THE PATTERN OF MENINGITIS IN ADULT ZIMBABWEANS

A DISSERTATION PRESENTED TO THE FACULTY OF MEDICINE,

UNIVERSITY OF ZIMBABWE (MEDICAL SCHOOL) HARARE,

AS PART

FULFILMENT FOR THE DEGREE OF M.MED (MEDICINE)

University of Zimbabwe Library

1993

BY

TAPIWANASHE BWAKURA

M.D., D.T.M. & M.P

CONTENTS PAGE

ACKNOWLEDGEMENTS

Thanks are due to Dr Ndiweni (Department of Medicine), Dr A Malin (Department of Clinical Pharmacology) and Dr V Robertson (Department of Medical Microbiology) for the supervision and advice rendered during the course of the study. Also many thanks to laboratory staff in the Public Health Laboratories, Mrs Musvaire and Mrs Jongwe (Department of Medical Microbiology) and Mr W Murambiwa (Department of Clinical Pharmacology) for their assistance. I owe a lot of gratitude to the junior medical staff at Parirenyatwa hospital for assisting in case collection and Miss C Zambezi for typing the manuscript.

LIST OF ABBREVIATIONS

AIDS	Acquired Immunodeficiency Syndrome
CNS	Central Nervous System
HIV	Human Immunodeficiency Virus
USA	Untied States of America

INTRODUCTION

Meningitis still poses a major clinical problem worldwide and is a significant cause of morbidity and mortality. Formerly, untreated meningitis was fatal with rare exceptions (1). Since the advent of antibiotics there has been a significant reduction in mortality. However, despite fifty years of antibiotic use, the case fatality rate especially in the developing world (2-9) remains unacceptably high.

Several factors appear to influence the relative frequency with which the various pathogens produce meningitis. Among these are season, geographical location and age. Baird et al. (11) drew attention to the high mortality among patients in tropical Africa who developed meningitis due to pneumococcus although the study could not attribute their finding to any one particular cause.

Meningitis occurs commonly in Zimbabwe. Except for a few studies done in paediatric cases (62,63), however, there is no information on the prevalence and aetiology of meningitis in the adult Zimbabwean population. Since the advent of human immunodeficiency virus (HIV) infection, there appears to be a drastic shift in clinical presentation, outcome and types of meningitis. HIV infection is a major problem in Zimbabwe and, as the underlying pathology, accounts for a significant percentage of hospital admission (60). Recent data published by the AIDS control Programme - Zimbabwe (59) gives the number of Acquired Immuno-deficiency syndrome (AIDS) cases for the year ending

December 1992 as 18 731. A seroprevalence study for HIV done on antenatal women in Harare (Zimbabwe) showed a high prevalence rate of 18% (61). The data is in pregnant women who do not represent a so-called high risk group for HIV infection . The sero-prevalence rate for HIV infection among healthy preselected blood donors for the period 1990 to 1992 is 2,46-4,67% (59). Therapeutic decisions are made in patients with infectious meningitis before the results of spinal fluid cultures become available. Decisions are usually based on the results of laboratory studies that can be rapidly performed and viewed in the context of the clinical and epidemiologic characteristics of each case and the hospital experience. Appropriate therapy depends to a large extent on the ability to distinguish bacterial, mycobacterial, and fungal causes of meningitis. Information regarding the pattern of meningitis under these circumstances is valuable for both diagnostic, public health purposes and treatment.

AIMS OF THE STUDY

1. To establish the aetiology and clinical/laboratory features of adult infective meningitis in Zimbabwe.

1.1 to determine the aetiology of meningitis in adult Zimbabweans

1.2 to determine the clinical features in relation to types of meningitis

1.3 to determine the laboratory and CSF findings n relation to types of meningitis

2. To assess the influence of human immunodeficiency virus (HIV) infection on the pattern of meningitis.

REVIEW OF LITERATURE

Meningitis, the most common and notable infection of the central nervous system, can progress rapidly, and result in death or permanent debilitation. Meningitis is much more common in the developing world than in the industrialised world. Morbidity in some parts of Africa has been reported to be as high as 300-400 cases per 100 000 population during epidemics (12). In 1963 Lapeysonnie (17) in an epidemiological study drew attention to the existence in an area of sub-Saharan Africa of the "African meningitis belt" which includes: Burkina Fasso, Niger, Northern Cameroon, Central African Republic, Southern Chad and Southern Sudan. The meningitis belt stretches from the Atlantic Ocean to the Red Sea, lying between the desert to the north and the equatorial forest to the south. The northern limit is defined as the 300 mm rainfall isohyet and southern limit as the 1000 mm isohyet covering an area of about 10 million square kilometres. In this area epidemic outbreaks of meningococcal meningitis occur every 5-10 years during the hot, dry dusty months attacking predominantly older children and young adults (4,13,14). The serogroup A of **Neisseria meningitides** is the cause of the outbreaks in Africa, although towards the end of an

epidemic serogroup B and other organisms may appear (4). Case fatality rates during such epidemics can be as high as 45%. All types of bacterial meningitis are a common clinical problem outside the meningitis belt of Africa (2-9). The few comprehensive studies of the aetiology of meningitis in tropical Africa (2,3,5,6,10) done outside the "meningitis belt" showed **Streptococcus pneumoniae** to be the commonest etiological agent.

In temperate climates, epidemics disappeared at the beginning of this century and were replaced by sporadic outbreaks in groups of young children and adults and the causative organisms usually belong to **Neisseria meningitis** serogroups B or C (14).

Very little accurate data is available regarding meningitis in the developing world and Africa in particular. The problems of under-reporting of confirmed cases and poor diagnostic and surveillance facilities have contributed to the unavailability of data. Epidemics of meningococcal meningitis have been reported outside the "meningitis belt of Africa" with very high mortalities of 10-44% (14,18). Most of the surveillance data in Africa comes from the era prior to the HIV epidemic when there was an emphasis on paediatric and bacterial meningitis (2,3,5,6,7,8,20,21,25,26). Cryptococcosis was not specifically looked for and rarely or never commented on. Tuberculosis was not believed to play a significant role as a cause of meningitis (6,10). Cadoz et al (9) in a study in Senegal (outside the meningitis belt) over a 10 year period (1970-79) showed the

average incidence of meningitis to be 50 cases per 100 000 population. Figures for the ten year period are shown in Table 1. The overall mortality was 44,2% with 53,9% of all cases being children below two years of age.

