol use	92/373 (24.7)	23/63 (36.5)	1.76 (1.00-3.09)	0.05	-	-
Unemployed	109/357 (30.5)	13/61 (21.3)	0.62 (0.32-1.18)	0.15	-	-
HIV-positive	288/370 (77.8)	54/64 (84.4)	1.53 (0.75-3.15)	0.24	1.26 (0.49-3.21)	0.63
Chronic lung disease	11/371 (3.0)	3/61 (4.9)	1.69 (0.46-6.23)	0.43	-*	-
Chronic heart disease	2/370 (0.5)	1/61 (1.6)	3.07 (0.27-34.35)	0.36	-*	-
Renal disease	0/371 (0)	1/61 (1.6)	-	-	-*	-
Pre-presentation symptoms >7 days	138/374 (36.9)	36/63 (57.1)	2.28 (1.33-3.92)	0.003	2.78 (1.40-5.54)	0.004
Travel time ≥1 hour	278/373 (74.5)	51/62 (82.3)	1.58 (0.79-3.16)	0.19	-	-
Previous review	231/375 (61.6)	42/63 (66.7)	1.25 (0.71-2.19)	0.44	-	-
Temperature <35 or ≥40 °C	13/375 (3.5)	1/64 (1.6)	0.44 (0.06-3.44)	0.44	-*	-
Systolic BP <90 mmHg	66/371 (17.8)	17/63 (27.0)	1.71 (0.92-3.16)	0.09	-	-
Diastolic BP ≤60 mmHg	112/371 (30.2)	28/63 (44.4)	1.85 (1.07-3.19)	0.03	-‡	-
Mean arterial BP <65	46/371 (12.4)	15/63 (23.8)	2.21 (1.14-4.26)	0.02	-‡	-
Heart rate ≥125 /min	135/374 (36.1)	37/64 (57.8)	2.43 (1.42-4.16)	0.001	2.99 (1.48-6.06)	0.002
Resp. rate≥30 /min)	172/364 (47.3)	33/62 (53.2)	1.27 (0.74-2.18)	0.39	-	-
Oxygen sat[¤] <90 %	45/368 (12.2)	27/63 (42.9)	5.38 (2.99-9.70)	<0.0001	4.40 (2.03-9.51)	<0.001
BMI <18.5 kg/m^2	108/366 (29.5)	20/61 (32.8)	1.17 (0.65-2.08)	0.61	-§	-
MUAC <230 mm	103/371 (27.8)	14/63 (22.2)	0.74 (0.39-1.40)	0.36	-	-
Confusion	2/374 (0.5)	3/64 (4.7)	9.15 (1.50-55.87)	0.02	-*	-
Inability to stand	57/375 (15.2)	30/64 (46.9)	4.92 (2.79-8.67)	<0.0001	3.59 (1.72-7.50)	0.001
Haemoglobin <8 g/dL	55/368 (15.0)	18/61 (29.5)	2.38 (1.28-4.43)	0.006	-	-
White cell count <4 x 10^9/L	50/367 (13.6)	15/61 (24.6)	2.07 (1.07-3.98)	0.03	-	-
Platelets <100 x 10^9/L	58/368 (15.8)	14/61 (23.0)	1.59 (0.82-3.08)	0.17	-	-
Urea >7 mmol/L	107/370 (28.9)	27/60 (45.0)	2.01 (1.15-3.51)	0.01	-	-
Creatinine >120 µmol/L	56/369 (15.2)	15/59 (25.4)	1.91 (0.99-3.65)	0.05	-‖	-
Glucose ≥14 mmol/L	0/330 (0)	0/53 (0)	-	-	-†	-

Definition of abbreviations: BP = blood pressure; BMI = body mass index; CI = confidence interval; MUAC = mid-upper arm circumference; OR = odds ratio; Resp. = respiratory

For age (in *italics*) data shown as median and interquartile range. Otherwise data shown as n/N (%) with variation in denominator compared to column header reflecting missing data. Univariable and multivariable analyses by logistic regression. For age, odds ratio indicates change in risk of mortality with each year increase. 20 patients of overall study cohort of 459 excluded due to unknown 30-day outcome. Final multivariable analysis based on 380 patients with complete results for all included parameters.

*Excluded from multivariable analysis because of prevalence ≤5%.

†Excluded from multivariable analysis because data were missing for >5% of patients.

‡Excluded *a priori* from multivariable analysis because of assumed collinearity with systolic blood pressure.

§Excluded *a priori* because of assumed collinearity with MUAC.

‖Excluded *a priori* because of assumed collinearity with urea.

Table 4. Accuracy of pneumonia severity-assessment tools for predicting 30-day mortality in a cohort of Malawian adults hospitalised with community-acquired pneumonia cohort.

Score group	*n**	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	Positive LR (95% CI)	Negative LR (95% CI)	AUROC (95% CI)
CURB65 ≥3	412	14.0 (6.3-25.8)	91.5 (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	421	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	280	89.7 (72.6-97.8)	36.7 (30.7-42.9)	14.1 (9.4-19.9)	96.8 (91.0-99.3)	1.42 (1.21-1.65)	0.28 (0.10-0.83)	0.66 (0.57-0.75)
Modified IDSA/ATS minor criteria ≥3	272	48.3 (29.4-67.5)	72.0 (65.9-77.6)	17.1 (9.7-27.0)	92.1 (87.3-95.5)	1.73 (1.13-2.64)	0.72 (0.50-1.03)	0.66 (0.56-0.75)
SWAT-Bp ≥3	427	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)

Definition of abbreviations: AUROC = area under receiver-operating characteristic curve; CI = confidence interval; CURB65 = tool based on presence of confusion, urea >7mmol/L, respiratory rate ≥30/min, systolic blood pressure <90mmHg and/or diastolic blood pressure ≤60mmHg, age ≥65 (29); CRB65 = as per CURB65 with exclusion of urea (29); IDSA/ATS = modified version of Infectious Disease Society of America/American Thoracic Society criteria based on presence of respiratory rate ≥30/min, oxygen saturations ≤90% (used as a surrogate for arterial oxygen pressure/fraction of inspired oxygen (PaO_2/FiO_2) ratio ≤250 criterion included in the published tool), multilobar infiltrates, confusion/disorientation, urea ≥7.1 mmol/L, white blood cell count <4 x10^9 cells/L, platelets <100 x10^9 cells/L, temperature <36°C, systolic blood pressure < 90 mmHg (used as a surrogate for hypotension requiring aggressive fluid resuscitation; (35); LR = likelihood ratio; NPV = negative predictive value; PPV = positive predictive value; SMRT-CO = tool based on presence of systolic blood pressure < 90 mmHg, multilobar consolidation, respiratory rate ≥25/min if ≤50 years or ≥30/min if >50 years, heart rate ≥125/min, confusion and oxygen saturations ≤93% if ≤50 yrs or ≤90% if >50 yrs (34); SWAT-Bp = tool based on male sex, wasting, non-ambulatory status, temperature <35°C or >38°C and systolic blood pressure <100 mmHg or diastolic blood pressure <60 mmHg (28). For each tool, the performance characteristics displayed are those using the scoring threshold for "severe CAP" as suggested by the authors. *Score calculated in varying number of patients depending on availability of results for component parameters; SMRT-CO & modified IDSA/ATS minor criteria include radiological parameter hence only calculated in those with radiographic pneumonia.

