PROFILE OF ACUTE BACTERIAL MENINGITIS IN CHILDREN AGED BETWEEN 1 AND 59 MONTHS ADMITTED TO THE PAEDIATRIC WARDS AT THE UTH, LUSAKA.

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CONTENTS

		Pages
COPYRIGHT		v
DECLARATION		vi
APPROVAL		vii
ABSTRACT		viii
ACKNOWLEDGEMENT		x
GLOSSARY		xi
CHAP 1	**INTRODUCTION**	
1.1.0	Background	1
1.1.1	Etiology	2
1.1.2	Pathophysiology	6
1.1.3	Clinical Features	9
1.1.4	Diagnosis	10
1.1.5	Complications	11
1.2.0	Literature Review	13
1.3.0	Study Justification	22
1.4.0	Study Hypothesis	24
CHAP 2	**STUDY OBJECTIVES**	25
2.1	General Objectives	25
2.2	Specific Objectives	25

CHAP 3	**METHODOLOGY**	26
3.1	Study Design	26
3.2	Study Site	
3.3	Study Duration	26
3.4	Study Population	27
3.5	Subject Selection	27
3.6	Sample Size and Sampling	27
3.7	Study Procedure	28
3.8	Laboratory Management	29
3.9	Data Collection and Analysis	31
3.10	Ethical Considerations	32
CHAP 4	**RESULTS**	33
4.1	Socio-demographic Aspect	33
4.2	Clinical Parameters	38
4.3	Laboratory Results	43
CHAP 5	**DISCUSSION**	50
5.1	Socio-demographic aspect	50
5.2	Clinical Manifestations and Outcome	53
5.3	Laboratory Results	55
CHAP 6	**CONCLUSIONS**	58
6.1	Conclusions	59
6.2	Recommendations	59

6.3 Study Limitations 60

I. REFERENCES 61

II. APPENDICES 68

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DECLARATION

I hereby declare that this dissertation represents my own work and has not been presented either wholly or in part for a degree at the University of Zambia or any other university.

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ABSTRACT

A hospital based descriptive, prospective study on the **profile of acute bacterial meningitis in children aged between 1 and 59 months admitted to the paediatric wards at the UTH, Lusaka** was carried out in the Department of Paediatrics and Child health, University Teaching Hospital, Lusaka from 1st April 2002 to 31st December 2002 (9 months).

The objectives of the study were to determine the prevalence of acute bacterial meningitis, the social status of affected children, the clinical features, the common causative pathogens and their antibiotic sensitivity, and finally, to document Immediate complications.

Out of 210 children admitted with a provisional diagnosis of acute bacterial meningitis, only 92 were eligible for the study.

It was found that socioeconomic and demographic factors have a bearing on the incidence of acute bacterial meningitis in children who, most of them, lived in highly populated areas and overcrowded families (average family size: 6.2 persons) without adequate sanitation (61.5%) and source of clean water (81.3%).

There was no sexual predilection, with the male to female ratio of 1.1: 1.

Four in five patients admitted with acute bacterial meningitis had received an antibiotic before being referred to UTH, with penicillin being the most administered antimicrobial.

The mean duration of illness prior to admission was 6.2 days with 85% of patients having been admitted within the first one week of illness.

The commonest presenting complaints were body hotness (96.7%), neck stiffness (69.6%), excessive crying (59.8%), fits (56.5%) and bulging of anterior fontanel (42%).

On examination:

Neck stiffness (83,7%), bulging of anterior fontanel (51.6%) and seizures (41.3%) were the positive signs of meningeal irritation.

Pneumonia (18.5%) was the most common condition besides meningitis, emphasizing the septicaemic nature of the illness.

The most common pathogens isolated were *S.pneumoniae* (61.9%), *H.influenzae* (19.5%), *N. meningitidis* (9.8%).

Penicillin and chloramphenicol still show good efficiency against these common pathogens, whereas ampicillin appeared to no longer be effective against haemophilus.

Hypertonia was the common immediate event (20.7%) and the case fatality rate was 27.2%.

The duration of the illness prior to admission did not seem to singularly determine the outcome.

ACKNOWLEDGEMENT

Special thanks to Dr B.C Amadi for encouraging me to take up this study and rendering me the support and guidance I needed to complete this work.

My gratitude to Professor G J Bhat for his words of guidance and encouragement.

To all the senior consultants in the Department, for their valued advise, I am greatly indebted to you.

To fellow doctors who have embraced me and made me feel at home by their friendship and support, I thank you all.

To the nurses, ward clerks who kindly provided me with the information I needed to complete this work, thank you for your support.

To the maids and porters who, at awkward time and against all odds, made sure the specimen reach the laboratory, may the Good Lord be with you.

At last, to my dear wife and friend Julie and "my clan" namely: Bernadette, Denis, Emile, Christian, Joshua, Amanda, Angeline and Allegra, I say: Thank you for enduring my long days away from home.

May God receive my thanks and praises for His loving kindnesses.

Jean Desire B Kabamba

October 2003

GLOSSARY

ABM: Acute Bacterial Meningitis

AIDS: Acquired Immune Deficiency Syndrome

BBB: Blood Brain Barrier

CBF: Cerebral Blood Flow

CSF: Cerebro-Spinal Fluid

Hib: Haemophilus influenzae type b

UNZA: University of Zambia

UTH: University Teaching Hospital

CHAPTER 1

1.0 INTRODUCTION

1.1.0 Background

Acute Bacterial Meningitis is a pyogenic infection of the meninges (the 3 envelopes around the central nervous system) of less than 28 days duration[1].

The common pathogens, that cause acute bacterial meningitis, colonize the nasopharynx, penetrate the epithelial cells of the upper respiratory tract causing bacteraemia, and invade the central nervous system[2].

The available data based on reviews of hospitalized patients, across the world suggest that endemic acute bacterial meningitis is mostly a disease of the young infant within the first two years of life, though it can occur at any age[3, 4].

This infection is an important cause of childhood death and neurological sequelae throughout the world, though mortality related to the disease is much higher in the developing countries than the industrialized world[5, 6,7]

In developing countries with fewer resources, the incidence of the disease in children is approximately ten times greater than that in the developed countries[7].

Sequelae are reported in 15 to 20% of children in developed countries, whereas they are under-reported in developing countries[7, 8].

Between 12 and 50% of individuals with the infection die in poorly resourced countries, compared with 5% in well-resourced countries[7, 8].

1.1.1 Etiology

The most common pathogens in acute bacterial meningitis in both industrialized and developing countries are *Streptococcus pneumoniae*, *Haemophilus influenzae* type b and *Neissseria meningitidis*, although other bacteria may be implicated, especially in the neonatal period (e.g. *Listeria monocytogenes*, salmonella spp, group b streptococcus) [9-11].

1.1.1.1 *Streptococcus pneumoniae*

Of the three outstanding pathogens, ***Streptococcus pneumoniae*** (pneumococcus) is responsible for a considerable part of the disease burden in developing countries particularly in sub-Saharan Africa. Pneumococci are the leading causative agents of non-endemic meningitis and other bacteremic diseases[12, 13, 14].

Since 1967 when the first case of drug resistance strain emerged there has been an increase in the incidence of Penicillin resistance among several stains and serotypes.

However Penicillin resistance of *Streptococcus pneumoniae* may vary country to country and within the country[15].

Of the 90 known pneumococcal serotypes, 18 are responsible for 82% of cases of bacteremic pneumococcal pneumonia, with close correlation between bacteremic subtypes and those implicated in meningitis[16].

Serious infection may occur in patients with various underlying conditions, including asplenic states, splenectomy, hypogammaglobulinaemia and renal diseases due to the impairment of the opsonisation process that leads to phagocytosis of encapsulated organisms[17].

Pneumococcal vaccines have been developed and are in use predominantly in developed countries, however their prohibitive cost[18, 19] and their limited immunogenicity to some strains make their use in sub- Saharan Africa, particularly in Zambia a remote prospect.

1.1.1.2. ***Haemophilus influenzae***

Haemophilus influenzae is fastidious, Gram-negative, pleomorphic coccobacillus that requires factorX (i.e, phosphopyridine nucleotide, heat labile) for growth. This factor is found inside erythrocytes, hence the name haemophilus.

Humans are the only hosts for *Haemophilus influenzae.* It colonizes the respiratory tract in 60 – 90%. However colonization by subtype b organisms is infrequent.

The proportion of cases of invasive disease in children younger than two years of age is relatively high, with the peak attack occuring at six to twelve months of age.

Haemophilus influenzae is the second most common cause of acute meningitis in children below 5 years of age after *S. pneumoniae* worldwide.

It accounts for 100.000 to 160.000 child deaths every year in sub-Saharan Africa [20, 21, 22].

Among the six encapsulated strains (a through f), type b causes invasive disease.

However the burden of *Haemophilus influenzae* type b (Hib) disease in many developing countries has been underestimated because of technical difficulties surrounding the culture of the organism, particularly when community antibiotic use is prevalent leading to sterile cultures as is the case in Zambia[23].