Table 1

	Morbidity (per 1000000 per year)			Mortality (per 1000000 per year)
	Meningococcal	S. pneumonia	H.Influenzae	Total
Zaria (Nigeria)	63	12	10	110	24
Dakar (Senegal)	6	14	10	38	17
U.K.	2	1-2	2	8	1
U.S.A.	1	1	3-5	8	1

The incidence of acute bacterial meningitis in two areas of tropical Africa, one northern Nigeria within the African meningitis belt and one (Dakar) outside it. The data from Dakar cover a 10 year period 1970-1979. Estimates from the U.K. and the U.S.A. are derived from a number of studies .

Less comprehensive data collected in hospitals elsewhere in tropical Africa (2,3,5,6,10,12,20), where meningitis accounts for 1-3% of all hospital admissions, suggests that the figures obtained in Dakar are representative of the situation that prevails in other parts of tropical Africa outside the meningitis belt. Figures for the incidence of different forms of meningitis in Zaria (within the meningitis belt) are also represented in Table 1.

Estimates of the incidence of the main forms of meningitis in the United Kingdom and in the United States of america, derived from variety of sources, are also shown in Table 1. These data demonstrates the very high incidence of **Neisseria meningitis** in Zaria as compared with outside the meningitis belt. This incidence rate is greater than fifty times that of the United States of America. The incidence of **H.Influenzae** is probably only a little higher in tropical Africa than in the United States of America. Overall **Neisseria meningitides, Streptococcus pneumoniae** and **Haemophilus influenzae** account for about 75% of bacteriologically diagnosed cases of meningitis (before the HIV-era) throughout tropical Africa, as is the case in countries with a temperate climate. Thus it is not etiological agents but size that differentiates the problem of meningitis in Africa from that in Europe and the United States of America.

There are no common causes of meningitis in tropical Africa that are not found elsewhere. However, salmonella species, responsible for 91 of 2 515 bacteriologically diagnosed cases of meningitis in Dakar (9) and a similar proportion of cases in a smaller series from Togo (26) are a more important cause of meningitis in tropical Africa than in industrialised countries.

The incidence of pneumococcal meningitis in tropical Africa (2,3,6,9,10,18,20,26,27,28) is higher than in temperate countries (15,16,29,31,31). A factor is thought to be the strong association between sickle cell disease and pneumococcal meningitis found throughout tropical Africa. At Kinshasa in Zaire, the haemoglobin genotype SS was found 28-times more frequently among children with pneumococcal disease than among controls (27). At Dakar a 14-fold difference between patients and controls was found (9). A characteristic feature of pneumonococcal meningitis in tropical Africa is its high mortality, averaging around 40% (2,6,9,11,20,27,28). A mortality of 40-50% is about twice as high as that recorded in most studies from industrialised countries (15,16,29,31,32) although there have been occasional reports of higher mortality among patients studied in Europe (19) and in the United States of America (22). In the latter study, many of the patients were black and the in USA, morbidity and mortality from pneumococcal disease are in general higher in blacks than in whites (30). The high mortality from pneumococcal meningitis in tropical Africa may be simply a reflection of late diagnosis and poor medical care, but whilst these factors may play a role, they do not seem to be

the only explanation. A number of studies have shown that mortality from pneumococcal meningitis is highest among those with a short history. Furthermore mortality from meningococcal meningitis in tropical Africa (24) is in general similar to that in series done in Europe and the USA (15,16,29,31,32) indicating that many African centres can provide adequate care for patients with severe infections.

Human Immunodeficiency Virus (HIV) and Meningitis

Infection with the Human Immunodeficiency Virus (HIV) has a profound effect on cell-mediated immunity and thus increases the risk of diseases caused by pathogens that are held in check by this arm of the immune response. Central nervous system (CNS) complications are often observed in patients infected with HIV. The most common causes include primary disease due to HIV and other infectious agents such as Mycobacterium tuberculosis, Toxoplasma and Cryptococcus neoformans.

HIV is known to infect T -lymphocytes and macrophages, altering B-cell function and thus increase a patient's risk of bacterial infection (33-35). Gilks et al (71) in a surveillance study in Kenya (East Africa) found a significantly higher rate of streptococcus pneumonia and salmonella typhimurium bacteraemia among HIV-positive patients. Pallangyo et al (78) in a recent study in Tanzania (East Africa) did not find an association

between HIV-infection and pyogenic meningitis (HIV-infected 24% vs non-HIV-infected 17%). However, they found a significantly higher mortality rate in the HIV-seropositive group with pyogenic meningitis, especially pneumococcal meningitis. Reports on the impact of HIV infection on the pattern of meningitis have otherwise concentrated mainly on **Mycobacterium tuberculosis** and **Cryptococcus neoformans** (38,39,40,41,42,43). Epidemiological information strongly suggests an association between HIV and Tuberculosis. In 1985 the Centres of Disease Control (CDC) modified the definition of AIDS to include extra pulmonary tuberculosis in any person known to be seropositive for HIV (36). This has recently been modified to include all cases of tuberculosis. Mann et al (1986) in a study in Zaire (37) found 30% of patients diagnosed as cases of tuberculosis to be HIV positive. Epidemiological data in Zimbabwe has shown a doubling of tuberculosis cases from 4 759 in 1985 (56 per 100 000 population) to 115 000 cases in 1991 (118 per 100 000 populations) (65). This increase is more marked in the adult population aged 25 to 55 years. With a 40-60% seroprevalence rate for HIV-infection among the tuberculosis cases, the HIV epidemic has been found to be the most important reason for this increase (64,65). Similar figures have been reported in the United States of America, where an increase , thought to be due to HIV, in the incidence of tuberculosis has been noted. Although **M.tuberculosis** has been described as causing central nervous system manifestations in patients with HIV, reports are scarce and limited to case reports or short series of patients (39,40,42).

One of the few large series reported by Berenguer et al (43) from two large referral hospital in Madrid (Spain) found that all tuberculosis meningitis cases during the study period, 59% occurred in patients with HIV infection. Also central nervous system involvement of patients with tuberculosis was five times higher in sero-positive than in sero-negative patients. However, most studies have shown that infection with HIV does not appear to change the clinical manifestations or the outcome of tuberculous meningitis (39-43).

Cryptococcal meningitis has been reported as one of the most important neurological manifestations of AIDS and that it ranks third in frequency to the HIV-Virus itself and toxoplasmosis in infectious agents causing neurological disease in patients with AIDS (44,45). Meningitis is the most common manifestation of cryptococcosis. It may occur at any time during the course of HIV infection, either as the initial opportunistic infectious disease or as a later complication in cryptococcal meningitis presenting as the first opportunistic infection (46,47). The incidence of HIV related cryptococcosis in different Central African countries has been reported to be as high as 13 to 35% (55,56). This is thought to be due to the prevalence of Cryptococcus neoforman in the domestic and general environment (48,51). In North America, cryptococcal meningitis is a frequent manifestation of AIDS occurring in about 7% of AIDS cases (53,54,55).There have been case reports from the North American literature suggesting an increase in Salmonella meningitis in HIV

infected patients (57). Salmonella infections have been reported to be 20-100 fold more common in AIDS patients than in the general population, with bacteraemia occurring n 50-75% (58,71). Although the pathogenesis of salmonella meningitis in AIDS is unknown, it is probably associated with bacteraemic seeding of the CSF. Prevalence of salmonella infections is much higher in the African tropical environment than in temperate climates and a correspondingly higher incidence of salmonella meningitis has been reported from Africa (9,26) before the AIDS era. There is however no up-to-date literature from Africa to indicate that impact HIV-infection has had on the prevalence of salmonella meningitis.

