ACUTE BACTERIAL MENINGITIS IN ZAMBIAN CHILDREN

HIGHLIGHTING THE CHANGING PATTERN IN THE AETIOLOGY OF BACTERIAL MENINGITIS IN ZAMBIA

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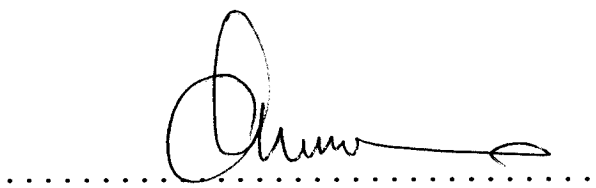
A DISSERTATION
SUBMITTED IN ACCORDANCE WITH THE PARTIAL REQUIREMENTS
FOR THE

MASTERS DEGREE IN PAEDIATRICS AND CHILD HEALTH

UNIVERSITY OF ZAMBIA
(SCHOOL OF MEDICINE)
LUSAKA

1997

I hereby state that this dissertation is entirely a result of my own efforts.



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DECLARATION

I hereby declare that, this dissertation is entirely the result of my own work, and that it has not been previously submitted for a degree at this, or another University

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This dissertation of Dr Chipepo Kankasa is approved as fulfilling the partial requirements for the award of a masters degree in Paediatrics, by the University of Zambia, Lusaka.

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Examiner3.....

DEDICATION

To my little daughter Chilufya
for all the time and love denied
her while pursuing my masters degree.
To my mother Chibesa Kankasa for
being my source of inspiration,
and my pillar of strength all the
way.

ABSTRACT

A hospital based prospective study on Acute Bacterial Meningitis (ABM) in Zambian Children was done in the department of Paediatrics, University Teaching Hospital Lusaka over a period of six months in the hot dry season (1st August to the end of November) of the years 1992 and 1993.

The aim and objectives of the study were to determine the prevalence, aetiology, risk factors, poor prognostic signs, clinical profile and outcome of ABM. Nine hundred children were recruited aged one month to 15 years as cohorts, 29 were excluded, 871 were followed up.

It was found out that almost all age groups were at risk, with ABM being commonest around 5 and half years of age. There was no sexual predilection, male to female ratio was 1.2:1, almost 90% of cases came from high density areas of Lusaka.

Clinical manifestations ranged from fever with neck stiffness alone, to associated septic shock with petechial rash. The commonest complaints were fever (99%), anorexia (88.5%), headache (73.8%), vomiting (71.3%), arthralgia (about 60%), the commonest signs were; neck stiffness (96.9%), Kernigs (77.4%), Brudzinski (73%), whilst in infants fever, irritability, refusing to suck and bulging anterior fontanelle were common.

The most common pathogens isolated were *N.meningitidis* (77.9%), *S. pneumoniae* (15.4%), *H. Influenzae* (2.7%), others (2.6%). Young age, HIV sero positivity, *S.Pneumoniae* as pathogen , altered level of consciousness and seizures on admission were associated with a poor outcome.

Case fatality rate was 10.7%. The highest mortality was seen in children with meningitis caused by *S. Pneumoniae* (38.75%), compared to influenzal meningitis (14.2%) and *Meningococcal* meningitis (6.6%). Follow up was very difficult because more than 50% of the study group defaulted.

ACKNOWLEDGEMENTS

Special thanks to Professor Bhat - for having banished me to ward A06, as doctor in charge of the meningitis ward during the outbreak of Acute Bacterial Meningitis in 1992 and 1993. I worked long hours, tirelessly, weekends included. It was the most challenging and most difficult time in my medical career, but Professor Bhat was always there, leading me on, inspiring, making me feel I was not alone in this tedious task.

I would like to thank Dr. Luo C. and Mr. Mwansa Salamu for the statistical advice, methodology and for the encouragement I received from them, Mr C. Mwakamui, Mr J. Banda of the Virology Laboratory for the secretarial services as well as Eddie Banda, Richard Tumeo, Hector Chimese of the Health Information Systems Department for data analysis.

Special thanks to Professor Chintu my teacher, mentor, and supervisor. I do appreciate his occasional scoff. I know it is done in good faith.

Thank you to Dr. Osborne my unit consultant during the study period, acknowledgements to Dr Uma for all the help given to me and to all doctors and nurses in our department for providing a conducive working atmosphere.

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ABM	-	Acute Bacterial Meningitis
CSF	-	Cerebral Spinal Fluid
SP	-	Streptococcus pneumonia
HI	-	Haemophilus influenzae
NM	-	Neisseria meningitidis
ATT	-	Anti Tuberculosis Treatment
SKA	-	Serum Killing Activity
UTH	-	University Teaching Hospital
UNZA	-	University of Zambia
ARI	-	Acute Respiratory Infection
CNS	-	Central Nervous System
AF	-	Anterior Fontannel
LP	-	Lumbar Puncture
IV	-	Intravenous
BS	-	Blood Slide
MPs	-	Malaria Parasites
MOH	-	Ministry of Health
H/O	-	History of
BBB	-	Blood brain barrier
MPs	-	Malarial parasites
Lab	-	Laboratory
Chrystapen-		Crystalline penicillin
CFR	-	Case Fatality Rate
HIV	-	Human Immune Deficience Virus
AIDS	-	Acquired Immuned Deficiency Syndrome
TNF	-	Tumor Necrosis Factor
BBB	-	Blood Brain Barrier
OR	-	Odds Ratio
PEM	-	Protein Energy Malnutrition
PICU	-	Paediatric Intensive Care Unit

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CHAPTER 1

1.0.0 INTRODUCTION

Bacterial Meningitis continues to be an important cause of morbidity and mortality, despite the availability of effective bactericidal antibiotics. Case fatality rates of 10-30% have not changed in the past thirty years, and continue to leave a high incidence of neurological sequelae all over the world [1,2,3].

Outbreaks of *Meningococcal* disease continue to occur in industrialised and non industrialised countries[2,4,5] Africa has a so called *Meningococcal* belt which lies over countries in the Southern Sahara, extending from Ethiopia and Sudan on the Eastern coast, through Northern Uganda, Niger, Benin, right up to the Gambia on the Western coast[1,5]. Here *meningococcal* meningitis epidemics have been known to recur in 5-12 years cycles during the hot dry season. Outbreaks occurring outside the meningitis belt like those in Tanzania 1989/90, have been rare in the past[5,6,7].

Zambia has experienced only two documented outbreaks of *meningococcal* meningitis. The first one was in Kitwe in 1974/75 and the second was in the dry hot season of 1992, after which we continue to experience elevated rates of the same disease in 1995. Bacterial meningitis is a problem for public health that has to be reviewed periodically. Most of the infections are due to *N. meningitidis, Haemophilus influenzae* or *Streptococcus pneumoniae*.

This study is necessary, because it will help identify the commonest pathogens causing ABM in Zambian children, it might demonstrate the effectiveness of the empiric choice of antibiotics used in the treatment of ABM in Zambia and hopefully the conclusions deduced from this study, might be adopted to improve the quality of health care in any epidemic of ABM.

1.2.0 ZAMBIA

1.2.1 PHYSICAL SETTING

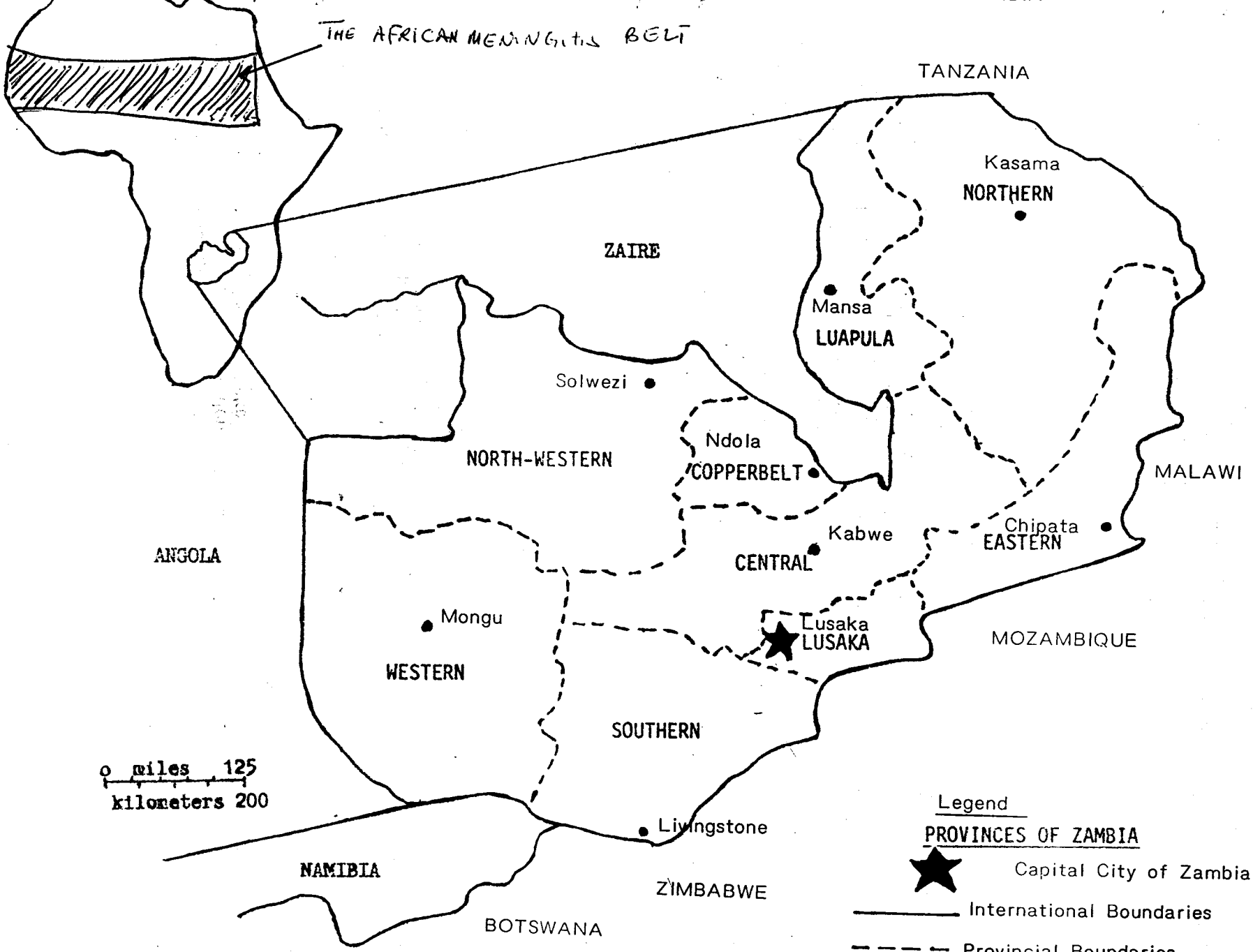
Zambia lies in South Central Africa between 8-18 degrees South latitudes and between 20-35 degrees East longitudes. It lies like a large butterfly sprawling over the Central African plateau with an average altitude of 1,127 metres above sea level. Zambia is landlocked covering an area of 752,614 Sq kilometres and consisting of about 2.5% of Africa. It shares borders with Zaire 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. Zambia is divided into 9 provinces; Eastern, Southern, Central, Lusaka, Western, Copperbelt, Luapula, Northern, North Western[10] (Graph I).

1.2.2 CLIMATE

Zambia's climate is mainly subtropical. There are three distinct seasons: with a hot dry season from September to October with temperatures of 26 - 30°C; the warm wet season from late November to early April, a cool dry season stretches from Early May to August with temperatures of 14° - 28°. The Copperbelt, Northwestern, Northern and Luapula province get the most rain with over 1000mm per annum. There is a decrease of rainfall towards the south and East with an annual rainfall of about 600mls.

Over the past 20 years, mean average annual temperatures have remained fairly constant, but there has been a drop in the mean average annual rainfall, starting from the 1991/92 rainy season (Graph No. 8).

Typical vegetation is Savanna grasslands with a mixture of various types of trees and tall grass. The woodland is mostly deciduous found on the main plateau. Tropical forests are found in the Northern tips of Zambia, in the North Western and Northern provinces. However the past 20 years has witnessed massive deforestation of Zambia's once rich forests and woodlands by charcoal burners and villagers, who utilise this natural resource as a source of fuel.


THE AFRICAN MENINGITIS BELT
TANZANIA
Kasama
NORTHERN
ZAIRE
Mansa
LUAPULA
Solwezi
Ndola
NORTH-WESTERN
COPPERBELT
MALAWI
Kabwe
Chipata
EASTERN
ANGOLA
CENTRAL
Mongu
Lusaka
LUSAKA
MOZAMBIQUE
WESTERN
SOUTHERN
0 miles 125
kilometers 200
Livingstone
NAMIBIA
ZIMBABWE
BOTSWANA
Legend
PROVINCES OF ZAMBIA
Capital City of Zambia
International Boundaries
Provincial Boundaries

1:2:3 POPULATION

The 1969 , 1980, 1990, 1992 National census reported total population of 4.0 million, 5.7 million, 7.8 million and 8.3 million end of 1992. Zambia had a mean growth rate of 3.1 percent per annum between 1969 - 80 and 1980 - 90, the highest being in Lusaka at 5.6%[8,9].

Zambia has a young population with under 15s accounting for close to half the population. The most vulnerable group is the under 5 which amounts to one fifth of the total population.

The overall population density has increased from 5.3 people per square kilometre in 1965 to 7.5 in 1980 and 10.4 per square kilometre in 1990. The average density in 1990 ranged from 55 people per square kilometre in Lusaka province, and 50 in the Copperbelt which are both heavily urbanised, to 5.3 per square kilometre both in Western and Northwestern provinces [8,9].

There has been continuous migration of people to Urban centers, which has resulted in a steady increase of urban population from 29% in 1969 to 42% in 1990. Whilst the population of rural areas has increased by 2.8%, that of urban areas continue to grow at about 3.7% making Zambia the most urbanised country in the region. In Lusaka urban the paediatric population as per 1980 census was 275,250, it rose to 355,692 in the 1990 census. The under 15s constitute 46.2% of the urban population. An average household has 5 people[8,9,10].

1.2.4 HISTORY OF GOVERNMENT

In October 1964 Zambia became independent from Britain and adopted a multiparty system with United National Independence Party (UNIP) as the ruling party. It had been under British colonial rule from 1924. In 1953 the Federation of Rhodesia and Nyasaland (Malawi) was formed. This federation was dissolved in 1963 to make way for independence and majority rule in 1964. By 1973 Zambia had become a one party state under Dr Kaunda's UNIP. The present Government headed by Frederick Chiluba came to power in 1991. The President is elected by universal suffrage for a term of 5 years.

Zambia is a unitary republic and has over 73 tribes. The major tribes are the Bemba group, Nyanja group, BantuBotatwe and Lozis. The majority of the people in Zambia are christians, but other religions and beliefs are well tolerated.

1.2.5 ECONOMY

Zambia has a mixed economy consisting of a modern and urban-oriented sector confined to the line of rail (apart from the Zambia-Tanzania railway) and a rural agricultural sector. Copper mining remains the country's main economic activity accounting for 95% of export earnings and contributing to about 45% of government revenue[10].

Principal non traditional exports are primarily agricultural products, fresh fruits and vegetables, cut flowers, semi precious stones, textiles and building materials, timber and wood products etc. but the development of these exports continue to remain below expectations[8,9,10].

The fall in copper prices, rising oil prices and slow pace of industrialization with a heavy dependence on imports have retarded economic growth.

As a result of an apparent decline in the national economy, the provision of social services such as health and education have been drastically affected. In an effort to halt the economic recession the Movement for Multiparty Democracy (MMD) has launched an economic recovery programme (ERP) to turn the protracted decline of the economy into a sustained positive growth.

1.2.6 PROVISION OF HEALTH SERVICES

Health services are provided by the government, mission (church) and industrial institutions, private practitioners and the traditional sector. The structure for provision of health and medical services in Zambia is as follows:

(a) Community health centers
(b) Health centers (stage 1 & 2 and mobile clinics)
(c) District hospitals
(d) General hospitals
(e) Central and specialised hospitals

Health Centers provide services mainly to the Rural population, districts without hospitals are served by large Rural health centers, Community health workers provide basic health to the community.