Developing countries where Hib disease has been studied, it has been found to be responsible for a large proportion of meningitis cases in infancy, with incidence rates in

the first year of life much higher than those that were seen in developed countries before the introduction of Hib vaccines[24, 25].

The clinical pattern of the disease also differs. Pneumonia is commoner than meningitis in developing countries, whereas epiglotitis is rare.

Nasopharyngeal carriage of Hib is commoner and occurs in younger children in developing than in industrialized countries.

Studies from the Gambia, Senegal, Niger and South Africa have shown steady rates of *Haemophilus influenzae* type b meningitis (Hib) ranging from 50 to 60 cases per 100.000 children less than 5 years old[26].

The introduction and implementation of Hib immunization both in Western Europe and North America in the early eighties, and in some sub-Saharan countries in the mid-nineties, has brought the incidence of Hib related infections under control [27, 28, 29].

1.1.1.3 ***Neisseria meningitidis***

Neisseria meningitidis is a Gram-negative diplococcus. It is a common commensal of the human nasopharynx.

The meningococci have been divided into serogroups based on antigenic differences in their capsular polysaccharides (A, B, C, D, X, Y, Z, W-135, and 29-E).

Groups B, C, Y, and W-135 are the predominant serogroups associated with invasive disease in the developed countries, whereas the group A strain accounts for epidemic disease in many other countries, especially in the sub-Saharan Africa[30].

Neisseria meningitidis (meningococcus) is the third most common pathogen of acute bacterial meningitis worldwide. Meningococcal meningitis is endemic in the " **meningitis belt** " of *sub*-Saharan Africa (which extends from Mali eastward to Ethiopia) and occurs in outbreaks in other parts of Africa [31, 32].

Massive epidemics of meningococcal diseases occur with a periodicity of 5 to 12 years during the dry season from December to May, against a background of hyperendemic disease[33, 34].

Serogroup A has been responsible of most dramatic outbreaks of meningococcal meningitis across sub-Saharan Africa[33].

Serogroup C is occasionally responsible for epidemics in the tropical Africa (Niger, Chad, Burkinafaso and Mali) and endemic in the Meningitis belt.

Serogroup B is mainly found in Southern Africa, along the Mediterranean coast, in the Americas and Europe.

The World Health Organization (WHO) reported a total of over 700 000 cases in African countries in the 1988 – 97 ten years period. Even with appropriate treatment, 5 – 10% of patients die, and 10 – 15% of survivors suffer neurological sequelae[34].

1.1.2 Pathophysiology of Acute Bacterial Meningitis

Live meningeal pathogens are not by themselves responsible for the harmful effects on the Central Nervous System, and clinical expression of meningitis arises largely from the host immune response triggered by organisms in the subarachnoid space[35-37].
The intensity and duration of this inflammatory process will ultimately determine the severity and the outcome from the disease[38, 39].

Host exposure to a meningeal pathogen via colonization of the nasopharyngeal mucosal epithelium constitutes the initial step for development of bacterial meningitis [40,41].
Bacteria achieve invasion of mucosal epithelium, which is normally protected by secretory immunoglobulines A (Ig A), through secretion of Ig A proteases. These enzymes cleave the proline – rich hinge region of Ig A, leaving it n on-functional and allowing the pathogen to attach to the epithelium [42].

The specific patterns of invasion across the nasopharynx are thought to be different for the various meningeal pathogens. It is believed also that an antecedent viral infection of the upper respiratory tract can facilitate the invasion of the blood from colonized mucosal sites[42].
Once mucosal attachment and invasion have been achieved, the pathogen enters the intravascular space. To survive intravascularly, it must evade complement, particularly the alternative complement pathway, which represents the primary host defense against sustained bacteremia. In case of S.pneumoniae, it does so means by of its polysaccharide

capsule, specifically because C3b binds inefficiently to factor B on the pneumococcal capsular surface, activation of C5 – C9 is prevented. With sustained intravascular growth, the bacteria cross the blood brain barrier into the cerebro-spinal fluid (CSF) and meningeal inflammation ensues[42].

The release of bacterial products within the subarachnoid space initiates the pathophysiologic events leading to meningeal inflammation, subsequent cerebral edema, and alteration in CSF hydrodynamics and brain damage.

These products stimulate macrophage – equivalent brain cells (e.g.: astrocytes, microglia) and cerebral capillary endothelium to produce potent pro inflammatory cytokines, notably tumor necrosis factor – alpha (TNFalpha) and interleukin – 1 (IL – 1)[39, 42].

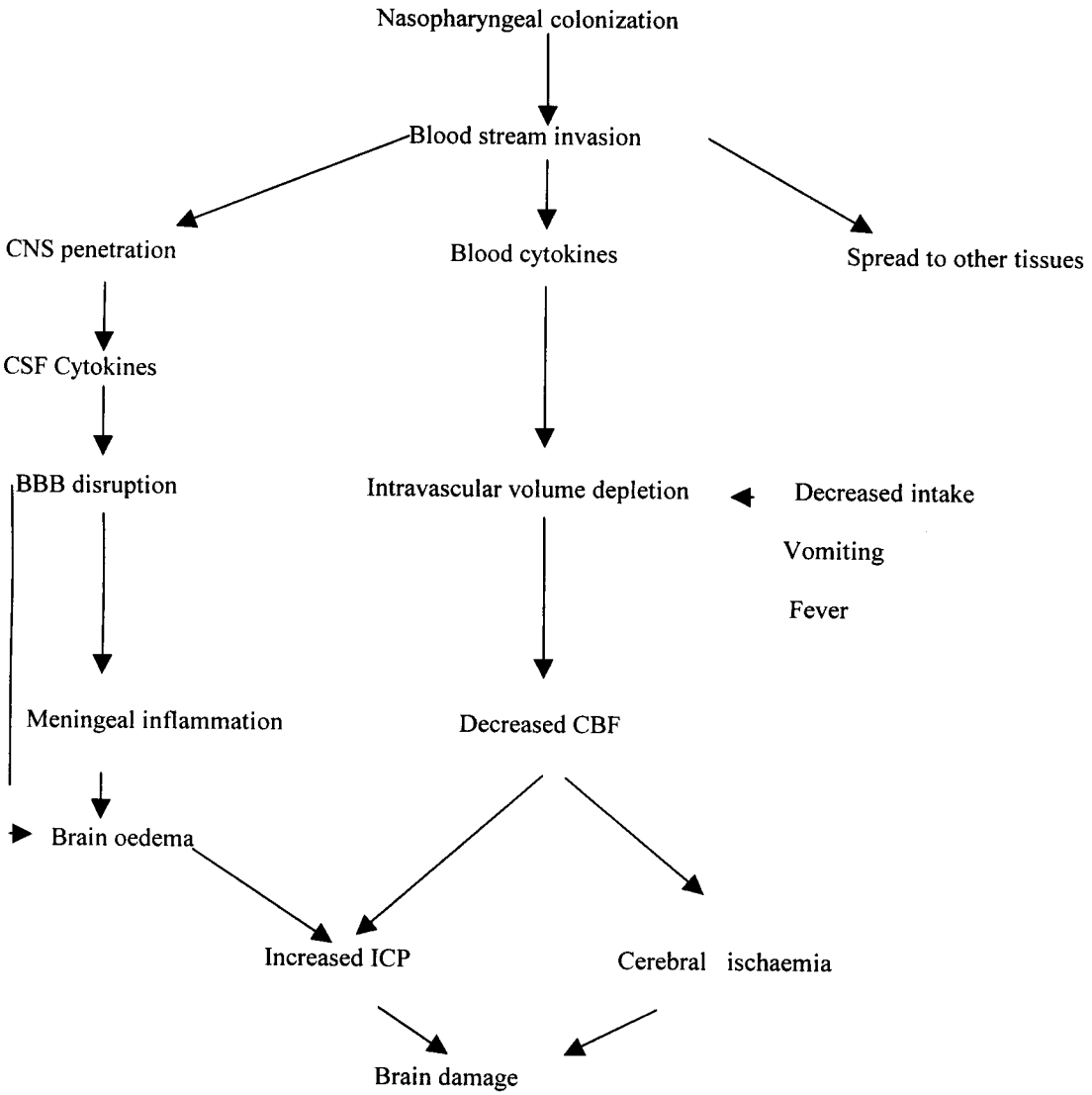
These two polypeptide mediators will activate surrounding cells to liberate other inflammatory substances (IL – 6, IL – 8, phospholipase A2, platelet activating factor, arachidonic acid metabolites, granulocyte macrophage colony stimulating factor) enhancing thus, cerebral endothelial permeability, altering cerebral blood flow and causing direct neuronal damage disrupting the blood brain barrier.

The insufficiency of humoral factors (antibody complement) and phagocytic activity in the CSF allows the bacteria to reach the subarachnoid space, multiply rapidly and produce endotoxin teichoic acid and peptidoglycans.

Following these initial steps, the pathological events of meningeal inflammation result in clinical manifestations of Central Nervous System infection.