MATERIALS AND METHODS

Study Population

All patients, 18 years of age or above, on the day of presentation to hospital, admitted with a clinical diagnosis of meningitis to adult medical wards at Parirenyatwa hospital, (Harare) and fulfilling the criteria described below. Cases were recruited consecutively over a six month period (1 November 1992 to 30 April 1993).

Inclusion Criteria

1. All sequential patients admitted to the adult medical wards through casualty or out-patients departments of Parirenyatwa hospital with the presence of any two of the following symptoms:-
   - (i) fever
   - (ii) headache
   - (iii) photophobia
   - (iv) stiff neck
   - (v) fits
   - (vi) confusion

The above criteria were chosen so as to include as many atypical presentations as possible eg. the patient with an unexplained fever who has cryptococcal meningitis.

2. Informed consent to enter the study .

3. Informed consent have an HIV-test

4. 18 years of age or above on day of admission.

Exclusion Criteria

A clinical picture suggesting a diagnosis other than meningitis e.g. Sub-arachnoid haemorrhage.

STANDARD CASE MANAGEMENT

A detailed baseline examination including both clinical and laboratory parameters was performed on all patients at the time of admission.

Clinical

The following data was recorded:

1. Name, age, sex and the hospital case file number.

2. Baseline clinical data including headache, neck pain photophobia, vomiting, fever, seizures (focal and/or generalised) and confusion and the duration of each at presentation.

3. Any medication taken by the patient, especially antibiotics, prior to presentation for admission.

Definition of Meningitis

For the purpose of analysis meningitis was defined as either

(i) CSF changes indicating meningeal inflammation (a protein >0.45 g/l and/or glucose CSF/plasma ratio < 50% and/or CSF glucose <2.1 mmol and/or CSF leucocytosis > 5 cells/ml) or by finding Acid alcohol fast bacilli, cryptococci or bacteria in the CSF.

Laboratory Data

Baseline full blood count including differential white count, urea and electrolytes, blood glucose were done on all patients. Also included in the work-up were chest X-ray and Human immunodeficiency Virus (HIV)-Serological test. HIV serodiagnosis was performed using a double ELISA technique as per national guidelines (Vironostika HIV MIXT, Organon Teknika B.V. and Enzynost Anti-HIV-1-HIV-2, Behring). Equivocal results were checked by repeating the double ELISA and if further doubt occurred, using a Western Blot (Ancoscreen immunoblot assay for HIV-1 and HIV-2, Ancos).

Definition of Specific types of meningitis

i) Cryptococcal Meningitis: evidence of cryptococcal infection as shown by positive India Ink, culture and or antigen test on CSF.

ii) **Pyogenic Meningitis:** typical CSF [Pleocytosis >5/ml and mainly polymorphs; CSF glucose <2,1 mmol/l or <50% of blood glucose, CSF protein >0,45 gl/l], positive gram stain or culture and/or antigen test.

iii) **Tuberculous Meningitis:** typical CSF changes (Glucose <2,1 mmol/l or 50% of blood glucose, pleocytosis > 5 cells/ml and mainly mononuclear cells, protein > 0,45 g/l) positive culture, without evidence of pyogenic or cryptococcal meningitis.

All CSF samples were then examined by standard methods (77) including cell and differential count estimation, glucose content and protein level. Since diagnostic usefulness of staining procedures depends on the concentration of organisms on the CSF of patients with meningitis, all CSF samples were centrifuged prior to staining and culture of the deposit. Gram and Ziehl-Neelsen stains and an India Ink preparation were done on all centrifuged deposits of CSF. Phillips and Millan (74), as well as other worker (75,76) found a high percentage of positive culture results in bacterial meningitis

patients with CSF cell counts of <10 leucocytes/mm^3. All deposits were thus cultured on blood agar and enriched chocolate agar. The plates were incubated overnight at 35°C in a CO_2 enriched atmosphere using candle (extinction) jars. If no growth was apparent after overnight incubation, the plates were re-incubated for a 48 hours before being discarded as negative. CSF samples with abnormal cell counts (white cell count $\geq$ 5 per mm^3) and or abnormal biochemical results were cultured on the Lowenstein Jensen medium. Isolated bacteria were identified by standard methods (2) and sensitivity to chemotherapeutic agents was determined by the disc diffusion method.

Bacterial antigen test using Latex agglutination method (Bactigen, Wampole Laboratories, Cranburg, N.J) for **Haemophilus influenzae, Neisseria meningitis** serogroups A,B,C,Y W135 and **Streptococcus pneumoniae** as has been recommended by other authors (74,75) was carried out on all CSF samples with cell counts and/or biochemical findings suggestive of meningitis. Lymphocyte phenotyping was performed by an APAPP (alkaline phosphatase, anti-alkaline phosphatase), technique (monoclonal Dako-T_4 and T-8 and APAPP, mouse, monoclonal Dakopatts). Absolute T-helper CD_4+ cells were calculated by multiplying the percentage of CD_4+ cells by the percentage lymphocytes in the differential white cells counts and by the total white cell count.

Statistical Analysis

Statistical analysis was performed by Epi-info software. Tests included Chi-square (Yates corrected), Fisher's exact test and Krusskal Wallis.

RESULTS

Over a six month period (from 1 November 1992 to 30 April 1993) of 285 patients who had a lumbar puncture 65 had meningitis. The majority of the remaining 220 cases had a lumbar puncture as part of either a neurological work-up (60 cases) or investigation of fever (160 cases).

Table 2 shows the age, sex, HIV-seroprevalence and CD_4 Counts by type of meningitis. Of the 65 cases, 53 (82%) were male. The average age for all cases was 32 years (Range 20-61). There was no statistically significant difference in sex and age distribution among the different types of meningitis. The overall HIV-seroprevalence was 86% (100% of cryptococcal, 88% of the tuberculous and 53% of the pyogenic meningitis cases). HIV-seroprevalence in the pyogenic group was lowest and this was statistically significant when compared to cryptococcal meningitis ($p<0.0001$; 2 tailed Fisher exact test) but not in comparison to tuberculous meningitis ($p = 0,0538$). Results of CD_4 counts were available from 16/34 (47%) cryptococcal meningitis cases, 6/61 (38%) cases of tuberculous and 7/15 (47%) pyogenic meningitis cases . The mean CD_4 count in the tuberculous meningitis group (275 cell/ul) was higher by 131 cells/ul than that for the cryptococcal meningitis group (144 cells/ul) however this did not quite reach statistical significance ($p = 0,0591$; Kruskal Wallis).