Private surgeries operate primarily in Urban areas. Practice is mainly for out-patient services only and payment is by fee for services rendered or on membership basis. There is no National Health Insuarance Scheme in Zambia

In the traditional sector health service are provided by traditional healers and traditional birth attendants who operate mainly in rural areas. Clients pay for services either in cash or in kind.

1.2.7. LEVELS AND TRENDS IN INFANT AND CHILD MORTALITY.

There is an apparent downtrend in child survival prospects over the last decade. From 1977-1981 to 1987-1991, the under five mortality had risen by fifteen percent from 152 to 191 per thousand live births. Much of this resulted from an increase in mortality under the age of one. Both neonatal and post neonatal infant mortality increased by 35 percent in the last 15 years. In this same period child mortality had risen by almost 20 percent[8,9].

These findings signal the beginning of an era of increased childhood mortality in Zambia, in which deteriorating economic conditions coupled with the HIV/AIDS epidemic have led to the break down of infrastructure and institutions that one time checked the downward trend of infectious diseases in Zambia.

CHAPTER 2

ACUTE BACTERIAL MENINGITIS (ABM) IN CHILDREN

2.0.0 THE PROBLEM

Acute bacterial meningitis continues to be an important cause of morbidity and mortality all over the world. It occurs sporadically or in outbreaks and it is sometimes seasonal. A substantial increase in the number of meningitis has been reported everywhere in Africa since 1988 [7,11]. Meningitis has a high mortality rate that can exceed 50% despite modern therapy.

Meningococcal meningitis is a notifiable disease in Zambia although it is under reported by community health centers, traditional healers and private surgeries, therefore, caution should be taken when using data derived from the "bulletin of health statistics" as indicative of community health status, because this data is derived from government institutions only and do not reflect the actual prevalence of the disease in the community. However, the number of *meningococcal* cases reported from all over Zambia to the Ministry of Health, increased sharply (graph no. 1 next page) from 1991, and one explanation given hypotheticaly is that a new strain of group A *Neisseria meningitis* has been responsible for this outbreak [9,11]. *Meningococcal* meningitis case fatality rates in Zambia in 1992 stood at 294/1000 in hospitals[9].

A variety of factors such as access to health facilities, medical fees etc influence the number of new cases being reported. Recent outbreaks in Tanzania and Uganda appear to indicate that the meningitis belt is spreading south of the endemic sub sahelian regions [3,7,12].

In Zambia four studies have been done on ABM. The first study was done by Sheila Johnston, former Medical Registrar at Lusaka Central Hospital. The study was published as **"Meningitis in Lusaka: A study of the natural history of patients seen in 1966/67"**[13]. The study embraced all age groups. Children aged from 1 - 24 months and adults were responsible for the majority

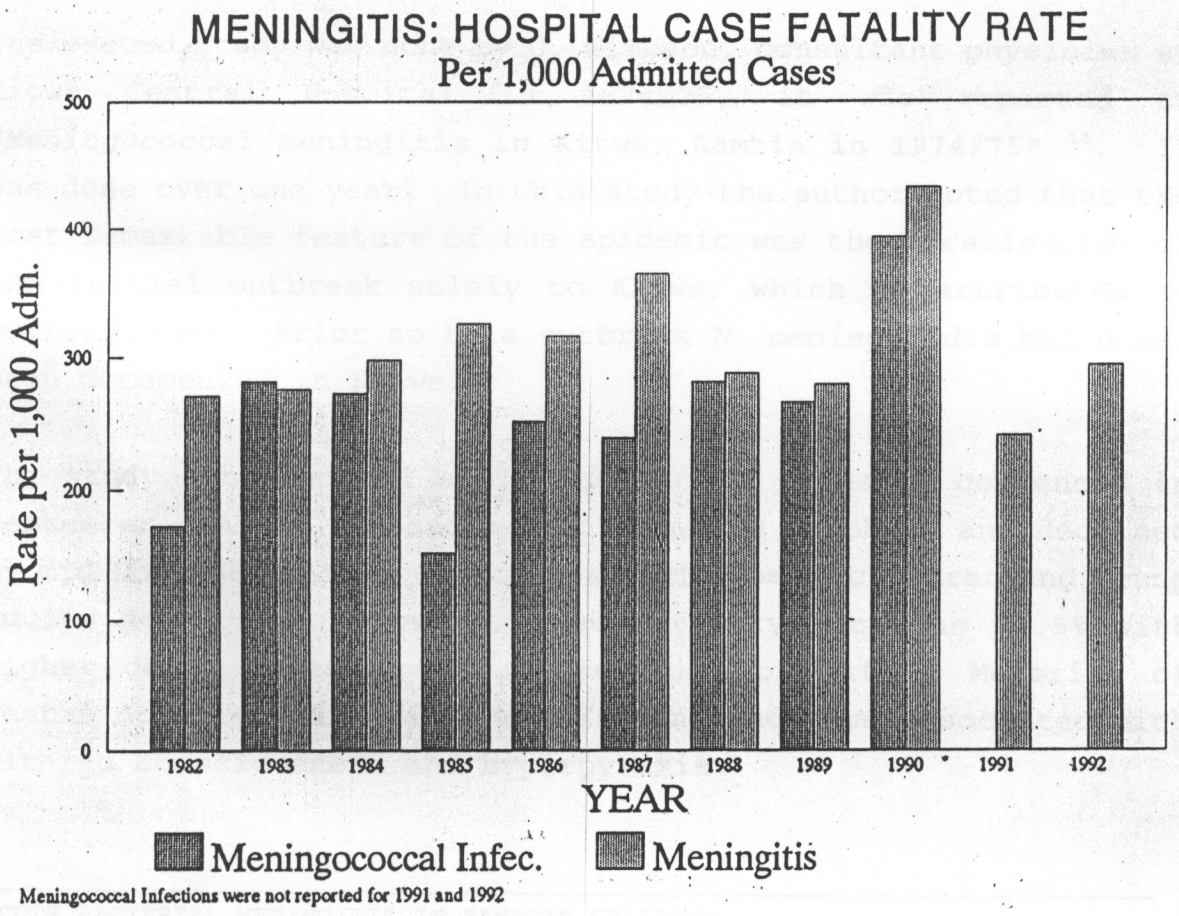
Table 1

MENINGOCOCCAL INFECTIONS AND MENINGITIS ,HOSPITAL ADMISSIONS, DEATHS AND FATALITY RATE PER 1,000 CASES 1982 – 1992

YEAR	Meningococcal Infections Admissions	Deaths	Case Fatality Rate per 1,000	Meningitis Cases	Deaths	Case Fatality Rate per 1,000 Cases
1982	168	29	172.6	1,410	383	271.6
1983	85	24	282.4	1,316	364	276.6
1984	84	23	273.8	1,245	371	298.0
1985	105	16	152.4	1,136	370	325.7
1986	99	25	252.5	1,370	433	316.1
1987	75	18	240.0	1,508	550	364.7
1988	39	11	282.1	1,480	427	288.5
1989	60	16	266.7	1,428	400	280.1
1990	33	13	393.9	1,772	766	432.3
1991	n.a.	n.a.	n.a.	3,272	790	241.4
1992	n.a.	n.a.	n.a.	3,622	1,065	294.0

NOTE: Data for the years 1991 and 1992 on Meningococcal Infections is not available due to change in reporting format.

Figure 1



TAKEN FROM "THE BULLETIN OF HEALTH STATISTICS 1989 - 1992 (9)"

of cases. Bacteriological isolation was successful in 39 out of 83 CSF samples (47%). The most common pathogens were *S. pneumoniae* 19 (48.7%), *H. influenzae* 15 (38.5%), *Meningococcus* 2 (5.1%) and dual *Meningococcal/Pneumococcal* infection 1 (2.5%).

Seasonal distribution showed maximal incidence occurring in September and October, the hottest and driest months of the year. *H. Influezae* meningitis was noted to be mainly the disease of the young below the age of 2 years. *S Pneumoniae* was fairly well distributed in all age groups, and among adults it was the commonest pathogen.

She concluded that the outcome of ABM appeared to be more related to the clinical state rather than to the CSF findings and that the presence of convulsions gave rise to a poor prognosis. She attributed the large numbers of convulsions and semicoma, as an indication of late presentation to hospital. She noted the rare occurrence of meningococcal meningitis in Lusaka, in contrast to the endemic *meningococcal* belt in the Sahel Region.

The second study was done by J. Simpson, consultant physician at Kitwe Central Hospital in 1974/75, it was reported as **"*Meningococcal* meningitis in Kitwe, Zambia in 1974/75"** [14]. It was done over one year. In this study the author noted that the most remarkable feature of the epidemic was the localisation of the initial outbreak solely to Kitwe, which he attributed to overcrowding. Prior to this outbreak *N. meningitidis* had never been documented in Kitwe.

The study embraced all age groups. The epidemic commenced in september, 1974, reached a quick peak in October, and declined by mid November, 1974. Commonly affected were children and young adults aged 0 - 30 years, case fatality rate was 14.5% with higher death rates at the extremities of life. Majority of deaths occurred early after admission, and were associated with altered consciousness and hyperpyrexia.

He concluded that the high mortality rate could be explained by a non immune population, mainly with poor nutritional background, and endemic malaria which might interfere with the immune mechanism. He noted that the Kitwe epidemic demonstrated that cerebral, spinal or, focal complications are commoner than previously recorded.

Two studies were done on ABM in children by Chintu and others. In the first study carried out over a period of one year (first August 1973-thirty first July 1974) [15], the prevalence rate of ABM among paediatric in-patients was 85:10,000 and the most common pathogens were *S.pneumoniae* about 37%, *H. influenzae* about 10,7%, *Salmonella Sp* about 4.6%. Miscellaneous organisms accounted for the rest. The second study was done over a period of one year (from the first of march 1978 to the 28/03/1979). The prevalence rate of ABM had risen to 138:10,000 among hospitalised children and the most common pathogens were; *Pneumococcus*-20.7%. *Meningococcus*-15.4%, *Staphylococcus* about 5%, *H. influenzae* about 5%. The authors pointed out that, bacterial meningitis was on the increase and highlighted the changing pattern of ABM's aetiological factors, and that *Neisseria Meningitides* had appeared on the scene only in the second study. They concluded that the *meningococcal* belt was moving southward[13].

From the studies done in Southern Uganda in 1990, it was also concluded that the *meningococcal* belt was spreading southward from it's endemic area. It was previously observed only in the dry Northern belt of the country. In addition, localized outbreaks of meningitis have also occurred during the rainy season, contrary to earlier epidemics, which were strictly seasonal and occurred in cycles of 8-12 years[7].

2.0.1. MENINGITIS DEFINITION

Meningitis is an inflammatory process of the meninges. It can be caused by a variety of pathogens, viral, bacterial, fungi etc. ABM is an acute Inflammatory process of the meninges caused by bacteria of less than 28 days duration [1,17,18].

2.1.0 AETIOLOGY

The most common pathogens causing bacterial meningitis in children aged from 1 month to 14 years today are:

1. *Neisseria meningitidis*
2. *Streptococcus pneumoniae*
3. *Haemophilus influenzae*

2.1.1 *STREPTOCOCCUS PNEUMONIAE*

It occurs in children under 2 years of age and older children with predisposing factors for example pneumonia, Sinusitis, Sickle cell disease and HIV/AIDS [17,19]. The illness is usually severe, insidious onset with an antecedent acute respiratory tract infection and usually run concomitantly with pneumonia, gastro intestinal manifestations and anaemia[17].

2.1.2 *MENINGOCOCCAL* MENINGITIS

Sporadically it is observed in infants and toddlers, but during epidemics affected are older children (3 - 14 years of age). It occurs commonly in the hot dry months of the year (and is favoured by drought) and declines when the rains come. *Meningococcal* meningitis can be rapidly progressive, deaths may occur during the first 24 hours of admission. The presence of a petechial rash indicates associated meningococcaemia. With early initiation of therapy children respond very well and case fatality is about 10%. The most common long term complication is hearing impairment, while gait disturbance, eye manifestations and other neurological signs are usually transient [1,17,18,20,21,22].

2.1.3 *HAEMOPHILUS INFLUENZAE* MENINGITIS

H.Influenzal type B is the most common bacterial cause of meningitis in children under 6 years of age all over the world. But this does not seem to be the case in Zambia, where it ranks third after the NM, SP [13,14,15,16]. The occurrence of *H.Influenza* in older patients should prompt efforts to exclude otitis media, other parameningeal foci of infection, CSF leak, or Immunodeficiency Syndrome[6,17,23].

The continuation or recurrence of decreased mentation or fever after antimicrobial therapy may indicate the presence of subdural effusions, there is an associated death rate of about 3-8% and 30 -50% of children remain with permanent neurological sequelae.

2.1.4 GRAM NEGATIVE BACILLARY MENINGITIS

Gram negative bacillary meningitis is usually hospital acquired, it can occur with head trauma or there may be medical conditions such as accompanying gram negative sepsis, ruptured brain abscess, impaired host defenses. The most likely gram negative bacilli to cause meningitis after the neonatal period are *klebsiella, pseudomonas, E.coli, Salmonella*. Although it is essential to start therapy early, initially gram stains maybe negative in up to 50% of the patients[17,18].

2.2.0 EPIDEMIOLOGY

A major risk factor for meningitis is the attenuated immunologic response to specific pathogens associated with young age. The risk is greatest among infants between 1 and 12 months of age, 95% of cases occur between 1 month and 5 years of age, but meningitis can occur at any age. Additional risk factors include recent colonisation with pathogenic bacteria, close contact with individuals having invasive disease (home, day care centres, schools, military barracks), crowding and poverty. The mode of transmission is probably person-to-person contact through respiratory tract secretions or droplets. The risk of meningitis is increased among patients with presumed occult bacteraemia. Other systemic infections are also associated with an increased risk of meningitis. Congenital or acquired CSF mucocutaneous communications such as cranial and middle ear or inner ear fistulas, CSF leakage through a rupture of the meninges due to a basal skull fracture into the cribriform plate or paranasal sinus are associated with an increased risk of *pneumococcal*, and less often, *H. influenzae* type B meningitis. Lumbosacral dermal sinus and meningomyelocoele are associated with *staphylococcal* and enteric bacterial meningitis. Penetrating cranial trauma and CSF shunt infections increase the risk of meningitis due to

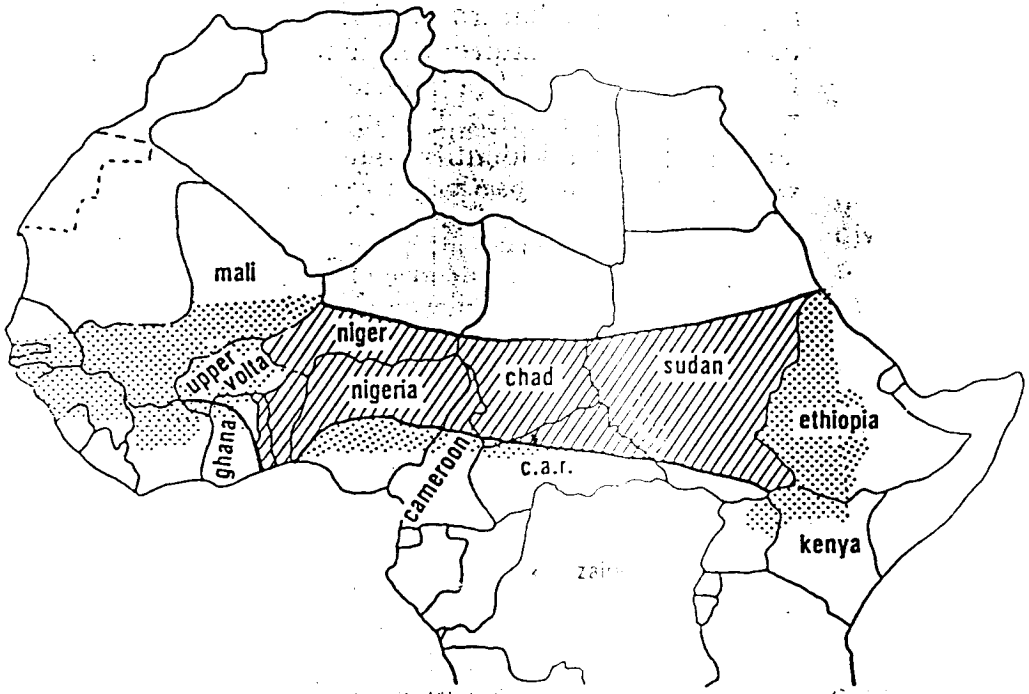


FIGURE 1. The African meningitis belt. The shaded area indicates the area of the belt as originally defined by Lapeyssonnie. Dotted areas indicate regions where outbreaks of meningococcal disease with epidemiologic features characteristic of the African meningitis belt have sometimes been recorded. (Adapted from Lapeyssonnie L: Bull WHO 28(Suppl 3):3, 1963.)