The above events clearly explain the worsening of the patient's clinical condition after initial administration of antibiotics. This results in the release of pro-inflammatory cytokines within the vascular and subarachnoid spaces as a result of massive lysis of the invasive organism[42].

FIG. 1 PATHOGENESIS AND PATHOPHYSIOLOGY OF BACTERIAL MENINGITIS



ABBREVIATIONS: CSF: Cerebral Spinal Fluid CBF: Cerebral Blood Flow

BBB: Blood Brain Barrier ICP: Intracranial Pressure

1.1.3 Clinical features

The clinical manifestations of Acute Bacterial Meningitis are varied and depend closely on the causative organism and age of the subject. Meningococcal and pneumococcal meningitides are characterized by a sudden onset associated with rapid deterioration and may lead to death within 24 hours. On the other hand, infection caused by *H.influenzae* type b is often preceded by several days of upper respiratory tract or gastro-intestinal symptoms[43].

Fever, lethargy, irritability, poor feeding, vomiting and bulging fontanel, shock, seizures are common signs in the infant. Whereas the older child may complain of headache, neck stiffness and photophobia in addition of above symptoms.

Meningeal irritation is characterized by nuchal rigidity, back pain, photophobia, *Kernig sign* (pain on lower leg extension, with hip flexed) and *Brudzinski sign* (involuntary flexion of knees and hips with neck flexion).

However the absence of these signs does not rule out the diagnosis of meningitis.

Certain signs and symptoms may suggest a specific etiologic diagnosis. In meningococceamia with or without meningitis, a proportion of patients will present with a prominent erythematous and macular rash, especially located on the extremities, which finally will evolve into petechiae. Such a rash is also found in splenectomized patients with *S.pneumoniae* and *H. influenzae* infection[44].

Cranial nerve palsies (mainly cranial nerves II, III, IV, VI, VII and VIII) and focal cerebral signs are present in some patients [45].

1.1.4 Diagnosis

In developing countries, and Zambia in particular, the differential diagnosis of meningitis includes malaria, and a wide range of viral encephalitides[46].

The diagnosis of meningitis depends not only on the correct clinical diagnosis, but also on the performance of the lumbar puncture, and the laboratory's ability to examine and culture the cerebrospinal fluid (CSF).

The diagnosis of Acute Bacterial Meningitis is based on:

1. The history from the patient and/or guardian with above listed complaints.
2. The clinical examination, which will elicit signs of meningeal irritation; bearing in mind that meningococcal meningitis might be devoided of meningeal signs.
3. The lumbar puncture and examination of the cerebral spinal fluid (CSF):
    a) Macroscopic examination determines the fluid appearance, which may be suggestive of the diagnosis, though a clear CSF does not exclude ABM.
    b) Microscopic examination on direct smear with Gram stain for pyogenic bacteria, Ziehl Nielsen for Koch bacilli, and Indian ink for *Cryptococcus neoformans.*
    c) CSF culture identifies the causative organism.

    In our setting where, for some reasons, the lumbar puncture may be delayed, the diagnosis of meningitis can still be made based on the cellular and chemical changes, which are present in the CSF up to 44 to 68 hours after the start of antibiotic treatment. As for the culture, it will likely be negative 2 hours after parenteral antibiotics are given in meningococcal

meningitis and 6 hours in pneumococcal meningitis, irrespective of the organism sensitivity pattern [47,48].

d) CSF biochemical investigation: protein greater than 0.4g/l and glucose less than 2/3 of blood sugar are significant indicators of meningeal infection.

e) CSF cellularity of more than 10 white cells / mm^3, predominantly neutrophils.

1.1.5 Complications

- Systemic circulatory problems: Peripheral circulatory collapse most frequently associated with meningococcaemia occurs, but can accompany other types of infection[49].
- Seizures occur before, or during the first few days after admission to hospital in as many as one-third of patients with meningitis. Focal seizures are more likely than generalized ones to be forerunners of adverse neurological outcome[50].
- Focal neurological findings such as hemiparesis, quadriparesis, facial palsy, and visual field defects arise early or late in about 10 – 15% of patients with meningitis[51].
- Inappropriate secretion of antidiuretic hormone is now believed to be an appropriate host response to unrecognized hypovolemia that requires consequent use of parenteral fluids[52]. This knowledge is important because systemic blood pressure should be maintained at levels sufficient to prevent compromise of cerebral perfusion.

- Gangrene of distal extremities can occur in patients with fulminant haemorrrhagic meningococcal meningitis.
- Extension of meningeal inflammatory process can implicate the cranial nerves that course through the subarachnoid space (II, III, VI, VII, and VIII). [52]
- Hydrocephalus, of either the communicating or obstructive type, is occasionally seen in patients in whom treatment has been either suboptimal or delayed.[53]
- Subdural effusions are present in more than one-third of patients with Hib meningitis and commonly resolve spontaneously with no permanent neurological abnormalities[54].

1.2.0 Literature Review

1.2.1 Morbidity and mortality

Acute bacterial meningitis remains a dreaded infection world over despite improved therapeutic endeavors of the last decade, mainly because of its association with high risk of mortality (even under favorable conditions) and resulting severe neurological complications.

This disease is quite common in the child under five years of age, with the infant around two years of age being highly at risk. This implies that the disease process affects the developing brain leading to devastating complications.

A recent review of almost 30.000 children in 50 studies from 25 African countries found Streptococcus *pneumoniae* and *Haemophilus influenzae* type B the most commonest causes of acute bacterial meningitis, with *Neisseria meningitidis* ranked third[12].

Annually there are 400.000 cases alone of Hib meningitis in the developing world, 80 % are infants, nearly 30% die, and another 30% have major impairments [49].

A review of approximately 4100 cases of acute bacterial meningitis at Couta Maia, Brazil, from 1973 through to 1982 revealed an overall case fatality rate of 33%, with 50% of deaths occurring within 48 hours of admission [57].

A study by Chintu *et al*, in 1975 at the paediatric wing of University Teaching Hospital, Lusaka, recorded 85 cases of acute bacterial meningitis. Fifty percent of these patients died within 24 hours of hospitalization[50].

Of all types of bacterial meningitis, pneumococcal meningitis has the highest morbidity and mortality.

1.2.2 Debilitating Sequelae

Survivors of acute bacterial meningitis face the possibility of chronic and debilitating sequelae. Short-term sequelae include among others, seizures, subdural effusion and transient cranial nerve palsies, whereas common long-term complications include neurologic abnormalities such as cerebral palsy, permanent cranial palsies.

Goetghebuer T *et al*, in his survey on the outcome of meningitis caused by *Streptococcus pneumoniae* and *Haemophilus influenzae* in children in the Gambia, found that 48% of children with pneumococcal meningitis and 27% of the ones with Hib meningitis died whilst in hospital. Of the surviving children with pneumococcal meningitis that were traced, 58% had clinical sequelae; half of them had major disabilities preventing normal adaptation to social life, 38% of the survivors of Hib meningitis had clinical sequelae with a quarter of them crippled by major disabilities.

Major handicaps found were hearing loss, mental retardation, motor abnormalities and epilepsy [51].

In another study Grimwood K. *et al* observed that 1 in 4 school-age meningitis survivors had either serious and disabling sequelae or a functionally significant behavior disorder, neuropsychological or auditory dysfunction adversely affecting academic performance.[52] Many cognitive skills not fully developed in children below the age of five years at the time of meningitis. Consequently, functionally important deficits may not appear until the children are much older, attending school, and expected to think and reason independently[53].

The pattern of results suggested that their greatest impairment was in verbal skills and organizational capacity. The risks for these adverse outcomes were greatest in those with meningitis during infancy and where there had been delays in diagnosis or neurological complications.[54-56]

Doctors need not only to check vision and hearing after bacterial meningitis but also to ensure that caregivers and schoolteachers are aware of possible language deficits and problems understanding language material.

1.2.3 Growing Antimicrobial Resistance

There is a growing concern brought about by the rising incidence of decreased susceptibility to penicillin and third generation cephalosporins among pneumococci, although prevalence varies substantially even within countries[57].

In 1997, the prevalence of resistance to penicillin among a sample of pneumococcal isolates from Australian laboratories was 25.4%, varying from13 to 38% between regions[58].

A study by Wenger *et al* have shown that any degree of penicillin resistance in pneumococcal meningitis was associated with failure of both penicillin and chloramphenicol treatment[59].

In the same study, it was found that vancomycin and high dose of cefotaxime were synergistic and able to prevent the emergence of resistance.

A study by the Centers for Disease Control and Prevention in the USA to estimate drug susceptibility patterns of *Streptococcus pneumoniae* revealed resistance to penicillin in 6.6 % of isolates. Six serotypes (6B, 23F, 14, 9V, 19A, and 19F) accounted for nearly 85% of strains resistant to at least one drug class [60].

It is estimated that 25 to 30% of pneumococcal strains in USA are resistant to penicillin and in some parts, up to 50% of these strains are resistant to routine antibiotics (penicillin, sulfa drugs, erythromycin, and cephalosporins). This resistance also appeared to be more among younger children.