There was no statistically significant difference in mean CD_4 Counts between cryptococcal and pyogenic (p = 0,8431) as well as between pyogenic and tuberculous (p = 0,1967) meningitis cases.

The cases of pyogenic and tuberculous meningitis were split into HIV-positive and negative sub-groups then compared for sex, age, CD_4-counts and CSF results (white cell count, protein and glucose concentrations) distribution. There was no statistically significant difference between these small groups.

Cryptococcal Meningitis

Cryptococcal meningitis was the commonest (34 cases = 54%) type. All cases were HIV positive and the average age was 32 years (range 25 - 50) and a male to female ratio of 4,7:1. In 27 cases both India Ink and culture were positive. The remaining 7 cases (21%) were India Ink negative but Culture positive for *Cryptococcus neoformans*. Of note was that 4/34 (12%) of cases with culture positive cryptococcal meningitis had normal CSF glucose, protein and white cell count.

Chest X-rays were available from eighteen cases, twelve of which were normal.Four X-rays showed bilateral hilar lymphadenopathy with normal lung parenchyma. Two cases had bilateral mid zone reticulo-nodular shadowing and one of these was positive for *Cryptococcus neoformans* on broncho-alveolar lavage.

Tuberculous Meningitis

The diagnosis was made in 16 cases (27%). The basis for the diagnosis was; typical CSF changes (glucose <50% of blood glucose or CSF glucose <2,1 mmol/l, protein >0,45 g/l, pleocytosis > $5mm^3$ with >50% being mononuclear cells). Without evidence of pyogenic or cryptococcal meningitis. The average age was 35 years (range 20 - 61) with a male to female ratio of 7:1, HIV-seroprevalence of 14/16 (88%) and then mean CD_4 count was 275 cells/ul. CSF Culture was positive for M.tuberculosis in only one case (1/12 = 8%). (Due to technical problems, culture results were not available on 4 cases).

Chest X-rays were available on ten patients, six of which were normal. Three of the abnormal X-rays showed bilateral hilar lymphadenopathy and one showed right upper zone consolidation.

Pyogenic Meningitis

All the fifteen cases diagnosed were due to Streptococcus pneumoniae . The average age was 30 (range 21-40) with a male to female ratio of 4:1 and 8/15 (53%) tested positive for HIV-infection. The mean CD_4 Count was 116 cells/ul. In eight cases the diagnosis of S.pneumoniae was established on positive Gram Stain and culture. Three cases with negative Gram Stain were positive at culture. The remaining four cases

had negative Gram Stain and culture results but positive antigen test. All blood culture results (15) were negative whilst 11 cases had positive CSF /culture and pneumococcal antigen testing was positive in all 15 samples. Four cases had received antibiotics before presenting to hospital. All the culture positive samples were sensitive to penicillin.

CSF Results

Table 3 shows CSF results by type of meningitis describing the rate occurrence of: raised white cell count, raised protein and low glucose. Raised CSF white cell counts occur more commonly in pyogenic meningitis (100%) and tuberculous meningitis (100%) with cryptococcal and pyogenic having a lower rate of occurrence (56%). The difference was significant when comparing both cryptococcal and pyogenic meningitis ($p<0,00072$) and Cryptococcal and tuberculous meningitis ($p<0,00009$) but not pyogenic and tuberculous meningitis ($p = 0,05515$). counts of <5 cell/mm^3 were seen in 44% of the cryptococcal meningitis cases , only two cases (6%) had white cell counts >100/mm2 compared to 10/15 (67%) in the pyogenic group and 8/16 (50%) in the tuberculous meningitis group. All the five cases in the pyogenic meningitis group with white cell counts of below 100/mm^3 had received antibiotics before presenting to hospital.

Protein

Five cases with cryptococcal meningitis had normal protein compared to one in the tuberculous meningitis group and none in the pyogenic group. There was however no significant difference in the protein levels among the three groups.

Glucose

A wide range of CSF glucose concentrations was seen in cryptococcal meningitis cases. Almost a third (26%) of the patients had a normal CSF glucose level compared to none in the pyogenic group and 2/16 (12%) in the tuberculous meningitis group. Differences were significant only between cryptococcal meningitis and pyogenic meningitis. ($p<0,024$; Kruskal Wallis).

Clinical Features

Table 5 shows the rate of occurrence of clinical features by type of meningitis. Headache was the commonest presenting complaint and was present in all cases of meningitis. Seizures were the least frequent feature observed in pyogenic, tuberculous and cryptococcal meningitis groups (occurring in 7%, 13% and 6% respectively). When comparing cryptococcal and tuberculous meningitis, differences were signficant for neck stiffness ($p<0,0042$), Kernig's sign ($p<0,003$) and confusion

($p<0,002$) (Chi-square Yates corrected). Confusion was a significantly distinguishing feature between pyogenic and tuberculous meningitis ($p<0,006$ Chi-square).

DISCUSSION

Several factors influence the relative occurrence of different types of meningitis. Historically important factors have included season, geographical location and age. This study looked at the aetiological pattern of meningitis in adult Zimbabweans with special attention to the influence of HIV-infection.

A total of 65 cases were diagnosed as having meningitis. The average age was 32 (Range 20-61) and the HIV seroprevalence rate was 86%. The age distribution of the cases corresponds with the age bracket [20-40 years] with the highest incidence of HIV-infection/AIDS in the general Zimbabwean population (59). Cryptococcus neoformans accounted for 52% of the cases, followed by tuberculous meningitis (25%) and pyogenic meningitis (23%) which were all due to Streptococcus pneumoniae. The diagnosis of tuberculous meningitis was presumptive (typical CSF changes and no evidence of other pathogen). This definition is limited in that a missed microbiological diagnosis could have been classified as Tuberculous meningitis e.g. early Cryptococcal meningitis or partially treated gram negative meningitis. The definitive diagnosis of tuberculous meningitis depends on culture of mycobacteria from CSF a technique which unfortunately is also known to give false negative results (70). Only 1/12 (8%) culture was positive for tubercle bacilli. Polymerase chain

reaction would be ideal in diagnosing tuberculous meningitis (68) but the method was not available for the purpose of this study.

