

Patient outcome in adults with pneumococcal meningitis or bacteraemia admitted to QECH

Stephen B Gordon

Malawi-Liverpool-Wellcome Trust Clinical Research Programme, Blantyre. Email: sgordon@mlw.medcol.mw

ABSTRACT

Pneumococcal infections are common in Malawian adults. We set out to determine which factors influence in-hospital mortality and long-term survival among these patients. Features of history and examination, inpatient mortality and long-term survival were described among consecutively admitted QECH patients with *S. pneumoniae* in blood or CSF. 217 patients with pneumococcal disease were studied over an 18-month period. Among these, 158 of 167 consenting to testing (95%) were HIV positive. Inpatient mortality was 65% for pneumococcal meningitis (n=64), 20% for pneumococcal pneumonia (n=92) and 26% for patients

with pneumococcaemia without localising signs (n=43). Lowered conscious level (OR 5.8, p<0.001), hypotension (OR 4.8, p=0.04) and age exceeding 55 years (OR 3.8, p=0.001) at presentation were associated with inpatient death but not long-term outcome in survivors. Outpatient death was associated with multilobar chest signs (HR 2.1, p=0.01), oral candidiasis (HR 1.8, p=0.03) and severe anaemia (HR 3.9, p=0.005) as an inpatient. In conclusion, most patients with pneumococcal disease in Malawi have severe disease, HIV co-infection and a poor prognosis. At discharge patients with multilobar chest signs or anaemia are at particular risk.

Introduction

It is well-known that *Streptococcus pneumoniae* is an important pathogen in HIV infected adults in Africa causing a high incidence of bloodstream and recurrent infections(2). HIV infected patients in the USA have also been shown to have an increased incidence of bloodstream and recurrent pneumococcal infections(3). A decrease in the incidence of pneumonia and pneumococcal infections has recently accompanied the increased use of highly active anti-retroviral therapy (HAART) in the USA(4). Blantyre has an estimated HIV seroprevalence of 35% among urban-dwelling adults(5) and *S. pneumoniae* has been described as the most common cause of bacterial meningitis(6) and a major cause of bacteraemia(7) among adult inpatients. We now report both the acute mortality and long-term survival patients admitted to hospital with invasive *S. pneumoniae* disease presenting as pneumococcal meningitis, bacteraemic pneumonia and bacteraemia without a detectable clinical focus.

Materials and methods

The Queen Elizabeth Central Hospital (QECH), Blantyre admits 9800 adults per year to the non-fee-paying medical wards from among the 395 000 outpatients seen in the Emergency department. The HIV seroprevalence among medical inpatients in a sample of 758 patients in 2000 was 75% (David Lewis, personal communication).

Patient recruitment, investigation treatment and follow-up

All febrile adult admissions during an 18-month period (October 1997 to March 1999) had samples collected for blood culture. In addition, patients with clinical features consistent with meningitis (2 of the following: fever, headache, neck stiffness, altered consciousness) were recommended diagnostic lumbar puncture. If *S. pneumoniae* was identified in any of these samples, patients were recruited with informed consent to an observational study of clinical features and disease outcome.

Patients were pre-counseled prior to HIV testing according to local guidelines and tested if consent was obtained (if the patient was unconscious, consent was sought from the accompanying relative or guardian). All patients were treated according to local guidelines. Patients with a clinical diagnosis of meningitis were

treated with intravenous benzyl penicillin (2.4g every 6 hours) and chloramphenicol (1g every 6 hours) for a minimum of 5 days; treatment was given orally when the patients were fully conscious and eating. Patients with pneumonia were treated with oral amoxicillin unless they had clinical features of severe disease - at least one of the following: respiratory rate greater than 40 per minute, systolic blood pressure less than 90mmHg, cyanosis, confusion or multilobar disease. In severe cases, combinations of intravenous benzyl penicillin (1.2g every 6 hours) and erythromycin (500mg every 6 hours) or gentamicin (240mg once daily) were used at the discretion of the attending physician.