A study conducted in England and Wales from 1990 to 1998 demonstrated an increased incidence of pneumococcal bacteremia among infants up to one year of age and antimicrobial resistance of these isolates. *S. Pneumoniae* showed an increase in resistance to penicillin from 1% (1990) to 7.4% (1997) [61].

Another study in the Southern Nigeria from 1985 to 1990 in infants aged over a month up to one year old showed that, out of 253 culture proven cases of bacterial meningitis, the proportions of sensitive strains of the common organisms to the three commonly used drugs were 95.3% for chloramphenicol, 83.9% for ampicillin and 67.6% for penicillin respectively.

Resistance to penicillin had increased while simultaneous resistance to ampicillin and chloramphenicol had emerged as a new problem among the three common bacteria [62].

The rising resistance of *S. pneumoniae* (the most common isolate in meningitis) to penicillin (the largely used antimicrobial in this instance) opens the door to the increase of dreadful outcomes of the disease in developing countries, and sub-Saharan Africa in particular.

1.2.4 Prophylaxis

As antimicrobial resistance grows and sequelae of acute bacterial meningitis continue to disable patients, disease prevention by routine use of vaccines presents the most realistic option.

2.4.1 *Haemophilus influenzae* type b vaccine (Hib)

In the USA, before the advent of conjugate vaccines, Hib meningitis or invasive disease developed in nearly 1 in 200 children by five years of age, and 70% of bacterial meningitis among children under five was attributable to *H. influenzae*.
Reports of dramatic declines in the disease from several countries after conjugate vaccines entered routine use suggest that the eradication of the disease is attainable.[63,64]

In the Gambia, bacterial pneumonia is far more common than bacterial meningitis. In the fully vaccinated cohort, 11 cases of meningitis and 38 cases of radiographic pneumonia were prevented, which suggests that the overall effect on pneumonia and meningitis is four to five- fold greater than the effect on meningitis alone.[65]

The introduction of Hib vaccines into developing countries should substantially reduce childhood mortality due to pneumonia and meningitis.[65]

Because of the high efficacy of conjugate Hib vaccines in the countries in which they have been tested, and their very low rate of adverse events, World Health Organization (WHO) and the Children's Vaccine Initiative (CVI) have recommended their widespread use in Expanded Programs of Immunization (EPI). However one deterrent to this prospect is the fact that Hib vaccines are currently more expensive to produce than those already in the EPI.

WHO, CVI and others are exploring approaches to reducing the cost of these vaccines for the non- industrialized countries.[65]

1.2.4.2 Pneumococcal vaccines

WHO estimated that 25 to 33% of deaths among children younger than five years are caused by acute respiratory infections, representing approximately 4 to 5 million deaths each year[66].

The prevalence of multidrug-resistant *S. pneumoniae* continues to perpetuate the mortality associated with pneumococcal disease. This fact further emphasizes the importance of preventing pneumococcal infection by immunization.

In the 1993 to 1994 CDC survey, 89% of all immediately susceptible invasive isolates and 100% of all highly resistant isolates were serotyped and included in the 23-valent-pneumococcal vaccines.

Multivalent pneumococcal conjugate vaccines have been developed and tested in phase II and III clinical trials. These studies have provided evidence that the conjugate vaccines

are safe and immunogenic in healthy adults, children and infants, as well as many high-risk groups [67].

However due to their prohibitive cost (US $ 58 per dose in some cases), pneumococcal vaccines have been limited to children at high risk, including those with sickle- cell disease or splenectomy and those with conditions resulting in rapid antibody decline such as nephrotic syndrome, renal failure, or renal transplantation [67]

1.2.4.3 Meningococcal vaccines

Prevention of meningococcal disease has been attempted by administration of meningococcal A and C polysaccharide vaccines. There is evidence supporting the efficacy of group A vaccine from a number of African countries and the group C component from Brazil in children over 24 months of age.[68]

No country is at present regularly vaccinating children with meningococcal vaccines. An apparent sparing of children under two years of age in epidemics and duration of protection of at least four years in older children suggest that vaccination of children at two-year intervals and adults every 4 to 6 years might keep meningococcal infections under control in the meningococcal belt.[69]

The vaccine that is available will protect against four strains of bacteria including type A (prevalent in Zambia), C, Y and W, but will not protect against B. A single dose of vaccine should offer protection for at least three years.[70]

1. 2.5 Meningitis background in Zambia.

1.2.5.1 Geographical, demographic and climatic aspects

Zambia is situated in the South Central Africa between 8-18 degrees South latitudes and between 20-35 degrees longitudes. It is a landlocked country, covering an area of 752,612 km^2 and shares borders with the Democratic Republic of Congo (D.R.C) and Tanzania in the North, Malawi and Mozambique in the East, Zimbabwe and Botswana in the South, Namibia in the South West and Angola in the West.

The 1980, 1990, and 2000 national census reported total population of 5.7 million, 7.8 million and 10.3 million, respectively, with a growth rate of 2.9 percent per annum with a density of 13.7 population per $km.^2$

Lusaka stands out as the most populated province in the country with 1.8 million inhabitants representing approximately 14% of the overall population with a density of 65 people per km^2 with the populated province being Northwestern province with only 5 people per square kilometre.

This distribution of population of Lusaka has increased by 1.1% since the last census carried out in 1990, demonstrating the ever-increasing migration from the rural to the urban areas.[71]

The climate in Zambia is mainly subtropical, consisting of three seasons: hot dry season from September to October; rainy season from late November to early April followed by a cool dry season that covers early May to August.

1.2.5.2 Situation of ABM in Zambia.

There has not been any nationwide survey to determine the prevalence of acute bacterial meningitis, however studies have been carried out in hospitals at different periods of time to assess the prevalence of the condition as a public health problem.

In 1966, Johnstone initiated a survey that embraced all paediatric age groups and a 47% successful bacteriological isolation was achieved. *Streptococcus pneumoniae* accounted for 48.7% of the isolates followed by *Haemophilus influenzae* with 38.5% whilst *Neisseria meningitidis* was found in only 5% of all cases.[72]

A study by Chintu *et al.* found 85 cases of meningitis out of approximately 10,000 annual admissions to the paediatric wards at UTH, Lusaka with a case fatality rate of 41,5%. Thirty-three percent of these cases were associated with immediate complications, ranging from generalized spasticity and followed by hydrocephalus, and cranial nerve palsy).

Out of the total number of CSF samples analyzed, bacteriological identification was estimated at 43.1% with *S.pneumoniae* being the most prominent causative organism isolated, followed by *H. influenzae*, with salmonella species making an appearance.[50]

A follow up study by Chintu *et al,* four years later, showed an increase in the number of cases of meningitis (138 per 10,000 admissions) with *S. pneumoniae* still remaining the most common isolate, followed this time by an ever-increased *N. meningitidis* isolates.[73]

This development was attributed to a possible southwards stretching of the meningococcal belt as also observed in Southern Nigeria where *N. meningitidis* had replaced *S. pneumoniae* as the commonest organism[62].

In the early nineties, a study by Kankasa, during an outbreak of meningococcal meningitis, found *N. meningitidis* to be the leading pathogen (77.9%) alongside *S. pneumoniae* (15.9%), *H.influenzae* (2.7%) and *Salmonella spp* (2.6%). The overall case fatality rate was 10.7%; significantly lower as compared to previous studies. This low mortality was explained by the fact that meningococcaemia with meningitis had a better prognosis. In this study, most neurological complications were transient. They ranged from ataxia to blindness.[74]

1.3.0 Study Justification

The previous survey on endemic **acute bacterial meningitis** at the University Teaching Hospital took place twenty seven years ago when the annual number of admissions on the paediatric wards was about half of the current average figure of 22,000 admissions yearly.

Besides the above trends, a number of parameters have since changed such as the emergence of new nosologic entities (e.g. HIV/AIDS pandemic), change in bacterial flora, socio-economic mutations characterized by ever-growing urban population and increasing poverty with a great risk of transmission of communicable diseases promoted by overcrowding. Therefore, a new study was needed to ascertain the prevalence and study the incidence of the meningitis causative organisms.

Acute bacterial meningitis, though at the bottom of the top 10 major causes of admission at the paediatric wing of the University Teaching Hospital (Lusaka, Zambia), accounts for the third highest case fatality rate (25%) after malnutrition (30%) and pneumonia (26%) according to the updated hospital statistics (year 2000).

Despite the overwhelming problem that **Acute Bacterial Meningitis** presents, the causative pathogen identification through microbiology has been quite poor as revealed by 8.1% of positive bacterial isolations (Microbiology Laboratory 1998 statistics); with the use of antibiotics prior to the cerebral spinal fluid collection being one of the contributing factors to this fact.

The Ministry of Health in Zambia has recommended the introduction Hib vaccine.