Previous surveillance studies in Africa, which are all from an era prior to the HIV-epidemic, showed Streptococcus pneumoniae to be the commonest cause of meningitis in adults with N.Meningitides, H.Influenzae and other (mainly Gram negative organisms) following in that order (2-7,9). In these earlier studies there was an obvious emphasis on bacterial meningitis. Cryptococcosis was not specifically looked for and tuberculosis was not believed to play a significant role. HIV-infection has changed the whole pattern of meningitis. There has been a dramatic increase in cryptococcosis and extrapulmonary tuberculosis reported in different African Studies (49-52,65,66). Gilks et al 1990 and 1991 (71,72) in Surveillance Studies in Kenya (East Africa) reported a general increase in bacteraemia among HIV-seropositive patients and in particular a higher rate of pneumococcal and **Salmonella typhimuirium** bacteraemia (HIV-seroprevalence 50% and 91% respectively). He however did not find an association between HIV-infection and meningococcal disease in adults. In this study, all cases of pyogenic meningitis were due to S.pneumoniae (HIV-seroprevalence 53%).

Interestingly, other bacterial meningitides (e.g. gram negative bacilli) or cases of aseptic meningitis were not

that it occurred with a frequency far higher than that of **Cryptococcus neoformans** or other identifiable organism. Cryptococcosis is a well recognised AIDS complicating opportunistic fungal infection. Its prevalence in AIDS patients living in or recently emigrated from central Africa has been reported to be as high as 13-35% (69). An explanation proposed to explain the high prevalence of cryptococcosis in AIDS patients from Central Africa has been the frequent exposure to saprophytic sources(48).

The commonest presenting features in this study were headache, neck stiffness, photophobia and Kernig's sign.Overall it was difficult to distinguish the types of meningitis on clinical grounds.However, features of meningism (Neck stiffness and Kernig's sign) were absent in 26% and 35% of the cases of cryptococcal meningitis respectively. This was statistically significant when compared to cases of pyogenic meningitis but not against tuberculous meningitis. Previous authors have stressed the point that cryptococcal meningitis may resent in an indolent manner or as an acute illness (46,47,67). In these series meningism occurred in only 30%, and photophobia in 20% and 10% of cases of cryptococcal meningitis were asymptomatic.Alteration of mental status previously reported as rare in cryptococcal meningitis (46,47) was present in 44% of the cases in this study and the difference was statistically significant when compared to pyogenic meningitis. Observations made in this study support

the general impresion in the literature that the presence of unexplained fever, headache or confusion in an individual at high risk of HIV infection should signal the need for a lumbar puncture.

A comparison of HIV positive and negative cases with pyogenic and tuberculous meningitis did not yield any distinguishing physical features. Results from recent studies [Berenguer et al 1992 (43), Dube et al 1992 (42), Richard et al 1989 (41)] looking at tuberculous meningitis have also shown that the clinical manifestations of tuberculosis do not seem to be modified by HIV infection. However in this study, the small sample size especially in the HIV negative group with tuberculous meningitis, could have easily masked any potential differences.

CSF pleocytosis could distinguish between cryptococcal and pyogenic meningitis as well as cryptococcal and tuberculous meningitis . Of particular interest is that 44% of the cases with cryptococcal menigitis had <5 white cell/mm^3. Compared to the other two groups cryptococcal meningitis patients were more likely to have normal CSF protein and glucose. Zuger et al (1986) and Kovacs et al (1988) in their series highlighted that patients with AIDS and cryptococcal meningitis often have a striking lack of inflammatory response to the disease. Up to 65% of cases in Kovacs' series (46) had a CSF white cell count <5mm^3. Similarly deranged CSF glucose and protein levels

were found in only 60-73% of cases . A normal or slightly abnormal CSF white cell count, protein and glucose level in patients with AIDS and suspected cryptococcal meningitis thus do not exclude the diagnosis. In this study 4/34 (12%) of cases with culture positive cryptococcal meningitis had normal CSF glucose, protein and white cell count. Greater diagnostic reliance should thus be placed on more specific tests for C.neoformans (India Ink stain, CSF culture and antigen test on both serum and CSF). Unfortunately Kits for doing cryptococcal antigen tests were not available. There is evidence in the literature that commercial latex antigen testing for Cryptococcus neoformans in both CSF and serum is highly sensitive (Detects >90%) and of particular significance is that India Ink and culture negative specimens can still be antigen positive (46,47,67). Analysis of serum for cryptococcal meningitis has been shown to be probably the most useful single diagnostic test (67). These findings demonstrate the need to culture all suspected cases of cryptococcal meningitis even in the absence of other CSF abnormalities.

The entity of extraneural cryptococcosis occurring in 20-60% of cases is well recognised in the literature (46,54,67). Common manifestations are skin, lungs, liver, bone marrow and urogenital system. Only one case of extraneural cryptococcosis (pulmonary) was documented in this study.

The fact that extraneural cryptococcosis is rarely considered as a diagnostic possibility and antigen testing is not done routinely, are partly responsible for the low pick-up rate of extra neural cryptococcosis.

A comparison of CSF findings in HIV positive and negative cases of tuberculous meningitis was statistically insignificant. The small sample size, in particular in the HIV negative tuberculous meningitis group (two) would account for this. There is however evidence in the literature that CSF findings are quite similar when comparing the two groups (42,43), although normal protein concentrations occurred with higher frequency in patients with HIV-infection and a higher incidence of intracerebral mass lesions in the HIV-infected individual has been reported (43).

CSF findings in the pyogenic meningitis group were quite similar when comparing HIV-positive and negative patients. This could be a reflection of a not so significant degree of immunosuppression in the HIV-infected individuals. Although this is not confirmed by the CD_4 Counts in this study, the small sample size could potentially mask differences.

Mean CD_4 Counts of the tuberculous meningitis group were higher than the cryptococcal group by 131 cells/ul. Although this did not reach statistical significance, it suggests a less

degree of immunosuppression in the tuberculous group. Similar to the observation of less marked inflammation in HIV-positive cases of cryptococcal meningitis, there are reports in the literature confirming that HIV-infected patients with tuberculous meningitis generally have higher CD_4 counts than those with Cryptococcal meningitis (42,47,53). The low CD_4 counts observed in HIV-negative patients with pyogenic meningitis (4 cases) are probably due to the severe infection and this is well recognised in the literature. Comparison of CD_4 counts in HIV-infected cases of pyogenic meningitis (3 cases) with the other two categories (tuberculous and cryptococcal) interestingly did not show statistically significant difference. The figures were too small to allow any meaningful conclusions.

CONCLUSION

There has been a dramatic shift in the aetiological picture of meningitis in adults with **Cryptococcus neoformans** accounting for the majority of cases (54%), **Mycobacterium tuberculosis** (25%) and **S.pneumoniae** (23%). The high HIV-seropositivity (82%) is responsible for the change in pattern.