Patients participating in the follow-up study were provided with transport home from hospital and a monthly outpatient appointment. Patients failing to attend the regular follow-up clinic were visited at home. Details of intercurrent illness were recorded, and treatment prescribed as appropriate. If patients died, details of the terminal illness and date of death were recorded.

Data analysis and ethical review

Patients were divided into three groups - meningitis, pneumonia and bacteraemia. Patients were defined as having pneumococcal meningitis if *S. pneumoniae* was identified in the CSF or if the CSF contained more than 50 neutrophils per ml in a patient with pneumococcaemia. Patients with neck stiffness but normal CSF were not included in the meningitis group. Patients were defined as having bacteraemic pneumonia if they had chest signs on clinical examination and pneumococcaemia. These two categories of patients were distinguished from those with bacteraemia with no focal symptoms or signs.

Comparisons were made between clinical groups and between survivors and patients who died both as inpatients and in follow-up. Continuous variables were compared using the Kruskal-Wallis test and categorical variables using the χ^2 test. Multiple logistic regression was used to determine risk factors for inpatient death with comparative risk expressed as Odds Ratios (OR). Cox's proportional hazard ratios (HR) were used to compare outpatient survival between groups.

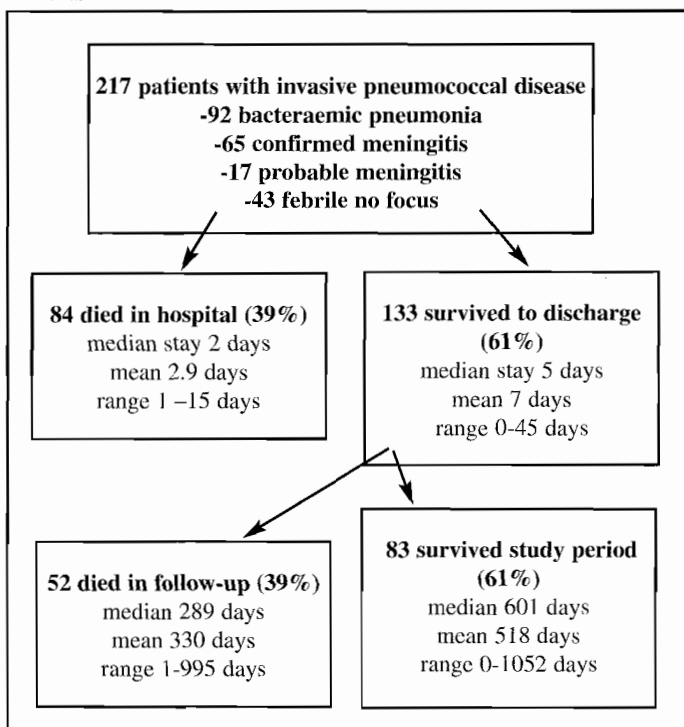
This study was reviewed and approved by the Health Sciences Research Committee of Malawi. All subjects or their relatives gave written informed consent to participation in this study.

Results

217 patients with invasive pneumococcal disease were recruited to the observational study (see Figure 1). 84 (39%) died during their hospital admission. Of the remaining 133, 52 died in follow-up bringing the total mortality during the study to 136 (63%). 82 patients had taken antibiotics prescribed by a pharmacy prior to admission (52% of 157 patients able to give a full drug history). The most common risk factors for invasive pneumococcal disease in this cohort were HIV infection and a prior history of lung disease. 167 of the 217 patients (77%) consented to HIV testing, of whom 158 (95% of those tested) were HIV positive. 41 patients had a prior history of lung disease, of whom 24 presented with pneumonia ($\chi^2=7.5$, $p=0.02$).

Figure 1.

Patient group studied. This flow chart shows the total number of patients followed in the study and their diagnoses. The numbers of patients dying as inpatients or during follow-up are also shown.



