COMMON BACTERIAL ISOLATES AND IN HOSPITAL TREATMENT OUTCOME OF ACUTE BACTERIAL MENINGITIS AMONG CHILDREN SUSPECTED WITH CENTRAL NERVOUS SYSTEM INFECTIONS ADMITTED AT DODOMA REGIONAL REFERRAL HOSPTIAL

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MASTER OF MEDICINE IN PAEDIATRICS AND CHILD HEALTH

THE UNIVERSITY OF DODOMA

OCTOBER, 2019

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By

NEEMA ERNEST KIPIKI

A DESERTATION SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF MEDICINE IN PAEDIATRICS AND CHILD HEALTH

THE UNIVERSITY OF DODOMA

OCTOBER, 2019

DECLARATION

AND

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I, **Neema Ernest Kipiki** declare that this thesis is my own original work and that it has not been presented and will not be presented to any other University for a similar or any other degree award.

Signature 

CERTIFICATION

The undersigned certify that they have read and hereby recommend for acceptance by the University of Dodoma thesis/dissertation entitled, "***Common bacterial isolates and in hospital treatment outcome of acute bacterial Meningitis among children suspected with CNS infections admitted at Dodoma Regional Referral Hospital***" in partial fulfilment of the requirements for the degree of Master of Medicine in Pediatrics and Child Health of the University of Dodoma.

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DEDICATION

I dedicate this work to my parents, Mr and Mrs Kipiki who are my daily inspiration

ABSTRACT

Background: Bacterial meningitis, is an inflammation of the meninges affecting the pia, arachnoid, and subarachnoid space that happens in response to bacteria and bacterial products invasion. The incidence of ABM has decreased significantly in developed countries especially after the addition of the Hib and pneumococcal conjugate vaccines to the routine childhood immunization schedule, but in most developing countries little is known on how the introduction of these vaccines has changed the incidence of ABM especially due to the existence of other comorbidities such as HIV and malnutrition.

Objectives: Determination of prevalence, bacterial isolates and their antimicrobial resistant pattern, and in hospital treatment outcome of acute bacterial meningitis among children aged 2 months and 15 years who are suspected to have CNS infection admitted at DRRH.

Methods: The study included a sample size of 101 patients aged 2 months to 15 years with features of CNS infection. The CSF obtained from these patients was analyzed by using culture, gram stain and latex agglutination test for identifying the etiological organism of ABM. MRDT, BS and CRAG to all HIV patients to rule out other causes of CNS infection.

Results: The prevalence of ABM was found to be 4 %(4/101). 1 species of *E. coli* and 3 species of *S. pneumoniae* were the main organism isolated. Severe acute malnutrution was found to be one of the major risk factors with a (OR5.3, 95%CI[2.005-5.924] p -value 0.04) while being immunized at least once against the common causative organisms was found to be protective against ABM with a p value of 0.04 (OR0.04,95CI[0.02-0.9] p value 0.04). This disease was among the risks factors for requirement of physiotherapy at the time of discharge with (OR2.36 95CI [1.18- 19.7] p value 0.047)

Conclusion: Despite wide spread of vaccination coverage, ABM is still prevalent with a local prevalence at Dodoma RRH of 4%. Children with Severe acute malnutrition were found to be at high risk for this ABM. *Streptococcus pneumoniae* which were the main isolates, had a resistance of about 50% to the first line antibiotics used for ABM. At discharge, children confirmed to have ABM were more likely to have neurological deficits requiring physiotherapy.

Hence more efforts should be placed on diagnosis and identification of etiological organisms by using high sensitive techniques so as to improve treatment and outcome among patients with ABM

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LIST OF ABBREVIATIONS

ABM	Acute Bacterial Meningitis
CNS	Central Nervous System
CSF	Cerebral Spinal Fluid
DRRH	Dodoma Reginal Referral Hospital
ESBL	Extended spectrum Beta lactamase producing strains
HIV	Human Immunodeficiency Virus
MRDT	Malaria Rapid Diagnostic Test
WBC	White Blood Cell count
WHO	World Health Organization

DEFINITIONS OF TERMS

CNS infection suspects; Adopted from (Page et al., 2017)

Included patients with fever or history of fever with a temperature of > 38.C who also met at least one of seven additional criteria:

Reduced level of consciousness; (Blantyre coma score [BCS] ≤4 for children aged 5 years or younger; or Glasgow coma score [GCS] ≤14 for children older than 5years.

Irritability

Neck stiffness

Photophobia

Kernig's sign/Brudzink sign

Tense fontanelle

Convulsions

CHAPTER ONE

INTRODUCTION

1.0 Background

Acute bacterial meningitis refers to an inflammation of the meninges affecting the pia, arachnoid, and subarachnoid space that occurs in response to bacteria and bacterial products invasion to the CNS, and it is one among the medical emergency in pediatric population due to its associated high morbidity and mortality(Kim, 2010a).

Worldwide, the prevalence of ABM ranges from 1.6% - 17.9 %.(Thigpen et al., 2011), but the global incidence of ABM is difficult to ascertain due to wide variation in surveillance mechanisms in different regions compounded with under reporting from many developing countries (Agrawal & Nadel, 2011).

The incidence of ABM has declined significantly in developed countries especially after the addition of the Hib and pneumococcal conjugate vaccines to routine childhood immunization schedules(Saez-Llorens & McCracken Jr., 2003). In developing countries, ABM remain a public health problem most likely due to the existence of other comorbidities such as HIV and malnutrition which pose a major risk for this disease (Oordt-Speets, Bolijn, Van Hoorn, Bhavsar, & Kyaw, 2018).

Though the impact of vaccination in inducing immunogenicity for prevention of meningitis caused by *Hemophilus influenza type b*, *StreptococcaLpneumoniae*, and *Neisseriameningitidis*has been demonstrated in high income countries, *Streptococcalpneumoniae*remains the most frequent cause of bacterial meningitis reported in children from developing countries and the rise of resistant strains of

Streptococcal. pneumoniae against the commonly used antibiotics is rapidly increasing while sensitive antibiotics are either too expensive (eg, vancomycin) or cannot be widely recommended (eg, rifampicin, which is the key drug to treat tuberculosis) in developing countries (Nigrovic, Malley, Macias, Kanegaye, & Moro-sutherland, 2008; Scarborough &Thwaites, 2008). Hence more studies are needed to determine the antimicrobial resistance pattern against various antibiotics in our local areas.

Several factors are reported to influence the mortality rate among children with acute bacterial meningitis including the type of an infectious agent, age of the child, the child's general health status, and the promptness of diagnosis and treatment(Kim, 2010b).

Despite improvements in antibiotic and supportive care, mortality and complication rates remain high for most children with ABM (Husain E, Chawla R, Dobson S, et al 2006). Among the most common pathogens, Pneumoccocal meningitis has the highest mortality and the antibiotic resistant strains can lead to longer hospital stay and more acute long term sequella (Mongelluzzo, Have, & Shah, 2015).

This study aimed to investigate the prevalence, bacterial isolates and antimicrobial sensitivity profile together with in hospital treatment outcome of ABM in children suspected to have CNS infection in Dodoma region so as to get a clear picture on the impact of this disease to our health system.

1.1 Problem Statement

Acute bacterial meningitis is still a major health problem in children and new-born infants especially in developing countries and the epidemiology of pathogens causing meningitis in many developing countries such as Tanzania is not well characterised as there is little data available to describe how the introduction of vaccines against the common etiological organism of ABM have changed the epidemiology of this disease.

Another challenge in developing countries is that, for most hospitals the first line antibiotic therapy for ABM are those recommended by WHO guidelines but local antibiotic sensitivity pattern for different isolates could be different especially in areas where antibiotic prescription is not controlled, therefore studies conducted at local hospitals can generate data regarding local sensitivities which may help to formulate local guidelines.