Staphylococci and other cutaneous organisms.
Epidemic group A *meningococcal* meningitis follows a unique distinctive pattern in Sub-sahara Africa[11] (Figure 3). Epidemics results from a complex combination of HOST, ORGANISM and ENVIRONMENTAL RISK FACTORS[23,24,25,26,27].

Recent studies suggest that "antigenic shifts" in group A *meningococcal* clones may trigger an out break of disease by suddenly decreasing herd immunity within a population[11,12]. Although the introduction of a new Group A *meningococcal* strain into a susceptible population may contribute to the likelihood of an epidemic, the presence of additional environmental factors like drought, immigrations, overcrowding plus coincidental respiratory infection are also necessary for an epidemic to occur.

Serogroup A is by far the dominate serogroup responsible for ABM in Africa. Isoenzyme typing suggest that the new epidemic strain belongs to the III - 1 clone of Olyhoeks classification [28].

This strain has been linked to the epidemic that started in China, passed through Northern Nepal, Northern India and caused a very large out break in Mecca in 1987, including Sub-Sahelian Africa as the pilgrims returned home from Hajji. This sulfonamide resistant clone had not been identified in Africa prior to 1983. In the *meningococcal* belt, although the new strain has been documented, the predominant serogroup still remains serogroup A, subtype A:4 P:19 [12,28].

SEROGROUP C is occasionally responsible for epidemic outbreaks in tropical Africa (Niger, Chad, Burkinafaso and Mali) and is endemic in the *Meningococcal* belt[12,28].

SEROGROUP B appears to be absent from the *Meningococcal* belt, it is found in South Africa, along the Mediterranean coast, in the Americas and Europe.

SEROGROUP X constituted 24% of *N. menengitidis* strains identified in Niger in 1991[12].

Studies done in the Inter epidemic periods in the *meningococcal* belts have shown that greater than 50% of childhood ABM are caused by *H. Influenzae* and the highest peak incidence is in infants less than 12 months of age [24,29]. However in Zambia before the out break of *meningococcal* meningitis in Kitwe, and in the inter epidemic periods the leading pathogen causing ABM in children has always been *S.pneumoniae* [13,14,15,16].

2.3.0 PATHOPHYSIOLOGY

The pathogenesis of ABM involves 6 steps:

1. Attachment of the organism to epithelial cells of nasopharyngeal and oral pharyngeal mucosa.
2. Transgression of the mucosal barrier.
3. Survival in the blood stream (avoiding phagocytic cells and bacteriologic activity).
4. Entry into the CSF.
5. Survival in CSF.
6. Production of disease in the meninges and brain.

Bacteria that most frequently cause ABM have a variety of virulence mechanisms, each of which play a unique role in one or more of the successive steps of the pathogenic process. Bacteria that cause ABM usually attach to and colonise host mucosal surfaces in the nasopharynx. They all have pili that appear to mediate attachment [1,17,30,31].

Bacteria are ingested without being killed by epithelial cells of the nasopharyngeal mucosa which aid their transgression through to the sub epithelial tissue where they gain access to the blood stream. There is a possible role of bacterial cell wall polysaccharide, as is suggested by the fact that only certain capsular types of *meningococcal, S.Pneumoniae, H.Influenzae,* Group B *Streptococcus* and *E.Coli* have a predilection for causing ABM.

Once in the blood stream successful meningeal pathogens appear to avoid phagocytosis by polymorphonuclear leucocyte and cells of the reticuloendothelial system by virtue of having anti phagocytic capsules.

How bacteria enter the CSF space from the blood stream is not known. It is postulated that they enter probably via the choroid plexuses of the lateral ventricles and then spread to the extra cerebral CSF along the normal paths of CSF flow.
Bacteria may also enter the CSF space directly through defects of congenital or traumatic origin, or from parameningeal suppurative foci (ears, mastoids and paranasal sinuses). The CSF is generally devoid of sufficient humoral factors or phagocytic cells to repel successfully the initial invasion.

Meningeal pathogens are generally limited to the subarachnoid space. Thus the functional disorder of the nervous system in ABM is likely to result from occlusion of blood vessels traversing the subarachnoid space and from intense inflammatory process, such as neutrophilic pleocytosis. Bacterial cell components stimulate the release of cytokines such as interleukin-1(il-1), prostaglandin and tumor necrosis factor(TNF). They in turn cause alteration of the permeability of the blood brain barrier (BBB) to various substances leading to cerebral oedema and raise in the intracranial pressure.

If there are defects in host defenses, bacteria that do not normally have the virulent factors to complete all steps of the pathogenic process may do so and cause ABM, or bacteria that can complete all steps may do so more easily and more often. Lack of humoral immunity, the presence of complement defects, loss of integrity of CSF space and other less well defined factors such as stress and viral infections all predispose to ABM [28].

2.3.1 PATHOPHYSIOLOGY OF ABM IN PATIENTS WITH HIV

Bacterial infections have emerged as a major threat to patients infected with human immunodeficiency virus (HIV). The respiratory tract is the primary focus of these infections. As in the general population, *Pneumococcus* is the most common respiratory pathogen with associated bacteremia and subsequent meningitis in patients affected with HIV [31,32].

Population based studies confirm the high incidence of pneumococcal meningitis among seropositive patients. It is usually a common complication of pneumonia and relapses occur frequently. Specific local and systematic defects in host defenses are markedly reduced.

It has been shown that seropositive patients have a decreased number of Ig A producing cells at mucosal sites which hamper Bacterial adherence to mucosal surfaces and prevent colonisation [31,32,33].

Opsonisation is required for effective phagocytosis and killing by human pulmonary alveolar macrophages. Although spontaneous killing of intracellular organism by mucosal macrophages from patients with AIDS is generally intact, CD4+ T-cell numbers and function are depressed in these patients. Decreased CD4+ T-cells mediated antibody dependent cellular cytotoxicity has been proposed to indicate in part, the predisposition to *salmonella* bacteremia and may impair the ability to kill *S.Pneumoniae*, predisposing this subset of patients to invasive *pneumococcal* infection [31,32].

2.4.0 RISK FACTORS ASSOCIATED WITH BACTERIAL MENINGITIS IN ZAMBIA

2.4.1 OVERCROWDING

The past 15 years has seen Zambia turn into the most urbanised country in the Region. There has been continuous migration of the Rural population to urban centers because of lack of opportunities in the rural areas. Health services that were planned for a much smaller population continue to get the same

funding from the government leading to inadequate health care [8,9].

2.4.2 MALNUTRITION

Malnutrition is a common condition in Zambian children. A malnourished child with less than 80% of weight for age will always have an impairment of the immune function, more so at less than 70% there's severe impairment. These children are highly susceptible to respiratory infections, Gastroenteritis and viral diseases which usually become invasive [35]. In Zambia, Lusaka province has the highest number of cases, 17,116 (6.2)% of under five years are malnourished [9].

2.4.3 RESPIRATORY DISEASES

Respiratory disease are a frequent reason for seeking medical care, in fact in the Zambian paediatric age group it is the leading cause of admission to hospital. According to a study done by MOORE and others[11], who investigated the role of coincidental respiratory viral and *mycoplasmal* agents in the pathogenesis of *meningococcal* meningitis type A during an epidemic in CHAD [34]. They found out that case patients were more likely than controls to have nasal colonisation or infection with respiratory viruses and mycoplasma species. Respiratory pathogens were found more commonly in older patients with Meningitis [11,36,37].

2.4.4 DIARRHOEAL DISEASES

Are the 5th most common cause of paediatric hospital admissions, and the 6th cause of paediatric mortality in UTH. Although the incidence of diarrhoeal diseases seems to be coming down over the decade, a few children are seen every year with invasive infection of enteropathogens, such as *salmonella, klebsiella, E coli*. They are mostly seen in infants, or in children that are immune compromised [35].

2.4.5 AGE

In the five year period of 1987 - 1991, one out of five Zambian children died before their first birthday.

INFANT AND CHILD MORTALITY BY 5 YEAR RATES

PER 1,000 LIVE BIRTHS 1979 -1992 [8]

TABLE 2

YEARS	NEONAT. MORTAL	POSTNEON. MORTAL	INFANT MORTAL	CHILD MORTAL	UNDER5 MORTAL
1989 TO 1992	42.5	64	107	93.6	190.7
1984 TO 1989	37.1	50	87.6	81.7	151.9
1979 TO 1984	31.6	47.9	79.5	78.6	151.9

Foot note: MORTAL.....Mortality
NEONAT.....Neonatal.
POSTNEONAT .....Post neonatal infant.

These findings suggest the beginning of an era of increased childhood mortality in Zambia, in which deteriorating economic conditions coupled with the spread of new infections such as HIV/AIDS and *Meningococcal* Meningitis, have led to the breakdown of infrastructures and institutions that one time supported the downward trend in childhood mortality.

2.5.0 CLINICAL FEATURES

The mode of onset of acute *meningococcal* disease has two predominant presentations. Sudden onset, with rapidly progressive manifestations of shock, purpura, disseminated intravascular coagulation, and reduced levels of consciousness, as a dramatic and often fatal presentation of *meningococcal* sepsis. Whilst *meningococcal* meningitis usually presents with the symptomatology of fever, headache, vomitting and neck

stiffness (or a bulging anterior fontanelle in the infants). It may be associated with the loss of consciousness and seizures. However, there may be an overlap in symptoms and signs when a patient presents with a meningitis associated with clinical *meningococcaemia*, it may lead to death within 24 hours. *H. influenzae* type B and *pneumococcus meningitis* (and some cases of *meningococcal* meningitis) is preceded by several days of upper respiratory tract or gastrointestinal symptoms. This subacute presentation may also be complicated by partial treatment with antibiotics (in 25-50% of patients) for associated otitis media or respiratory tract infections [1,17,18,37].

ABM is also associated with non specific findings such as fever (present in 90-95%), anorexia and poor feeding, upper respiratory tract infection, myalgias, arthralgias, tachycardia, hypotension, and various cutaneous signs such as petechiae (present in 10%), purpura, or an erythematous macular rash. Meningeal irritation is manifest as nuchal rigidity, back pain, Kernig sign and Brudzinski sign. In some children, particularly young infants, these signs may not occur. Increased intracranial pressure is suggested by headache, emesis, bulging fontanelle or diastasis of the sutures, oculomotor or abducens nerve paralysis, a combination of hypertension and bradycardia with apnea or hyperventi-lation, decorticate or decerebrate posturing, stupor, coma or signs of herniation. Papilloedema is uncommon in uncomplicated meningitis. Focal neurological signs may be due to vascular occlusion or abscess formation. Overall 14% of children with bacterial meningitis have focal neurologic signs[18].

Seizures (focal or generalised) due to encephalitis, infarction, or electrolyte disturbances are noted in 20-30% of patients with meningitis [18]. Seizures that occur on presentation or within the first 4 days of onset are usually of no prognostic significance. Seizures that persist after the 4th day of illness, those that are difficult to treat, and those that appear late in the course of meningitis are associated with poor prognosis [16,18].

Alterations of mental status and a reduced level of consciousness are common, and may be due to increased intracranial pressure, encephalitis or hypotension; manifestations include irritability, lethargy, stupor, obtundation, and coma. Comatose patients have a poor prognosis and neurologic complications include seizures, increased intracranial pressure, cranial nerve palsies, stroke, cerebral or cerebellar herniation, transverse myelitis, ataxia, thrombosis of dural venous sinuses, and subdural effusions [18].

2.6.0 PROGNOSTIC FACTORS

2.6.1 POOR PROGNOSTIC SIGNS FOR ABM

1. Coma and obtundation on admission with or without convulsions.
2. Decorticate and decerabrate posturing.
3. Seizures that persists after the 4^{th} day, those that are difficult to treat, and those that appear late in the course of meningitis.
4. Young age (less than 12 months).
5. Severe PEM.
6. Associated pneumonia
7. Shock

2.7.0 DIAGNOSIS

Meningitis is diagnosed from

1. The history collected from the patient or guardian (with complaints of fever, headache, vomiting, neck stiffness in the older child, or a bulging anterior fontanelle with irritability in the infants).

2. Clinical examination.
   In case of *meningococcal* meningitis which usually has a short history, meningeal signs might be absent, therefore a high index of suspicion is important with the performance of a lumbar puncture and prompt therapy. A petechial rash indicates associated *meningococcaemia*.

3. LP and Laboratory examination of the CSF:

i. Macroscopic examination of the CSF is usually helpful, although a clear CSF does not exclude ABM. Diagnosis is confirmed by;

ii. Microscopic examination of CSF on direct smear with Gram stain for pyogenic bacteria, *Ziel Nielsen* for *Mycobacterium tuberculosis*, and *Nigrosin Stain* for *Cryptococcus*.

iii. Positive CSF bacterial culture is the gold standard.

iv. CSF biochemical examination, high CSF protein greater than 0.4g/l, low CSF sugar less than two thirds of serum sugar or less than 2mMol/l.

v. CSF pleocytosis - a CSF cell count of more than 10 cells per $1mm^3$ predominantly neutrophils.

2.8.0 TREATMENT

Bacterial meningitis is presented as a clinical entity, because clinical manifestations usually do not allow the clinician to distinguish various etiological agents on admission. Initially antibiotic treatment and general supportive management are standard irrespective of the specific infective bacteria.

In Zambia the empiric choice in very young children under 2 months of age is *ampicillin* and *gentamicin*, and in older children *crystalline penicillin* and *chloramphenicol*. It is based on the antibiotic susceptibilities of the most common pathogens causing bacterial meningitis in Zambia (*H. Influenzae, S. Pneumoniae* and *N. Meningitides*). Ampicillin is given up to 300 mg/kg/day divided into 4 doses every 6 hours, chloramphenicol 100 mg/kg/day hours 6 hourly and Crystalline penicillin up to 400,000 IU /kg/day divided into 4 doses 6 hourly intravenously.

Subsequent antibiotic therapy when culture and sensitivity results are out after 48 to 72 hours, meningitis is treated in

line with the sensitivity pattern. Meningitis caused by

S. pneumonia and *H. influenzae* are treated for two weeks while that caused by *N. meningitids* is treated for 7 - 10 days [18].

Seizures are controlled immediately with intravenous diazepam (0.1-0.3mg/kg/wt/dose). The patient is maintained on phenobarbitone or phenytoin whatever is available.

In severe *meningococcal* infections rapid killing of bacteria by high concentrations of bactericidal antibiotics in the CSF effectively sterilizes the CSF but the liberated toxins can induce cytoxine mediated inflammatory response. In this condition *Dexamethasone* 0.15 - 0.4mg/kg/dose is given 6 hourly for two days with the initiation of antibiotic therapy to lessen the inflammatory process [27,28,28,36,39,40].

Mannitol is sometimes recommended when there is a very high rise in intracranial pressure (8mls/kg of 20% solution per dose 8 - 12 hourly for two days).

2.8.1 CRITERIA FOR DISCHARGE

i) Clinical improvement and the child should be afebrile for at least 3 days.
ii) Non progressive neurological sequelae.
iii) CSF cell count of less than 20/mm^3 (> 90% should be mononeuclear).
iv) Serum/CSF glucose ratio should not be less than 30%.
v) Gram stain should show no organism.
vi) culture should be sterile.