Clinical features and acute outcome (Table 1)

The clinical features and outcome of patients with pneumococcal disease is summarised by category in Table 1. The analysis of inpatient outcome is illustrated in Figure 2a. There was no significant difference between the mean ages of patients, or their gender distribution, between the diagnostic groups (see Table 1). There was a significant difference between the inpatient mortality of patients with confirmed meningitis compared to pneumonia (OR=7.5, CI 3.6-15.5, $p<0.0001$) or bacteraemia (OR=5.3, CI 2.3-12.5, $p<0.0001$) but not between patients with bacteraemia and those with pneumonia (OR 1.4, CI 0.6-3.3, $p=0.4$). There were 3 important features predictive of inpatient death in the whole group (see Table 2). These were confusion on admission (OR=5.8), age greater than 55 years (OR=3.8) and hypotension defined as systolic blood pressure less than 90mmHg (OR=4.8). The likelihood of survival and the presenting level of consciousness were significantly correlated. Among patients presenting with a normal Glasgow Coma Score (GCS), the mortality was 30%, compared to 50% with a GCS of between 9 and 14 and 74% in those with a coma score of less than 9 ($\chi^2=26$, $p<0.001$).

Table 1.

Patients compared by diagnostic group. In this table, basic demographic features are compared between patient groups, and the features of history and examination at presentation that distinguished one group from another are highlighted. In addition, differences in treatment prior to admission, features of AIDS and overall outcome are compared.

Clinical Features	Pneumonia	Meningitis	Bacteraemia	p value
Number in group (n=200)	92	65	43	
Demographics				
Age (mean)	33.9	32.1	31.5	0.7
Gender (F:M, % male)	39:53 (58)	36:29 (45)	23:20 (47)	0.2
Features of acute presentation with a difference between highlighted group and other groups, n (%)				
Cough	88 (97)	26 (40)	25 (58)	<0.001
Chills	43 (47)	9 (14)	8 (19)	<0.001
Dyspnoea	65 (71)	21 (32)	8 (19)	<0.001
Confusion	5 (5)	38 (58)	1 (2)	<0.001
Previous treatment				
Traditional medicine	30 (38)	9 (14)	10 (23)	0.03
Pharmacy outpatient antibiotics	42 (53)	24 (53)	16 (57)	0.9
Features of AIDS - excess in highlighted group				
Previous pneumonia	16 (17)	6 (9)	1 (2)	0.03
Wasting	64 (70)	26 (40)	19 (44)	<0.001
Prolonged fever	34 (37)	11 (17)	11 (26)	0.02
Persistent cough	14 (15)	1 (2)	2 (5)	0.006
Lymph nodes	14 (15)	1 (2)	2 (5)	0.006
Features on examination - excess in highlighted group				
Multilobar signs	34 (36)	7 (11)	0 (0)	<0.001
Herpes labialis [n (%)]	9 (10)	17 (26)	3 (7)	0.005
Reduced Glasgow coma score	3 (3)	38 (58)	0 (0)	<0.001
Hospital stay				
Inpatient mortality, n (%)	18 (20)	42 (65)	11 (26)	<0.001
-days in hospital (survived) mean (sd)	6.6 (6.3)	10 (4.7)	4.4 (2.6)	0.0001
-days in hospital(died) mean (sd)	5.1 (3.7)	2.1 (1.7)	3.3 (4.0)	0.004

*Continuous variables were compared using the Kruskal-Wallis test and categorical variables using χ^2 .

Table 2.

Factors associated with inpatient mortality are not associated with poorer long-term outcome. In the table, the 3 features confirmed by regression analysis to be most associated with inpatient mortality are presented together with their associated odds ratio (OR) and the confidence interval (CI and p value). The same features were then examined for any predictive value on long-term outcome and the associated hazard ratio (HR) and confidence interval (CI and p value) are presented in the right hand panel. In the lower panel, the reverse process was carried out – that is, features associated with a poor long-term prognosis were examined for their predictive value on inpatient mortality. It can be seen that factors associated with poor acute outcome are different from those predicting poor longer term survival

resistant isolates were obtained compared to patients with penicillin sensitive isolates. Antibiotic sensitivity was also determined for erythromycin (99%), chloramphenicol (76%), tetracycline (50%) and co-trimoxazole (6%). No significant difference was found in the antibiotic sensitivity of blood and CSF isolates.