The mortality rate associated with acute bacterial meningitis remains very high in some developing countries, ranging from 16–32%, (Shrestha et al., 2015). Additional factors, such as advanced HIV infection, malnutrition and the rise of resistant strains to the commonly used antibiotics, complicate the management of these children. For these reasons, acute bacterial meningitis presents an exceptional challenge to physicians working in resource-poor settings(Scarborough & Thwaites, 2008).

1.2 Rationale

The prevalence, aetiologies and treatment outcome of ABM may vary depending on geographical regions, and according to the age of the patients. Moreover, the effectiveness of treatment may be limited due to presence of antibiotic-resistant strains. Therefore, periodic reviews of meningitis cases are necessary.

This study looked into the pattern of this disease especially in Tanzania especially in Dodoma region. Also determined the extent of antimicrobial sensitivity pattern towards the WHO first line recommended antibiotics for treatment of ABM. Lastly this study evaluated the in hospital treatment outcome in children diagnosed with ABM and how investigations such as CSF analysis, latex agglutination tests, CSF culture and gram stain are important in improving our diagnostic accuracy and outcomes of children with ABM.

1.3 Research Question

I. What is the prevalence of ABM in children suspected to have CNS infection?

II. What are the bacterial isolates in ABM and their antimicrobial sensitivity pattern?

III. What are the in- hospital treatment outcomes of children with ABM

1.4 Broad Objective:

To Determine the prevalence, bacterial isolates, antibiotic sensitivity pattern and in hospital treatment outcome of acute bacterial meningitis among children aged 2 months to 15 years who are suspected to have CNS infection admitted at DRRH

1.5 Specific objectives:

I. To determine of prevalence of acute bacterial meningitis among children aged 2 months to 15 years who are suspected to have CNS infection admitted at DRRH.

II. To determine the antimicrobial sensitivity pattern of bacteria isolated in ABM among children aged 2 months to 15 years who are suspected to have CNS infection admitted at DRRH.

III. To assess the in-hospital treatment outcome of children with ABM among children aged 2 months to 15 years who are suspected to have CNS infection admitted at DRRH.

CHAPTER TWO

2.0 Literature Review

ABM Bacterial meningitis continues to be an important cause of mortality and morbidity in neonates and children throughout the world. The introduction of the protein conjugate vaccines against *Haemophilus influenzae* type b, *Streptococcus pneumoniae,* and *Neisseria meningitidis* has changed the epidemiology of bacterial meningitis. Suspected bacterial meningitis is a medical emergency and needs empirical antimicrobial treatment without delay.(Kim, 2010b)

2.1 Prevalence of acute bacterial meningitis

Worldwide, the prevalence of ABM ranges from 1.6% - 17.9 %.(Thigpen et al., 2011), but the incidence of ABM worldwide is difficult to ascertain because of wide variation in surveillance in different regions of the world, together with underreporting from many developing countries (Agrawal & Nadel, 2011).

The occurrence of this disease has decreased significantly in developed countries especially after the addition of the Hib and pneumococcal conjugate vaccines to the routine childhood immunization schedule, but in most developing countries it is still a burden due to the existence of other comorbidities such as HIV and malnutrition(Rogerson, Walsh, & Molyneux, 2003).

In Africa, most available information concerning meningitis comes from meningitis belt of sub-Saharan Africa, stretching from Senegal in the west to Ethiopia in the east. Around 30 000 cases of meningococcal meningitis are still reported each year from that area (WHO, 2018)

(Owusu et al., 2012) showed a prevalence of confirmed and probable meningitis were 3.3% and 2.1% respectively in a retrospective study done in Ghana. The low prevalence in this study was associated with the use of antibiotics before hospital admission, which is a common practice in many developing countries. Another study with similar result by (Nwadioha, Nwokedi, Onwuezube, Egesie, & Kashibu, 2013) in Nigeria showed the positive culture bacterial isolation rate of 3.3%. But both of these studies were retrospective.

A prospective descriptive study done in Uganda in 2013 showed that Bacterial meningitis was the second most common etiology for CNS infection after malaria, with a prevalence of 13.3%(Page et al., 2017). The high prevalence of ABM in this study was associated with the usage of a high sensitivity detection technique such as PCR. This shows that the prevalence of ABM in many African countries may be under estimated due to the use of low sensitive technique for diagnosing the disease.

In northern Tanzania a study done at Kilimanjaro region by al revealed a prevalence of ABM to be 2.5%, by using conventional methods such as gram stain and culture for diagnosis but a prevalence of 37.5% by using PCR (Abdallah et al., 2015). Another study in north-western Tanzania in 2017, showed a prevalence of 12.6%. This low prevalence was associated with usage of antibiotics before lumbar puncture (Jumanne, Meda, Hokororo, & Leshabari, 2017).

2.2 Antimicrobial sensitivity pattern of etiological agents isolated in bacterial meningitis.

The causative organisms for ABM varies with age, immune function, immunization status and geographical area.The most frequent pathogens varied according to age are as follows;

Neonates	Infants and children
Group B streptococci	Streptococcus pneumoniae
E. coli	H influenza
Listeria monocytogen	Neisseria Meningitidis
Klebsiella species	

Amongst the changes in the epidemiology of ABM is the increase in resistant strains of pneumococcus worldwide. One factor that may have contributed to the increasing prevalence of antibiotic resistant in meningitis was the use of antibiotics before hospital admission, a common practice in many developing countries (Iregbu & Abdullahi, 2015).

Research done in Yunnan province in China in 2017, showed that *E. coli* (51.3%) was the most frequently isolated pathogen in young infants aged ≤3 months, while *Streptococcus pneumoniae* (23.3%) was the most frequently isolated pathogen in young infants aged >3 months (Jiang et al., 2017).These results were quite different than those reported by previous studies, which identified *group B streptococcus* as the pathogen most frequently isolated from the CSF of paediatric patients ≤ 30 days of age followed by *Streptococcus pneumoniae* . All E. coli isolates exhibited intermediate resistance against third generation cephalosporins.Emerging resistance to third generation cephalosporins was also identified as a critical concern because increased use of cephalosporins is likely to result in a rapid increase in the prevalence of extended spectrum-lactamase (ESBLs)-producing strains.

From the same study of the *Streptococcus pneumoniae* isolates, 87.5% were susceptible to chloramphenicol, whereas 68.8% were susceptible to penicillin and 100% were susceptible to erythromycin, gentamycin, ofloxacin, linezolid and vancomycin. *Haemophilusinfluenzae type b* isolates exhibited considerable resistance to third generation cephalosporins but were susceptible to cefepime and imipenem. This study has revealed the need of continuous monitoring of resistant strains so as to provide a proper reference for the selection of appropriate antibiotics.

Another study in Namibia in 2013, showed that most common pathogens causing meningitis isolated from the CSF samples analysed were Streptococcus species, *N. meningitidis, Haemophilusinfluenzae, Staphylococcus*, and *E. coli*.*Staphylococcus* seemed to be the common cause of meningitis in all age groups, while ESBL *K. pneumoniae* was the most frequent isolate in CSF samples drawn from neonates. All common organisms isolated from CSF samples showed high resistance to penicillin. The overall resistance of Streptococcus species to penicillin was 34.3%. The highest percentage of resistance to a cephalosporin was seen among ESBL *K. pneumoniae, Klebsiella,* and *Staphylococcus.* This study also showed the need to do more research on the existence of ESBL producing bacteria(Mengistu et al., 2013).

In Tanzanian study, the commonest isolates were *E coli* and *S. pneumoniae*. Both of these agents were resistant to cloxacillin and cotrimoxazole but sensitive to ceftriaxone, gentamycin, chloramphenicol and amoxyclav. From this study it was difficult to draw a conclusion on antimicrobial resistantance, since cloxacillin and cotrimoxazole are not recommended in the treatment of ABM(Abdallah et al., 2015).