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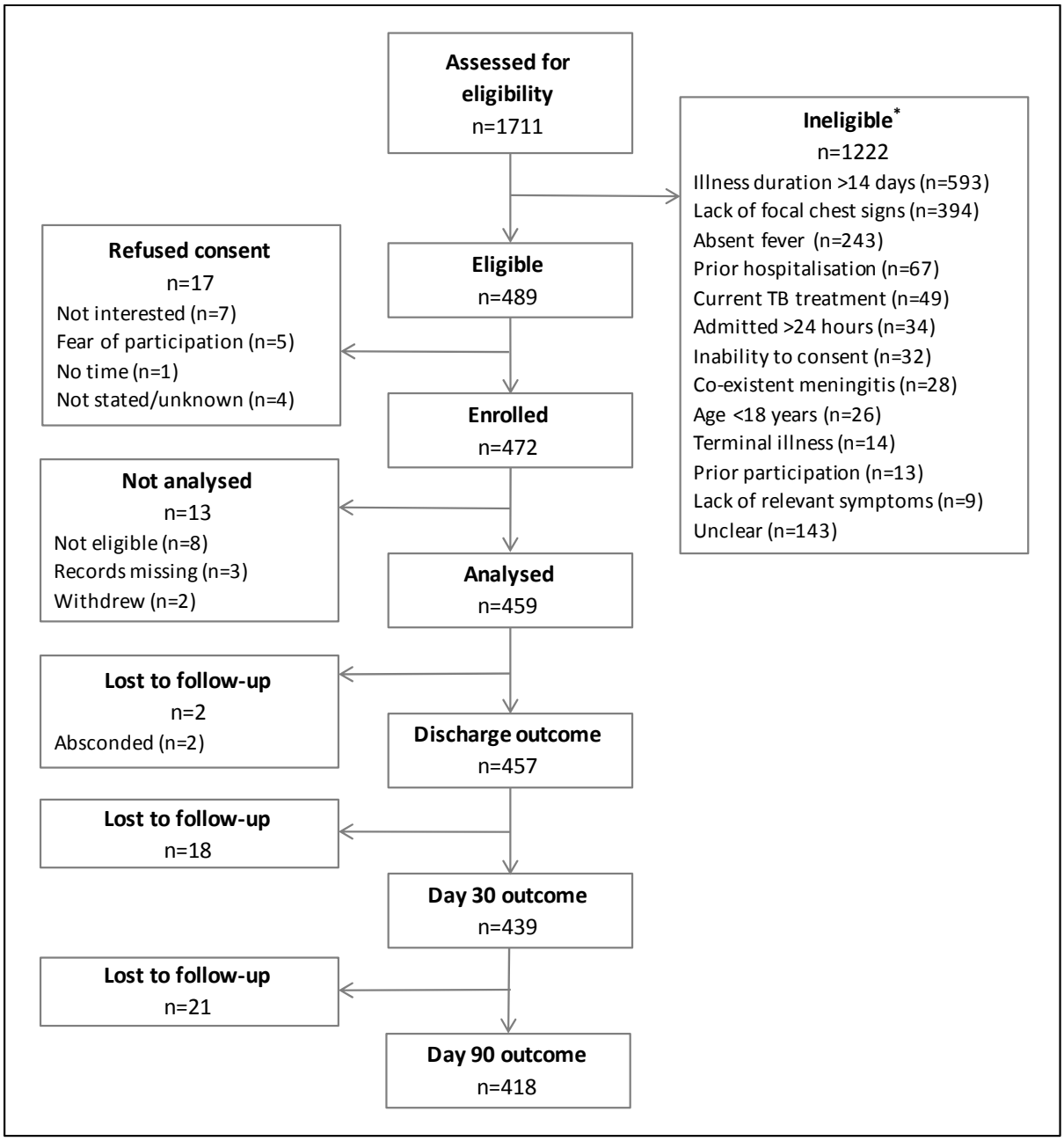

Figure 1

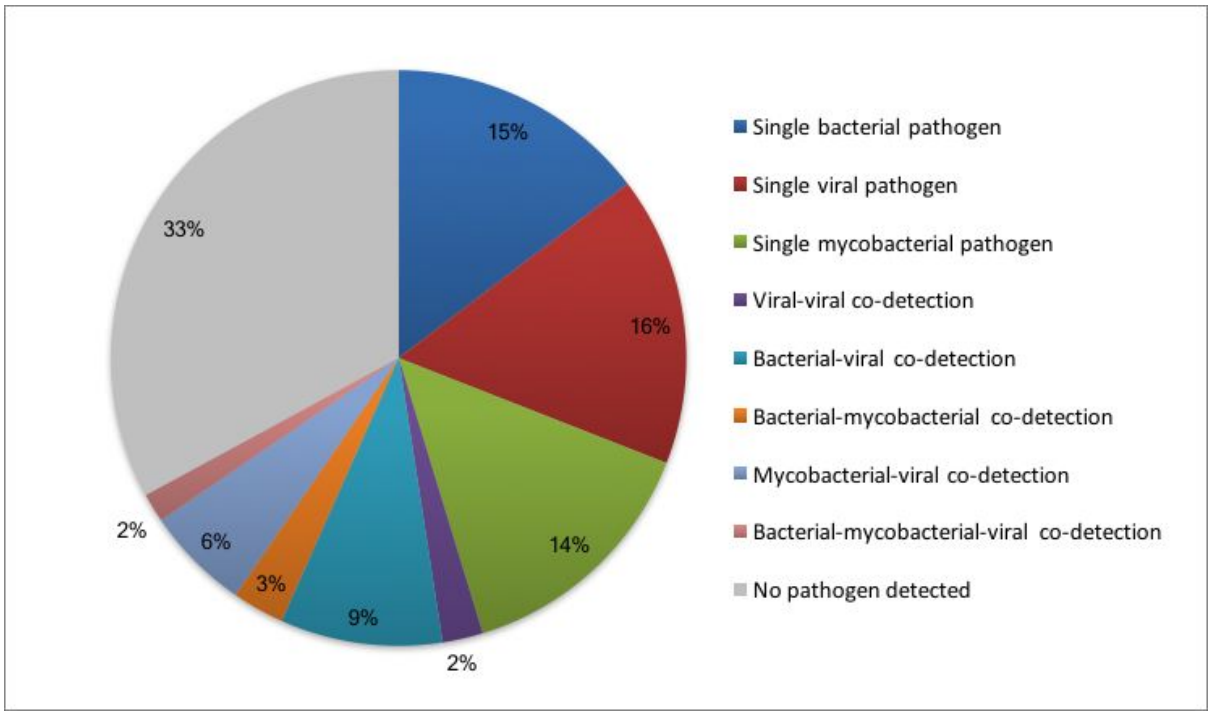

Figure 2

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Online Data Supplement

SUPPLEMENTARY METHODS

Study design and conduct

We conducted a prospective observational study of adults hospitalised with CAP at Queen Elizabeth Central Hospital (QECH) - a 1200 bed teaching hospital that provides free healthcare to the 1.3 million residents of Blantyre district in Southern Malawi. Recruitment commenced on 15th May 2013 and continued until 31st January 2015. Participant follow-up was completed by 28th May 2015.