Discussion

We have described clinical features and outcome in a cohort of 217 consecutive patients with invasive pneumococcal disease admitted to QECH. 39% of patients died of their acute illness, and only 38% of the cohort remained alive at the end of the 18-month study period. Pneumococcal disease is a severe illness in Malawi. Three modes of presentation were observed – meningi-

	Inpatient mortality			Long-term outcome		
Features associated with increased inpatient mortality						
Feature	OR	CI	p	HR	CI	p
Confusion	5.7	2.9-11.3	<0.001	0.91	0.41-2.0	0.82
Diastolic bp/mmHg	0.95	0.93-0.98	0.004	0.99	0.97-1.1	0.36
Age>55yr	3.8	1.7-8.7	0.001	1.8	0.56-5.8	0.3
Features associated with increased long-term mortality rat						
Feature	OR	CI	p	HR	CI	p
Oral candida	0.25	0.1-0.6	0.001	1.8	1-3.3	0.03
Multilobar disease	1.0	0.5-2.0	0.96	2.1	1.17-3.8	0.01
Anaemia	1.2	0.3-5.5	0.8	3.9	1.5-10.1	0.005

Patient long-term survival

133 patients were discharged from hospital. These patients had a median stay in hospital of 5 days and were followed up for up to 1052 days (median 414 days). Patient attendance at clinic was poor, and the bulk of follow-up was carried out actively in the community. Late in the study, patients were increasingly likely to be ill and to return to their rural homes from the city and this made follow-up more difficult. 51 patients (39%) died during the follow-up period, with a median survival of 330 days. The survival curves by clinical diagnostic groups for patients discharged from hospital are shown in Figure 2. Despite the differences in acute mortality, outpatient mortality did not differ between groups (37%, 37% and 40% respectively; $\chi^2=0.68$, $p=0.96$). Outpatient mortality was also not related to age, shock at presentation or low coma score – all of which were associated with high inpatient mortality (see Table 2). Increased outpatient mortality was associated with multilobar chest signs (HR=2.1), oral candida (HR=1.8) and with anaemia (HR=3.9) though haematological data was only available for 53 of 133 patients followed up.

Isolates of *S. pneumoniae* - source, antibiotic resistance

All isolates in this study were obtained from normally sterile sites in symptomatic patients. Early in the study, 130 blood cultures were taken from asymptomatic clinic attendees to establish if patients had asymptomatic bacteraemia. None grew *S. pneumoniae*. 145 isolates (145/173; 84%) from blood cultures and 55 isolates (55/63; 87%) from CSF culture were found to be fully sensitive to penicillin. There was no increase in inpatient, outpatient or overall mortality in the patients from whom the

isolation was made. The factors associated with inpatient death were confusion or lowered coma score, age greater than 55 years and hypotension. The median time to death was 2 days from admission to hospital. These data suggest that the patients who died in this series might not have been saved with altered medical therapy(8) but rather with a change in health seeking behaviour or health care delivery resulting in earlier admission to hospital. Over 50% of patients in this series had been treated in community pharmacies prior to admission, however, and many patients had approached both traditional healers and dispensary physicians before being admitted (Table 1). There is evidence, therefore, that health care provision, rather than health-seeking behaviour, must be improved to alter the mortality of this disease. In QECH, less than 2.5% of patients presenting to the emergency department are admitted to medical wards (9800/395000 = 2.4%) as bed occupancy is already between 100 and 200 percent.

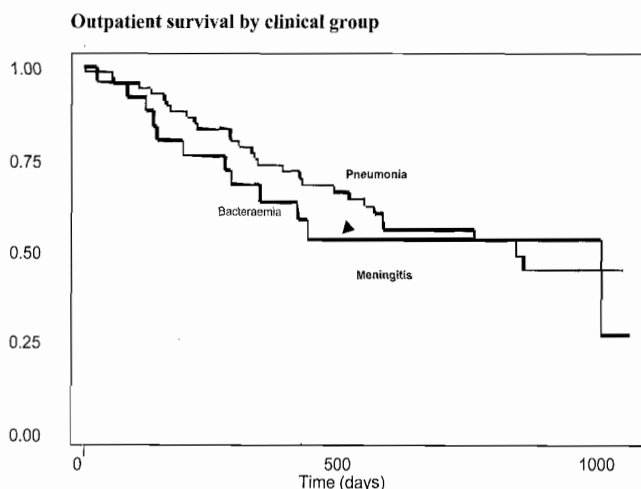
The mortality rate during outpatient follow-up in this study was 31% per year. Patients were followed in the community for up to 1052 days (median 414 days). During this time, 39% of the cohort discharged from hospital died. This overall mortality rate is similar to that of larger studies in which unselected HIV infected patients were followed up in a similar setting(9). The design of this study does not allow determination of whether pneumococcal infection is itself a poor prognostic factor in HIV infected adults.