With ***Haemophilus influenzae*** **type b Paediatric Bacterial Meningitis Surveillance** initiated by WHO/Afro in view of introducing Hib vaccine in the existing EPI schedule, we seized this opportunity to assess the overall burden of disease caused by **Acute Bacterial Meningitis.**

1.4.0 Study Hypothesis

There has been no recent study on the trends of acute bacterial meningitis in children after studies by Chintu *et al.* in the seventies, and Kankasa during the last meningococcal outbreak in the early nineties. Has the etiological pattern of acute bacterial meningitis in children changed over the years with the advent of HIV/AIDS pandemic, and the changes in the socio-economic and demographic parameters? . This study will, to some extent, quantify the burden of disease due to this problem among the population of children studied.

CHAPTER 2

2.0 STUDY OBJECTIVES.

2.1 General objective.

To study the profile of Acute Bacterial Meningitis in children below 5 years admitted to the paediatric wards at the University Teaching Hospital, Lusaka.

2.2 Specific objectives.

1. To determine the prevalence of Acute Bacterial Meningitis among the under five children.
2. To determine the social status of children admitted with meningitis.
3. To determine the clinical features of meningitis among the under five children.
4. To determine most common organisms causing Acute Bacterial Meningitis and their antibiotic sensitivity pattern.
5. To document the immediate complications due to Acute Bacterial Meningitis.

CHAPTER 3

3.0 METHODOLOGY

3.1 Study Design

This was a prospective, descriptive study involving children aged 1 to 59 months admitted to the paediatric wards with acute bacterial meningitis. Patients who were eligible to the study were followed up to determine the incidence, clinical course and outcome of the disease.

3.2 Study site

This study was carried out in the paediatric wing (A block), of the University Teaching Hospital, Lusaka.

The paediatric wing, which admits about 2000 sick children every month, has an OutPatient Department, where patients are attended to and admitted depending on the severity of each case. Beside this compartment, there are wards for in-patients with a capacity of approximately 364 beds with a bed occupancy that varies according to a number of factors (season, ability to afford admission, etc.).

Five units manage the Department of Paediatrics, each headed by a consultant.

3.3 Duration of the study

The study was carried out from the 1st April 2002 to 31st December 2002,covering a period of 9 months.

3.4 Study population

Children aged between 1 to 59 months, who were admitted to the paediatric wing / UTH with a provisional diagnosis of Acute Bacterial Meningitis during the study period and subsequently complied with the inclusion criteria to the study.

3.5 Subject selection

3.5.1 the criteria for inclusion were:

1. Children from 1 to 59 months of age, admitted to the paediatric wing with a provisional diagnosis of Acute Bacterial Meningitis.
2. Successful lumbar puncture.
3. Symptoms and signs of not more than 28 days duration. This criterion was mainly intended to include cases of partially treated acute bacterial meningitis.

3.5.2 the criteria for exclusion were:

1. Children aged below 1 month and above 59 months by the time of the study.
2. Children in whom the lumbar puncture was unsuccessful.
3. Children with other types of meningitis not included in the definition of acute bacterial meningitis.

3.6 Sample size and sampling

Sampling was carried out as consecutive sampling of all children admitted to A block with a provisional diagnosis of Acute Bacterial Meningitis during the study period.

3.7 Study procedure

The investigator conducted the study with the assistance of unit doctors, nurses and ward clerks both in the Outpatient Department and the wards.

Guardians were interviewed so as to document both the socio-demographic parameters and the course of the disease prior to the admission to the paediatric wards using a pre-tested questionnaire.

Children were examined, investigated accordingly and followed up by the investigator on the patient's respective ward, since there was no specific arrangement to keep all cases of meningitis in one location.

Once it was ascertained that the patient complied with the inclusion criteria, the lumbar puncture procedure was thoroughly explained to the guardian to allay the fear associated with this investigation, especially with its seemingly association with high fatality rate in the adult disease.

The lumbar puncture was then carried out under aseptic measures including swabbing of the site with methylated spirit and iodine. The cerebro-spinal fluid (CSF) specimen was labeled and attached to duly filled-in form, and immediately sent to the laboratory.

The patient was admitted and commenced on the meningitis standard treatment protocol that comprised crystalline penicillin, chloramphenicol, dexamethasone and any specific adjuvant support whilst awaiting the CSF microbiology report for any treatment changes.

The follow-up period was restricted to the patient's hospital stay, irrespective of the outcome.

3.8 Laboratory management

3.8.1 Collection and transport of CSF to the Laboratory

The CSF was collected directly into two sterile plain bottles (for biochemistry and microbiological investigations).

Once the CSF specimen was collected, the investigator made sure the samples reached the microbiology laboratory within the hour to allow successful plating, because *Haemophilus influenzae, Streptococcus pneumoniae* and *Neisseria meningitidis* are fastidious and fragile bacteria, and any delay in transport to the laboratory and plating of the specimen in culture media would have led to unsuccessful results and possible loss of the bacteria. It is in this regard that a register was made available in order to monitor fast transportation of CSF specimens from A block to the laboratory. The investigator called the laboratory technician each time a CSF sample was collected to make sure it was processed as soon as it reached the laboratory.

In the event the CSF specimen had not been taken immediately to the laboratory, it was kept under room temperature, and never in the refrigerator, whilst awaiting transport.

The biochemistry investigations, which would have been helpful in the diagnosis and management of acute meningitis, were so erratic and inconsistent that they had to be excluded from the data analysis.

3.8.2 Laboratory investigations

Once the CSF specimen reached the laboratory, it went through the following steps:

1. Macroscopic examination for color, turbidity or presence of blood.
2. Cell count:
    - Cell count was performed through improved Neubauer Counting Chamber using four large squares. Cells (red and white) were reported as per cubic millimeter.
    - The differential count: The ratio of neutrophils (polymorphonucleated cells) and lymphocytes (mononucleated cells) was done if there were more than 5 white cells per mm^3 using 2% acetic acid tinted with Crystal Violet or Gentian Violet.

3. Smear staining for organism identification
    - Gram stain to identify *S. pneumoniae, N.meningitides, H. influenzae,* Salmonella spp and any other bacteria.
    - Indian Ink or Nigrosin on a wet preparation to identify yeast cells (cryptococcus).
    - Ziehl Nielsen to identify Mycobacteria

4. Culture

Day 1

The CSF was laid for culture on three different media (Blood Agar, Chocolate Agar and McConkey) and incubated in 10% carbon dioxide between 35 and 37^0 C over 24 hours.

Day 2

The plates were then examined for growth.

If there was growth, we proceeded with identification and subsequent susceptibility.

If there was no growth, the plates were re-incubated for another 24 hours.

Day 3

If growth took place, we proceeded with identification and susceptibility testing; otherwise a final report was issued declaring the culture sterile.

3.9 Data Collection and Analysis

A pre-tested questionnaire was administered to collect socio-demographic and other relevant data at the time of recruitment. Additional information was obtained through physical examination of the study subjects and the results of laboratory investigations. The data collected was analyzed by EPI.INFO. 6.0.

3.10 Ethical considerations

No written consent was obtained from patient's parents or guardians since this cohort was part of routine admissions and the study did not include any form of intervention that might have had an impact on the disease outcome. However, an official consent and clearance were obtained from the Research Ethics Committee of the University of Zambia. .

As part of patient's management, the investigator explained the disease process, the lumbar puncture procedure and the CSF results as soon as they were made available.

CHAPTER 4

4.0 RESULTS

During the study period a total of 21,200 children were admitted.

210 children were admitted with provisional diagnosis of acute bacterial meningitis, 92 were eligible for the study. 118 were excluded for failing to meet the inclusion criteria. The explanation of the large number being excluded from the study lies in the fact that a number of guardians were uncomfortable with the lumbar puncture procedure on one hand, and some patients were in such a condition that invasive procedures had to be post-poned (including lumbar puncture) on the other hand.

4.1 socio-demographic parameters

TABLE 1: AGE DISTRIBUTION

AGE (months)	FREQUENCY	PERCENT
1 - 6	35	38.0%
7 - 12	22	23.9%
13 - 59	35	38.1%
TOTAL	**92**	**100%**

Table 1 clearly shows that acute bacterial meningitis affected more children within their first year of life as portrayed by almost 60% of the total number of cases. Within this age range, infants aged 6 months and below represented almost two-third of cases.

TABLE 2: SEX DISTRIBUTION

SEX	FREQUENCY	PERCENT
M	48	52.2 %
F	44	47.8 %
TOTAL	**92**	**100 %**

There was no significant difference in the sex distribution, with the males contributing 52.2% and females 47.8 % respectively. The male to female ratio standing at 1.1: 1.

TABLE 3: ASSOCIATION POPULATION DENSITY AND MORBIDITY

DENSITY	NUMBER	PERCENT
HIGH	69	75.0%
MIDDLE	10	10.9%
LOW	6	6.5%
RURAL	7	7.6%
TOTAL	**92**	**100%**

Three out of four children admitted with acute bacterial meningitis came from a high peri - urban density areas of Lusaka.

TABLE 4 : MORBIDITY IN RELATION WITH FAMILY SIZE

FAMILY SIZE	FREQUENCY	PERCENT
1 - 3	12	13.3%
4 - 6	54	59.3%
7 and more	25	27.4%
TOTAL	91	**100%**

Almost nine out of ten children suffering from acute bacterial meningitis came from medium size and large families (4 and more members).