Clinical features are not very helpful in differentiating types of meningitis as well as HIV-infected from non-HIV-infected cases. However, the study demonstrated the paucity of features of meningism and mild or absence of CSF-inflammatory response in cryptococcal meningitis. Thus a high degree of suspicion is required. The study shows there is need for change in policy in investigating suspected cryptococcal meningitis, i.e. to culture all CSF specimens even when India Ink is negative and or there is no inflammatory response. Antigen testing of both CSF and blood should provide the highest pick-up rate for cryptococcal meningitis and thus needs to be incorporated into future research.

The challenge in improving the diagnosis of tuberculous meningitis remains. The use of polymerase chain reaction and thorough microbiological techniques should be the way forward.

Table 1 Age and sex distribution by type of meningitis

	Cryptococcal meningitis	Pyogenic meningitis	Tuberculous meningitis	All types of meningitis
Average age (range)	32 (25-50)	30 (21-40)	35 (20-61)	32 (20-61)
Sex ratio (M:F)	4.7:1	2:1	7:1	4:1
HIV rate (%)	34/34 (100)	8/15 (53)	14/16 (88)	56/65 (86)
Total cases	34	15	16	65

Table 2 csf results by type of meningitis describing rate of occurence of feature

	cryptococcal meningitis rate (%)	pyogenic meningitis rate (%)	tuberculous meningitis rate (%)	all types of meningitis rate (%)
leucocytosis (≥ 5 cell/ml)	19/34 (56)	15/15 (100)	16/16 (100)	50/65 (77)
PMN* count >50%	0/21 (0)	14/15 (93)	0/16 (0)	14/52 (27)
raised protein (≥0.45 g/l)	29/34 (85)	15/15 (100)	15/16 (94)	59/65 (90)
decreased glucose (ratio <50% or <2.2 mmol/l)	25/34 (74)	15/15 (100)	14/16 (88)	54/65 (83)
India ink	27/34 (79)	0/15 (0)	0/16 (0)	34/65 (52)
gram stain	29/34 (85)	8/15 (53)	0/16 (0)	37/65 (57)
antigen test	N/A	15/15 (100)	N/A	N/A
culture	34/34 (100)	11/15 (73)	1/12 (8)†	43/61 (70)

*polymorphonuclear leukocytes
†cultures not taken in 4 cases

Table 3 csf results by type of meningitis and HIV serostatus with average white cell count per millitre and protein and glucose concentrations (range in brackets)

	cryptococcal meningitis ave. (range)			pyogenic meningitis ave. (range)			tuberculous meningitis ave. (range)		
	HIV+	HIV-	Total	HIV+	HIV-	Total	HIV+	HIV-	Total
csf white cell count per ml	43 (0-720)	N/A	43 (0-720)	552 (21-2000)	340 (35-995)	453 (21-2000)	99 (6-200)	181 (22-240)	109 (6-340)
protein (g/l)	0,97 (0,24-3,4)	N/A	0.97 (0.24-3.40)	3.62 (1.52-9.38)	2.46 (0.72-4.43)	3.08 (0.72-9.38)	3.06 (0.54-7,03)	1,49 (0,43-2,54)	2.86 (0.43-7.03)
glucose (mmol/l)	2,0 (0,1-4,2)	N/A	2.0 (0.1-4.2)	1,2 (0,1-2,5)	1,7 (0,8-2,8)	1.4 (0.1-2.8)	1,1 (0,2-2,6)	2,8 (1,9-3,7)	1.3 (0.1-2.8)

Table 4 rate of occurence of clinical features by type of meningitis

	cryptococcal meningitis rate (%)	pyogenic meningitis rate (%)	tuberculous meningitis rate (%)	all types of meningitis rate (%)
Headache	34/34 (100)	15/15 (100)	16/16 (100)	65/65 (100)
Neck pain	27/34 (79)	13/15 (87)	13/16 (81)	53/65 (82)
Photophobia	15/34 (44)	10/15 (67)	12/16 (75)	37/65 (57)
Vomiting	7/34 (21)	2/15 (13)	3/16 (19)	12/65 (18)
Fever	6/34 (18)	12/15 (80)	7/16 (44)	25/65 (38)
Seizures	2/34 (6)	1/15 (7)	2/16 (13)	5/65 (8)
Neck stiffness	25/34 (74)	15/15 (100)	15/16 (94)	55/65 (85)
Kernig's sign	22/34 (65)	15/15 (100)	13/16 (81)	50/65 (77)
Stigmata of HIVinfection	24/34 (71)	3/15 (20)	9/16 (56)	36/65 (55)
Confused	15/34 (44)	1/15 (7)	9/16 (56)	25/65 (38)

LITERATURE

1. Alexander H.E. Treatment of meningitides. Advances in Paedit. 1947; 2:121-150.

2. Bhusan V and Chintu C. Changing pattern of pyogenic meningitis in Lusaka.East Africa. J.Med. 1979; 56:548-556.

3. Oladeinole Ogundi. Pyogenic meningitis in Lagos. W.Afri.Med.J. 1970; 19:90.

4. WHO epidemiological surveillance and control of CSF meningitis in Africa. WHO Chron. 1973; 27:347.

5. Alausa K.D. and Osoba O.A. Aetiology of acute bacterial meningitis in Ibadan, Nigeria.J. Paediatr. 1974; 1:53.

6. Brown K.G.E. Meningitis in Queen Elizabeth Central hospital. Blantyre, Malawi. East.Afr.J.Med. 1975; 52:377-384.

7. Potter P.C.,Donald P.R.,Moodie L.,Slater C., Kibel M.A. Meningitis in Cape Town children. S.Afr.Med. J. 1984; 66:751-762.

8. Bryan J.P., de Silva H.R.,Tavares A.,Rocha H., Schield M. Aetiology and Mortality of bacterial Meningitis in North Eastern Brazil. Rev.Infect.Dis. 1990; 12:128-135.

9. Cadoz M., DenisF., Diop Mar I. Etude epidemiologique des cas de meningites purulentes hospitalises a Dakar pendant la decennie 1970-79. Bulletin de I'Organisation Mondiale de la Sante 1981; 59:575-84.

10. Foster W.D., Hawgood B.C. The aetiology and laboratory diagnosis of meningitis in Kampala. Uganda. East.Afr.J.Med. 1966; 43: 309-314.

11. Baird et al. Mortality from pneumococcal meningitis. Lancet 1976; 2: 13-44.

12. Wispeivey B., Tunkel A.R., Sheld W.M. Bacterial meningitis in adults. Infect.Dis.Clin.N.Am. 1990; 4: 645-659.

13. Greenwood B.M. Selective primary health care strategies for control of disease in the developing world XIII. Acute bacterial meningitis. Rev.Infect.Dis. 1984; 6: 374-89.