We found three main factors to be associated with poor outpatient outcome in this study – anaemia defined as haemoglobin less than 7g/dl (OR=7), oral candidiasis (OR=3.4) and multilobar pulmonary disease (OR=4.6). None of these factors were associated with acute inpatient death. The association of severe anaemia with poor outcome in HIV infected patients has been noted by other authors(10-12) and may in part be due to *Mycobacterium tuberculosis* infection involving bone marrow, as well as concurrent viral infections and nutritional deficiencies(13). Oral candidiasis is a feature of HIV disease progression and as such the association with poor outcome is unsurprising. Multilobar chest signs may reflect the severity of pneumococcal disease, but more likely represents *M. tuberculosis* co-infection(14).

What strategies for improved care can be developed from these observations? First, all patients presenting with meningitis, pneumonia or pneumococcaemia in Malawi must be suspected of being co-infected with HIV and be investigated and advised appropriately. Second, patients with multilobar chest sign should be investigated for tuberculosis. A recent study of pneumonia patients in Kenya has demonstrated that tuberculosis is under-diagnosed among patients presenting as an emergency(14). Sputum examination for acid fast bacilli in all inpatients with chest signs may be justified but will create an extra burden on already strained resources(15;16). Severely anaemic patients have a very poor prognosis. Potentially, nutritional support and treatment of other infections could make an important difference but it is more likely that the prognosis for these patients would only improve with HAART(17).

Figure 2.

Kaplan-Meier survival estimates by clinical group. In the upper panel, overall patient survival is plotted for the whole group divided according to diagnosis of pneumonia, confirmed meningitis or bacteraemia. There is a significant difference in mortality rates ($p < 0.0001$) which is due to inpatient mortality. In the lower panel, outpatient survival is plotted in the same manner and shows no significant difference in mortality rates after leaving hospital by clinical group ($p = 0.55$). Patients dying as inpatients do not appear in the lower figure.



Overall survival by clinical group

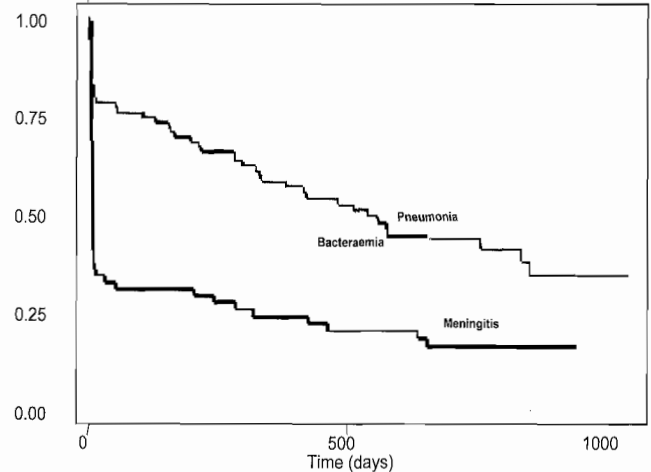
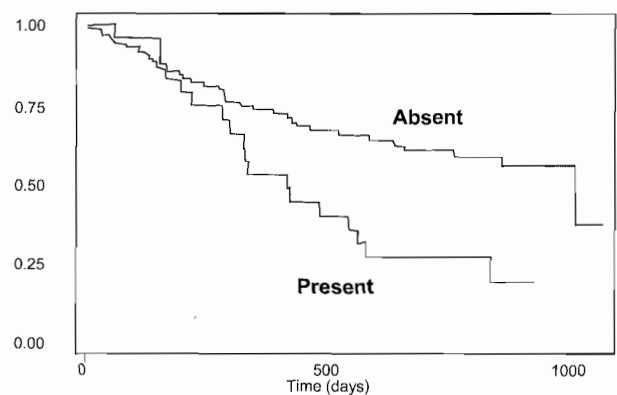


Figure 3.