Detailed inclusion and exclusion criteria

Clinical aspects of the study were completed by a dedicated team of research nurses and clinical officers who had received extensive training prior to study initiation. Study investigators (SA, AH, HJ, JH and TM) accompanied the clinical study team on their daily rounds at least weekly to evaluate data quality and consistency of data collection. Patients with features of respiratory illness or infection were screened on arrival in the hospital emergency department or on the medical wards within 24 hours of admission. Consenting adults with clinically diagnosed community-acquired pneumonia (CAP) as defined by the eligibility criteria below (summarised in the Methods section) were recruited.

Inclusion criteria

We recruited adults (≥18 years) hospitalised with clinically-diagnosed CAP defined as: reported or recorded fever (≥38°C); at least one relevant symptom (cough, chest pain, breathlessness, haemoptysis); and at least one focal chest sign (crepitations, pleural rub, bronchial breathing, percussive dullness or diminished breath sounds) (E1).

Exclusion criteria

Patients with any of the following were excluded from participation: symptoms for greater than 14 days; suspected co-existent meningitis; pre-admission diagnosis of terminal illness (e.g. metastatic malignancy, terminal AIDS); current anti-tuberculous treatment; admission to hospital more than 24 hours previously; prior hospitalisation within preceding 4 weeks; or prior participation in the study.

Clinical assessment and follow-up

For each participant, the study team completed a standardised clinical assessment consisting of a comprehensive medical history, physical examination and measurement of physiological observations. Information was obtained via direct questioning of the study participant (or accompanying guardian) and by reference to medical notes and health passport. Physiological observations were measured by the study team on admission or abstracted from the medical notes for patients recruited from the medical wards. 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.

Study participants were reviewed on a daily basis each morning until discharge or 14 days post-admission. At the point of hospital discharge or inpatient death, the study team reviewed the clinical notes and recorded details of treatment administered. 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 this information by phone call to the patient or their guardian; if unsuccessful field workers visited the patient's home.

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Patients with influenza formed the case population of a linked case-control study describing the impact of HIV on influenza severity (E2). Some patients with radiographic pneumonia who survived to discharge also participated in a further case-control study of the association of exposure to indoor air pollution with the occurrence of pneumonia (E3).

Radiographic assessment

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. 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. All study radiograph reports were generated by review of the set of digital images.

Chest radiographs were reported independently by two study radiologists (EJ and SG) and the study Principal Investigator (SA, an Infectious Diseases Resident Physician). All reporters were blinded to demographic and clinical data at the time of reporting. Radiographs were reported using a standardised form, that was piloted prior to use for study reporting to ensure consistent application. Definitions of radiological features were based on the Fleischner Society: Glossary of terms for thoracic imaging (E4).

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). Radiographic pneumonia was defined as the presence of consolidation or other parenchymal abnormality (including reticulonodular change, cavitation or miliary appearance) or pleural effusion (E5). 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. Study analyses were based on a consensus report for each specific feature. If there was disagreement between the reporters, the majority opinion was used. Variability of interpretation was assessed by calculating average agreement and kappa coefficient.

Specimen collection, processing and testing

Haematology and biochemistry

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

Bacteriology

Blood cultures were performed using standard aerobic bottles in the BacT/ALERT 3D automated system (bioMérieux, Marcy-L'Etoile, France) as previously described (E6). All isolates were identified using standard diagnostic procedures (E7). Coagulase-negative *Staphylococci*, *Bacillus* spp., *Micrococcus* spp. and diphtheroids were considered as contaminants.

Urine was collected in standard containers and refrigerated. The BinaxNOW® urine

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antigen test for *Streptococcus pneumoniae* (Alere, Massachusetts, USA) was performed in accordance with the manufacturer's instructions (E8). The same procedure was applied for pleural fluid specimens. The BinaxNOW® test for *Legionella pneumophila* urinary antigen was performed on urine specimens that had been stored at -80°C following collection.

Respiratory pathogen multiplex PCR

The nasopharyngeal aspirate (NPA) specimens were refrigerated immediately following collection and then divided into aliquots before being stored at -80°C in Universal Transport Medium (Copan, Brescia, Italy) for later batch-testing. 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). Influenza A and B viruses were detected by real-time reverse transcription polymerase chain reaction (qRT-PCR) using the CDC Human Influenza RT-PCR diagnostic panel (CDC Influenza Division) (E9). Adenovirus, bocavirus*, Chlamydia pneumoniae*, coronaviruses 229E, HKU1, OC43 and NL63, enterovirus, human metapneumovirus (hMPV), *Mycoplasma pneumoniae*, parainfluenza virus types 1, 2, 3 and 4, parechovirus, respiratory syncytial viruses (RSV) and rhinovirus were detected using the FTD Respiratory Pathogens 33 kit (Fast-track Diagnostics, Luxembourg) (E10). The results for the other organisms detected by the FTD 33 kit were disregarded. 5 or 10 µL of nucleic acid extract was used in each qRT-PCR reaction in combination with the AgPath one-step RT-PCR reagents (Applied Biosystems, Foster City, California, USA). For both kits, PCR conditions were according to the manufacturer's instructions. For the CDC Human Influenza RT-PCR diagnostic panel, samples with cycle threshold (Ct)-value <40 were recorded as positive; for the FTD 33 kit a cycle threshold (Ct)-value <33 was regarded as positive. Appropriate

negative and positive control specimens were run alongside each reaction.

Mycobacterial diagnostic tests

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 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 acid-fast bacilli (AFB) smear-positive.

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 (E11, E12). 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 AFB on ZN microscopy were positively confirmed as *Mycobacterium tuberculosis* complex by microscopic cording and MPT-64 lateral flow assay (Capilia; TAUNS Laboratories, Numazu, Japan). 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

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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.

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 (E13). The assay was performed in accordance with the manufacturer's instructions (E14).

Assignment of aetiology

A bacterial pathogen was determined to be present if: i) detected on blood or pleural fluid culture; ii) *S. pneumoniae* antigen was detected in urine or pleural fluid; iii) *L. pneumophila* antigen was detected in urine; or iv) *C. pneumoniae* or *M. pneumoniae* was detected by PCR in NPA. Certain bacterial blood culture isolates were considered to be contaminants. Mycobacterial infection was determined to be present if detected in sputum or pleural fluid by mycobacterial culture; or if *Mycobacterium tuberculosis* was detected by Xpert MTB/RIF assay. Positive AFB smear microscopy of sputum or pleural fluid in the absence of positive culture or Xpert MTB/RIF assay was assumed to be *M. tuberculosis* infection. Respiratory viral diagnosis was based on detection by PCR in NPA.

Data management

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). Prior to scanning the CRFs were checked by the clinical team and subsequently by study investigators (SA, AH, HJ and JH) and any discrepancies were queried. Automated validation checks were built in to the character recognition scanning process to identify outliers and erroneous values. Once all data were

entered into the study database, further systemic data checks were performed to detect potential errors, which were checked and corrected to create a final dataset.

Statistical methods

Statistical analyses were performed with Stata version 12.1 (StataCorp; Texas, US). The statistical methods for comparing microbial aetiology by radiographic and HIV status and for identifying independent risk factors for 30-day mortality are detailed in the main manuscript. The association of microbial aetiology with 30-day mortality for the most commonly identified pathogens (i.e. *S. pneumoniae*, *M. tuberculosis* and influenza) was estimated by multivariable logistic regression analysis with age, sex and HIV status included as covariates.