* NB Serial lumbar punctures are not indicated in patients with uncomplicated meningitis due to *H. influenzae*, *S. pneumoniae*, and *N. meningitidis*, but is indicated in some neonates, in patients with gram negative Bacillary meningitis and in those who do not respond to conventional anti microbial therapy within 48 - 72 hours [18].

2.9.0 PROPHYLAXIS

2.9.1 *MENINGOCOCCAL* VACCINE: Literature recommends that all household, institutional and personal contacts of *meningococcal* meningitis of all ages should receive prophylactic cotrimaxazole or Rifampicin which has 80-90% efficacy in eradicating carriage [1,17,18]. But several studies done in most African countries suggest that its efficacy has not been proved and many authors recommend against any form of chemoprophylaxis against epidemic meningitis in Africa[12], because the majority of isolates in tropical areas are now sulphonamide resistant. *Rifampicin* 10mg/kg twice daily for 2 days will eradicate nasopharyngeal carriage, but resistance may develop, however, it is costly and doubtful wether short courses of Rifampicin should be widely dispenced in areas where tuberculosis is prevalent.

VACCINES: There is an effective vaccine against Serogroup A and C. The vaccine is very expensive, and the organization of mass vaccinations is recognized as being formidable. Studies done during an epidemic out break in Chad, have shown the failure of selective vaccination restricted to only AT- RISK groups to halt the epidemic, but showed a 100% efficacy in mass vaccination campaigns aimed at the whole population and which must be carried out in the shortest possible time [38].

TREATMENT OF CASE CONTACTS

The efficacy of a single injection of an oily suspension of chloramphenicol in the treatment of patients of all ages with *meningococcal* meningitis has been demonstrated. This antibiotic is therefore recommended for the disease under epidemic conditions. However, it is not adequate for treatment or prophylaxis of patients with meningitis caused *by Strep. pneumonia* and *Haemophilus influenza* [25].

Serogroup A and C *meningococcal* vaccine is available with only mild and infrequent adverse reactions. The immunisation is valid

10 - 14 days after administration, and protective immunity is estimated to last three to five years [25,38,44].

2.9.2. *PNEUMOCOCCAL* VACCINE:

Contains 23 capsular serotypes, although the spectrum of immunity elicited is broad, it is not expected to prevent all *Pneumococcal* infections. *Pneumococcal* vaccine is recommended for persons over 2 years of age who are at special risk because of asplenia, diabetes, cardiohepatic, renal disease or those that are immune compromised [18,28,36].

2.9.3. *H. INFLUENZAE*

CHEMOPROPHYLAXIS: Rifampicin is used to treat contacts of *H. Influenzae* type B meningitis in a single daily dose of 20mg/Kg weight (up to a maximum dose of 600mg) for 4 days. Most authors agree that prophylaxis should always be given when there are children less than two years of age [17,18].

Although young children are at particular high risk from *meningitides* caused by *Strep. pneumococci*, *H. influenza* or *E.coli*, vaccines that protect against these micro organism are not effective in this age group [35]. Therefore sustained protection of children of this age group will require development of vaccines that are immunogenetic in infants and that can induce T-cell memory [32,33].

CHAPTER 3

3.0.0 METHODOLOGY

3.1.0 OVERVIEW

The study is a descriptive longitudinal study of 871 children aged one month to 15 years, admitted to the University Teaching Hospital's Department of Paediatrics with a provisional diagnosis of acute bacterial meningitis.

The study was conducted over six months, during the high risk season for ABM in the hot dry months of 1992 and 1993 (from the first of August to the end of November). From routine admissions and laboratory results, it was noted that there was a sharp rise in the prevalence of ABM, which prompted the review of ABM de novo.

The study was carried out in ward A06 (a ward which was specifically designated to admit patients with a provisional diagnosis of ABM).

The **AIMS and OBJECTIVES** of the study were to determine the commonest pathogens responsible for the ABM outbreak, to revisit the epidemiology, clinical profile of ABM, and to detect the risk factors associated with ABM in Zambia.

The study was done without special funding, everything was done within normal hospital routine. This was deliberate, because it was also hoped that short comings in the hospital management of patients with ABM will be highlighted and suggestions on how to improve these shortcomings could be discussed.

3.2.0 SITE

The study was done at the University Teaching Hospital's Department of Paediatrics, Lusaka, Zambia. Lusaka is the capital of Zambia with a population of over one million people (46.2% are aged 0 - 15 years). It is the only hospital serving this population and more, because UTH is the largest referral hospital and the only University Teaching Hospital in Zambia.

3.4.0 DESIGN

This was a descriptive longitudinal study involving children aged between 1 month to 15 years admitted to ward A06 with ABM. All cases were registered and followed up to determine the incidence, clinical profile and outcome of ABM in children in Lusaka.

The children (guardians) were interviewed and examined by the principal investigator, who was also the Doctor in charge of ward A06, responsible for treating, discharging and following up of these patients.

The children were followed up at 2 weeks, 6 weeks, 12 weeks after discharge. Those with neurological sequelae were followed up much longer to help facilitate their rehabilitation quickly. Losses to follow up were documented and analysed.

3.5.0 SAMPLING AND SAMPLE SIZE

3.5.1 SAMPLE SIZE

All children admitted to ward A06 with a provisional diagnosis of ABM during the study period were recruited. Sample size was not calculated since the study was done during an epidemic of ABM and any child who met the criteria was recruited to the study.

3.5.2 SAMPLING

Every child aged 1 month to 15 years admitted to ward A06 with a provisional diagnosis of ABM was recruited by consecutive convenient sampling from 08:00 hours to 17:00 hours. Those admitted overnight were recruited in the morning, and all deaths occuring during the day and night were recorded.

3.5.3 INCLUSION CRITERIA

1. Children between 1 month to 15 years of age admitted to Ward A06 with a provisional diagnosis of ABM.
2. No formal consent was obtained from parents and guardians since the admissions where routine.
3. Successful lumbar puncture with turbid CSF, or clear CSF with a classical clinical picture of ABM (page seventeen).

4. Symptoms and signs of not more than 14 days duration.

3.5.4 EXCLUSION CRITERIA

1. Children under 1 month of age who routinely are not admitted to ward A06.
2. Dry tap on lumbar puncture.
3. Children with meningitis other than ABM comfirmed by laboratory results.
5. Clinical meningococcaemia without meningitis.

3.6.0 DATA COLLECTION

A preset, pretested questionnaire was used as data base. Information obtained on the questionnaire was collected by interviewing the parents or guardians. Added information was obtained by physically examining the study subjects and from the results of laboratory investigations.

3.7.0 LABORATORY MANAGEMENT

CSF was collected into two universal sterile bottles, and was sent to the Microbiology and Biochemistry laboratories in the shortest possible time.

3.7.1 BIOCHEMISTRY LABORATORY

CSF glucose concentration was determined by the enzyme test (Glucose oxidase), and CSF protein by the calorimetric method.

3.7.2. MICROBIOLOGY LABORATORY

CSF was inoculated onto Chocolate agar, *McConkey* or blood agar. Incubation was done in 10% carbon dioxide jars at 37°c for at least 24 hours. Smears were prepared for cell count, and for staining by Gram, *Ziehl Nielsen* and *Nigrosin* stains.

3.7.3 OTHER INVESTIGATIONS

Patients who had clear CSF, had blood slides for malarial parasites taken. Random sampling for retroviral screening test was done in 585 patients. Haemogrammes, blood cultures, ear, throat, nasal or swabs from skin lesions were not done due to constraints in the study. [The Haematology, Biochemistry and part of the Microbiology Labs were closed during the period under review due to operational problems].

3.8.0 ETHICAL CONSIDERATIONS

No consent was obtained from the parents or guardians since the cohort was part of routine admissions. Official consent and clearance was obtained from the Research and Ethics Committee of the hospital and from the Board of higher studies UNZA before doing the study. And for those children whose blood had been tested for HIV, results were kept under strict confidentiality. (Random sampling for HIV was done to help confirm or refute any association between HIV and ABM).

3.9.0 DIAGNOSTIC CRITERIA

A diagnosis of ABM was suspected by a typical clinical presentation and hospital course consistent with ABM (page seventeen), supported by either a history of a positive contact with a meningitis patient, a suggestive peripheral smear or biochemical CSF profile and ABM was confirmed by bacterial isolation on gram stain of a direct CSF smear on microscopy, or on CSF bacterial culture.

1. Suggestive Biochemical CSF analysis of high proteins > 0.4g/l, low sugars of < than 2mMol/l.
ii. Predominantly CSF polymorphonuclear pleocytosis.
iii. Positive CSF bacterial culture and/or a positive gram stain on a direct CSF smear.

3.10.0 DATA ANALYSIS

Data collected from 871 cases with a provisional diagnosis of ABM on admission was received and analysed. Various variables were looked at, such as sex, age, residence density, mothers education and occupation, size of house, and number of people per house hold. Noted also were the duration of illness prior to admission, history of a positive contact at home or at school, symptoms on admission. Records of monthly admissions for 1992 and 1993 were collected and analysed, in order to define the trend of admissions of ABM through out the year.

The clinical profile consisted of symptoms and signs of ABM , laboratory results, duration of hospital stay and out come. Immediate complications of ABM were also noted. The data was analysed using EPI-INFO (computer software epidemiological package Version 6.0) to analyse various variables. The odds ratio and their 95% confidence limits were calculated in order to identify associated factors that were statistically significant.

3.11.0 DEFINITIONS

3.11.1 FEVER Was defined as axillary temperature greater than 37.5°C, and hyperpyrexia as fever of more than 41°C. Patients were described as hypothermic if their axillary temperature was less than 36°C.

3.11.2 SHOCK was defined as systolic pressure of less than 70mm Hg in children older than 7 years, in younger children shock was a clinical diagnosis characterised by cold, pale or cyanotic distal extremities and depressed mentation.

3.11.3 PURPURA FULMINANS was considered present if there was progressive intravascular thrombosis (purpura) associated with shock.

3.11.4 A co-primary case of *meningococcal* disease was defined as illness in a house hold contact with onset of symptoms 24 hours after hospitalisation of the index case.

3.11.5 A secondary case was one with onset more than 24 hours but less than 31 days after hospitalisation of the index case.

3.11.6 CSF Pleocytosis was CSF WBC count greater than 10 cells /mm^3 in older children, and 15/mm^3 cells in infants.

CHAPTER 4

4.0.0 RESULTS

900 children with a provisional diagnosis of ABM were admitted and interviewed. 871 were recruited in the study, 29 were excluded for failing to meet the inclusion criteria.

4.1.0 EPIDEMIOLOGY

It was observed that greater prevalence was in the child population coming from Lusaka's peri urban high density and shanty areas, with the highest numbers coming from compounds situated in the South West of Lusaka (Figure 3) where prevalence rates of up to 9.7:1000 per Paediatric population were recorded compared to none at all in some more central and easterly low density areas.

TABLE NO 3: ASSOCIATION BETWEEN POPULATION DENSITY AND MORBIDITY

DENSITY	NUMBER	PERCENT
HIGH	775	89
MIDDLE	22	2.5
LOW	33	3.8
RURAL	41	4.7
TOTAL	871	100

Almost 90% of patients were from high density areas, situated in the south of Lusaka. However it was not clear why the equally densely populated compounds in the North West and East of Lusaka had less patients coming in (Figure 3)

4.1.1 AGE & SEX

The age distribution of patients was as listed below
174 cases (20.2%) were infants aged 1 - 12 months of age,
276 cases (31.8%) were aged 13 months to 60 months.
416 cases (48%) were aged over 60 months.

SEX DISTRIBUTION

TABLE 4

SEX	NUMBER	PERCENTAGE
F	393	45.1%
M	478	54.90%
TOTAL	871	100%

There was no obvious difference in the sex ratio, with females contributing 45.1% and males 54.9% respectively. A male to female ratio of 1.2:1.

DURATION OF ILLNESS PRIOR TO ADMISSION

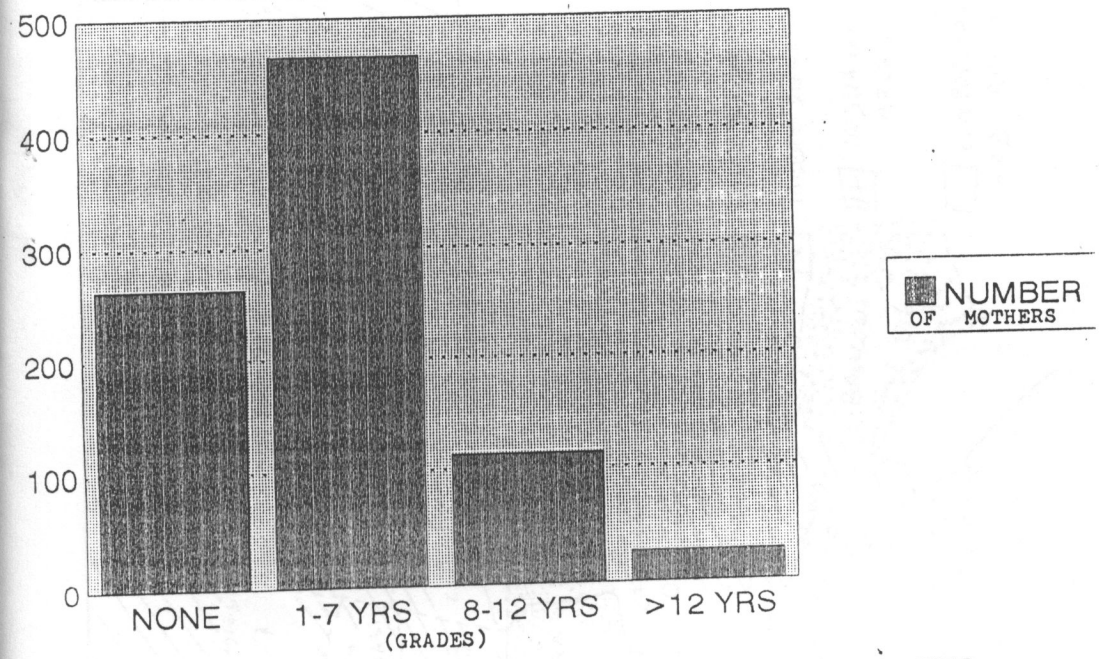
TABLE NO.5

DAYS	FREQUENCY	PERCENTAGE
1	193	22.2%
2	341	42.6%
3	162	18.6%
4	58	6.7%
5	40	4.6%
6	7	0.8%
7	45	5.2%
8	8	0.9%
9	2	0.2%
14	14	1.6%
TOTAL	**871**	**100%**

The duration of illness prior to admission ranged from less than a day to 14 days, with the mean average of 2.8 days and a standard deviation of ± 2.5 days.
97.9% of the cases were admitted by the end of the first week of symptoms.