Outpatient risk factors. Kaplan Meier plots showing survival among patients with multilobar chest signs (panel A) or oral candida (panel B) compared to the survival of the rest of the group. In panel C, all patients with a recorded haemoglobin result ($n = 53$) were divided according to whether or not they had anaemia ($Hb < 7g/dl$ at presentation, $n = 16$) or not ($Hb > 7g/dl$ $n = 37$). There was a significantly increased mortality rate in patients with multilobar disease compared to the rest of the group ($HR = 2.1$, $CI = 1.2-3.8$, $p = 0.01$). There was also increased mortality in the group with oral candida compared to those without oral candida ($HR = 1.8$, $CI = 1.1-3.3$, $p = 0.03$) and among patients with anaemia compared to those without anaemia ($HR = 3.9$, $CI = 1.5-10.1$, $p = 0.005$).

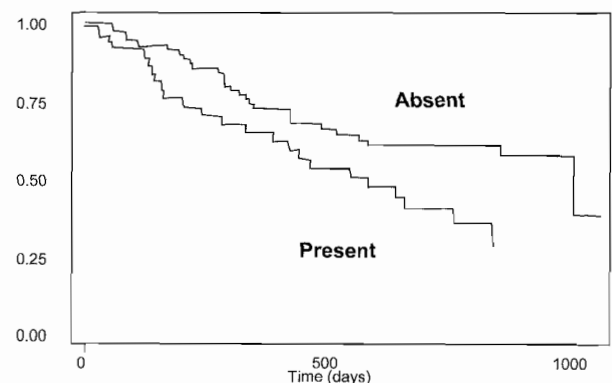
Panel A

Multilobar chest signs



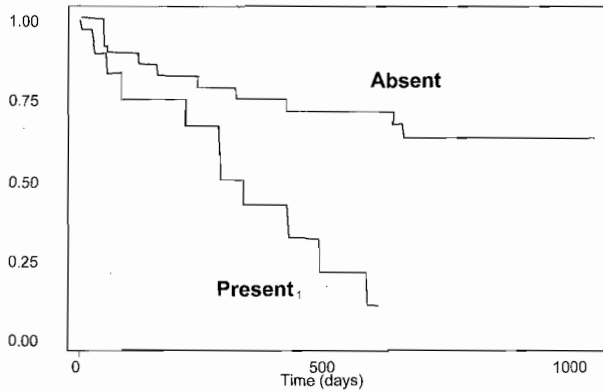
Panel B

Oral candidiasis



Panel C

Anaemia (Hb<7g/dl)



Acknowledgements

This is not an original piece of work but is an abridged version of work published in *AIDS(1)*. We thank the co-authors of the original work. That work received financial support from the Wellcome Trust of Great Britain and forms part of the Malawi-Liverpool-Wellcome Trust Programme of Research in Clinical Tropical Medicine.