2.3 Treatment outcome among children with acute bacterial meningitis.

In this study treatment outcome will be assed in terms of numbers of days required for hospital admission, requirement of physiotherapy after discharge and the mortality rate of ABM.

Bacterial meningitis continues to be an important cause of mortality and morbidity in neonates and children throughout the world. It has been estimated that over 75%of all cases of ABM occur in children under 5 years of age, mainly because of their immature immunity and it is one of the most common life-threatening infections in children worldwide, (S.Agrawal, S.Nadel 2011).

Despite the availability of potent newer antibiotics, the mortality rate associated with acute bacterial meningitis remains very high in some developing countries, ranging from 16–32%, (Shrestha RG, Tandukar S, Ansari S, Subedi A, Shrestha A, Poudel R, et al 2015).

A study done in Ethiopian adults from 18 years and above showed that Outcome in patients treated for ABM at the hospital was poor. Impaired mentation, treatment with adjunctive dexamethasone and persistent fever were found to be associated with poor outcome and the overall mortality rate was found to be as high as 22.2%, (Gudina, Tesfaye, Wieser, Pfister, & Klein, 2018). Hence from this study there is a need to evaluate the in hospital treatment outcome in paediatric patients.

A study in Northern Tanzania on assessment of clinical predictors and treatment outcome among febrile children with altered mentation showed a high mortality rate of about 5.33% among patients with no pathogen identification, followed by a mortality rate of 4.35% in patients with ABM and a 2% mortality rate in patients with malaria. From this study factors which associated with poor hospital outcome include HIV status, multiple seizures and severe AMS (GCS<8, BCS<2).(Jumanne et al., 2017). Hence more studies are required in assessment of in hospital treatment outcome as they may help to create awareness and possible to provide preventive measures to reduce mortality rate of ABM.

A retrospective study in Turkey showed a crude mortality rate of 13.7% among adult patients with pneumococci Meningitis with factors such as advanced age, critical status including ICU admission or poor GCS score increased the chance of death among patients. (Erdem et al., 2014). One set back on this study was the retrospective nature of the study and since it was done in adults and only focused on pneumococci meningitis, there is still a need in assessment of outcome in children and predictors of mortality to be assessed in all causative organism of ABM.

CHAPTER THREE

METHODOLOGY

3.0 Study design

This was a cross-sectional hospital based study designed to determine the prevalence, bacterial isolates , antimicrobial sensitivity and in hospital treatment outcome of acute bacterial meningitis among children aged between 2 months to 15 years who will be suspected to have CNS infection admitted at Dodoma regional referral hospital(DRRH**).**

3.1 Study Area

This study was conducted in Dodoma Regional Referral Hospital which is located in the center of Tanzania within the municipality of Dodoma city. It was started in 1920's as a health center. This Hospital has twenty-onewards with a bed capacity of 434 and 540 workers with different specialties and operates in line with the national health policy. Dodoma Regional Hospital serves as a Referral hospital serving areas such as Bahi, Dodoma urban, Mpwapwa, Kondoa and Chemba and Kongwa. The hospital also attends few referred cases from neighboring regions of Morogoro, Manyara, and Singida. The Hospital has thirteen departments which are; outpatient, emergencies, internal medicine, surgical department, pediatric, obstetrics and gynecology, laboratory, radiology, ophthalmology, orthopedic and traumatology, preventive services, pharmacy and oral and dental department.

The pediatric department has one pediatrician, 3 medical officers, pediatric residents and intern doctors. In daily patient management intern doctors are the first on call, residents and registrars, are the second on call and the third on call is the pediatrician. The nurse in-charge is the one who supervises daily activities within the ward.

The pediatric department has two special clinics, one of which is care and treatment clinic (pediatric CTC) and the other is a general pediatric clinic which operates on regular basis.

3.2 Study population

The study included all children aged between 2 months to 15 years who were suspected to have CNS infection admitted at DRRH in a period of 6 months from October 2018 to March 2019.

3.3 Selection criteria

3.3.1 Inclusion criteria

- Patients who were suspected of CNS infection admitted at DRRH during the study period
- Patients aged between 2 months to 15 years

3.4.2 Exclusion criteria

- Children with a septic wound at the lumbar puncture site.
- Children with spine abnormality such as spinal bifida or tethered spine.
- Children with metabolic conditions presenting with altered mental status such as DKA
- Children with CNS condition likely to cause neurological deficits such as stroke or epilepsy

3.4 Sample size

The sample size was calculated using Leslie Kish formula (1965):

$$N = \frac{Z^2 P(1-P)}{d^2}$$

Where: N = sample size

Z = Score for 95% Confidence Interval which is 1.96

P = Prevalence of ABM in children 6.9%(Mado SM, Aikhionbare HA, 2013)

d = tolerable error set at 5%.

Therefore N = 98 this was the minimum sample size but our study enrolled 101children with suspicious CNS infection.

3.5 Sampling method

Recruitment was done serially until the predetermined sample size was met.

3.6 Data collection

All children aged between 2months to 15 years suspected to have CNS infection, who met the above inclusion criteria who were admitted at DRRH during the study period were invited to participate in the study. The investigator provided consent forms and explained the aim of the study to the parents or guardians. The enrolment was done after obtaining an informed consent. Parents and guardians were interviewed for demographic details and symptoms using a standardized questionnaire. Physical examination was performed to look for features of CNS infection on the patients.

Laboratory investigations performed included peripheral blood smear for malaria parasites and rapid test for malaria and lumbar puncture for cerebrospinal fluid (CSF) analysis. The CSF was analysed for macroscopic appearance sugar, protein level, total white blood cell count and Gram stain. A portion of CSF (3 ml) was sent for latex agglutination tests, culture and sensitivity pattern. For the HIV-infected children, cryptococcal antigen test was performed for cryptococcal meningitis. CSF Latex agglutination test was performed using the Pastorex TM Meningitis latex agglutination test kit manufactured From Guangdong Huankai Microbial Sci.& Tech. Co.,Ltd in Guadong, China. The test was for detection of soluble antigen and identification of *Neisseria meningitidis A, C, Y, W135*, *Escherichia coli*, *Hemophillusinfluenzae type B (Hib),Streptococcus pneumoniae* and *Streptococcus group b*. CSF culture was done after centrifuging a portion of CSF specimen then inoculated on chocolate agar plate and incubated in both aerobic and anaerobic conditions.

Thick blood smear for malaria parasites was Giemsa stained, and malaria rapid diagnostic test (MRDT) was done using SD Bioline Malaria Ag P.f/Pan kit and HIV tests was done using the SD Bioline HIV- ½ 3.0 kit. Both were manufactured by Standard Diagnostic, Inc., 65, Borahagal-ro, Giheung-gu in the republic of Korea.

Malaria and bacterial meningitis was managed using National and WHO recommended guidelines for management of severe malaria and ABM, respectively, with intravenous artesunate at 3 mg/kg for children less than 20 kg and 2.4mg/kg for older children at 0,12hours and 24 hours. Or until the patient was able to take oral artemetherlumefantriene. For meningitis 100 mg/kg intravenous cefrtriaxone was administered once per day for 7–10 days depending on clinical response.

Other supportive treatments including maintenance fluids, blood transfusion, fever medication and anticonvulsants were provided depending on the clinical presentation of the patient. Patients were reviewed daily to monitor progress, including vital signs, level of consciousness, inputs and outputs, and at discharge treatment, outcome was documented.