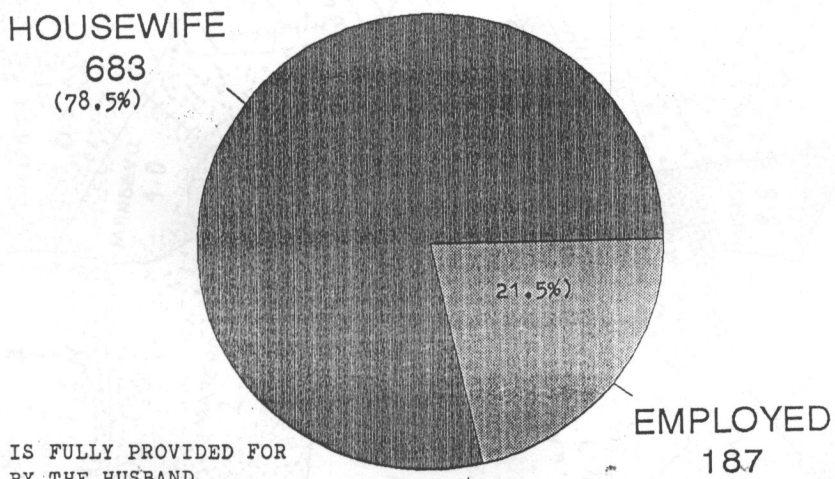
IOTHERS EDUCATION STATUS

FIGURE: 8



% OF MOTHER WERE EITHER SEMI LITERATES OR ILLITERATES

)CCUPATION OF THE MOTHERS

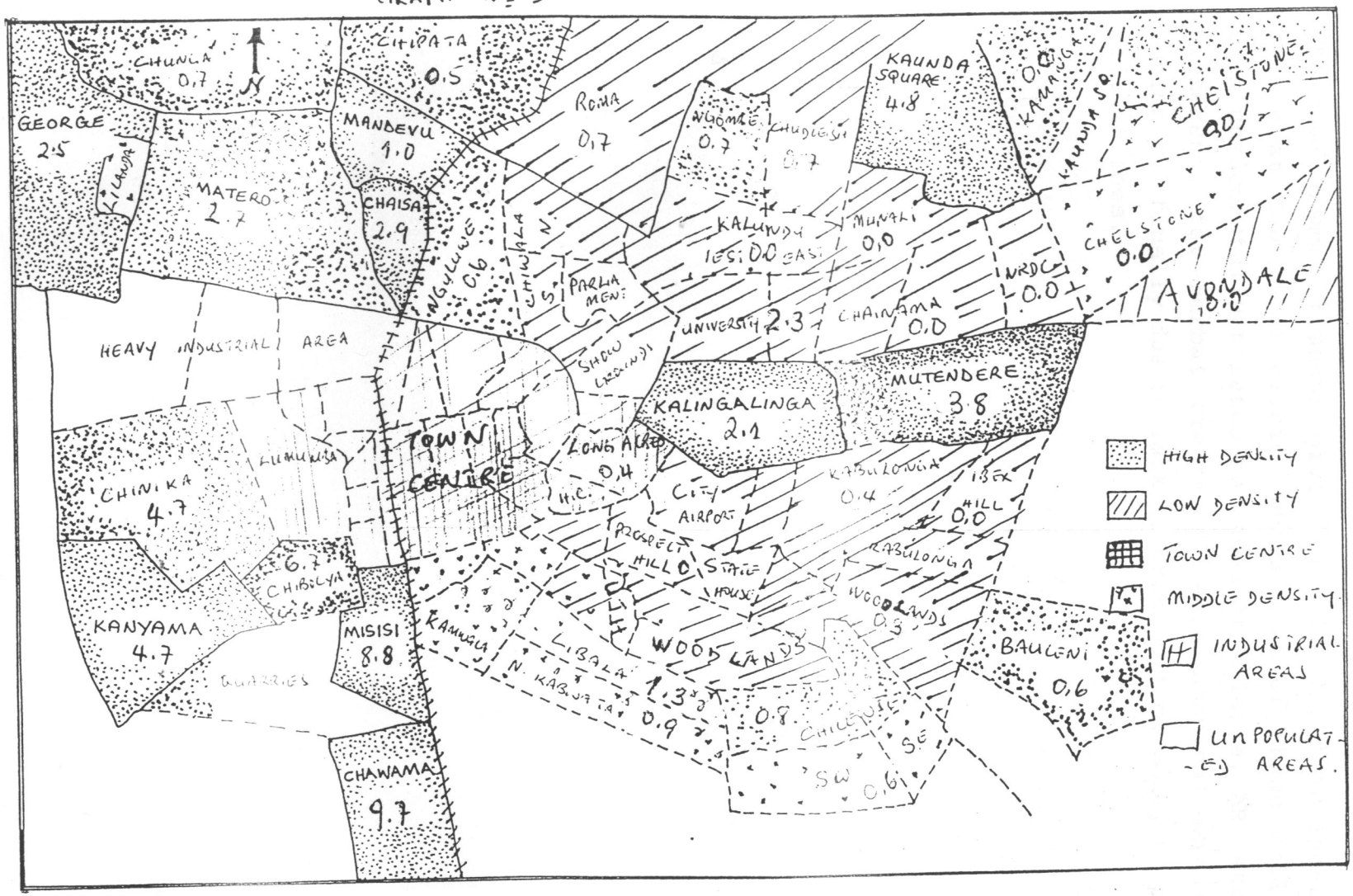


USEWIFE: IS FULLY PROVIDED FOR BY THE HUSBAND

PLOYED: INFORMAL, PRIVATE OR SELF EMPLOYMENT

FIGURE 1 INDICATED THAT THE EDUCATION STATUS OF MOTHERS WAS LOW WITH MOST OF THE MOTHERS ONLY ATTENDING THE FIRST YEARS OF EDUCATION OR NONE. HENCE AS DEPICTED IN FIGURE 2 THE MAJORITY OF MOTHERS WERE HOUSEWIVES.

GRAPH No 3



RESIDENTIAL MAP OF LUSAKA SHOWING PREVALENCE RATE OF ABM PER 1000 PAEDIATRIC POPULATION. PREVALENCE RATE WAS HIGHER IN THE HIGH DENSITY COMPOUND SITUATED IN THE SOUTH-WEST OF LUSAKA. IT IS POSSIBLE THAT THIS AREA MIGHT HAVE BEEN THE EPI CENTRE.

The most common reasons given for the delay included; delays at the local clinic, where most of these children had been unsuccesfully treated as cases of malaria, ARI etc, preference for herbal treatment hence hospital was the last option and finally due to lack of transport or money to pay their medical fees.

4.1.2 COMPLAINTS

The presenting symptoms are presented in Table: 6

COMMONEST PRESENTING SYMPTOMS

TABLE 6

COMPLAINT	PRESENT	PERCENT
1. FEVER	862	99%
2. LOSS OF APPETITE	771	86.5%
3. HEADACHE	642	73.8%
4. VOMITING	621	71.3%
5. ARTHRALGIA	509	58.4%
6. ARI	419	48.2%
7. LOSS OF CONSCIOUSNESS PRIOR TO ADMISSION	344	39.5%
8. IRRITABILITY	326	37.5%
9. GIT SYMPTOMS	315	36.2%
10. DELIRIUM	207	22.6%
11. REFUSE TO SUCK	197	22.6%

From the table it is clear that fever was the leading symptom on admission(99%). This was followed by loss of appetite(86.5%), headache(73.8%), vomiting(71.3%) and arthralgia(58.4%) in descending order. Irritability, gastro-intestinal symptoms and refusing to suck, were common in infants.

The majority of patients had a typical presentation of ABM, with positive meningeal signs (see page 18) in older children, and a bulging anterior fontanelle, irritability, refusing to breast feed in the infants. These symptoms were associated with fever, anorexia and vomiting (See Table 6 & 7).

COMMONEST SIGNS

TABLE 7

SIGNS & SYMPTOMS	PRESENT	PERCENT
1. Neck Stiffness	842	96.9%
2. Kernings	674	77.4%
3. Brudzinski	636	73%
4. Herpes Labialis	443	50.9%
5. Lethargy	397	45.6%
6. Seizures	315	36.2%
7. Coma	198	23.8%
8. Refusing to Breast feed	197	22.6%
9. Pneumonia	190	21.8%
10.Bulging AF	171	19.6%
11.G/Lymphadenopathy	157	18.0%
12. Arthritis	36	4.1%

Foot note; Bulging AF.....Bulging anterior fontanelle

G/lymphadenopathy....Generalised lymphadenopathy

There were some important variations from the classical picture of ABM such as;

i. 53.4% cases were mentally clear and showed no signs of delirium or semicoma.

ii. 5(0.6%) cases ran a completely afebrile course (might have had partially treated meningitis)

iii. 158(18%) cases vomited or passed a worm, commonly ascaris lumbricoides at the height of fever.

iv. Herpes labialis was quite common (50.9%), and was usually extensive, extending to the nares, into the mouth causing severe stomatitis, and externally on to the maxilla and chin.

v. 31(3.1%) cases with a classical presentation of ABM, on lumbar puncture yielded clear CSF, with normal or virtually normal laboratory results, but grew *N. Meningitidis* on culture. 79(9%) clear CSF had abnormal biochemical results with low grade pleocytosis, with no growth on culture..

vi Arthritis was seen in 36 (4.1%), 7(0.8%) had clinical septic arthritis. Twenty nine (3.5%) patients had reactive arthritis, which appeared towards the end of the first week or early second week of illness.

61 (7%) cases had clinical meningitis with purpura. Other signs seen in the study were hemorrhagic conjunctivitis in about 11%, cranial nerve palsies mostly involving the 6th cranial nerve in 12.7%, which were transient and resolved in 4 - 6 days. Generalised lymphadenopathy was seen in about 18%, splenomegaly in 28.9%, hepatomegaly in 33.2%. Shock was seen in 15 cases presenting with unrecordable blood pressure associated with cold extremities. 3 cases (0.3%) had suppurative otitis media and 45(5.2%) were admitted in respiratory distress.

Nutritional status was analysed using the Wellcome classification. Also documented and analysed were other clinical signs of florid malnutrition such as severe wasting and oedema. Severe PEM was defined as frank marasmus, kwashiorkor or marasmic kwashiorkor. It was found that, only 35.8% of cases were well nourished (the weight was more than 80% of the standard mean for age without oedema). 50.4% were underweight (60 - 80% of expected standard mean for age without oedema), while 13.8% were severely malnourished.

Severely malnourished children had a higher morbidity, almost 85% had associated diarrhoea, where as 69% had pneumonia (69%) and were also likely to be HIV seropositive (61%). CSF culture was likely to be sterile (58%) because

most of them had received antibiotics prior to admission. *S. Pneumonia* was prevalent in this subset of patients (27%). Of interest is the fact that, only one case of severe PEM had *Haemphilus influenzal* meningitis.

CONSCIOUSNESS GRADING

On admission, the childrens' mental status was assessed and they were put into three groups:

Grade 1 - Fully conscious and able to communicate well. (for the infant- ability to suck, alertness).

Grade 2 - Delirious or stuporous children. (infant- unconsolable crying or severe irritability).

Grade 3 - Comatose (an unarousable coma) (Table 8).

415 (47.6%) of cases had presented with altered consciousness grade 2 & 3. Severe obtundation was an ominous sign, but in those who survived, the signs were of short duration with total recovery. Seizures were seen in 36.2% of cases, mostly of the grand mal type.

CONSCIOUSNESS GRADING

TABLE 8

GRADE	NUMBER	PERCENT
1	456	52.4%
2	217	24.9%
3	198	22.7%
TOTAL	871	**100%**

6(0.7%) patients had transient transverse myelitis characterised by paraplegia and urinary retention. These signs resolved by the fourth day.

4.1.3 LABORATORY RESULTS

87.4% of the CSF sent to the laboratory had a typical CSF profile

of ABM on direct microscopy and biochemistry, 12.6% were atypical, some with normal CSF glucose levels, low protein, low cell counts which were predominantly lymphocytes.

TABLE NO. 9: LABORATORY CSF PROFILE

	RANGE	MEAN
Protein	< 0.4 g/L - > 6g/L	1.52 g/L ± 0.82 g/L
Sugar	Undectable levels ---> 3,8 mmol/L	0.62 mmol/L ± 0.6 mmol/L
Cell Count	None --> 3,500 cells/mm^3	925 cells/mm^3 ± 633 cells/mm^3
Differentials		
Lymphocytes	1% - 65%	16% ± 11.8%
Neutrophils	45% - 99%	84.3% ± 10.5%

Foot Note: Cell Counts > 3,500 cells/mm^3 are recorded as numerous by the hospital laboratory.

CSF CULTURE RESULTS

TABLE 10

CULTURED	FREQUENCY	PERCENTAGE
POSITIVE	502	59%
N.MENINGITIS	391	46.2%
S.PNEUMONIAE	80	9.7%
H.INFLUENZAE	14	1.7%
SALMONELLA SP	4	0.5%
OTHERS	13	1.5%

Almost 60% CSF culture grew some pathogen. The leading pathogen was *N. Meningitis* which was isolated in almost half of all the CSF sent to the laboratory.

Out of 502 CSF positive cultures 77.9% were due to

N.Meningitidis, *S. Pneumoniae* 15.9% was the second commonest, whereas *H.Influenzae* ranked third at 2.7% *Salmonella Sp* was fourth at 0.5%. Others (2.6%) included; 1 case of *cryptococcal* meningitis, 4 cases of E.Coli, 2 mixed growths, 2 *S. Epidermidis*, 2 *K.Pneumoniae* and 2 group A *beta haemolytic Streptococcus*.

Hundred and ten (12.6%) of the total CFS was "atypical", that is clear CSF with abnormal biochemical or microbiological findings. 31(28.2%) of these specimens grew *N. Meningitidis* on CFS culture.

ASSOCIATION BETWEEN AGE AND PATHOGEN

TABLE 11

AGE/MONTH	SP	NM	HI	SLM	OTHERS	TOTAL
1 - 12	44	30	10	4	6	94
13 - 60	24	138	3	0	2	167
> 60	12	223	1	0	3	239
TOTAL	80	391	14	4	13	502
Chi Square	88.15	152	5,25	-	-	-
P.Value	<0.001	<0.001	<0.01	-	-	-

Chi square < 5 not valid

* N/B 24 CSF culture results were untraceable

1 *Pneunmococcus* was commonest in the younger age group (<12 months), whilst in children >60 months other pathogens were more prevalent with a P value of less than 0.001 which was highly significant.

2 The most common pathogen in children aged >60 months was *Neisseria meningitidis* and the association was significant with a P value of less than 0.001.

3 *Haemophilus influenza* was commonest in those below 12 months and was hardly seen in those aged >60 months.

OTHER LABORATORY INVESTIGATIONS

202 patients admitted with delirium, convulsions or severe ARI, who yielded a clear CSF on lumbar puncture, or a turbid CSF but upon clinical assessment needed further investigations, had blood slides for malaria, urine microscopy and culture and chest xrays taken. Full blood counts and blood cultures were not done as routine due to constraints in the study.

The Results of these investigations indicated that; 69 (7,9%) had concomitant malaria with ABM, 190 (21.8%) patients had associated bronchopneumonia with meningitis. One patient had *Klebsiella sp* isolated from the urine.

DEFINITION OF CHILDREN EXCLUDED FROM THE STUDY

Twenty nine cases were excluded from the study on the basis of their CSF results which had ruled out ABM. 19 were found to be suffering from cerebral malaria with high parasite counts, 5 had lobar pneumonia, 3 had aseptic meningitis (2 Had prodromal measles, and had chicken pox, the characteristic rash erupted on the second and third hospital day). One patient was an undiagnosed insulin dependant diabetes mellitus in ketoacidotic coma, while the last one turned out to be an undiagnosed sickle cell anaemia patient in vasocclusive crisis with subsequent cerebral vascular accident.

HIV TESTING

Random HIV screening test was done on 585 patients out of which 140 (23.9%) were positive.

DURATION OF STAY

Duration of hospital stay ranged from a few hours among cases who died within hours of admission and 36 days in one patient with *Salmonella SP meningitis*, with a mean of 7.9 days and a standard deviation of 4.70 days. Patients suffering from uncomplicated *meningococcal* meningitis were discharged on their sixth hospital day, whilst those suffering from uncomplicated *pneumococcal* and *H. Influenzae* meningitis were discharged on the tenth day of hospitalisation.

ASSOCIATION BETWEEN DURATION OF ILLNESS AT HOME AND ISOLATION OF PATHOGEN

TABLE 12

DUARATION	POSITIVE CULTURE	NEGATIVE CULTURE	TOTAL
< 7 days	490	329	819
> 7 days	12	16	28
Total	502	345	847

Pathogens were likely to be isolated in patients regardless of wether they had presented early or not. Odds ratio was 1,97, an association which was statistically significant .

4.2.5. OUTCOME

Of the 871 cases that were recruited, 94 died giving a case fatality rate of (10.8%), 10 (1.1%) absconded, and 767 (88.1%) were discharged 66 out of the 94 (70.2%) cases that had died, died within 24 hours of admission. Out of the dead 53 (55%) were infants aged 1-12 months of age, and case fatality rate in this age group was 30%(Table 12), compared to 5.7% and 6% in children aged 13-60 and >60 months respectively.

Factors associated with poor outcome (Table 13) were young age, convulsions and coma on admission (Talbe 14), HIV sero positivity (Table 15), poor nutritional status, associated bronchopneumonia, and *Pneumococcus* meningitis, which had a CFR of 38,7% compared to *meningococcal* meningitis - (6.6%).