References

- Gordon SB, Chaponda M, Walsh AL, Whitty CJ, Gordon MA, Machili CE et al. Pneumococcal disease in HIV-infected Malawian adults: acute mortality and long-term survival. *AIDS* 2002; 16:1409-17.
- Gilks CF, Ojoo SA, Ojoo JC, Brindle RJ, Paul J, Batchelor BI et al. Invasive pneumococcal disease in a cohort of predominantly HIV-1 infected female sex-workers in Nairobi, Kenya. *Lancet* 1996;347:718-23.
- Hibbs JR, Douglas-JM J, Judson FN, McGill WL, Rietmeijer CA, Janoff EN. Prevalence of human immunodeficiency virus infection, mortality rate, and serogroup distribution among patients with pneumococcal bacteremia at Denver General Hospital, 1984-1994. *Clin.Infect.Dis.* 1997; 25:195-9.
- Sullivan JH, Moore RD, Keruly JC, Chaisson RE. Effect of antiretroviral therapy on the incidence of bacterial pneumonia in patients with advanced HIV infection. *Am J.Resp.Crit.Care Med* 2000; 162:64-7.
- Taha ET, Dallabetta GA, Hoover DR, Chipangwi JD, Mtimavalyc LAR, Liomba GN et al. Trends of HIV-1 and sexually transmitted diseases among pregnant and postpartum women in urban Malawi. *AIDS* 1998; 12:197-203.
- Gordon SB, Walsh AL, Chaponda M, Gordon MA, Soko D, Mbwini M et al. Bacterial meningitis in Malawian adults: pneumococcal disease is common, severe, and seasonal. *Clin.Infect.Dis.* 2000; 31:53-7.
- Gordon MA, Walsh AL, Chaponda M, Soko D, Mbwini M, Molyneux ME et al. Bacteraemia and mortality among adult medical admissions in Malawi--predominance of non-typhi salmonellae and Streptococcus pneumoniae. *J.Infect.* 2001; 42: 44-9.
- Austrian R, Gold J. Pneumococcal bacteraemia with especial reference to bacteremic pneumococcal pneumonia. *Ann Int Med* 1964; 60:759-76.
- French N, Nakiyingi J, Carpenter LM, Lugada E, Watera C, Moi K et al. 23-valent pneumococcal polysaccharide vaccine in HIV-1-infected Ugandan adults: double-blind, randomised and placebo controlled trial. *Lancet* 2000; 355: 2106-11.
- Moore RD. Human immunodeficiency virus infection, anemia, and survival. *Clin Infect Dis* 1999; 29: 44-9.
- Antelman G, Msamanga GI, Spiegelman D, Urassa EJ, Narh R, Hunter DJ et al. Nutritional factors and infectious disease contribute to anemia among pregnant women with human immunodeficiency virus in Tanzania. *J Nutr* 2000; 130: 1950-7.
- van den Broek NR, Letsky EA. Etiology of anemia in pregnancy in south Malawi. *Am J Clin Nutr* 2000;72 (1 Suppl): 247S-256S.
- Lewis DK, Peters RP, Schijffelen MJ, Joaki GR, Walsh AL, Kublin JG et al. Clinical indicators of mycobacteraemia in adults admitted to hospital in Blantyre, Malawi. *Int J Tuberc Lung Dis* 2002; 6: 1067-74.
- Scott JA, Hall AJ, Muyodi C, Lowe B, Ross M, Chohan B et al. Actiology, outcome, and risk factors for mortality among adults with acute pneumonia in Kenya. *Lancet* 2000; 355: 1225-30.
- Harris A, Hargreaves N, Kemp J, Kwanjana J, Salaniponi F. Diagnosis of tuberculosis in Africa. *Lancet* 2000; 355: 2256.
- Harries AD. Tuberculosis in Africa: clinical presentation and management. *Pharmacol.Ther.* 1997; 73: 1-50.
- Weidle PJ, Malamba S, Mwebaze R, Sozi C, Rukundo G, Downing R et al. Assessment of a pilot antiretroviral drug therapy programme in Uganda: patients' response, survival, and drug resistance. *Lancet* 2002; 360: 34-40.

Invitation and Call for Abstracts

COLLEGE OF MEDICINE RESEARCH
DISSEMINATION MEETING

November 15th, 2003

Mahatma Ghandi Campus, College of Medicine University of Malawi



The Annual Research Dissemination Meeting is an important opportunity to present data from research relating to any aspect of health in Malawi and to be informed of the wide range of current research activities.

Submitted abstracts are peer-reviewed and presentations will be oral or poster presentation. Available media for presentation include Powerpoint presentation, slides and overhead projector.

Forms for abstracts are available from:
Ms Thandi Kumwendo,
College of Medicine Research Office,
P/Bag 360, Blantyre 3.
Tel: 671 911 ext: 204; or 08 824 432