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 (E15, E16). 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.

CAP severity assessment tools

The following CAP severity-assessment tools were calculated as published and their prognostic performance to predict 30-day mortality was assessed.

- **CURB65:** One point awarded for each of the following components present: confusion; urea >7 mmol/L; respiratory rate ≥30/min; systolic blood pressure <90 mmHg or diastolic blood pressure ≤60 mmHg; age ≥65 years (E17).
- **CRB65:** Derived as per CURB65 with the exclusion of urea >7 mmmol/L (E17).
- **SMRT-CO:** Summation of points for each of the following components present:

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systolic blood pressure <90 mmHg (2 points); multilobar involvment (1 point); respiratory rate ≥25/min if ≤50 years or ≥30/min if >50 years (1 point); heart rate ≥125/min (1 point); confusion (1 point); oxygen saturations ≤93% if ≤50 years or ≤90% if >50 years (2 points; E18).

- **Modified IDSA/ATS minor criteria:** One point awarded for each of the following components present: respiratory rate ≥30/min; oxygen saturations ≤90% (used as a surrogate for arterial oxygen pressure/fraction of inspired oxygen (PaO_2/FiO_2) ratio ≤250 criterion included in the published tool); multilobar infiltrates; confusion/disorientation; urea ≥7.1 mmol/L; white blood cell count <4 $x10^9$ cells/L; platelets <100 $x10^9$ cells/L; temperature <36°C; systolic blood pressure < 90 mmHg (used as a surrogate for hypotension requiring aggressive fluid resuscitation; E19).
- **SWAT-Bp:** One point awarded for each of the following components present: male sex; wasting; non-ambulatory status; temperature <35°C or >38°C; systolic blood pressure <100 mmHg or diastolic blood pressure <60 mmHg (E20).

To calculate the prognostic performance characteristics of severity assessment tool, the recommended cutoffs used to define "severe pneumonia" were used: CURB65 ≥3; CRB65 ≥2; SMRT-CO ≥2; modified IDSA/ATS minor criteria ≥3; and SWAT-Bp ≥3. For each severity score, sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratios and area under the receiver-operating characteristic curve with 95% confidence intervals were calculated using standard methods. Patients with incomplete data were excluded from the analysis.

SUPPLEMENTAL RESULTS

Supplemental Table E1. Demographic, clinical and radiographic characteristics of 459 Malawian adults hospitalised with community-acquired pneumonia.

Characteristic	No. (%) of episodes	
Demographics		
Male sex	285/459	(62.1)
Age (yrs)*	34.7	(29.4-41.9)
18-24	53/459	(11.6)
25-34	185/459	40.3)
35-44	136/459	(29.6)
45-54	43/459	(9.4)
56-64	24/459	(5.2)
≥65	18/459	(3.9)
Socioeconomic factors		
Employment status		
Paid employment	157/455	(34.5)
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)
Main household 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)
HIV status		
HIV positive†	355/453	(78.4)
Newly diagnosed	124/355	(34.9)
CD4 cell count (cells/mm^3)†		
All HIV-positive*	99	(44-193)
<50	88/315	(27.9)
50-199	158/315	(50.2)
≥200	69/315	(21.9)
Newly diagnosed HIV-positive*	93	(43-179)
ART use in 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)

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Characteristic	No. (%) of episodes
CPT use on admission[†]	
All HIV-positive	151/355 (42.5)
Known HIV-positive	151/188 (80.3)
Medical history	
Any other comorbid condition	31/451 (6.9)
Chronic lung disease[‡]	15/452 (3.3)
Chronic heart disease[§]	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[‖]	84/458 (18.3)
Previous pneumonia in last 5 years[**]	108/457 (23.6)
Pregnancy	2/174 (1.2)
Current smoker	50/457 (10.9)
Regular alcohol intake	122/456 (26.8)
Pre-hospital attendance & treatment	
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)
Attended another health facility[††]	283/458 (61.8)
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)
Antibiotics within 2 weeks[‡‡]	280/455 (61.5)
Antimalarials within 2 weeks	79/457 (17.3)
Traditional remedies within 2 weeks	40/456 (8.8)
Clinical features	
Symptoms	
Cough	451/458 (98.5)
Sputum production	357/458 (78.0)
Dyspnoea	440/458 (96.1)
Fever	457/458 (99.8)
Weight loss	277/458 (60.5)
Night sweats	299/457 (65.4)

Characteristic	No. (%) of episodes
Examination features	
Crepitations	387/457 (84.7)
Bronchial breathing	167/458 (36.4)
Pleural effusion	79/457 (17.3)
Confusion/disorientation	5/458 (1.1)
Inability to stand	87/459 (19.0)
Oral thrush	28/458 (6.1)
Kaposi's sarcoma	14/458 (3.1)
Baseline 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	67/448 (15.0)
≥15	x63/448 (14.1)
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)
Radiological features§§	
Radiographic pneumonia	317/417 (76.0)
Consolidation	251/313 (80.2)
Multilobar involvement	73/247 (29.6)
Cavitation	20/317 (6.3)
Pleural effusion	118/315 (37.5)
Outcome¶¶¶¶	
Inpatient mortality	51/457 (11.2)
Day 30 mortality	64/439 (14.6)
Day 90 mortality	87/418 (20.8)

Definition of abbreviations: ART = antiretroviral therapy; BP = blood pressure; CPT = co-trimoxazole preventative therapy; IQR = interquartile range.
Data are n/N (%) unless indicated by * where median and interquartile range are shown. Variation in denominator reflects missing data unless further specified.
†HIV status missing in 6 patients; CD4 count missing in 40 of all with HIV; CPT and ART usage missing in 4 and 43, respectively, with known HIV; ART duration missing in 32 reporting ART use.
‡Chronic lung disease includes asthma, COPD and bronchiectasis.
§Chronic heart disease includes congestive cardiac failure, cor pulmonale and dilated cardiomyopathy.
||Any previous episode of treated tuberculosis regardless of site and confirmation.
**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.
††Included attendance to other hospital, health centre, private clinic, traditional healer or pharmacy.
‡‡Excluded co-trimoxazole prophylaxis in HIV-infected individuals.
§§Chest radiographs available in 421 patients; reports based on consensus grading of assessors and denominator may vary when consensus not obtained.
¶¶¶¶Status at hospital discharge, day 30 and day 90 missing in 2, 20 and 41, respectively.

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Supplemental Table E2. Radiological features with inter-report agreement in Malawian adults hospitalised with community-acquired pneumonia.