3.7 Variables

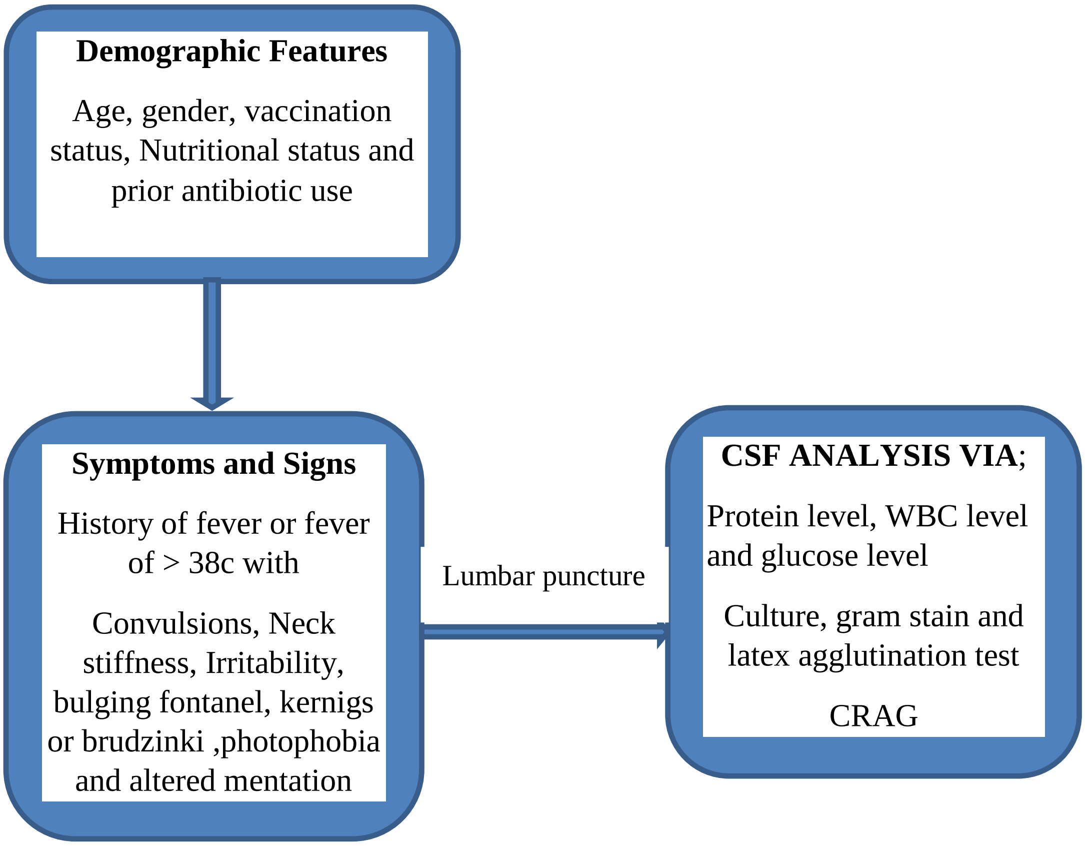
a) Independent variables (associated factors)

    - Categorical variables – Sex, vaccination status, fever, HIV status and Nutritional Status.
    - Numerical Discrete variables – Age.

b) Dependent variables (outcome)

    - Categorical variable- CSF culture and gram stain positivity
    - Numerical Discrete variables-WBC level, protein level, Glucose level of the CSF.

Conceptual frame work



MRDT and HIV test

3.8 Data processing and analysis:

Data entered into Microsoft Excel and cleaned. Analysis was performed using SPSS version 20. Results were described using proportions (%) for categorical data and means or median for continuous variables according to distribution. Categorical variables were compared using Chi - Square or Fishers Exact test while Continuous variables were compared using T- Test or Rank Sum Test. Predictors with a p- value of < 0.05 by univariate analysis were included in the multivariate analysis which was performed using logistic regression. P values < 0.05 were considered significant.

3.9 Ethical consideration

Permission to conduct the study was requested from UDOM research board, ethical issues were observed and patients, who guarantee informed consent to participate in the study, were enrolled. Unique identification number was used to maintain patient confidentiality. All patients received proper management for ABM and Malaria as to the WHO and hospital guide line and HIV positive patients were referred to CTC.

CHAPTER FOUR

4.0 RESULTS

This study was done in a period of six months from October 2018 to March2019. During this period there was a total admission of 1571 children at the pediatric ward. Among these patients 135 (8.6%) patients had features of CNS infection, and from this group 101(74%) met the inclusion criteria of the study as shown in **figure 1.**

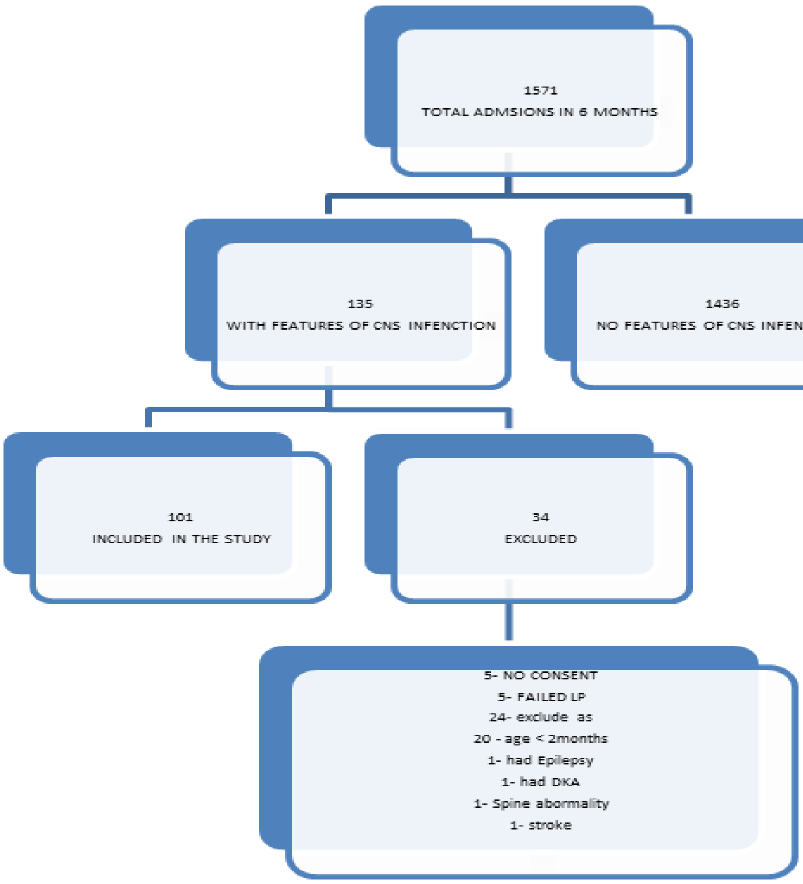


Figure 1: Consort diagram; showing enrollment of the study participants

4.1 Baseline characteristics

Half of the study participants were in age group of 2 months to 2 years, while the remaining belonged in the age group between 2years and 15 years. The minimum age recruited was 2 months and the maximum was 15 years with a mean age being

49 months. Male gender was predominant in the study population with a prevalence of 57% (58/101).

Majority of the patients 88 %(89/ 101) were fully immunized against pneumococcal and *Haemophilus influenza type b* diseases and the remaining were either immunized once, not immunized at all and those whom immunization status was unknown.

Some of the outstanding sings among the enrolled children were either history of fever or fever of more than 38c, bulging fontanel, altered mentation and neck stiffness .None of the patients had a positive kernings orbrudzinski sign.