TABLE 5: MORBIDITY IN RELATION TO HABITAT

NUMBER OF ROOMS	FREQUENCY	PERCENT
1 AND 2	51	56.7%
MORE THAN 2	41	43.6%
TOTAL	92	**100%**

About 6 out of 10 children with acute bacterial meningitis came from families that lived confined in one or two- roomed houses.

TABLE 6: MORBIDITY AND ACCESS TO BASIC SERVICES

	PRIVATE WATER	%	PRIVATE TOILET	%
Yes	17	18.7%	35	38.5%
No	74	81.3%	56	61.5%
TOTAL	**91**	**100%**	**91**	**100%**

Four out of five in the study group came from homes depending on a communal source of water for their daily needs, whereas 6 out of 10 lived in homes that did not have access to a private toilet.

TABLE 7: MORBIDITY AND GUARDIAN'S EMPLOYMENT STATUS

	WORK. MOTHER	%	WORK. FATHER	%
Yes	22	24.2%	72	79.1%
No	69	75.8%	19	20.9%
TOTAL	**91**	**100%**	**91**	**100%**

One out of four children in the studied population lived in a home where the mother contributed to the family livelihood, whereas almost 80% of them had their father being the sole family breadwinner.

It was a hard task to determine the income families disposed of since most mothers, who constituted 99% of informants, did not know how much money their spouses brought home at the month end. In some cases, casual work, with no regular revenue, was the only source of income.

Most working mothers held a small scale, home based, subsistence business made of daily basic consumable essential commodities.

TABLE 8: DISEASE MONTHLY DISTRIBUTION

YEAR	MONTH	NUMBER	PERCENT
2002	APRIL	4	4.3 %
	MAY	13	14.1 %
	JUNE	12	12.9 %
	JULY	10	10.7 %
	AUGUST	8	8.6 %
	SEPTEMBER	13	14.1 %
	OCTOBER	13	14.1 %
	NOVEMBER	12	12.9 %
	DECEMBER	6	6.4 %
	TOTAL	**92**	**100%**

The low incidence during the months of April and December 2002 may be explained by the fact that was the transition period between the dry and rainy seasons, whereas the drop during August could not be clearly explained.

4.2 Clinical Parameters

TABLE 9: DURATION OF ILLNESS PRIOR TO ADMISSION

DURATION (DAYS)	FREQUENCY	PERCENT
First 2	20	21.7 %
3 – 7	58	63.0 %
More than 7	14	15.3 %
TOTAL	**92**	**100 %**

The duration of illness prior to admission ranged from 1 to 21 days, with the mean average of 6.2 days and a standard deviation of +/- 5.8 days.

85% of patients were admitted within the first week of onset of symptoms.

Out of 14 patients, 10 attended the local clinic erratically, whereas the remaining four were being treated at home until just before admission when they were taken to the near clinic.

TABLE 10 ANTIBIOTICS AND OTHER DRUGS PRIOR TO ADMISSION

ANTIBIOTIC	FREQ.	1 DOSE	2 AND MORE DOSES
PENICILLIN	50	27	23
COTRIMOXAZOLE	17	5	12
GENTAMYCIN	7	4	3
CLOXALLICIN	1	0	1
CYPROFLOXACIN	1	0	1
AMPICILLIN	3	1	2
CHLORAMPHENICOL	8	3	5
OTHER DRUGS			
FANSIDAR	9		
QUININE	6		
ARTEMEETHER	1		
CHLOROQUINE	6		
NYSTATIN	1		

Eighty-two percent of the patients admitted with acute bacterial meningitis received at least one antibiotic prior to their admission to the children's wing of the UTH. Penicillin was the most prescribed antibiotic, accounting for almost half of the administered antimicrobials, followed by cotrimoxazole with 18.5% of cases. Eighty-seven of the 92-study population were referred from their respective local clinic. Twenty-three patients in the penicillin group received a single dose, whereas 27 had two or more doses.

The same table shows that the most common adjuvant treatment was mainly antimalarial drugs, such as quinine, Fansidar, artemether, and chloroquine.

TABLE 11 COMMONEST COMPLAINTS

COMPLAINTS	FREQUENCY	TOTAL	PERCENTAGE
SWELLING OF AF	27*	64*	42.2%
FEVER	89	92	96.7%
EXCESSIVE CRYING	55	92	59.8%
LOSS OF APPETITE	49	92	53.3%
ALTERED CONSCIOUSNESS	13	92	14.1%
HEADACHES	9**	27**	33.3%
VOMITING	39	92	42.4%
FITS	52	92	56.5%
NECK RIGIDITY	64	92	69.6%
COUGH	38	92	41.3%
DIARRHEOA	10	92	1.1%
PURULENT EAR DISCHARGE	2	92	
ORAL THRUSH	2	92	
DIFFICULT BREATHING	3	92	
CHICKEN POX	1	92	
RASH ON THE LEGS	1	92	

Body hotness was the most common symptom on admission (96.7%), followed by neck rigidity (69.6%), excessive crying (59.8%), fits (56.5%), loss of appetite (53.3%), vomiting and cough present in 42.2% and 41.2% respectively.

**The percentage of swelling of the anterior fontanelle was based on a total of 64 infants who were aged between 1 and around 18 months, and had a patent fontanelle.*

***Headache was recorded from 27 children who were able to communicate.*

TABLE 12 COMMONEST SIGNS

SIGNS	FREQUENCY	TOTAL	PERCENTAGE
FEVER	68	92	73.9%
FOCAL NEUR. SIGN.	7	92	7.6%
BULGING OF AF	33	64	51.6%
NECK STIFFNESS	77	92	83.7%
ALTERED CONSCIOUSNESS	35	92	38.0%
PETECHIAL RASH	3	92	3.3%
SEIZURES	38	92	41.3%
POOR FEEDING	60	92	65.2%

Neck stiffness was the leading sign, accounting for 83.7%, followed by fever and poor feeding with 73.9% and 65.2% respectively.

Petechial rash was only seen in 3.3% of the children. It is a common feature in meningococaemia, though it might be present in meningitis caused by other pathogens.

Nutritional status was determined using the Welcome classification with severe malnutrition being defined as marasmus, kwashiorkor or Marasmic kwashiorkor.

Out of 89 cases, 34 (38.2%) were labeled as underweight and only one of them had clinical malnutrition requiring intensive nutritional rehabilitation. This one patient had ***H. influenzae*** isolated in the CSF and did not survive.

Sixty-six (78.6%) out of 84 children had received their immunization regularly at the time of the study.

Eight (8.9%) of the study population did not produce their under-five card.

Table 13 ASSOCIATED MORBID CONDITIONS

CO-MORBID CONDITION	FREQUENCY	TOTAL	PERCENTAGE
PNEUMONIA	17	92	18.5%
ORAL CANDIDIASIS	6	92	6.5%
MALARIA	3	92	3.3%
OTITIS MEDIA	3	92	3.3%
CHICKEN POX	1	92	1.1%
SICKLE CELLANAEMIA	1	92	1.1%
CONGENITAL HYDROCEPHALUS	1	92	1.1%

Pneumonia featured prominently as a morbid condition besides meningitis. It accounts for 18.5% of the total number of acute bacterial meningitis cases. This suggests the septicaemic nature of the illness.

Oral candidiasis was recorded in 6 cases, all of them infants. It might have been a feature of an underlying immuno-suppression in these patients.

Malaria was ascertained in three patients and was treated accordingly. Three other patients presented with purulent ear discharge, 2 of them had acquired the infection within a week prior to onset of meningeal signs, whereas the remaining one had had it for months.

The only case of obvious sickle cell anaemia yielded *S.pneumoniae* on CSF culture and responded favourably to the combination of penicillin and Chloramphenicol.

The issue of antibiotic prophylaxis in such a patient becomes quite relevant, especially in the absence of pneumococcal vaccine.

4.3 Laboratory Results

CSF RESULTS

TABLE 14: CSF APPEARANCE

CSF APPEARANCE	FREQUENCY	PERCENTAGE
CLEAR	13	14.1%
CLOUDY	26	28.3%
TURBID	43	46.7%
HAEMORRHAGIC	5	5.4%
XANTHOCHROMIC	5	5.4%
TOTAL	**92**	**100%**

Eighty-six percent of the CSF specimens displayed an abnormal appearance, with the turbid appearance leading with 46.7% of cases, followed by the cloudy aspect with 28.3%.

The haemorrhagic CSF specimen had a white cell to red blood cell ratio of more than 1:500, confirming that this appearance was as a result of the disease inflammatory process rather than trauma during the lumbar puncture.

TABLE 15: CSF WHITE CELL COUNT

RANGE / mm^3	FREQUENCY	PERCENTAGE
< 10	17	18.4%
10 - 100	33	35.8%
> 10	42	45.8%
TOTAL	**92**	**100%**

Eighty-two percent of CSF samples had a white cell count of 10 and above per cubic millimeter.

S.pneumoniae was isolated in three of the CSF specimens that had less than 10 white cells per cubic millimeter.