	Individual scorer's assessment			Consensus interpretation[†]	All scorer's agreement	
	Radiologist 1 (n=419)[*]	Radiologist 2 (n=407)[*]	Clinician (n=417)[*]		Avg. agree (%)[‡]	Kappa (95% CI)[‡]
Radiographic pneumonia	323 (77.1)	297 (73.0)	314 (75.3)	317/417 (76.0)	90.6	0.75 (0.69-0.81)
Any parenchymal abnormality	300 (71.6)	266 (65.3)	268 (64.3)	282/414 (68.1)	86.0	0.68 (0.61-0.74)
Consolidation	245 (58.5)	251 (61.7)	260 (62.4)	251/413 (60.8)	83.3	0.65 (0.59-0.70)
Quality						
Confluent	159/244 (65.2)	135/251 (53.8)	161/260 (61.9)	145/233 (62.2)	74.5	0.46 (0.37-0.55)
Patchy	85/244 (34.9)	116/251 (46.2)	99/260 (38.1)	88/233 (37.8)		
Extent						
Segmental	77/245 (31.4)	78/250 (31.2)	83/260 (31.9)	62/225 (27.6)	65.9	0.48 (0.42-0.56)
Lobar	73/245 (29.8)	73/250 (29.2)	89/260 (34.2)	73/225 (32.4)		
Multifocal	95/245 (38.8)	99/250 (39.6)	88/260 (33.9)	90/225 (40.0)		
Multilobar	85/255 (34.7)	65/251 (25.9)	76/260 (29.2)	73/247 (29.6)	83.3	0.55 (0.46-0.63)
Cavitation	27/417 (6.5)	26/406 (6.4)	15/416 (3.6)	20/418 (4.8)	94.9	0.51 (0.35-0.65)
Reticulonodular change	140 (33.4)	35 (8.6)	24 (5.8)	35/418 (8.4)	76.9	0.15 (0.07-0.24)
Miliary appearance	2/414 (0.5)	2/405 (0.5)	8/416 (1.9)	2/417 (0.5)	98.4	0.17 (-0.01-0.34)
Pleural effusion	111 (26.5)	106 (26.0)	155 (37.2)	118/416 (28.4)	83.7	0.61 (0.55-0.67)
Pneumothorax	2/410 (0.5)	1/406 (0.3)	3/405 (0.7)	2/416 (0.5)	99.3	0.32 (-0.02-0.49)
Mediastinal lymphadenopathy	40 (9.6)	34 (8.4)	50 (12.0)	28/417 (6.7)	87.4	0.30 (0.19-0.42)
Volume loss	76 (18.1)	35 (8.6)	44 (10.6)	30/421 (7.1)	84.1	0.28 (0.17-0.38)
Bronchiectasis	31 (7.4)	8 (2.0)	3 (0.7)	3/421 (0.7)	93.7	0.03 (-0.04-0.11)

Definition of abbreviations: CI = confidence interval.

Data are n/N (%) unless otherwise specified. Chest radiographs were available in 421 of 459 patients; chest radiographs unavailable because of death prior to radiograph (n=14), hospital discharge without radiograph or prior to digital capture (n=18) and unclear reason (n=6).

[*]Radiologist 1, radiologist 2 and clinician considered 2, 14 and 4 radiographs, respectively, as uninterpretable.

[†]Consensus values calculated by majority rating of all assessors; denominator may vary when consensus not obtained, most notably for specific features of consolidation which were reported only when assessor regarded consolidation as present.

[‡]Average agreement and three-way kappa (estimated 95% confidence intervals) calculated for all three assessors.

Supplemental Table E3. Clinical features and outcome by chest radiograph availability and radiographic status in Malawian adults hospitalised with community-acquired pneumonia.

Characteristic	Chest radiograph available (n=417)			Chest radiograph unavailable (n=38)	
	Radiographic pneumonia (n=317)	No radiographic pneumonia (n=100)	*P*[†]		*P*[‡]
Male sex	210/317 (66.3)	59/100 (49.0)	0.002	23/38 (60.5)	0.85
Age[*]	35 (30-42)	33 (27-38)	0.01[§]	37 (30-44)	0.22[§]
HIV positive[ll]	247/313 (78.9)	73/98 (74.5))	0.36	31/38 (81.6)	0.60
Pre-presentation symptoms >7 days	122/316 (38.6)	42/103 (42.0)	0.55	15/37 (40.5)	0.90
Temperature <35 or ≥40 °C	10/317 (3.2)	3/100 (3.0)	1.00[**]	1/38 (2.6)	1.00[**]
Systolic BP <90 mmHg	61/314 (19.4)	13/99 (13.1)	0.15	11/37 (29.7)	0.08
Diastolic BP ≤60 mmHg	98/314 (31.2)	26/99 (26.3)	0.35	16/37 (43.2)	0.10
Heart rate ≥125 /min	127/316 (40.2)	35/100 (54.0)	0.35	14/38 (36.8)	0.80
Respiratory rate ≥30 /min	155/307 (50.5)	36/98 (36.7)	0.02	18/37 (48.7)	0.86
Oxygen saturations <90 %	52/308 (16.9)	7/100 (7.0)	0.02	13/38 (34.2)	0.002
BMI <18.5 kg/m^2	94/306 (30.7)	28/98 (28.6)	0.69	10/37 (27.0)	0.69
Inability to stand	51/317 (16.1)	18/100 (18.0)	0.65	16/38 (42.1)	<0.001
Haemoglobin <8 g/dL	45/313 (14.4)	22/96 (22.9)	0.048	6/37 (16.2)	0.98
White blood cells <4 x10^9 /L	41/312 (13.1)	19/96 (19.8)	0.11	7/37 (18.9)	0.49
Urea >7 mmol/L	98/313 (31.3)	27/98 (27.6)	0.48	12/37 (32.4)	0.80
Creatinine >120 µmol/L	46/313 (14.7)	22/96 (22.9)	0.06	7/37 (18.9)	0.72
Day 30 mortality	31/304 (10.2)	16/98 (16.3)	0.10	17/36 (47.2)	<0.001

Definition of abbreviations: BMI = body mass index; BP = blood pressure

Data are n/N (%) unless indicated by [*] where median and interquartile range are shown. Variation in denominator compared to column header reflecting missing data.

[†]Comparison between patients with and without radiographic pneumonia by χ^2 test unless otherwise stated.

[‡]Comparison between all patients with and all without available interpretable chest radiograph by χ^2 test unless otherwise stated; 4 patients who had chest radiograph but without consensus interpretation excluded from analysis.

[§]Wilcoxon rank-sum test

[ll]HIV status missing in 6 patients

[**]Fisher's exact test

[††]Status at day 30 missing in 19 patients.

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Supplemental Table E4. Intravenous antibiotic treatment duration, length of stay and 30-day mortality by antibiotic treatment group in Malawian adults hospitalised with community-acquired pneumonia.

Antibiotic treatment group	n	Intravenous antibiotic duration, days Median (IQR)	Length of stay, days Median (IQR)	30-day mortality n/N (%)
Ceftriaxone monotherapy	251/450 (55.8)	5 (3-7)	7 (4-9)	38/242 (15.7)
Ceftriaxone-based combination	114/450 (25.3)	5 (3-7)	8 (5-11)	15/108 (13.9)
Penicillin & Chloramphenicol	65/450 (14.4)	4 (3-6)	6 (4-8)	8/61 (13.1)
Penicillin & Chloramphenicol-based combination	15/450 (3.3)	3 (2-7)	12 (4-18)	0/14 (0)
Amoxicillin (oral)	5/450 (1.1)	- -	9 (5-11)	1/5 (20)

Definition of abbreviations: IQR = interquartile range.
Patients assigned to treatment group on the basis of all antibiotics prescribed during admission, excluding anti-tuberculous treatment. Patients in 'combination' groups received additional intravenous and/or oral agents. Data missing in 8 patients.

Supplemental Table E5. Organism identification by specimen type and diagnostic test stratified by HIV status.