Table 1: Baseline characteristics (history, clinical features and laboratory findings) of enrolled children (N=101

VARIABLE	Frequency	Percentage (%)
Age(months)		
2months- 24months	50	49.5
>24months-60months	20	19.8
>60months	31	30.7
Gender		
Male	58	57
Female	43	42.6
Vaccination status		
Fully immunized	89	88.1
Immunized once	5	5.0
Not immunized	2	2.0
Unknown	5	5.0

VARIABLE	Frequency	Percentage (%)
Nutritional Status		
Normal	96	95.5
SAM	2	3.0
Chronic malnourished	3	2.0
Prior antibiotic usage		
Yes	77	76.2
No	24	23.8
History of fever		
Yes	98	
No	3	97
Presence of convulsion		3
Yes	89	88.1
No	12	11.9
Type of Convulsion		
Focal	3	3.0
Generalized	86	85.1
Not applicable	12	11.9
Frequency of convulsions		
Once	40	39.6
More than once	49	48.5
Not applicable	12	11.9

VARIABLE	Frequency	Percentage (%)
Fever temperature (>38.C);		
Yes	98	97
No	3	3
Brudzinski sign/Kerning sign:		
Yes	0	0.0
No	101	100.0
Neck Stiffness;		
Yes	5	5.0
No	96	95.0
Bulging fontanel;		
Yes	3	3.0
No	67	66.3
Not applicable	31	30.7
Photophobia		
Yes	0	0.0
NO	100	100.0
Altered level of consciousness;		
Normal	17	16.8
BCS <4	55	54.5
GCS < 14	29	28.7

VARIABLE	Frequency	Percentage (%)
Malaria Infection		
+VE	24	23.8
-VE	77	76.2
Cryptococcocal		
Yes	3	3.0
No	2	2.0
None HIV Patients	96	95.0
CSF Protein level		
Normal	100	99.0
High	1	1.0
CSF Glucose level		
Normal	97	96.0
Low	4	4.0
CSF WBC		
Normal	91	90.1
High	10	9.9

4.2 Prevalence of Acute Bacterial Meningitis among 101 children with suspected CNS infection

In the majority of the patients 70% (70/101) no diagnosis was confirmedbut among those with identified etiologythe leading cause was found to be malaria with a prevalence of 24% (24/101), followed by ABM with a prevalence of 4%(4/101) and Cryptococcal meningitis with a prevalence of 3%(3/101).

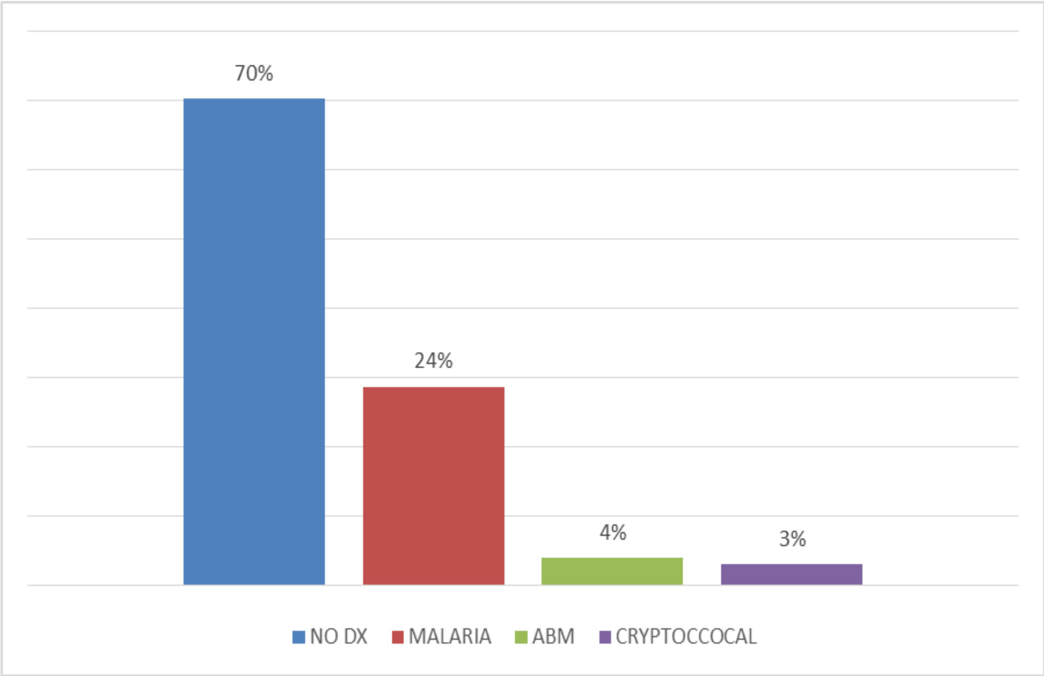


Figure 2: Distribution of participants according to the etiology of CNS infection.

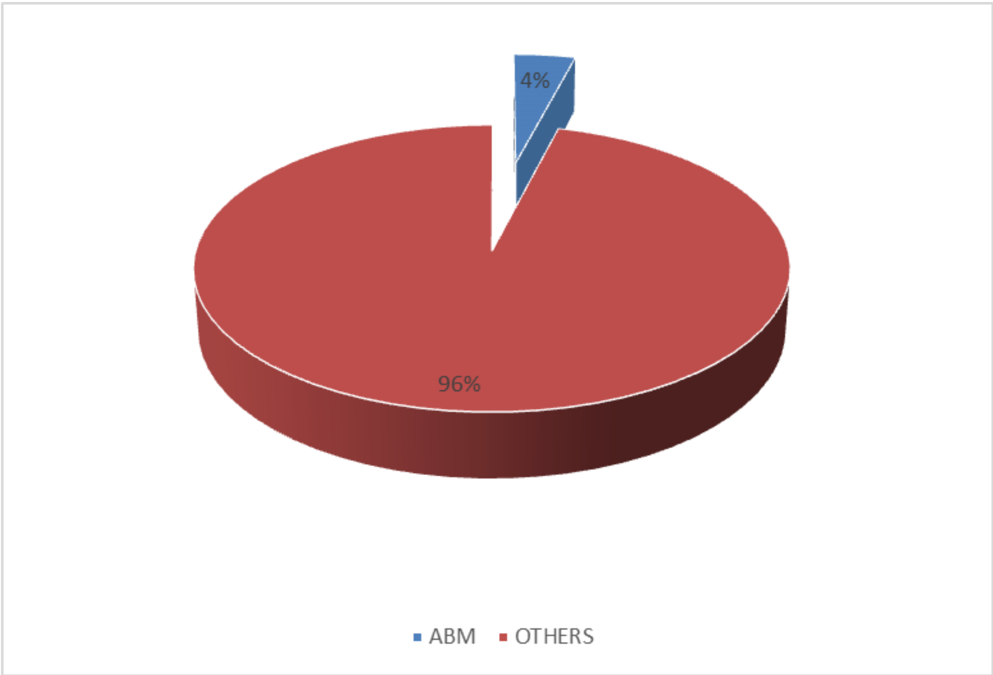


Figure 3: Prevalence of ABM among children aged 2 months to 5 years hospitalized with features of CNS infection at Dodoma Regional Referral Hospital.

4.3 Factors associated with ABM among children clinically suspected with CNS infections

On univariate analysis poor nutritional status and incomplete immunization were found to be two major risk factors for acquiring ABM. Poor nutrition status (OR3, (95%CI2.58-16.98] p-value =0.029,), severe acute malnutrition was observed to increase the risk of acquiring ABM by about 3 folds. Receiving immunization shots at least once was protective against ABM (OR0.2, 95%CI [0.08-2.09] p-value= 0.045).

Other demographic features had no significance effect on ABM. In the line of clinical signs and symptoms, history of fever or presence of fever at the time of admission together with bulging fontanel were mostly observed in patients with ABM with (OR7,95%CI[2.3-78.9]p- value = 0.030). Abnormal counts of WBC in the CSF was observed to be associated with ABM infection with a (OR 7.5 95%CI [3.2-244 p value=0.048) in **Table 2.**

On multivariate analysis poor nutrition status and incomplete immunization were also revealed to be major risks for ABM. Poor nutrition status (OR5.3, 95%CI [2.005-5.94] p value=0.04), severe acute malnutrition was observed to increase the risk of acquiring the infection about 5 times. Receiving immunization at least once was revealed to be protective against the infection (OR0.04, 95%CI [0.02-0.9] p value= 0.04). Having a bulging fontanel as a clinical feature was highly related with ABM (OR15, 95%CI [0.663-339] p value= 0.001) while an elevated WBC in the CSF was associated with ABM (OR4.2, 95%CI [1-108] p value = 0.024).