TABLE 16.1 : CSF CULTURE RESULTS

CULTURE	FREQUENCY	PERCENTAGE
NEGATIVE	51	55.5%
POSITIVE	41	44.5%
TOTAL	92	100%

TABLE 16.2: CSF ISOLATES

ISOLATES	FREQUENCY	PERCENTAGE
S. PNEUMONIAE	25	61.9%
H. INFLUENZAE	8	19.5%
N. MENINGITIS	4	9.8%
SALMONELLA	2	4.9%
OTHERS	2	4.9%
TOTAL	**41**	**100%**

Forty-one (44.5%) out of 92 yielded a positive culture with *streptococcus pneumoniae* accounting for 61.9% of cases, followed by far by *Haemophilus influenzae* with only 19.5%, and Neisseria meningitidis with 9.8%.

Eleven (48%)of the 25 pneumococcal isolates were found in children who were below 12 months of age with one of them barely a month old.

All the cases of Hib meningitis were below 2 years of age with the three of them being below 12 months of age.

Two of the 4 meningococcal isolates were found in children within their first one year of life with one presenting with an early gangrenous process on the skin of the toes. Luckily, the infant improved with no sequelae.

Salmonella was isolated in 2 infants aged 2 and 3 months respectively and both died.

E. Coli accounted for one case, and the last case resulting into a mixed growth.

TABLE 17: ASSOCIATION BETWEEN AGE AND ISOLATE

AGE / MONTH	SP	HI	NM	SLM	OTHERS	TOTAL
1 - 12	11	3	2	2	2	20
13 - 59	14	5	2	0	0	21
TOTAL	25	8	4	2	2	41

SP: *Streptococcus pneumoniae* HI: *Haemophilus influenzae* NM: *Neisseria meningitides.* SLM: *Salmonella spp.*

Streptococcus pneumoniae was the commonest isolated pathogen across the board.

Salmonella was specifically isolated in children below one year.

ISOLATES SENTIVITY PATTERN

TABLE 18: STREPTOCOCCUS PNEUMONIAE ISOLATE SENSITIVITY PATTERN

ANTIBIOTIC	TESTED ISOLATES	SENSITIVE ISOLATES	PERCENTAGE
Penicillin	23	22	95.7%
Chloramphenicol	23	22	95.7%
Cefotaxime	20	20	100%
Ciprofloxacin	19	16	84.2%
Vancomycin	3	3	100%

Ninety-six percent of *S.pneumoniae* isolates were sensitive to both penicillin and chloramphenicol. All isolates tested against cefotaxime and vancomycin were sensitive. About 16% of the isolates tested against ciprofloxacin were resistant.

TABLE 19: HAEMOPHILUS INFLUENZAE

ANTIBIOTIC	TESTED ISOLATES	SENSITIVE ISOLATES	PERCENTAGE
Chloramphenicol	5	4	80%
Cefotaxime	7	6	85.7%
Ciprofloxacin	8	8	100%
Ampicillin	4	1	25%

One in five *Haemophilus influenzae* isolates was resistant to Chloramphenicol.

Cefotaxime was ineffective in one out of 7 isolates.

All the *H. influenzae* isolated strains were sensitive to ciprofloxacin.

Three out of 4 strains were resistant to ampicillin, which, years back was the second-choice antibiotic in Hib related infections.

TABLE 20: NEISSERIA MENINGITIDIS

ANTIBIOTIC	TESTED ISOLATES	SENSITIVE ISOLATES	PERCENTAGE
Chloramphenicol	2	2	100%
Cefotaxime	2	2	100%
Ciprofloxacin	2	2	100%
Ampicillin	2	2	100%

All the strains were sensitive to both chloramphenicol, cefotaxime ampicillin and ciproflaxacin.

Neisseria meningitidis was not tested against penicillin, which is known to be quite efficient in this case, due to lack of sensitivity disks.

TABLE 21: IMMEDIATE COMPLICATIONS

COMPLICATIONS	FREQUENCY	TOTAL	PERCENTAGE
Hypertonia	19	92	20.7%
Hemiplegia	5	92	5.4%
Blindness	3	92	3.3%
Deafness	1	92	1.1%
Hydrocephalus	1	92	1.1%
Facial palsy	2	92	2.2%

Of note was the fact that some patients had simultaneously 2 or more complications

The above table lists them as they occurred in every individual patient.

Hypertonia featured highly in this survey with 20.7% of cases affected.

Hemiplegia was the second most common complication with 5.4 % whereas blindness was detected in three of the 92 patients.

Deafness, hydrocephalus, and facial palsy were each observed in one case, respectively.

TABLE 22: OUTCOME

OUTCOME	FREQUENCY	PERCENTAGE
No sequelae	45	48.9%
Sequelae	22	23.9%
Died	25	28.2%
TOTAL	92	100. %

Out of the 92 patients that were recruited, 25 died giving a case fatality rate of 27.2%. 77 (72.8%) were discharged. 22 (28.5%) of the survivors developed sequelae as described in table 21. Of the dead, 15 (60%) were below one year. Meningitis due to salmonella and pneumococcus gave the worst outcome.

TABLE 23: ASSOCIATION BETWEEN DURATION OF ILLNESS PRIOR TO ADMISSION AND OUTCOME

DURATION (days)	FREQ.	OUTCOME		
		NO SEQUELAE	SEQUELAE	DEATH
1-2	20	7	6	6
3-7	58	35	8	15
More than 7	14	3	8	14
TOTAL	92	45	22	25

Chi-square: 31.48 Expected is < 5. Chi square is not valid.

The duration of illness, before admission, did not relate to the outcome.

This might be due to a number of other associated factors such as the severity of the illness at the time of admission, the associated morbid conditions, the treatment received prior to admission, the individual response to treatment, and the pathogen sensitivity to antibiotics administered.

CHAPTER 5

5.0 DISCUSSION

This study was carried out between April and December 2002 covering a period of 9 months. During this period, a total of 21200 children were admitted. 210 aged between 1 and 59 months had acute bacterial meningitis as the diagnosis on admission, giving a prevalence rate of about 100:10,000.

This study cannot be compared to two previous studies by Chintu ***et al*** in the seventies[50] and Kankasa in the early nineties[74] due to the fact that their respective prevalences were inclusive of the whole paediatric range (from 0 to 15 years).

However a study by de Louvois J *et al* in England and Wales in a similar population gives a prevalence of sixteen in ten thousands[8].

Due to a number of constraints as cited by Wright P.F such as lack of skill and motivation to perform the lumbar puncture[2], only 92 were successfully enrolled on this survey.

5.1 socio-demographic aspects

Acute bacterial meningitis affects the highest number of children within their first year of life as supported by Chintu *et al.* and Mulholland K.*et al*[26] respectively.

In this study, the male-to- female ratio was 1:1.1 comparable to previous studies[50, 74].

Most children with acute bacterial meningitis lived in crowded peri-urban areas and came from large families (average of 6.5 persons per household), which in 60% of cases shared 1 or 2 rooms as living space with lack of easy access to basic services such as water in 80% and sanitation 61.5%of cases respectively.

This confirms findings by Kankasa and Nelson[1], that poverty and overcrowding are predisposing factors to acute bacterial meningitis.

The disease monthly distribution pattern shows a decline in April and December, which are transitional months between the dry and rainy seasons. Study by Chintu showed similar trends, whereas August showed a sharp increase in the study by Kankasa, which recorded an important rise in the cases of group A meningococcal meningitis from July through to November as a result of an outbreak.

Eighty two percent of children admitted with ABM received at least one antibiotic prior to their admission to UTH as per the disease management protocol advised by the Integrated Management of Childhood Illnesses (IMCI) for any patient suspected to have a "severe disease classification".

An ambulance is supposed to be at hand to timely ferry the very sick ones, but this does not happen all the time, leading to delay in receiving their next antibiotic dose. This fact has a bearing on the low causative pathogen isolation rate and emergence of resistant strains to commonly used antimicrobials as observed by Emele FE[62] and Akpede[14] in other parts of Africa and Paris MM *et al* in Australia[12].

5.2 Clinical manifestations and Outcome

Body hotness (96.7%) was the common symptom on admission.

Swelling of the anterior fontanelle (42%) and neck rigidity (69.6%) were the most common specific symptoms of ABM.

Cough (41.3%) stood as the most frequent extra-meningeal associated complaint.

These figures correlate well with findings by Chintu *et al*[50].

The commonest signs were neck stiffness (83.7%), fever (73.9%) and poor feeding (65.2%). Twenty-six percent of children did not have fever and yet displayed variable signs of meningeal irritation.

Two of patients were admitted after being unwell for more than 14 days. Partially treated meningitis was thought to be the reason for the afebrile course of their illness. This finding is in line with the observation made in the study by Kankasa[74].

Pneumonia was the most common morbid condition associated with meningitis. This condition was part of the septicaemic process in some patients, as often is the case in infections due to both ***Streptococcus pneumoniae*** and ***Haemophilus influenzae.***

This study has shown that the most common early event related to acute bacterial meningitis was hypertonia (20.7%). Other common complications of note were blindness and deafness.