Organism	All* (n=459)	HIV-positive (n=355)	HIV-negative (n=98)
Blood cultures†			
Streptococcus pneumoniae	5/450 (1.1)	4/350 (1.1)	1/94 (1.1)
Salmonella Typhi	9/450 (2.0)	3/350 (0.9)	5/94 (5.3)
Salmonella Typhimurium	6/450 (1.3)	6/350 (1.7)	0/94 (0)
Salmonella Enteritidis	1/450 (0.2)	1/350 (0.3)	0/94 (0)
Staphylococcus aureus	2/450 (0.4)	1/350 (0.3)	1/94 (1.1)
Escherichia coli	2/450 (0.4)	2/350 (0.6)	0/94 (0)
Enterobacter cloacae	1/450 (0.2)	1/350 (0.3)	0/94 (0)
Pleural fluid culture			
Salmonella Typhi	1/31 (3.2)	1/19 (5.3)	0/11 (0)
Mycobacterium tuberculosis	7/35 (20.0)	4/22 (18.2)	2/12 (16.7)
***Streptococcus 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)
***Legionella pneumophila* antigen test**			

Urine	0/193 (0)	0/154 (0)	0/38 (0)
Sputum mycobacterial diagnostic tests			
AFB smear microscopy	36/305 (11.8)	30/241 (12.4)	6/60 (10.0)
Sputum culture			
Mycobacterium 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)

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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)
Chlamydia pneumoniae	2/455 (0.4)	0/355 (0)	2/98 (2)
Coronavirus HKU1	3/455 (0.7)	3/355 (0.9)	0/98 (0)
Coronavirus 229E	19/455 (4.2)	16/355 (4.5)	3/98 (3.1)
Coronavirus OC43	6/455 (1.3)	6/355 (1.7)	0/98 (0)
Coronavirus NL63	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)
Metapneumovirus	9/455 (2)	8/355 (2.3)	1/98 (1.0)
Mycoplasma 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)

Definition of abbreviations: NTM = nontuberculous mycobacteria; RSV = respiratory syncytial virus.
Data are n/N (%) specimens positive for specific organism; variation in denominator reflects the availability of the relevant clinical specimen.
*In the 6 patients with unknown HIV status the following positive results were obtained: blood culture - *S.* Typhi, 1; pleural fluid culture – *M. tuberculosis*, 1; nasopharyngeal aspirate PCR – 1 each of influenza A, parainfluenza and RSV.
†A further 12 blood cultures (3%) yielded organisms regarded as contaminants: coagulase-negative *Staphylococci*, 8; *Micrococcus* spp., 2; *Bacillus* spp., 2.

Supplemental Table E6. Aetiology of community-acquired pneumonia in Malawian adults stratified by radiological appearance and HIV status.

	Radiographic pneumonia (n=317)*			No radiographic pneumonia (n=100)*			
Organism	**All**	**HIV-pos.**	**HIV-neg.**	**All**	**HIV-pos.**	**HIV-neg.**	***P* for difference†**
Streptococcus pneumoniae	83/316 (26.3)	56/247 (22.7)	27/65 (41.5)	8/100 (8.0)	5/73 (6.9)	3/25 (12)	<0.001
Salmonella Typhi	2/309 (0.7)	2/243 (0.8)	0/62 (0)	8/99 (8.1)	2/72 (2.8)	5/25 (20)	<0.001
Nontyphoidal *Salmonella*‡	1/309 (0.3)	1/243 (0.4)	0/62 (0)	5/99 (5.1)	5/72 (6.9)	0/25 (0)	<0.001
Other GNEB§	2/309 (0.7)	2/243 (0.8)	0/62 (0)	1/99 (1)	1/72 (1.4)	0/25 (0)	0.66
S. aureus	1/309 (0.3)	0/243 (0)	1/62 (1.6)	0/99 (0)	0/72 (0)	0/25 (0)	0.53
Atypical bacteria‖	5/314 (1.6)	4/247 (1.6)	1/66 (1.5)	1/99 (1)	0/73 (0)	1/25 (4)	0.66
Mycobacterium tuberculosis	58/232 (25)	47/186 (25.3)	10/42 (23.8)	13/68 (19.1)	13/50 (26)	0/17 (0)	0.39
NTM	3/194 (1.6)	2/158 (1.3)	1/33 (3)	4/57 (7.0)	2/41 (4.9)	2/15 (13.3)	0.046
Influenza	25/313 (8)	20/246 (8.1)	4/66 (6.1)	11/99 (11.1)	9/73 (12.3)	2/25 (8)	0.26
Adenovirus	22/314 (7)	19/247 (7.7)	3/66 (4.5)	7/99 (7.1)	5/73 (6.9)	2/25 (8)	0.95
Coronavirus	22/314 (7)	19/247 (7.7)	3/66 (4.6)	9/99 (9.1)	9/73 (12.3)	0/25 (0)	0.43
Parainfluenza	10/314 (3.2)	9/247 (3.6)	1/66 (1.5)	6/99 (6.1)	5/73 (6.9)	0/25 (0)	0.34
Rhinovirus	11/314 (3.5)	9/247 (3.6)	2/66 (3)	4/99 (4)	4/73 (5.5)	0/25 (0)	0.76
Bocavirus	9/314 (2.9)	9/247 (3.6)	0/66 (0)	3/99 (3)	3/73 (4.1)	0/25 (0)	0.85
Metapneumovirus	9/314 (2.9)	8/247 (3.2)	1/66 (1.5)	0/99 (0)	0/73 (0)	0/25 (0)	0.09
RSV	4/314 (1.3)	1/247 (0.4)	2/66 (3)	3/99 (3)	2/73 (2.7)	1/25 (4)	0.16
Enterovirus	2/314 (0.6)	2/247 (0.8)	0/66 (0)	1/99 (1)	1/73 (1.4)	0/25 (0)	0.66
Parechovirus	2/314 (0.6)	2/247 (0.8)	0/66 (0)	1/99 (1)	1/73 (1.4)	0/25 (0)	0.66
No pathogen detected	123/317 (38.8)	95/247 (38.5)	26/66 (39.4)	37/100 (37)	25/73 (34.3)	11/25 (48)	0.85

Definition of abbreviations: GNEB = Gram-negative enteric bacilli; NTM = nontuberculous mycobacteria; RSV = respiratory syncytial virus.
Data are n/N (%). Denominators indicate number of patients with at least one relevant test available. *S. pneumoniae* diagnosis based on combination of blood and pleural fluid culture and antigen assay of urine and pleural fluid. *M. tuberculosis* based on combination of sputum microscopy, culture and Xpert MTB/RIF and pleural fluid culture. Other organisms based on single test. *In the 42 patients without available chest radiograph or consensus report for radiographic pneumonia, the following organisms were detected: *S. pneumoniae*, 7; nontyphoidal *Salmonella*, 1; *S. aureus*, 1; atypical bacteria, 2; *M. tuberculosis*, 4; NTM, 1; influenza, 4; adenovirus, 6; parainfluenza, 1; rhinovirus, 2; bocavirus, 1; RSV, 1; enterovirus, 2; parechovirus, 2; no pathogen detected, 21. †Association of organism with radiological appearance controlling for effect of HIV by Mantel-Haenszel χ^2 test. ‡S. Enteritidis and S. Typhimurium combined. §*Escherichia coli* and *Enterobacter cloacae* combined. ‖ *Chlamydia pneumoniae* and *Mycoplasma pneumoniae* combined.