Table 2: Factors associated with ABMU nivariate and Multivariate analysis (Social demographic, clinical features and laboratory findings) N=101

Variable	ABM		Univariate			Multivariate		
	Positive 4 (4%)	Negative (96%)	P value	OR	95% CI	AOR	95% CI	P value
Age								
2months - 24months	3(6%)	47(94%)						
>24months- 60months	0(0%)	20(100)						
>60months	1(3.2%)	30(96.8%)	0.416	1.416	0.595-0.991			
Gender								
Male	3	55	0.634	4.68	0.5-3.64			
Female	1	42						
Vaccination status								
Fully immunized	1	88	Constant	0.2	Costant			

Immunized once	1	4	0.045	0.68	0.08-2.09	**0.04**	**0.002-0.9**	**0.04**
Not immunized	1	1	0.037	2	0.45-3.98	1	0.045-22	0.98
Unkown	1	4	0.02		0.115-34	4	0.117-137	0.4
Nutrition state								
Normal	3	93	Costant		Costant		2.005-5.924	
SAM	1	2	**0.029**	3	2.58- 16.98	5.3		**0.04**
Prior Antibiotic use								
Yes	2	75						
No	2	22	0.239	1.2	2- 12.6			
Presense of convulsions								
Yes								
NO	3	86	0.4	0.6	1.8-23.7			
	1	11						

Neck stiffness								
Yes	0	5	0.68	0.21	0.8-12.5			
No	4	92						
Bulging Fontanel								
Yes	1	2	0.03	7	2.3-78.9	**15**	**0.663-39**	**0.001**
No	2	65						
Altered level of consciousness								
Yes	4	80	0.593	1.044	4.6-43.9			
No	0	17						
HIV Status								
+VE	1	4	0.186	3.5	6.2- 28.7			
-VE	3	93						

CSF protein								
Normal	3	94						
High	1	3	0.838	0.042	0.2-19.6			
CSF glucose								
Normal	3	94						
Low	1	3	0.669	1	2.5-76.8			
CSF WBC								
Normal	2	89						
High	2	2	**0.048**	7.5	3.2-244	**4.2**	**2.58-108**	**0.024**
Malaria								
+VE	1	23	0.689	1	2.5- 76.8			
-VE	3	74						

4.4 The bacterial isolates in from children clinically suspected with ABM enrolled

Two organisms were isolated as etiological agents for ABM namely; *E.coli* and *S. Pneumoniae*. Only 1 *E coli* was identified by latex agglutination test in an infant aged 2 months while the other 3 species of *S. pneumoniae* were identified by using either gram stain, culture or latex test. One of the *S pneumoniae* was identified in an infant aged 2 months who was HIV exposed with severe malnutrition by Latex agglutination test. The remaining 2 species of *S.pneumoniae* were identified with gram stain, culture and latex agglutination test. These two were identified in an infant aged 21months who was fully immunized, while another child 9 years old had unknown vaccination status.

4.5 Sensitivity pattern of the isolated organism

In this study vancomycin, kanamycin and ciprofloxacin proved to be sensitive against S. pnemoniae, while ceftriaxone, ampicillin, Gentamycin and chloramphenicol were resistant by 50%. **Table 3**

Table 3: Antimicrobial sensitivity patterns of the CSF isolated organisms (N=2).

DRUGS	Streptococcus pneumonia	
	Sensitive N (%)	Resistance N (%)
Ceftriaxone	1 (50)	1 (50)
Ampicillin	1 (50)	1 (50)
Gentamycin	1 (50)	1 (50)
Chloramphenicol	1 (50)	1 (50)
Vancomycin	2 (100)	0 (0)
Kanamycin	2 (100)	0 (0)
Ciprofloxacin	2 (100)	0 (0)

*One of the *S. pnemoniae*and *E.coli* were identified by the latex agglutination, hence sensitivity was not tested.

4.6 In- hospital treatment outcomes of children

The in- hospital treatment outcomes in this study was assessed by observing the mortality rate, duration of admission and requirement of physiotherapy at the time of discharge.

4.6.1 Mortality rate

The overall mortality rate of CNS infection was found to be 13.8 %(14/101). 1 patient out of 4 patients confirmed with ABM died. High mortality rate 5.9 % (6/101) was observed in the group of undiagnosed and malaria patients.

Table 4: Distribution of Death according to the etiology of CNS infection

DIAGNOSIS	MORTALITY		TOTAL
	YES N (%)	NO N (%)	
Undiagnosed Patients	6 (8.6)	64 (91.4)	70 (100)
Malaria	6(25)	18 (75)	24 (100)
Cryptoccocal Meningitis	1(33)	2(67)	3 (100)
ABM	1(25)	3(75)	4 (100)

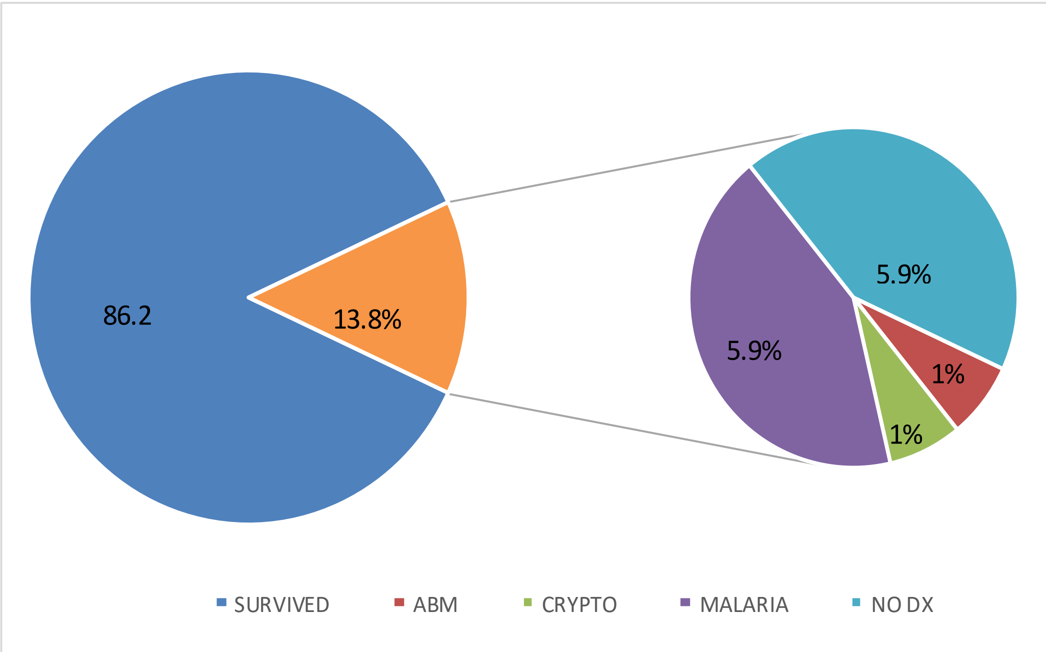


Figure 4: Mortality Rate of CNS infection among children aged 2 months to 5 years hospitalized at Dodoma Regional Referral Hospital