ASSOCIATION BETWEEN AGE AND OUTCOME

TABLE 13

Age in months	Discharged	Died	Total
1 - 12	119	53(30%)	172
13 - 60	257	16(5.7%)	273
> 60	387	25(6.7%)	412
Total	763	94(10.8%)	757

An expected value < 5 not valid

Chi square 69.88

Degree of freedom 4

P value <0.001

Fourteen patients not analysed had absconded.

NUTRITIONAL STATUS

Poor nutritional status was also a determinant of a fatal outcome, mortality rate in the well nourished was 8.7%, in the underweight it was 11%, whilst in the severely undernourished children it rose to 23%.

FACTORS CONTRIBUTING TO HIGH MORTALITY RATE

TABLE NO.14

SYMPTOMS & SIGNS	PRESENT MORTALITY RATE	ABSENT MORTALIT Y RATE	ODDS RATIO	P-VALUE
CONVULSIONS	26%	2.6%	11.36	0.003
COMA	23.2%	2.1%	14.64	0.00000071
PNEUMONIA	27%	6%	5.79	0.00006
SEV PEM	23%	8.7%	3.02	0.006

A child with ABM presenting with coma was 14 times more likely to die than those presenting without coma with a p-value of

0.00000071 which was highly significant, one presenting with convulsions was 11 times more likely to die, one presenting with pnemonia was 6 times more likely to die where as, those presenting with malnutrition were 3 times more likely to die from ABM.

Poor prognostic signs were; convulsions, severe prostration and coma on admission, associated pneumoniae and PEM.

ASSOCIATION BETWEEN HIV SEROPOSITIVITY AND OUTCOME

TABLE 15

	OUTCOME			
	DISCHARGED	DIED	TOTAL	ABSCONDED
HIV SERO POSITIVE	107	28	135	4
HIV SERO NEGATIVE	423	18	441	5
TOTAL	530	46	576	9

Odds Ratio 6.15 (3.15 < or < 12.09)

p-value <0.001

There seemed to be an association between risk of mortality from meningitis and HIV seropositivity.

Mortality was higher among HIV sero positive infants - 38.2% compared to those aged 13 to 60 months - 12.7% and 9% in children over 5 years of age. Sixty four (3%) of the HIV sero positive children that died were infants. CFR among HIV Positive children was much higher (20%) compared to HIV Negative children (4%). HIV seropositivity therefore was a risk factor in this study.

After discharge, children were followed up at 2 weeks, 6 weeks and 12 weeks. follow up was very difficult and documentation of the immediate and late complications of ABM was done. On first review less than half- 399 children came, on second review, the number had dropped to 157, and on third review only 120 (13.8%) children from the original study group were reviewed. The loss

to follow up was attributed to improvement in the general condition of the children, hence review was deemed unnecessary by most parents.

A clinical assesment was made on discharge, complications were noted, the same were done on subsequent review. The commonest immediate complications are documented in table 17.

COMMONEST IMMEDIATE COMPLICATIONS

TABLE NO. 16

SYMPTOMS & SIGNS	ON DISCHARGE	ON 1st REVIEW 2 weeks after discharge	ON 3rd REVIEW 12 weeks after discharge
ATAXIA	80	10	2
DEAF	65	10	6
G/WEAKNESS	50	5	3
PSYCHOSIS	10	2	2
ARTHRITIS	7	0	0
HYPERTONIA	4	3	2
SPASTIC P.	6	4	4
FLACCID P.	2	2	2
BLIND	7	2	2
HYDROCEPH	0	2	2
SEIZURES	0	2	2
ANAEMIA	15	22	41

Foot note: G/weakness.....Generalised weakness
Spastic P.....Spastic palsy
Hydroceph.....Hydrocephalus
Flaccid P.....Flaccid paralysis

Most Neurological complications were transient.

The commonest complication was ataxia, followed by deafness, gait

weakness, psychosis and athritis in descending order. However, most of these patients had recovered fully by the third week post discharge. Residual complications remained in 27(3%) of those followed up. Of note is increasing levels of anaemia amongst the children on subquent review.

The decline in numbers of complications on first follow up compared to the third, was thought to be both the function of resolution and of poor follow up.

CHAPTER FIVE

DISCUSSION

In the study period, there were 13,828 admissions to the Department of Paediatrics out of which 1,419 had ABM, a prevalence rate of 1026:10,000. Records of monthly admissions for the years 1992 & 1993 were analysed, it was found that, the prevalence rate for 1992 was 552:10,000, while that for 1993 was 540:10,000. This compared to the 2 Chintu studies were prevalence rates of 85:10,000 and 138:10,000 were recorded, one would deduce that, there has been un upward swing in the prevalence of ABM over the past 15-20 years. Although one might argue that about 10 - 15 years ago, the child population of Lusaka was much smaller than it is today and that might explain the lower prevalence of ABM in patients seen at UTH. However, according to the 1980 census Lusaka's urban child population stood at 275,250, compared to 355,692 in the 1992 census, an increment of 29% over 10 years, whilst the prevalence rate of ABM has risen from 138:10,000 in 1979 to 552: 10,000 in 1992 an increment of greater than 300%.

The hyperendemic conditions experienced in 1992 and 1993, provided an opportunity to review the epidemiology, clinical manifestations, laboratory findings and to re-examine what seems to be the changing pattern of ABM in Zambia.

EPIDEMIOLOGY:

From literature review, it has been learnt that there is a global epidemic being caused by *N. Meningitidis* Sero Group A clone III-1 which, started in China in 1986 and caused a large outbreak in Mecca in 1987 [12]. It was brought to African countries by pilgrims coming from Hajji, mostly to the African Moslem countries of North and East Africa. It is possible that, it was brought into Zambia mostly by refugees escaping civil strife in the Horn of Africa in the early ninenties. This is in agreement with the hypothesis made by Simpson, that introduction of a new Group-A meningococcal strain into a susceptible population may trigger

an outbreak [11,14].
The CSF samples that were sent from Zambia to France and Sweden in 1993, confirmed the serotype and clone as the one that is causing the current epidemic in the meningococcal belt, Group A clone III-1, and it seems to be spreading Southward with each year [6,24,25].

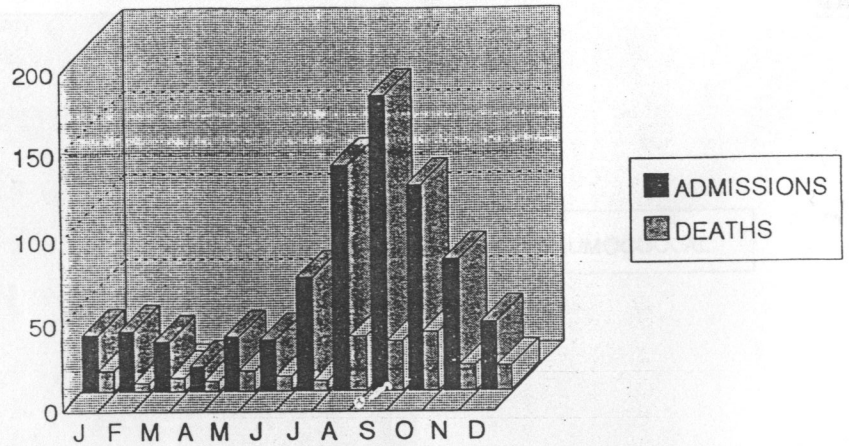
Among infants, the common pathogens were *S. Pneumoniae* and *H. Influenza*, while *meningococcal* meningitis was prevalent in children >60 months of age. Male to female ratio was 1,2:1. This is in agreement with Bushanam and Chintu[16], Johnston[13], who showed equal attack rates in both sexes.

The population at risk were children from high density areas, with mothers with a poor educational background, from low income groups. The average affected family had 6.7 persons per house hold[9], compared to the national average of 5 persons per house hold, this was over crowding (coupled with the fact that, these house holds have no running water with poor sanitation) and in total agreement with Simpson[8] and Nelson [18] who cite over crowding and poverty as predisposing factors to ABM.

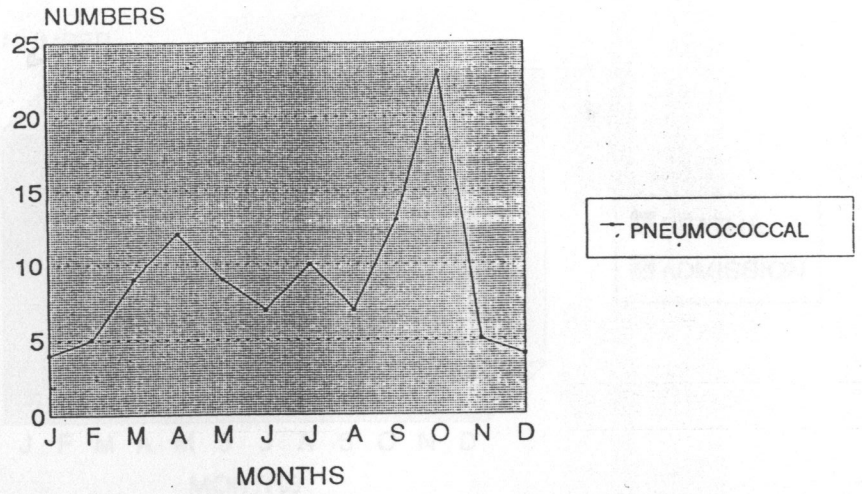
The increased prevalence rate of ABM in the study was due to a sharp rise in the cases of group A *meningococcal* meningitis, there was a high prevalence rate from July through to November, with a peak in september/october (see graph 6 & 7). This could represent a fresh epidemic. Since there are unreliable statistics on ABM, the exact epidemiological situation cannot be determined, but the same trend was seen in the Kitwe epidemic of *meningococcal meningitis* of 1975-76 [14].

CLINICAL MANIFESTATIONS of ABM noted in the study ranged from neck stifness with fever alone in older children, to shock coma and death. Meningeal signs associated with petechial rash or purpura were classically noted in patients with meningitis associated with *meningococcaemia*.

GRAPH: 6



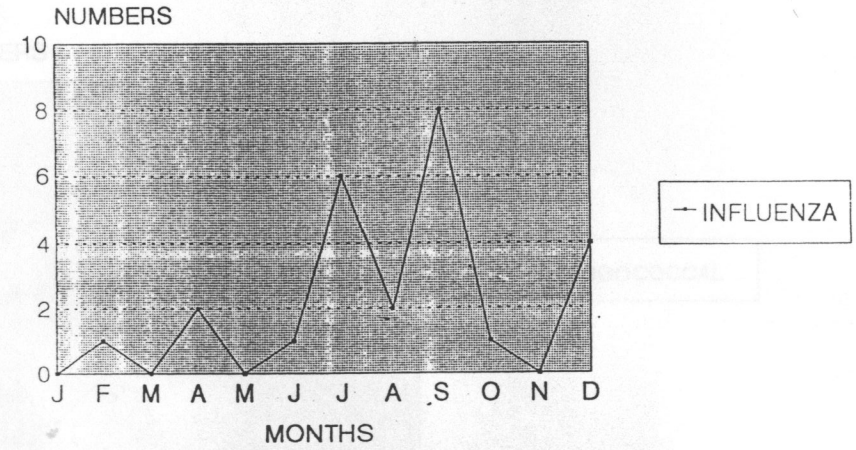
THE ANNUAL INCIDENCE RATE FOR 1992 WAS 552/10000/PAEDIATRIC IN PATIENTS. IT WAS MOSTLY DUE TO A RISE IN THE NUMBER OF CHILDREN BEING ADMITTED WITH MENINGOCOCCAL MENINGITIS.



THERE WERE 108 CONFIRMED CASES OF PNEUMOCOCCAL MENINGITIS. SPORADIC CASES WERE OBSERVED THROUGH OUT THE YEAR, WITH A PEAK IN OCTOBER.

INCIDENCE RATE OF INFLUENZAL MENINGITIS

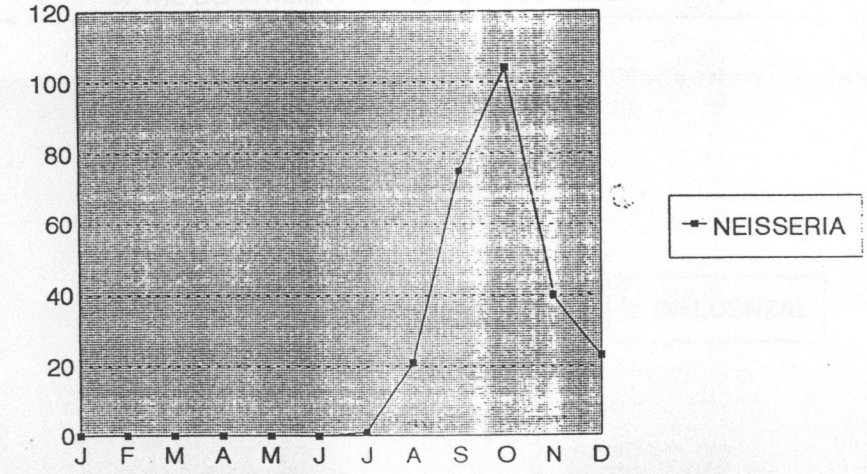
IN THE DEPARTMENT OF PEADIATRICS, 1992



THERE WERE ONLY 25 CONFIRMED CASES OF INFLUENZAL MENINGITIS. MOST CASES WERE OBSERVED IN THE SECOND HALF OF THE YEAR WITH A PEAK IN JULY AND SEPTEMBER.

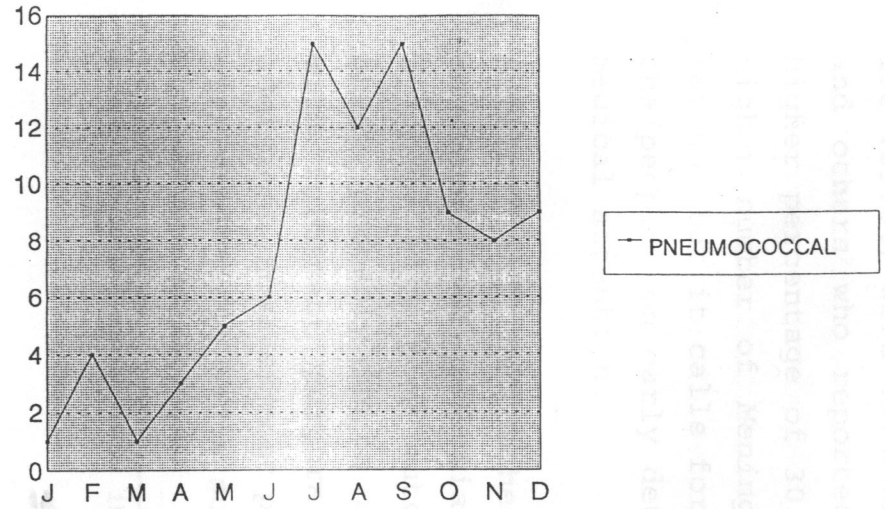
INCIDENCE OF ACUTE MENINGOCOCCAL MENINGITIS

AT THE DEPARTMENT PAEDIATRICS UTH LUSAKA, ZAMBIA 1992

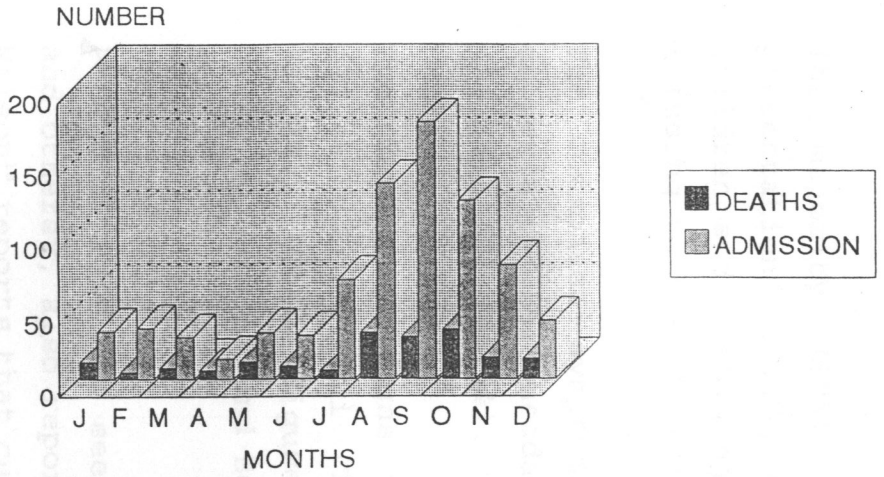


THERE WERE 264 CONFIRMED CASES OF MENINGOCOCCAL MENINGITIS WHICH HAD A SEASONAL VARIATION WITH A PEAK IN THE HOT DRY SEASON OF THE YEAR, AUGUST TO NOVEMBER.