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Supplemental Table E7. Radiological features of community-acquired pneumonia in Malawian adults stratified by microbial aetiology.

Radiographic feature*	Organism		
	Streptococcus pneumoniae† (n=69)	*Mycobacterium tuberculosis*‡ (n=51)	Influenza (n=16)§
Any parenchymal abnormality	65/68 (95.6)	43/51 (84.3)	16/16 (100)
Consolidation	61/68 (89.7)	40/51 (78.4)	11/16 (68.8)
Quality§			
Confluent	46/60 (76.7)	17/37 (46.0)	4/9 (44.4)
Patchy	14/60 (23.3)	20/37 (54.1)	5/9 (55.6)
Extent§			
Segmental	11/57 (19.3)	5/37 (13.5)	1/8 (12.5)
Lobar	23/57 (40.4)	8/37 (21.6)	3/8 (37.5)
Multifocal	23/57 (40.4)	24/37 (64.9)	4/8 (50.0)
Multilobar	20/61 (32.8)	20/51 (39.2)	3/14 (21.4)
Cavitation	2/69 (2.9)	6/51 (11.8)	0/16 (0)
Reticulonodular change	4/69 (5.8)	14/51 (27.5)	3/16 (18.8)
Miliary appearance	0/69 (0)	0/50 (0)	0/16 (0)
Pleural effusion	22/69 (31.9)	23/50 (46.0)	3/16 (18.8)
Mediastinal lymphadenopathy	2/69 (2.9)	8/51 (15.7)	1/16 (6.3)

Data area n/N (%). Analysis restricted to patients with radiographic pneumonia who did not have co-infection involving more than one of *S. pneumoniae*, *M. tuberculosis* and influenza to achieve three mutually exclusive groups.

*Based on consensus values of all assessors; denominator may vary when consensus not obtained.

†Additional 6 patients with *M. tuberculosis* and 7 with influenza co-infection excluded. Other co-infections detected in 24: bacterial, 5; viral, 18; mixed viral-non-tuberculous mycobacterial, 1.

‡Additional 6 patients with *S. pneumoniae* and 1 with influenza co-infection excluded. Other co-infections detected in 15: bacterial, 2; viral, 11; mixed viral-bacterial, 2.

§Additional 8 patients with *S. pneumoniae* and 1 with *M. tuberculosis* co-infection excluded. Other co-infections detected in 4: bacterial, 1; viral, 3.

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Supplemental Table E8. Matrix showing co-infection combinations in Malawian adults hospitalised with community-acquired pneumonia.

	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**

Definition of abbreviations: GNEB = Gram-negative enteric bacilli; NTM = nontuberculous mycobacteria; NTS = nontyphoidal *Salmonella*; RSV = respiratory syncytial virus.
Analysis performed in 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; 152 excluded for lacking results for one or more of these investigations. Darkly shaded squares indicate mono-infection.

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Supplemental Table E9. Association of aetiology with 30-day mortality for three commonest pathogens in Malawian adults with community-acquired pneumonia.

Organism	30-day mortality		
	No. (%)	aOR (95% CI)*	*P*
Streptococcus pneumoniae			
Yes	7/94 (7.5)	0.40 (0.17-0.91)	0.03
No	57/344 (16.6)		
Mycobacterium tuberculosis			
Yes	17/74 (23.0)	2.44 (1.19-5.01)	0.02
No	22/241 (9.1)		
Influenza			
Yes	2/39 (5.1)	0.39 (0.09-1.67)	0.20
No	61/396 (15.4)		

Definition of abbreviations: aOR = adjusted odds ratio; CI = confidence interval; IQR = interquartile range.
Data are n/N (%). Status at day 30 determined in 439 of 459 patients overall; individual analyses for each pathogen restricted to those for whom relevant specimens available: *S. pneumoniae* (n=438); *M. tuberculosis* (n=315); influenza (n=435).
*Odds ratios calculated by logistic regression and adjusted for age, sex and HIV status.

Supplemental Table E10. Association of candidate clinical and laboratory risk factors with 30-day mortality in HIV-infected Malawian adults hospitalised with community-acquired pneumonia.

Characteristic	Day 30 survivors (n=288)	Day 30 mortality (n=54)	Univariable analysis		Multivariable analysis	
			OR (95% CI)	*P*	aOR (95% CI)	*P*
Male sex	170/288 (59.0)	45/54 (83.3)	3.47 (1.63-7.37)	0.001	1.94 (0.81-4.67)	0.14
Age (yrs)	*34 (30-41)*	*36 (32-41)*	1.01 (0.98-1.03)	0.72	1.00 (0.96-1.04)	0.98
Current smoker	23/286 (8.0)	3/54 (5.6)	0.67 (0.19-2.32)	0.53	-	-
Pre-presentation symptoms >7 days	99/288 (34.4)	32/53 (60.4)	2.91 (1.59-5.31)	0.001	3.56 (1.60-7.93)	0.002
Temperature <35 or ≥40 °C	10/288 (3.5)	1/54 (1.9)	0.52 (0.07-4.18)	0.54	-*	-
Systolic BP <90 mmHg	58/284 (20.4)	15/54 (27.8)	1.50 (0.77-2.90)	0.23	-	-
Heart rate ≥125 /min	117/287 (40.8)	33/54 (61.1)	2.28 (1.26-4.14)	0.007	3.06 (1.40-6.71)	0.005
Resp. rate ≥30 /min)	128/277 (46.2)	28/53 (52.8)	1.30 (0.72-2.35)	0.38	-	-
Oxygen sat^{n} <90 %	33/282 (11.7)	23/54 (42.6)	5.60 (2.92-10.73)	<0.0001	2.97 (1.28-6.88)	0.01
MUAC <230 mm	82/285 (28.8)	13/53 (24.5)	0.80 (0.41-1.58)	0.53	-	-
Inability to stand	47/288 (16.3)	26/54 (48.2)	4.76 (2.57-8.84)	<0.0001	4.25 (1.84-9.79)	0.001
Haemoglobin <8 g/dL	51/283 (18.0)	17/51 (33.3)	2.27 (1.18-4.38)	0.01	-	-
White cell count <4 x 10^9/L	41/282 (14.5)	14/51 (27.5)	2.22 (1.11-4.47)	0.03	-	-
Platelets <100 x 10^9/L	48/283 (17.0)	11/51 (21.6)	1.34 (0.64-2.81)	0.43	-	-
Urea >7 mmol/L	90/285 (31.6)	22/50 (44.0)	1.70 (0.92-3.14)	0.09	-	-
CD4 count <50 cells/mm^3	65/257 (25.3)	23/47 (48.9)	2.83 (1.50-5.35)	0.001	2.30 (1.07-4.92)	0.03

Definition of abbreviations: BP = blood pressure; BMI = body mass index; CI = confidence interval; MUAC = mid-upper arm circumference; OR = odds ratio; Resp. = respiratory

For age (in *italics*) data shown as median and interquartile range. Otherwise data shown as n/N (%) with variation in denominator compared to column header reflecting missing data. Univariable and multivariable analyses by logistic regression. For age, odds ratio indicates change in risk of mortality with each year increase. 13 of 355 HIV-infected patients within study cohort excluded due to unknown 30-day outcome. Final multivariable analysis based on 287 patients with complete results for all included parameters.