14. Peltola H. Menigococcal disease. Still with us. Rev.Infect.Dis. 1983; 5: 71-91.

15. Wenger J.D., Hightower A.W., Facklam R.R., Gaventa S., Broome C.V.Bacterial meingitis in the United State, 1986. Report of a multistate surveillance study. J.Infect.Dis. 1990; 162: 1316-1323.

16. Walter F., Schlech III, M.D., Ward J.I., Band J., Hightower A., Fraser W.D., Broome C.V. Bacterial meningitis in the United States, 1978 through 1981. The national bacterial meningitis surveillance study. J.Am.Med.Assoc. 1985; 253: 1749-1754.

17. Lapeyssonnie L. (1963) Le meningite cerebro-spinale en Afrique. Bulletin of the World Health Organisation, 28 supplement, 1-114.

18. Hutton P.W. Neurological disease in Uganda. East Afr.Med.J. 1956; 33: 210-223.

19. Ispahani P. Bacterial meningitis in Nottingham J.Hyg. (Camb) 1983; 91: 189-201.

20. Montefiore D., Alausa O.K. and Sobayo E. Pyogenic meningitis in Ibadan, Nigeria. A 15-month prospective study. Scand.J.Infect.Dis. 1978; 10: 113-117.

21. Nottidge V.A. Meningococcal meningitis in childhood. A five-year study of meningococcal meningitis in Ibadan, Southern Nigeria. J.Infection 1983; 7: 39-45.

22. Richter R.W and Brust J.C.M. Pneumococcal meningitis at Harlen hospital New York State. J.Med. 1971; 71: 2747-2754.

23. Wadely B.B. African epidemic cerebro-spinal meningitis. J.Trop.Med.Hyg. 1957; 60: 179-189.

24. Greenwood B.M., Bradley A.K., Cleland P.G., Haggie M.H.K., Hassan-King M., Lewis L.S., MacFarlane J.T., Tagi A., Whittle H.C., Bradley-Moore A.M. and Ansari Q. An epidemic of meningococcal infection at Zaria, Northern Nigeria. 1.General epidemiological feature. Trans.R.Soc.TRop.Med.Hyg. 1979; 23: 557-562.

25. Greenwood B.M., Blakeborough I.S., Bradley A.K., Wali S and Whittle H.C. Meningococcal disease and season in Sub-Saharan Africa. Lancet 1984; 1: 1139-1342.

26. Amedome A., Boulay E., D'Almeida A., Agbetra Begne P., Kekeh K and Rey M. Le meningites purulentes an Togo Med d'Afrique Noire 1980; 27: 11-13.

27. Omanga U., Ntihinyurwa M., Shako D., Muaku M.M., Shango L and Luangambi M. Aspects etiologiques et evolutifs des meningites purulentes de l'enfant a Kinshasa. Amalyse de 471 Cas.Med. d'Afrique Noire 1980; 27: 25-34.

28. Perreve C. Les menigites purulentes en Haute-Votta. These medicale. Universite de Clermont Ferrand, France (cited in Cadoz et al. 1981).

29. Davey D.G., Cruikshank J.K., McManus I.C., Mahood B., Snow M.H and Geddes A.M. Bacterial Meningitis - ten year experience. J.Hyg.Camb. 1982; 83: 383-401.

30. Henneberger P.K., Galaid E.I and Marr J.S. The descriptive epidemiology of pneumococcal meningitis in New York City. Am J Epidemiol. 1983; 117: 484-491.

31. Centres for Disease Control, Annual Summary 1983: reported morbidity and mortality in the United States of America. Morbidity and Mortality Weekly Report 1984; 32: 35.

32. Bohr V., Hansen B., Jessen O., Johnson N., Kjersem H., Kristensen H.S., Nyobe J and Rasmussen N. 875 cases of bacterial meningitis. (Part 1) J.Infection 1983; 7: 21-30.

33. Lane H.C., Maur H., Edgar L.C., Whalen G., Rook H.H., Fanci A. Abnormalities of B Cell Activation and immunoregulation in patients with the acquired immunodeficiency syndrome. N.Engl.J.Med. 1983; 309: 453-458.

34. Montagnies L., Guest J., Chamaret S. et al: Adaptation of lymphadenopathy associated views to replication in EBV transformed B lymphoblastoid cell lines. Science 1984; 225: 63-66.

35. Pahwa S.G., Quilop M.T.J., Aauge M., Pahwa R.N., Grieco M.H: Defective B-lymphocyte function in homosexual men in relative to the acquired immuno-deficiency syndrome. Am.Intern.Med. 1984; 101: 757-763.

36. Centres for Disease Control. Tuberculosis and acquired immunodeficiency syndrome - New York City. MMWR 1987; 36: 785-95.

37. Mann J., Snider D.E., Francis H., Quinn T.C., Colenbunders R.L., Piot P., Curran J.W., Nzilambi N., Bosenge N.,Malonga M.,Kalunga D.,Nzingg M.M.,Bagala N: Association between HTLV III/LAV infection and tuberculosis in Zaire JAMA 1986; 256: 346.

38. Pitchenik A.E., Burr J., Suarez M., Fertel D., Gonzalez G., Moas C: HTLV III Seropositivity and related disease among 71 consecutive patients in whom tuberculosis was diagnosed. Am. Rev.Resp.Dis. 1988; 137: 121a.

39. Bishburg E., Sunderam G., Reichman L.B., Kapila R: Central nervous system tuberculosis with the acquired immunodeficiency syndrome and its related complex. Ann Intern Med 1986; 105: 210-213.

40. Tischl M.A., Pitchenick A.E., Spira T.J. Tuberculosis brain abscess and toxoplasma encephalitis in a patient with acquired immunodeficiency syndrome. JAMA 1985; 253: 3428-3430.

41. Richard E., Chaisson and Gary Slutkin. Tuberculosis and Human immunodefiency virus infection. J Infect Dis 1989; 159(1): 96-100.

42. Dube M.P., Holtom P.D., Larsen R.A., Tuberculous meningitis in patients with and without Human immunodefiency virus infection. Am.J.Med. 1992; 93: 520-524.

43. Berenguer J. et al. Tuberculous meningitis in patients infected with the human immunodeficiency virus. N Engl J Med 1992; 326: 668-72.

44. Gobudza D.H., Hirsch M.S. Neurological manifestations of HIV clinical features and pathogenesis. Ann Intern Med 1987; 107: 383-391.

45. Levy R.M., Bredesen D.E., Rosenbaum M.L. Neurological manifestations of AIDS: experience at UCSF and review of literature. J Neurosurg 1985; 62: 475-495.