GRAPH: 7



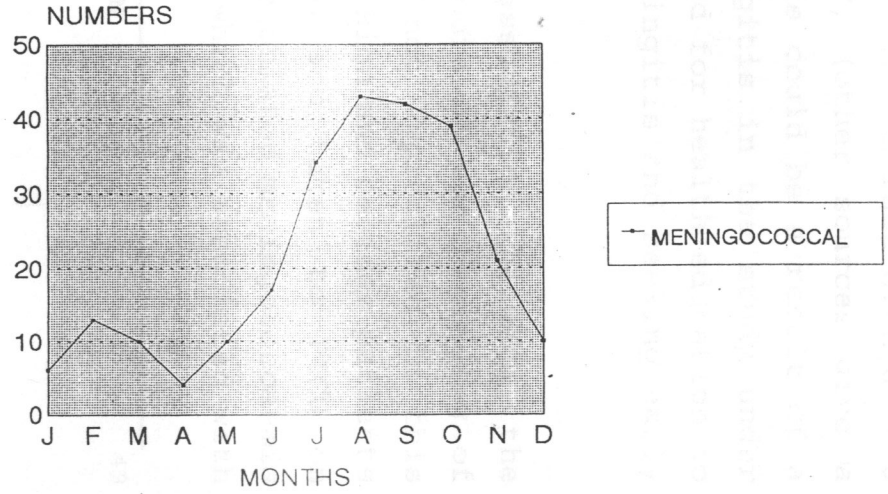
THERE WERE 88 CONFIRMED CASES OF PNEUMOCOCCAL MENINGITIS, SPORADIC CASES WERE OBSERVED THROUGH OUT THE YEAR WITH A PEAK FROM JULY TO SEPTEMBER.



INCIDENCE RATE OF ABM IN 1993 WAS 540/10000 AMONG PAEDIATRIC IN PATIENTS, AND IT WAS DUE TO A HIGH NUMBER OF CHILDREN ADMITTED WITH MENINGOCOCCAL MENINGITIS.

INCIDENCE RATE OF MENINGOCOCCAL MENINGITIS

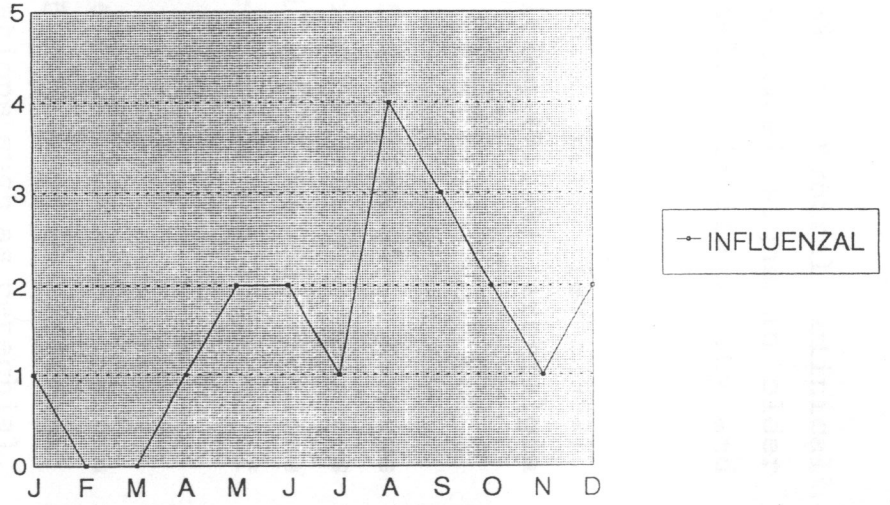
IN THE DEPARTMENT OF PEADIATRICS, 1993



THERE WERE 249 CONFIRMED CASES OF MENINGOCOCCAL MENINGITIS. SPORADIC CASES WERE OBSERVED THROUGH OUT THE YEAR, WITH A PEAK IN THE HOT DRY MONTHS OF AUGUST - NOVEMBER.

INCIDENCE RATE OF INFLUENZAL MENINGITIS

IN THE DEPARTMENT OF PEADIATRICS, 1993



THERE WERE 19 CONFIRMED CASES OF INFLUENZAL MENINGITIS, WITH THE MAJORITY OF CASES BEING ADMITTED IN THE SECOND HALF OF THE YEAR.

The majority (87%) of cases showed a typical clinical presentation of ABM, with positive meningeal signs in older children and a bulging anterior fontanelle, irritabillity and refusing to breast feed in infants.

The commonest symptoms in older children were; fever(99%), anorexia (88.5%), headache (73.8%), vomiting (71.3%), arthralgia (59.5%), ARI (48.2%).

The commonest signs were; neck stiffness (96.9%), Kernigs (77.4%), Brudzinski (73%), herpes labialis (50.9%), seizures (36.2%). These figures correlate well with the descriptions given by Nelson[18] and Bennet[17] on clinical signs and symptoms of ABM.

Petechial rash was seen in 58 cases (6.66%). Simpson[14], Chintu and others[13], also reported a paucity of this sign in Africans, Nelson[18] reports that cutaneous manifestations such as petechial, purpura and erythematous macular rash are present in about 10% of ABM cases.

Altered mentation was seen in 405 cases (46.4%), out of which 198 (23.8%) were comatose on admission, in contrast with Chintu and others who reported only 7.1% [16], (other sources give a higher percentage of 30 - 50%[17,18]. This could be a result of a higher number of *Meningococcal* meningitis in the study under review, but it calls for an urgent need for health education to the people, on early detection of meningitis and seeking early medical attention.

Stielnn and Damrosche noted an association between the development of petechiae within 12 hours of the beginning of symptoms with poor outcome[45], it was not appreciated in this study, probably due to paucity of this sign and besides patients with fulminant purpura were excluded and taken to PICU on admision. However most patients with associated *meningococcaemia* with meningitis had a sub acute onset which was associated with

meningits, the rash usually began insidously with a peripheral distribution, in the soles and palms of feet and hands. Prior to this, most of these patients had demonstrated hyperaesthesiae, everywhere you touched hurt, a highly prognostic sign that rash will erupt in the next 6-24 hours, a sign which has not been documented in all the literature under review. Two patients had cellulitis type socks and gloves with subsequent transdermal ulcerations.
Mortality among patients with associated *meningococcaemia* was low (3 out of 58 (5.2%) which highlighted the fact that, *meningoccaemia* with meningitis (turbid CSF) has a better prognosis than that with a clear CSF (fulminant *meningoccaemia*).

Poor prognostic signs were; shock, progressive or late onset convulsions, coma with obtundation, short history of less than 12 hours. In infants the most ominous sign was severe irritability. Johnston also noted that, outcome was mostly related to the clinical state[14]. Like in the Johnston study most the patients died early after admission. This could have been a result of an overwhelming infection, or that the children were simply brought in late.

Suppurative arthritis was a presenting sign in only 7(0.8%) patients, but late onset arthritis (reactive) was much more common - 29 cases(3.5%). It presented towards the end of the first week or early second week of illness. The latter group of children responded well to Aspirin.

Three percent of the children in the study group who had positive meningeal signs, but had crystal clear CSF, had *N. meningitidis* isolated from the clear CSF despite a lack of pleocytosis, low CSF sugar or organisms on gram stain. The lack of inflammatory response might have been due to sampling of the CSF early before the development of pleocytosis, alternatively the absence of an inflammatory response may have been due to an overwhelming infection, or inadequate host response. This demonstrated that, clear normal CSF in the presence of a typical clinical

presentation of ABM did not rule out a provisional diagnosis of ABM (as is commonly believed by our residents[18]). Such patients were treated with high dosages of antibiotics until CSF results were out.

LABORATORY RESULTS

The results of CSF culture can depend on various factors such as antibiotic treatment at home prior to admission, unsterility of lumbar puncture and the age of the sample.

In the study, it was noted from the history that, some of these patients had been treated unsuccessfully at their local clinics as cases of ARI's 126 (14.5%), malaria 133 (15.3%) and acute diarrhoeal disease 67 (7.7%). 150 (17.2%) had received antibiotics prior to admission. This might partially explain the high proportion of negative CSF cultures. This emphasised the need of training all primary care health personnel on early detection and treatment of meningitis.

On the sterility of the lumbar puncture, it was assumed that these were efficiently done because, only 2 (0.3%) results came back as contaminated samples. Age of sample was a bone of contention. Despite strict orders given to take CSF specimens to the laboratory within an hour of collection, over weekends 69 (7.9%) specimens were delayed for as long as 48 hours in the ward (a few were even frigerated), *N.meningitidis* being a fastidious organism can never grow from such a sample, worse still, the cells are likely to disintegrate and the cell count would be inaccurate.

The late taking of specimen to the laboratory was blamed on the distance of the main laboratory from the Department of Paediatrics, and female maids were reluctant to traverse this distance alone at night. Hence the need for a proper laboratory in A block. Failure to this, an effective portal system for specimen collection should be worked out, that would be able to cover weekends and public holidays. Despite various constraints, we had a positive yield of (59.2%) CSF bacterial culture, which

was comparable to the Chintu 1975 and Chintu 1978 results of 56.9% and 55.48% respectively.

Out of the 29 patients that were excluded from the study, 2 had prodromal measles associated with generalised convulsions, one had prodromal chicken pox, one was an undiagnosed IDDM in ketoacidotic coma, another one was an undiagnosed SCD patient in vasocclusive crisis with CVA, the rest had cerebral malaria. These common diseases in our set up should always be included in the differential diagnoses of ABM.

The commonest pathogens isolated were *Neisseria meningitidis, S. pneumoniae, H. influenzae* and *Salmonella Sp*. in that order. This was the second time *N. meningitidis* had emerged as the number one pathogen, the first being in the Kitwe Simpson study almost twenty years ago, and like in that study the initial out break was localised to one town only. In between epidemics *S. pneumoniae* has been the leading pathogen[13,15, 16].

In the study, *Salmonella Sp* was seen as an invasive infection in 4 children, 3 infants and 1 toddler. One was HIV positive, and died on admission. Three were HIV negative, 1 died, 1 developed ventriculitis confirmed by ultrasound, he finally got discharged on the thirty sixth day with spastic palsy.The last child absconded.

Pleocytosis ranged from 0 - 3,200 cells, because our laboratory record counts of more than 3,200 cells/1mm^3 as numerous. An indicator that our Microbiology Lab needs to update their workmanship and machinery.

In contrast to Chintu and Bathirunathan[15] who found Gram stains to be more informative than culture and attributed it to partial treatment, most of our Gram stains were negative. Since the mean duration of illness prior to admission was 2.6 days, this could mean that patients were brought in early before critical bacterial concentration for Gram stain to be positive were

reached, or could have been a result of poor technique. There is an urgent need on the part of the microbiologists to regard microscopy of direct smears as an important tool in the express diagnosis of most bacterial infections, and will help reduce the poly pharmacy used in the empiric treatment of ABM.

A biochemical profile suggestive of pyogenic meningitis was a very useful tool in this study, since these results were ready the same or next day, and could be used for express diagnosis, as opposed to bacteriological results which usually took a minimum of two days.

TREATMENT

The choice of an antimicrobial agent to treat ABM depends on many factors. One factor is antibiotic penetration into the CSF, which is usually enhanced by inflammation, high lipid solubility, low protein binding capacity, but most important in our set up is the bactericidal efficacy of the antibiotics, and the delivery of rapid high concentration of these drugs in the CSF.

Empiric penicillins given intravenously did very well in the study against the still penicillin sensitive NM and SP. For HI because of the increasing prevalence of Beta-lactamase producing strains, the choice of chloramphenicol to which HI is still sensitive was justified.

Duration of antimicrobial therapy still remains largely empiric and based on a tradition which recommends treatment to be continued for 10 to 14 days, and often longer for Gram Negative Bacillary Meningitis. In the study shorter courses given for NM were equally efficacious. Most patients with NM were treated for 7 days, but generally the treatment was individualised, it was longer in patients with complications like associated *Meningococcaemia*, Ventriculitis, severe PEM and gram negative bacillary meningitis.

Many studies have now proved the importance of adjunct

dexamethasone therapy early in the disease with appropriate antimicrobials to reduce the incidence of neurological sequelae[38, 41, 42, 43]. The use of this drug in the study was too sporadic for comment.

HIV AND ABM

Sero Prevalence among patients admitted with ABM was 23.8% which correlated well with Dr Luo's findings of 23.7%(46) of HIV Seropositivity among paediatric in-patients. *S.Pneumoniae* has emerged in this study as the most common bacterial meningeal pathogen in patients with HIV in all age groups. In many of these children, the disease run a protracted course with concomitant pneumoniae and septicaemia. Many had generalised lymphadenopathy, 4 were on ATT. Prognosis was poor especially in infants. This association was also seen in the studies done by Janoff, and others who have done various studies on *pneumococcal* disease in HIV infection[31,32].

The study highlights the absence of association between *Meningococcal* Meningitis and HIV infection. The prevalence of 23% of HIV positivity in patients with *Meningococcal* infection correlates with the figures found by Luo and others on the *prevalence of HIV among hospitalised children*[46]. *The absence of* this interaction was also noted in the study done in Western Uganda in 1992 (on *Meningococcal* Meningitis and HIV infection)[7].

Sero positive children were likely to be infants aged 1 - 12 months (43.5%) compared to older children (15.3%). This may mean that maybe these children were still carrying maternal antibodies, or most HIV positive patients should have died by the age of 2 years.

CASE FATALITY RATES

Case fatality rates of ABM has been noticed to have an ambiguos character. It is much higher "out of" and in the "inter epidemic" *periods, and drops drastically during meningococcal* outbreaks.

The Johnston[13] and the first Chintu study[15] were done before the first documented outbreak of *meningococcal* meningitis in Kitwe[14], very high Case fatality rates of 43.5% and 41.2% were recorded. Whilst the second Chintu study[16] done during an inter epidemic period had a Case fatality rate 21.3%. In the Simpson[14] and the study under review which were done during an outbreak of *meningococcal* meningitis, fairly low case fatality rates of 14.2% and 10.8% were recorded.

This can be explained by the fact that *meningococcal* meningitis is very acute onset, with a typical symptomatology of ABM, besides there is usually a high public awareness of the disease during an outbreak, as well as a more alert and sensitised medical personnel which leads to early diagnosis and specific adequate treatment.

Sixty-one percent of the children who presented with severe PEM were HIV positive this correlated well with Dr Luo and others[46] who found sero prevalence among children with failure to thrive in the Department of Paediatrics to be 76.9%.

Case fatality rate (42.4%) was highest among children who were HIV positive and suffering from pneumococcal meningitis, than in any other subset of children (p value < 0.1). This result is supported by Janoff and others[32] who reported that most infected patients who develop invasive *pneumococcal* infections such as meningitis and septicaemia are at an advanced stage of HIV disease, have low CD4 cell counts and death is inevitable.

27(3.1%) children developed neurological sequelae which included 6(0.7%) deaf, 2(0.23%) post meningitis convulsive disorder and 2(0.23%) had hydrocephalus. Definite conclusions were difficult to be arrived on post ABM sequelae, because many children were lost to follow up.

CONCLUSIONS

1. Socioeconomic factors contributed greatly to the ABM outbreak.

   Most mothers were either illiterate (30.2%) or semiliterate (57.3%), and full time housewives (78.5%). Almost 90% came from high density areas. An average affected household had 6.7 persons compared to the national mean of 5 persons per household, high lighting a possible association between over crowding, poverty, and high morbidity for ABM.