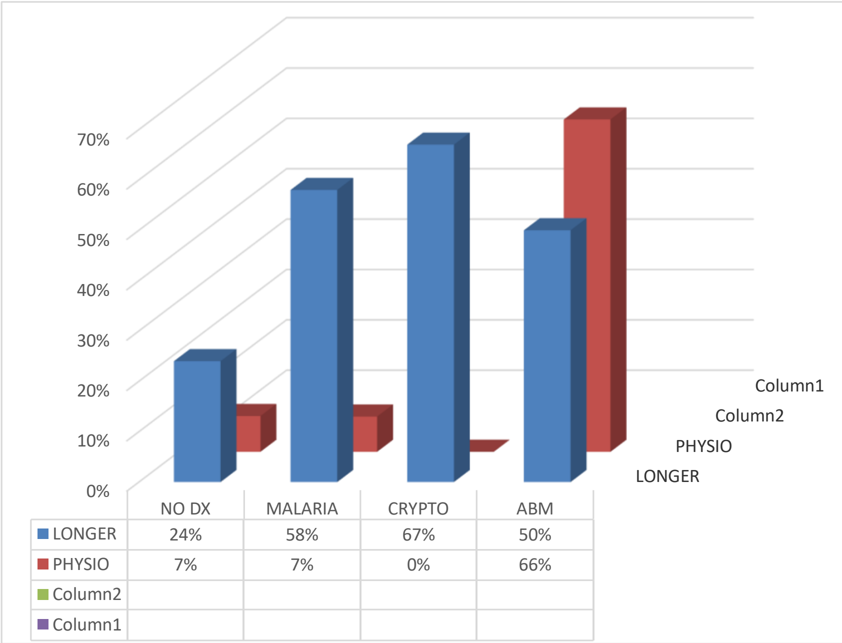
4.6.2 Duration of hospital stay and requirement of Physiotherapy at the time of patient discharge.

Duration of hospital stay was categorized as either longer hospital stay; that is hospital stay more than 2 weeks or shorter hospital stay of less than 2 weeks Longer hospital stay at a rate of 67%(2/3) was observed among patients with cryptococcal meningitis ..50% (2/4) among ABM patients required longer hospital stay while undiagnosed and malaria patients required longer hospital stay at a rate of 24%(18/70) and 58%(14/24).

Among patients with ABM 66 %(2/3) required physiotherapy while one of them died. Patients with either malaria or those without proven diagnosis required physiotherapy at a rate of 7 % shown in **Figure 4**

ABM infection was among the risks factors for the requirement of physiotherapy at the time of discharge together with being undiagnosed and malaria infection with significant p values of 0.047, 0.019 and 0.023 respectively. **Table 5**

ABM infection was among the risks factors for the requirement of physiotherapy at the time of discharge together with being undiagnosed and malaria infection with significant p values of 0.047, 0.019 and 0.023 respectively. **Table 5**



	NO DX	MALARIA	CRYPTO	ABM
LONGER	24%	58%	67%	50%
PHYSIO	7%	7%	0%	66%
Column2				
Column1				

Figure 5: Distribution of number of admission days and requirement of physiotherapy by the patients with features CNS infection according to the etiology.

Table 5: Distribution of requirement of physiotherapy and hospital stay among patients with features CNS infection according to the etiology obtained by univariate and multivariate analysis).N=101

DIAGNOSIS	PYSIOTHERAPY		UNIVARIATE		MULTIVARIATE	
	YES	NO	P VALUE	OR, CI	AOR, CI	P VALUE
Undiagnosed patients	5(7%)	65(93%)	**0.041**	6.384,(5.74-37)	4.148, (2.69- 13.527)	**0.019**
Malaria	4(7%)	10(93%)	**0.012**	6.38,(3.09-33.3)	4.133(1.269-9.942)	**0.023**
Cryptoccocal	0(0%)	2(100%)	0.45	3.682(3.351-26)		
ABM	2(66%)	1(34%)	**0.046**	6.158(4.708-51)	2.36(1.18- 19.7)	**0.047**
LONGER HOSPITAL STAY						
	YES	NO				
Undiagnosed patients	18(24%)	52(76%)	**0.021**	5.345(2.690-11.36)	2.69, (1.11.69- 6.53)	**0.035**
Malaria	14(58%)	10(24%)	**0.012**	6.4(6.205-8.79)	3.25(1.75-12.98)	**0.023**
Cryptoccocal	2(67%)	1(33%)	0.501	1.321(1.320-73)		
ABM	2(50%)	2(50%)	0.41	0.321(0.309-1.47)		

CHAPTER FIVE

5.0 DISCUSSION

ABM stands as the second most common cause of CNS infections following malaria and is among the major cause of mortality and morbidity in developing countries. The effective treatment for this disease ideally depends on the local epidemiological pattern of the prevalent bacteria, hence periodic reviews of meningitis cases are required for improving evidence-based treatment strategies.

5.1 Prevalence of ABM among children suspected to have CNS infection

The prevalence of ABM in this study was found to be 4%. This finding lies within the provided worldwide prevalence range of 1.6% - 17.9 % stated by (Thigpen et al., 2011).

In Africa, a study done in Ghana showed a prevalence of confirmed and probable meningitis were 3.3% and 2.1% respectively (Owusu et al., 2012). The low prevalence in this study was associated with the use of antibiotics before hospital admission, which is a common practice in many developing countries. Another study with similar result in Nigeria showed the positive culture bacterial isolation rate of 3.3%. But both of these studies were retrospective studies (Nwadioha et al., 2013).

The actual prevalence of ABM among children in Tanzania is difficult to ascertain due to lack of uniform nationwide surveillance hence most of the available data are generated from isolated facility-based studies. A study conducted in northwestern Tanzania reported a prevalence of 12.6% which is high compared to our findings. The difference in the prevalence could be attributed to the difference in the definition of ABM as in this study they used the WHO definition of ABM blood culture in a child with neurological features while we strictly relied on identification ofpathogen from CSF (Jumanne et al., 2017) . It is also possible that there is a progressive decline in the prevalence of ABM with increasing vaccine coverage of the common bacterial causes of ABM such as *Streptococcus pneumoniae a*nd *Hib*given the time difference between the two studies

Another study in Tanzania by (Abdallah et al., 2015) revealed a prevalence of about 2.5% by using conventional diagnostic method such as culture and gram stain, but a prevalence of about 37.5% by using PCR. The 37.5% prevalence in this study is probably because more neonates were enrolled who are generally more prone to ABM compared to older children, and using techniques with high sensitivity such as PCR .Hence despite the wide spread use of vaccination, ABM is still prevalent and more efforts should be placed on diagnosis and identification of etiological organisms by using high sensitive techniques.

5.2 Factors associated with ABM among children clinically suspected to have CNS infection

Children with severe acute malnutrition in our study had high likelihood of having ABM an association which was also reported in a study from Iran among children with bacterial meningitis (Jarousha&Afifi, 2014). Children with severe acute malnutrition are generally at risk for invasive bacterial infections as a result of impaired immunity. Poor nutritional status, not only pose as a risk factor but also complicate the management of the infected patient (Scarborough &Thwaites, 2008)

Children with incomplete vaccination in our study were also likely to have ABM compared to those who had complete vaccination in keeping with the reported impact of the pneumococcal and Hib vaccines in reducing the incidence of invasive bacterial infections(Mokaddas & Albert, 2012).

The common features observed in enrolled patients from this study was fever with either generalized convulsions or altered mentation or Neck stiffness or bulging fontanel. But presence of fever with bulging fontanel was mostly associated with ABM infection with a p value of 0.001. This finding was also observed in a study by (Kostenniemi, Norman, Borgstr, & Silfverdal, 2015) were by bulging fontanel was observed mainly in infants. Hence in an infant presence of fever and bulging fontanel are highly associated with ABM infection.

5.3 Common bacterial isolates for IBM among children suspected to have CSN infection

The two organisms identified in this study as the causative organisms of ABM are E. coli and S.pneumoniae. These two organism were also identified as the main etiological agents of ABM in a study by (Abdallah et al., 2015). E. coli related infection is found to be rising among infants less than 3 months instead of group B streptococcus, while S. pneumonia still remains the common infection among older infants. These findings are similar to the study done in China by (Jiang et al., 2017).