*Excluded from multivariable analysis because of prevalence ≤5%.

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Supplemental Table E11. Association of clinical and laboratory risk factors with 30-day mortality in hospitalised Malawian adults with radiographic community-acquired pneumonia.

Characteristic	Day 30 survivors (n=274)	Day 30 mortality (n=31)	Univariable analysis		Multivariable analysis	
			OR (95% CI)	*P*	aOR (95% CI)	*P*
Male sex	179/274 (65.3)	24/31 (77.4)	1.82 (0.76-4.38)	0.18	1.39 (0.53-3.61)	0.51
Age (yrs)	*35 (30-42)*	*37 (32-44)*	1.01 (0.98-1.03)	0.70	1.02 (0.98-1.05)	0.39
Current smoker	28/272 (10.3)	3/31 (9.7)	0.93 (0.27-3.27)	0.92	-	-
Pre-presentation symptoms >7 days	99/273 (36.3)	19/31 (61.3)	2.78 (1.30-5.97)	0.009	3.30 (1.37-7.96)	0.008
HIV-positive	216/271 (79.7)	25/31 (80.7)	1.06 (0.41-2.71)	0.90	1.11 (0.36-3.42)	0.86
Temperature <35 or ≥40 °C	10/274 (3.7)	0/31 (0)	-	-	-*	-
Systolic BP <90 mmHg	52/271 (19.2)	7/31 (22.6)	1.23 (0.50-3.00)	0.65	-	-
Heart rate ≥125 /min	104/273 (38.1)	20/31 (64.5)	2.95 (1.36-6.41)	0.006	2.66 (1.08-6.57)	0.03
Resp. rate ≥30 /min)	134/265 (50.6)	16/30 (53.3)	1.12 (0.52-2.38)	0.77	-	-
Oxygen sat^{n} <90 %	42/267 (15.7)	9/30 (30.0)	2.30 (0.98-5.36)	0.06	-	-
MUAC <230 mm	79/270 (29.3)	5/30 (16.7)	0.48 (0.18-1.31)	0.15	-	-
Inability to stand	41/274 (15.0)	10/31 (32.3)	2.71 (1.19-6.17)	0.02	2.63 (1.00-6.89)	0.05
Haemoglobin <8 g/dL	38/270 (14.1)	6/31 (19.4)	1.47 (0.56-3.81)	0.43	-	-
White cell count <4 x 10^9/L	34/269 (12.7)	5/31 (16.1)	1.33 (0.48-3.70)	0.59	-	-
Platelets <100 x 10^9/L	37/270 (13.7)	6/31 (19.4)	1.51 (0.58-3.93)	0.40	-	-
Urea >7 mmol/L	83/270 (30.7)	13/31 (41.9)	1.63 (0.76-3.48)	0.21	-	-
Multilobar	56/266 (21.1)	14/30 (46.7)	3.28 (1.51-7.13)	0.003	2.75 (1.17-6.47)	0.02
Cavitation	18/274 (6.6)	2/31 (6.5)	0.98 (0.22-4.44)	0.98	-	-
Pleural effusion	98/272 (36.4)	16/31 (51.6)	1.86 (0.88-3.93)	0.10	-	-

Definition of abbreviations: BP = blood pressure; BMI = body mass index; CI = confidence interval; MUAC = mid-upper arm circumference; OR = odds ratio; Resp. = respiratory

For age (in *italics*) data shown as median and interquartile range. Otherwise data shown as n/N (%) with variation in denominator compared to column header reflecting missing data. Univariable and multivariable analyses by logistic regression. For age, odds ratio indicates change in risk of mortality with each year increase.

12 of 317 patients with radiographic pneumonia within study cohort excluded due to unknown 30-day outcome. Final multivariable analysis based on 278 patients with complete results for all included parameters.

*Excluded from multivariable analysis because of prevalence ≤5%.

Supplemental Table E12. Accuracy of pneumonia severity-assessment tools for predicting 30-day mortality in hospitalised Malawian adults with radiographic community-acquired pneumonia.

Score group	*n**	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	Positive LR (95% CI)	Negative LR (95% CI)	AUROC (95% CI)
CURB65 ≥3	288	6.7 (0.8-22.1)	89.9 (85.6-93.3)	7.1 (0.9-23.5)	89.2 (84.8-92.7)	0.66 (0.17-2.65)	1.04 (0.94-1.15	0.53 (0.43-0.63)
CRB65 ≥2	292	20.0 (7.7-38.6)	79.8 (74.4-84.5)	10.2 (3.8-20.8)	89.7 (85.1-93.3)	0.99 (0.46-2.10)	1.00 (0.83-1.21)	0.50 (0.39-0.60)
SMRT-CO ≥2	280	89.7 (72.6-97.8)	36.7 (30.7-42.9)	14.1 (9.4-19.9)	96.8 (91.0-99.3)	1.42 (1.21-1.65)	0.28 (0.10-0.84)	0.66 (0.57-0.75)
Modified IDSA/ATS minor criteria ≥3	272	48.3 (29.4-67.5)	72.0 (65.9-77.6)	17.1 (9.7-27.0)	92.1 (87.3-95.5)	1.73 (1.13-2.64)	0.72 (0.50-1.03)	0.66 (0.56-0.75)
SWAT-Bp ≥3	297	40.0 (22.7-59.4)	65.9 (59.9-71.6)	11.7 (6.2-19.5)	90.7 (85.7-94.4)	1.17 (0.73-1.88)	0.91 (0.67-1.23)	0.54 (0.43-0.65)

Definition of abbreviations: AUROC = area under receiver-operating characteristic curve; CI = confidence interval; CURB65 = tool based on presence of confusion, urea >7mmol/L, respiratory rate ≥30/min, systolic blood pressure <90mmHg and/or diastolic blood pressure ≤60mmHg, age ≥65 (29); CRB65 = as per CURB65 with exclusion of urea (29); IDSA/ATS = modified version of Infectious Disease Society of America/American Thoracic Society criteria based on presence of respiratory rate ≥30/min, oxygen saturations ≤90% (used as a surrogate for arterial oxygen pressure/fraction of inspired oxygen (PaO_2/FiO_2) ratio ≤250 criterion included in the published tool), multilobar infiltrates, confusion/disorientation, urea ≥7.1 mmol/L, white blood cell count <4 x10^9 cells/L, platelets <100 x10^9 cells/L, temperature <36°C, systolic blood pressure < 90 mmHg (used as a surrogate for hypotension requiring aggressive fluid resuscitation; 32); LR = likelihood ratio; NPV = negative predictive value; PPV = positive predictive value; SMRT-CO = tool based on presence of systolic blood pressure < 90 mmHg, multilobar consolidation, respiratory rate ≥25/min if ≤50 years or ≥30/min if >50 years, heart rate ≥125/min, confusion and oxygen saturations ≤93% if ≤50 yrs or ≤90% if >50 yrs (31); SWAT-Bp = tool based on male sex, wasting, non-ambulatory status, temperature <35°C or >38°C and systolic blood pressure <100 mmHg or diastolic blood pressure <60 mmHg (28). For each tool, the performance characteristics displayed are those using the scoring threshold for "severe CAP" as suggested by the authors. *Score calculated in varying number of patients depending on availability of results for component parameters.

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