2. The mean duration of illness prior to admission was 2.6 days, more than 90% patients had been admitted by the end of the first week, demonstrating the acute nature of ABM.

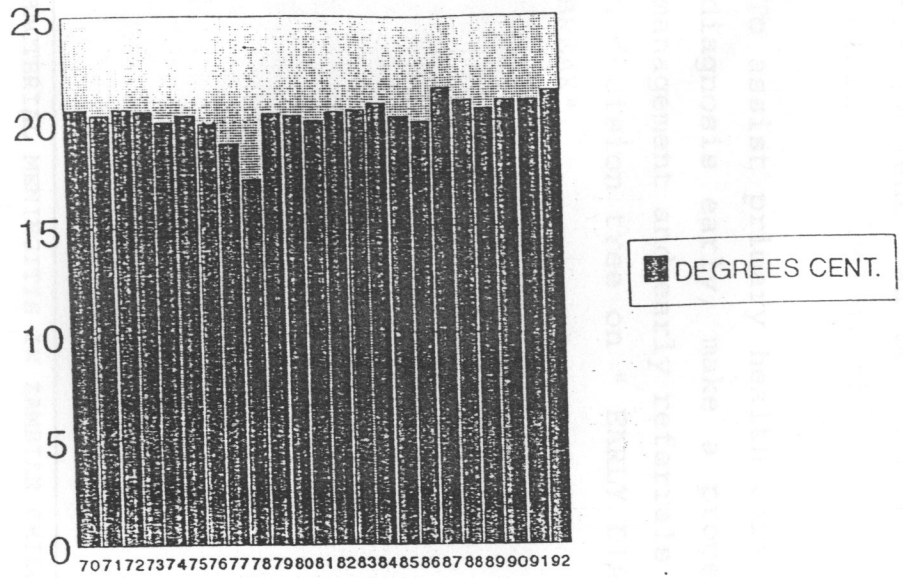
3. All age groups were affected, 20% were infants aged 1-12 months, 32% were children aged 13-60 months, and 48% were aged more than 60 months, this is consistent with the increasing risk to ABM with age during an out break.

4. There was no sexual predilection, male to female ratio was 1,2:1.

5. The commonest symptoms were fever (99%), poor appetite (88.5%), vomiting (71.5%). Specific to the older children were headache (79.5%)and arthralgia (59%). In infants, the commonest symptoms were irritability (37.5%), bulging anterior fontanelle (19.4%) and refusing to suck (22.6%).

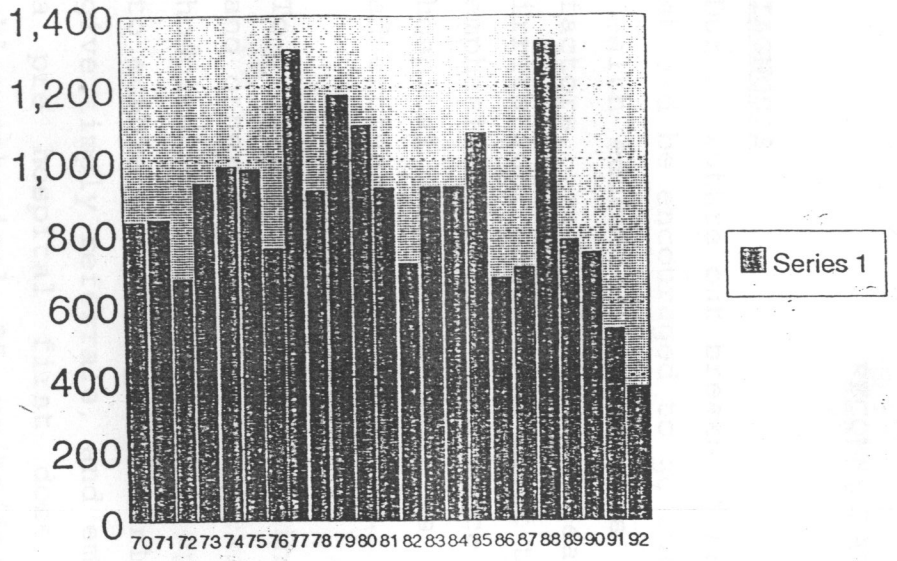
6. Positive signs of meningeal irritation and a bulging anterior fontanelle were the commonest signs. Herpes labialis and stomatitis were common (50.9%), associated *meningococcaemia* was rare (7%), cranial nerve palsies (commonly the 6th nerve) were common(23%), but transient. Eighth nerve palsy in 6 children became permanent.

MEAN AVERAGE TEMPERATURES FROM THE YEAR 1970 TO 1992



The temperatures from 1989 to 1992 were fairly static

MEAN AVERAGE RAINFALL FOR THE YEAR 1970-1992



From the 1989/90 rain season there has been a gradual fall in the mean average rainfall reaching a a nadir in 1992, the year we had the ABM outbreak.

PREVAILING DROUGHT FROM 1991, WAS AN IMPORTANT ENVIRONMENTAL FACTOR IN THE OUTBREAK. OF MENINGOCOCCAL MENINGITIS WHICH IS FAVOURED BY DRY HOT WEATHER.

RECOMMENDATIONS

(i) **DIAGNOSIS**:

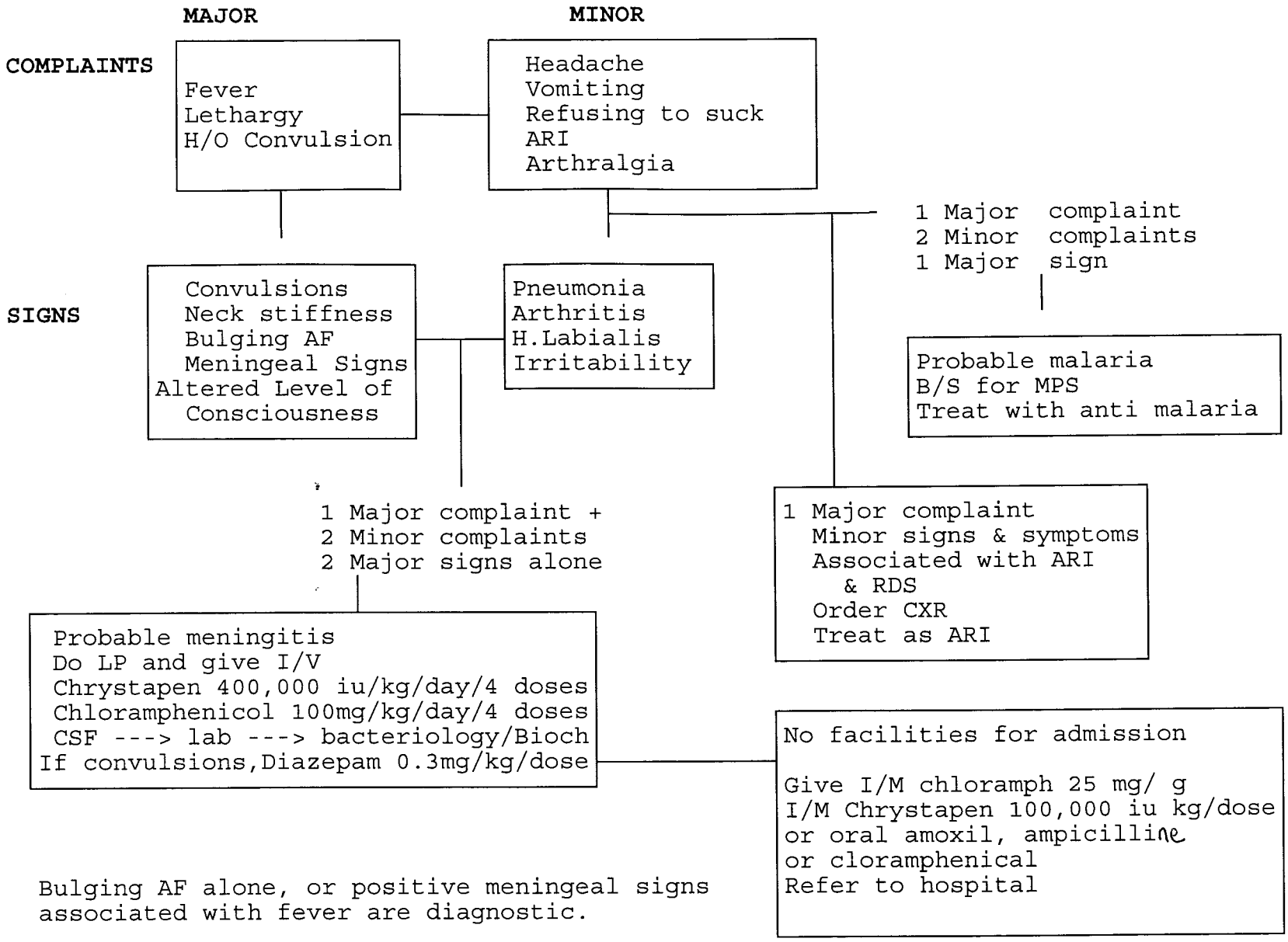
1. During future out breaks of ABM, community health workers should be encouraged to go out into the community, to give health education to mothers and other guardians on risk factors, recognition of early symptoms of meningeal irritation, teach them about the nature of the disease, and emphasise on the importance of taking the children to hospital early, as well as sensitise every one through advertisements on the media.

2. To organise in service training courses for doctors, nurses and other health workers working in peripheral clinics and hospital filter clinics, to update their knowledge on ABM, to enable them recognise early symptoms and signs of ABM, give timely referrals, and emphasise on the importance of a pre hospital first dose of antibiotics (parenteral *chloramphenicol 25 mg/kg/dose, or I/M crystapen 50 - 100,000 i.u kg/dose. (If none of these drugs are available the patient can be started on oral ampicillin, amoxil, chloramphenicol in the right dose for age).*

3. To assist primary health care workers arrive at the right diagnosis early, make a proper decision on pre hospital management and early referrals to hospital, I have proposed a decision tree on " EARLY DIAGNOSIS OF ABM DURING AN OUT BREAK".

DECISION TREE ON EARLY DIAGNOSIS OF ABM DURING AN OUTBREAK: FOR PRIMARY HEALTH WORKERS

FIGURE 9



Bulging AF alone, or positive meningeal signs associated with fever are diagnostic.

methods on early detection of threshholds of future outbreaks of ABM, draw protocols on how to manage such outbreaks, and if possible to maintain an emergency fund specifically for use in times of epidemics.

At community level to embark on programs targeted at improving the literacy level and accessibility to formal employment, especially for the Zambian woman.

UTH - ADMINISTRATION: I urge them to work out their priorities right, to afford proper planning and provision of adequate funding to vital departments, to avoid situations like the one that arose in 1992/93, when virtually the whole laboratory ground to a stand still because of non availability of reagents.

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QUESTIONNAIRE OF A STUDY ON MENINGITIS AND HIV INFECTION IN LUSAKA

1 (STUDY NUMB)ER ###
2 (DATE OF INT)ERVIEW <dd/mm/yy>
3 (INTERVIEWER _____
4 (AGE) ## YEARS 5 (SEX) __ 6 (RESIDENCE) _____
(DENSITY) _____ (HIGH, MID, LOW, RURAL)
7 (MOTHERS' ED)UCATION _____ (NON, PRIM, SEC, HIGHER)
8 (MOTHERS' OC)CUPATION _____ (HOUSE WIFE, EMPLOYED)
9 (FAMILY SIZE) ### (PARENTS+CHILDREN+DEPENDANTS)
10 (SIZE OF HOUS)E _____ (L4, 4-6, M6)

PRESENTATION

11 H/O POSITVE CONTACT WITH ANYONE HAVING MENINGITIS.

12 (DUR)ATION OF (ILLNESS) ### DAYS
13 (FEVER) <Y>
14 (VOMITING) <Y>
15 (POOR APPET)ITE <Y>
16 (HEADACHE) <Y>
17 (ARI) <Y>
18 (LOSS OF CONS)CIOUSNESS <Y>
19 (DELIRIUM) <Y>
20 ECK ACHE / (STIFFNESS) <Y>
21 (BUL)GING OF (A)NT (F)ONTANELLE <
22 IRRITABIL)ITY <Y>
23 (LETHARGY) <Y>
24 (REFUS)ING TO (SUCK) <Y>
25 GIT SYMPTONS
26 ARTHRALGIA\MYALGIA

CLINICAL SIGNS AND SYMPTOMS

27 (TEMP)ERATURE ##.# DEGREE
28 (PETECHIA)L RASH <Y>
29 (HERPES LAB)IALIS <Y>
30 (NECK STIFF)NESS <Y>
31 (BRUDZINSKI) <Y>
32 (KERNIGS) <Y>
33 SIGNS OF (PNEUMONIA) <Y>
34 (ARTHRITIS) <Y>
35 (BULGING AF) <Y>
36 POOR FEEDING
37 (CONS)CIOUSNESS (GRAD)ING __ (BLANTYRE 1,2,3,)
38 (DELIRIUM) <Y>
39 NUTRITIONAL STATUS

40 SEIZURES
41 FOCAL NEUROLOGICAL SIGNS
SIXTH NERVE PALSY

CSF FINDINGS

42 (PROTEIN) #.## g/l
43 (SUGAR) #.## m mol/l
44 (CELL COUNT) ##### /mml
45 (DIFFERENT)IAL
P ## %
L ## %

BACTERIOLOGY

46 (PNEUMOCOC)CUS <Y>
47 (HAEM. INFL)UENZA <Y>
48 (N. MENING)ITIDIS <Y>
49 (SALM)ONELLA (SP). <Y>
50 (CRYPT)OCOCCUS <Y>
51 (T.B.) <Y>
52 IF (OTHERS) SPECIFY_____

53 (HIV) STATUS ___ (POS,NEG)
54 (DUR)ATION OF HOSPITAL (STAY) ### DAYS

COMPLICATIONS ON DISCHARGE

55 (ARTHRITIS) <Y>
56 (DEAFNESS) <Y>
57 (SPACITIC)ITY <Y>
58 (GAIT DIST)URBANCES <Y>
59 (BLINDNESS) <Y>
60 (GANGRENE) <Y>
61 (PSYCHOSIS) <Y>
62 HYDROCEPHALUS
63 BRAIN DAMAGE
64 FLACID PARALYSIS
65 HYPERACTIVITY
66 IF (OTHERS SP)ECIFY_____

67 (OUTCOME) _____ (DISCHARGED, DIED, ABSCONDED)

FOLLOW UP 1

68 (STUDY NO) ####

PRESENTATION

69 (NO COMPL)AINTS <Y>
70 (ARTHRITIS) <Y>
71 (HEADACHE) <Y>
72 (FEVER) <Y>
73 GENERAL (WEAKNESS) <Y>
74 (LOC)ALISED (WEAK)NESS<Y>
IF YES WHICH LIMB_____
75 (DEAFNESS) <Y>
76 (BLINDNESS) <Y>
77 (GANGRENE) <Y>
78 (POST) (MEN)INGITIS (SEQ) <Y>
79 (PERS)ONALITY (CHANGE)S <Y>
80 (GAIT DIST)URBANCES <Y>
81 ATAXIA <Y>
82 MUSCULAR HYPERTONIA <Y>
83 HEMI OR QUADRIPARESIS <Y>
84 MENTAL RETARDATION <Y>
85 OBSTRUCTIVE HYDROCEPHALUS <Y>
86 PERMANENT SEIZURE DISORDERS <Y>
87 IF OTHERS SPECIFY_____

FOLLOW UP 2

PRESENTATION

88 (NO COMPL)AINTS <Y>
89 (HEADACHE) <Y>
90 GENERAL (WEAKNESS) <Y>
IF YES WHICH LIMB_____
91 (DEAFNESS) <Y>
92 (GANGRENE) <Y>
93 (PERS)ONALITY (CHANGE)S <Y>
94 ATAXIA <Y>
95 HEMI OR QUADRIPARESIS <Y>
96 OSTRUCTIVE HYDROCEPHALUS <Y>
97 PERMANENT SEIZURE DISORDERS <Y>
98 IF OTHERS SPECIFY_____