Deafness as a complication has attracted a lot of interest when it comes to its prevention with the use of dexamethasone. A study by Molyneux *et al* in Malawi, using dexamethasone in a randomized trial, did not show any improvement in the overall outcome in children with bacterial meningitis of all causes.[75]

Results of a number of studies using steroids in ABM in developed countries have been varied. Gieman and Smith reported no change in mortality, but reduced numbers of patients with neurological and hearing sequelae in the long term with the addition of steroids.[76]

In 1997, Quagliarello and Scheld advised that steroids should be used for all children older than two months of age, especially if infected with *H.influenzae* to prevent deafness.[42]

The study by Kankasa has shown a later emergence of other complications, not present during the acute phase of the disease, such as epilepsy and hydrocephalus.

Need for follow-up is vital, but adequate treating of meningitis should prevent hydrocephalus.

Twenty-five of the 92 patients died, giving a case fatality rate of 27.2%. This mortality rate is far much lower as compared to the one recorded by Chintu *et al.* This could partly be explained by the widespread use of antibiotics at the community level on one hand, and the hospital use of much efficient, alternative antimicrobials, such as cefotaxime, on the other hand.

Twenty one (84%) out of the 25 deaths had fallen sick within the week before admission, whereas the remaining four presented after two weeks of illness. *S.pneumoniae* was isolated in six cases; all of them being underweight. *H.influenzae* was identified in two cases, and salmonella in two other cases. Nineteen children (76%) died within the first of admission. Hypotonia was a clinical feature at the time of death in fifteen cases (60%). In 9 cases (36%), death was attributed to severe pneumonia.

We have picked up two cases that illustrate connections between acute bacterial meningitis and other entities.

In one instance, a well grown, five-month old, who had fallen sick 2 days before admission, died of respiratory failure 48 hours after admission, despite treatment with penicillin, chloramphenicol and dexamethasone. The CSF Gram stain showed pneumococcus and the chest radiograph was compatible with broncho-pneumonia, stressing the septicaemic nature of the disease.

In another case, a two-month old infant was admitted with extensive oral thrush and irritability. She was then treated as a case of septicaemia, but died within 24 hours of admission. The CSF culture would later grow salmonella spp.

Circumstances, at the time, did not allow counseling and testing for HIV, which we thought, was most likely the underlying condition.

Twenty-two of the survivors developed immediate complications with hypertonia being top on the list. The duration of illness before admission did not relate to the outcome due to some other associated factors, such as treatment before referral.

5.3 Laboratory results

Due to erratic and inconsistent results from the biochemistry laboratory, CSF sugar and proteins could not be included in this study.

Our laboratory results were mainly based on CSF microbiology findings.

Eighty-six percent of CSF specimens displayed an abnormal appearance, with 75% of them ranging from cloudy to turbid. Only 14% of the study cases had clear CSF.

5.3.1 CSF appearance

In a study by James A *et al,* CSF turbidity was subjectively scored so as to see whether it correlated with diagnosis accuracy of acute bacterial meningitis and it was observed that the more turbid the CSF was, the more accurate the diagnosis was.

However, this fact should not be taken as a golden rule in the diagnosis of meningitis as the CSF may be clear in about 30% of culture confirmed acute bacterial meningitis[77].

In our survey, 2 of the clear CSF specimens surprisingly yielded *H. influenzae* on culture.

5.3.2 CSF culture

Forty-one (44.5%) CSF specimens yielded a positive culture with *S.pneumoniae* leading with 61.95% of cases, followed by *H.influenzae* (19.5%) and *N.meningitidis* (9.8%).

This isolation rate ranking concurred with previous studies at the exception of the one done during a meningococcal outbreak by Kankasa.

Haemophilus influenzae was a difficult pathogen to isolate; hence our figures may not reflect the real burden of disease caused by this germ. Improved diagnostic methods are required, such as the antigen testing by latex agglutination.

Salmonella was isolated in two infants aged 2 and 3 months respectively. This pathogen seems to be closely associated with acquired immuno-suppression in our setting. Kankasa had reported four cases, with three of them in infants. One was HIV positive and died on admission. A further study would be required to ascertain these trends.

5.3.3 CSF isolates sensitivity pattern

Ninety six percent of *S.pneumoniae* isolates were sensitive to both penicillin and chloramphenicol, which are the most used antibiotics as first line management of acute bacterial meningitis in our setting. The emergence of resistance of pneumococcus to these antibiotics is of great worry in the sense that they are the cheapest many, in developing countries, could afford in the absence of an effective vaccine. Emele reports a reducing antimicrobial susceptibility of the 3 common pathogens to both ampicillin and benzyl penicillin in Southern Nigeria.

Cefotaxime and ciprofloxacin were effective on all the pneumococcal strains.

Eighty percent of the haemophilus strain was sensitive to chloramphenicol, and showed 75% resistance to ampicillin. Thus, ampicillin should not be considered as alternative antibiotic in acute bacterial meningitis. All *N. meningitidis* isolates were sensitive to chloramphenicol, ampicilllin, cefotaxime, and ciprofloxacin.

There was no sensitivity test done for penicillin due to lack of disks.

CHAPTER 6

6. CONCLUSIONS

6.1 Conclusions

This study has shown that acute bacterial meningitis is still a devastating disease among children below five years of age admitted to the University Teaching Hospital.

This was demonstrated by the high case fatality rate (27.2%), with infants paying the heavy toll (60%).

The unfavorable socio-economic and demographic factors largely contribute to the incidence of this condition as illustrated by the family size and the area where most of these affected children lived in.

Streptococcus pneumoniae is still the most common causative organism of acute bacterial meningitis and seems to be distributed evenly across this age range.

Penicillin and chloramphenicol are still efficient as first line treatment for acute bacterial meningitis in our setting when initiated on time.

Finally, it was observed that the duration of illness prior to admission did not necessarily determine the disease outcome.

6.2 Recommendations

6.2.1 Community level

Knowing well that acute bacterial meningitis is most the disease of the under-five child and complications arising from this illness may cripple the child for life, health workers should embark on a sensitization campaign in the community, teaching about the nature of the disease, emphasizing on early consultation where the case arises and making sure no delay is taken between the health center and the next level of care.

A health worker should always accompany a suspected case of meningitis to the referral hospital so as to avoid patient side tracking for one reason or the other.

6.2.2 Referral hospital level

In the midst of the multitude of referred patients, a health worker at the hospital should be able to select very sick ones, including cases of ABM, for prompt medical attention. To achieve this, health workers need to be assisted in making the right diagnosis and managing the patient appropriately through job-on training and other possible means.

To allow easy and efficient follow up, there is need to create an exclusive space for such patients.

6.2.3 Laboratory level

Equip the laboratory in A block to process CSF specimen so as to avoid delay and, at times, loss of specimens.

6.3 Study limitations

The study was limited to the hospital stay and, for this fact, fell short of carrying out a further follow-up to monitor the final outcome of the disease.

Due to financial constraints, it was not possible to efficiently equip the laboratory for the identification of causative organisms, i.e.: antigen testing by Latex Agglutination both for *Streptococcus pneumoniae* and *Haemophilus influenzae* type b. This may have led to low isolation rate.

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II. APPENDICES

QUESTIONNAIRE / PROFILE OF ACUTE BACTERIAL MENINGITIS

GENERAL INFORMATION

1. Name: 2.Study number: 3. Date:

4.Informant: . 5. Interviewer: . 6.Age: months. 7.Sex:

8.File num: . 9. Ward: . 10.Residence: . 11. Referring clin:

12. Family size: . 13. Number of rooms: . 14.Nber of households sharing the premises: .

15. Own toilet: Y / N. 16. Own tap of water: Y / N. 17. Father's job: 18. Mother's:

PRESENTATION

19. Duration of illness: days. 20.Fever. 21. Headaches. 22. excessive crying. 23.Refusal to feed.

24. Bulging of A.F. 25.Altered consciousness. 26.vomiting. 27. Fits. 28. Neck stiffness. 30. Other:

MEDICATION RECEIVED PRIOR TO ADMISSION

31. Antibiotics: . 32. Nber of doses:

33. Other medication:

VACCINATION SCHEDULE

33. Up-to-date for age: Y / N. (Check under five card)

CLINICAL FINDINGS

34. Temp: 0C. 35. weight: Kg. 36. Head circum: cm. 37. Focal neur. Signs:

38. Petechial rash. 39. Bulging of A.F. 40. Poor feeding. 41. Seizures. 42. Neck stiffness.

43. Altered consciousness. 44.Nutrition (normal / underweight) 45. Other:

CSF CHARACTERISTICS

46. Lumbar puncture done: / / 02. 47. CSF appearance:

47. Cell count: WBC: / mm3 48. Diff: Polymorph: % Lymph: %

49. Rbc: / mm3 50. Gram stain: 51. Indian ink:

52.Culture / sensitivity:

COMPLICATIONS ON DISCHARGE

53. State:

OUTCOME

54. Discharge. 55. Death. 56. Absconded. Hospital stay: days