One of the challenges in the management of ABM in developing countries is the rise of streptococcal resistant strains against our first line antibiotics such as penicillins and cephalosporin. This study has conquered with this observation as the isolated *S.pneumoniae* has shown a resistance of about 50% towards both of the first line drugs, while vancomycin, kanamycin and ciprofloxacin had resistance of 0%. This intermediate resistance was also observed in a study by (Jiang et al., 2017) . This observation highlights a critical concern as the continuation ofuncontrolled antibiotic prescription especially cephalosporins may lead to a rapid increase of the prevalence of ESBL producing strain.Current guidelines recommend the use of third generation cephalosporins in suspected bacterial meningitis, with the addition of vancomycin in areas of high levels of penicillin and cephalosporin resistance in *S. pneumoniae.* (Ranawaka, 2016).

Majority of patients in this study about 70% had no confirmed diagnosis despite effective CSF studies done to increase chances of organism isolation. This finding was relatively high compared to the study done in Uganda where the rate of un diagnosed cases was 45.1%(Page et al., 2017). This difference may be explained with the use of PCR in isolation of organism in the study.

High rates of poor organism isolation in CNS infection reflects the common challenge in many developing countries as the CSF isolation rates in these countries are lower compared to developed countries(Ranawaka, 2016). These findings highlight the need to utilize molecular diagnostics for improving pathogen identification for CNS infections(Akhvlediani et al., 2014).

The overall mortality rate of CNS infection in this study was found to be 13.8%. This was low to compared to the 18% obtained by (Page et al., 2017). The high rate in this study could be explained by the large sample size.

5.4 In-hospital treatment outcome of children suspected with CNS infection

The mortality rate of ABM in this study was 25% as only one patient out of four died. Despite the fact that this rate is in line with the estimated mortality rate of 16%- 32% in developing countries stated by (Shrestha et al., 2015) it is difficult to conclude on this finding as there were only four patients with ABM.Hence more studies with more sensitive and specific techniques are required to provide a clear prevalence and hence the mortality rate. ABM infection has shown to be among the risks factors for requirement of physiotherapy togetherwith being undiagnosed and malaria infection.

Requirement of physiotherapy at the time of discharge highlights the occurrence of neurological sequel as one of the longstanding complication of ABM. Hence follow-up of these patients after discharge is important as the rate of neurological sequel in these patients can be as high as 47% (Ramakrishnan et al., 2009)

CHAPTER SIX

6.0 CONCLUSION

Despite the wide spread use of vaccination, ABM is still prevalent with a local prevalence of 4% and Malnutrition was found to be one of the major risk factor for this disease. The isolated organism were mainly *S. pneumoniae* and *E. coli* who had a resistance of about 50% towards the first line antibiotics against ABM.

This disease was among the risks factors for requirement of physiotherapy at the time of discharge highlighting the occurrence of neurological sequel as one of the longstanding complication of ABM. Hence more efforts should be placed on diagnosis and identification of etiological organisms by using high sensitive techniques so as to improve treatment and outcome among patients with ABM

6.1 Limitation

Blood culture was not done this may lead to under estimation of the reported prevalence

6.2 Recommendations

1. More emphasis to be placed on Immunization coverage as it is still the best preventive measure against ABM**.**
2. Increase availability of medications that can be used as alternatives to cephalosporin's resistant strains
3. Improving diagnostic techniques for ABM apart from culture and gram stain
4. Frequent periodic review of ABM pattern
5. Control of antibiotic prescriptions to decrease bacterial resistance

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APPENDICES

Appendix 1: Informed Consent

You are invited to participate in a study on Acute bacterial meningitis. We are studying the prevalence, aetiologies, and treatment outcome of ABM in children less than 15 years, admitted at our hospital, Dodoma regional Hospital. Participation is strictly voluntary and unwillingness to participate in this study will not affect your treatment in one way or another. If you are willing to participate, you need to sign this form indicating your willingness. You may withdraw from the study at any time. Such a decision will be respected, and will not affect your treatment.

Participants will undergo an interview, a physical examination, lumbar puncture and blood test.

Other investigations will depend on the condition of the patients. The blood test and lumbar puncture may involve some pain at the time of drawing the sample but overall, there is no physical harm expected from participation. To minimize risk of microbial infections, the needle site will be sterilized. When the results of the research are published or discussed in conferences or used in any form, no information will be included that would reveal your identity.

Participants will benefit from this study by knowing whether or not they have ABM. If they have ABM they will receive treatment according to Tanzanian guidelines.

In case of any questions regarding this study, please contact:

Dr.NeemaKipiki, principal Investigator, Univeristy of Dodoma, Dept of Pediatrics and child health.: P. O. Box259, Dodoma. Tel: +255-714-366426

Participant

I ____

I have understood the above information. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

____

Signature of Patient / Next of Kin__________________________________Date

Appendix 2: Questionnaire

Thank you for participating in our study. I will read each question loud and wait for your response. For some questions I will also read aloud some answers from which you can choose. Please take as long as you need to remember or think about your answer. If a question is unclear, please say, I will repeat and explain it. Please remember all your answers will be kept confidential and this questionnaire does not have your name on it.

Social and demographic characteristics

1. Patient No: ………………..
2. Patient Initials: …………....
3. Patient Age: ………………
4. Patient Sex: ……………….
5. Maternal/ Care taker education
    a. Not been to school
    b. Standard seven incomplete
    c. Standard seven complete
    d. Secondary education
    e. College / University education.
6. Maternal/Caretaker job
    a. House wife
    b. Peasant/small scale business
    c. Informal employment
    d. Formal employment

7. PCV vaccination status:
    a. Well immunized
    b. Immunized only once
    c. Immunized only twice
8. Hib vaccination status;
    a. Well immunized
    b. Immunized once
    c. Immunized twice
9. Prior treatment with antibiotics
    a. Yes
    b. No
10. history of fever within the previous week
    a. Yes
    b. No
11. Presence of any Chronic illness
    a. Yes
    b. No
12. Presence of convulsions.
    a. Yes
    b. No
13. Frequency of convulsions
    a. Once
    b. More than once

B: Physical examination signs and symptoms

14. Presence of fever

    a. Yes (Axillary T > 38.5)

    b. no

15. Reduced level of consciousness

    a. BCS] ≤4 for children aged 5 years or younger;

    b. Glasgow coma score ≤14 for children older than 5years.

    c. altered mentation

16. Patient nutrition status;

    a. Chronic malnourished

    b. SAM

17. Presence of neck stiffness

    a. Yes

    b. No

18. Presence of photophobia

    a. Yes

    b. No

19. Kernig's sign/Brudzinski sign

    a. Positive

    b. Negative

20. Presence of Tense Fontanelle

    a. Yes

    b. No

C: Laboratory results:

21. PITC status

    a. Positive

    b. Negative

22. MRDT

    a. Positive

    b. Negative

23. BS results

    a. Positive

    b. negative

24. Csf analysis:

    a. Macrospicapearance;
    b. Protein level ……………
    c. Wbc count ……………
    d. Glucose level …………….

25. Cryptococcal antigen test

    a. Positive
    b. Negative

26. CSF gram stain results;

    a. Gram-positive diplococci suggest *S. pneumoniae*
    b. Gram-negative diplococci suggest *N. meningitidis*

    c. Small pleomorphic gram-negative coccobacilli suggest Hib

d. Gram-positive cocci or coccobacilli suggest group B streptococcus

e. Gram-positive rods and coccobacilli suggest *L. monocytogenes*

27. CSF culture results

    a. Positive

    b. Negative

28. Latex agglutination test results;

a. Neisseria meningitidis A, C, Y, W135.

b. Escherichia coli,

c. Hemophillusinfluenzae Type B (Hib).

d. Streptococcus pneumoniae.

e. Group B Streptococcus.

Section D; Treatment Outcome

29. Number of days of admission …………

30. Treatment outcome

    a. Dead

    b. Alive

31. Requirement of Physiotherapy after discharge.

    a. Yes

    b. No