46. Kovacs A.A., Polis M., Wright W.C., Gill V.J., Tauzon C.U., Gilman E.P., Lane H.C., Longfield R., Overtierf G., Macher A.M., Fanci A.S., Parillo J.E., Bennett J.E., Masur H. Cryptococcosis in AIDS, Ann Intern Med 1985; 103: 533- 538.

47. Zuger A., Lorie E., Holzman R.S., Simberkoff M.S., Rahral J.J. Cryptococcal disease in patients with AIDS. Ann Intern Med 1985.

48. Swinne D., Deppner M., Maniratunga S., Laroche R., Flock J.J. and Kadende P.J. AIDS-associated cryptococcosis in Bujumbura, Burundi, an epidemiological study. J Med Vet Mycology 1991; 29: 25-30.

49. Desmet P., Kaumbe K and De Veroy: The Value of Cryptococcal antigen screening among HIV and AIDS patients in Kinshasa, Zaire. AIDS 1989; 3: 77-78.

50. Rinaldi M.G., Drutz D.J., Howell A., Sande M.A., Woesy C.B and Hadley W.K. Serotypes of cryptococcus neoformans in patients with AIDS. J Infect Dis 1986; 153: 642.

51. Swine D., Deppner M., Laroche R and Flock J.J. Isolation of cryptococcus neoformans from houses of AIDS associated cryptococcosis patients in Bujumbura, Burundi. AIDS, 1989; 6: 389-390.

52. Chuck S., Sande M.A. Infections with cryptococcus neoformans in the acquired immunodefiency syndrome. N Engl J Med 1989; 321: 794-799.

53. Dismukes W.E. Cryptococcal meningitis in patients with AIDS. J.Infect.Dis. 1988; 157: 624-628.

54. Eng R.H., Bishburg E., Smith S.M., Kapila R. Cryptococcal infection in patients with AIDS. Am.J.Med. 1986; 81: 19-23.

55. Piot P., Tallman B.M., Kapita N., Mbendi K., Ndangi K., Kanyembe K., Bridts C.T., Quin F.M., Feinsod W., Odio P., Mazebo W., Stevens S., Mitchell S., MacCormic: Acquired immunodeficiency syndrome in a heterosexual population in Zaire. The Lancet, 1984; July 14: 65-69.

56. Katlama C., Leport C., Matheron S., Brun-Vezinet F., Rouzioux C., Vittecoq D., Lambolez T., Lebras R., Petitprez P., Offenstedt G., Vachon F., Vilde J.L., Couland J.P., Saimot A.G. Acquired Immunodeficiency Syndrome (AIDS) in Africans. Ann Soc Belce Med Tropicale 1984; 64: 379-389.

57. Traimow H.S., Wormser G.P., Coburn K.D., Small C.B. Salmonella meningitis an infection with HIV: AIDS, 1990; 4: 1271-1273.

58. Cellum C.L., Chaisson R.E., Rutherford G.W., Barnhart J.L., Echenberg D.F. Incidence of Salmonellosis in patients with AIDS. J.Infect.Dis. 1987; 156: 998-1002.

59. HIV and AIDS Surveillance Report. 1992 Annual Report (AIDS Control Programme - Ministry of Health and Child Welfare, Zimbabwe).

60. Ternouth I., Malin A., Sarbah S. The small epitrochlear node: not to be underestimated. IXth International AIDS conference, Berlin 1993, PO BO3 0954.

61. Mahomed K., Kasule J., Makuyana D., Moyo S., Mbizvo M., Tswana S. Seroprevalence of HIV infection amongst antenatal women in greater Harare, Zimbabwe, C.Afr.J.Med. 1991; 37: 322-325.

62. Kendall A.C. Acute bacterial meningitis in childhood. Centr.Afr.J.Med. 1971; 5: 98-101

63. Glyn Jones R. S.Afr.Med.J. 41, 75:1967.

64. Report of a joint government of Zimbabwe and WHO Review team. Comprehensive review of the tuberculosis programme in Zimbabwe. 24 April 1992.

65. Houston S et al. The association of tuberculosis and HIV infection in Harare, Zimbabwe. (Unpublished Data)

66. Laroche R. et al. Cryptococcal meningitis associated with acquired immunodeficiency syndrome (AIDS) in African patients: treatment with fluconazole. J.Med.Vet.Mycology 1992; 30: 71-78.

67. Patterson T.F., Andriole V.T. Current concepts in cryptococcosis, Eur.J.Clin.Microbiol.Infect.Dis 1989; 8: 457-465.

68. Kohlk et al. Detection of Mycobacterium tuberculosis in clinical samples by using polymerase chain reaction and a non-radioactive detection system. J.Clin.Microbiol. 1992; 30: 2567-2575.

69. Katlama C., Leport C., Matheron S., Brun-Vezinet C., Rouzioux C. AIDS in Africans. Ann Soc Belge Med tropicale 1984; 64: 379-389.

70. Piot P., Taelman H., Kapita B.M., Mbendi N., Ndangi K., Kayembe K. AIDS in a hetero-sexual population in Zaire. The Lancet, 1984: 65-69.

71. Gilks C.F. et al. Life threatening bacteraemina in HIV-1 seropositive adults admitted to hospital in Nairobi, Kenya. Lancet; 1990, 336: 545-549.

72. Gilks C.F., Bundde R., Simani P., Newnham R., Waiyaki R. No association between meningococcal disease and human immunodeficiency virus in adults in Nairobi, Kenya; Trans Roy Soc Trop Med. Hy 1991; 85:651.

73. Karamandis D., Shulman J.A. Recent survey of infectious meningitis in adults. Review of laboratory findings in bacterial, tuberculous and aseptic meningitis. South. Med. J. 1976; 6: 449-457.

74. Phillips S. and Millan J.C. Reassessment of Microbiology protocol for CSF specimens. Lab Med 1991; 22:619-622.

75. Onorato I.M., Wormer G.P., Nicholas P. Normal CSF in bacterial meningitis. JAMA 1980; 244: 1469-1471.

76. Polk D.B and Steele R.W. Bacterial Meningitis presenting with normal cerebrospinal fluid. Paediatr Infect Dis 1987; 6:1040-1042.

77. Gray L.D and Steele R.W. Laboratory diagnosis of bacterial meningitis. Clin Microbiol Rev 1992; 5: 130-145.

78. Pallangyo K., Hakansson A., Mtesa M., Lera L., Murjas J., Bredberg P., Rader U., Mhalu F., Bitefeld G., Britten S. High HIV-seroprevalence and increased HIV-associated mortality among hospitalised patients with deep bacterial infections in Dar-es-Salaam. Tanzania. AIDS 1992; 6: 971-976.