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Neurological Disorders in Rural Tanzania: Characteristics of Patients with Febrile Seizures and Meningitis

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Neurological Disorders in Rural Tanzania: Characteristics of Patients with Febrile Seizures and Meningitis

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2 List of abbreviations

AIDS	acquired immune deficiency syndrome
CI	confidence interval
CSF	cerebrospinal fluid
ELISA	enzyme-linked immunosorbent assay
FS	febrile seizure
HIV	human immunodeficiency virus
HLH	Haydom Lutheran Hospital
ILAE	International League Against Epilepsy
MCH	mother and child health center
SD	standard deviation

3 List of publications

The thesis is based on the following original publications:

1. Storz C, Meindl M, Matuja W, Schmutzhard E, Winkler AS. Community-based prevalence and clinical characteristics of febrile seizures in Tanzania. Pediatr Res 2015;77:591-6.

2. Storz C, Schutz C, Tluway A, Matuja W, Schmutzhard E, Winkler AS. Clinical findings and management of patients with meningitis with an emphasis on Haemophilus influenzae meningitis in rural Tanzania. J Neurol Sci 2016;366:52-8.

4 Summary

Neurological disorders, especially those of infectious origin, seem to be more frequent in low-income countries like sub-Saharan Africa. But not only the prevalence estimates seem to be higher in low-income countries, mortality rates tend to be higher compared to high-income countries, too. Seizures as well as meningitis are often reported as one of the leading causes for neurological disorders in patients in sub-Saharan Africa. As shown in our studies, symptoms and signs of neurological diseases like febrile seizures (FSs) and meningitis can appear very similar and render an exact diagnosis difficult, as they often include impairment of consciousness, for example. Several African studies reported that neurological diseases, especially epileptic seizures, FSs and meningitis/meningoencephalitis as leading causes of impairment of consciousness, are often accompanied with adverse outcome such as neurological sequelae and especially infectious diseases such as meningitis may contribute to the high mortality in sub-Saharan Africa. The lack of appropriate diagnostic methods and imaging modalities as well as unqualified workers and the often late presentation at medical services and, last but not least, the lack of appropriate vaccination coverage in rural areas complicate the detection of the exact diagnosis and concomitant diseases and the exclusion of important differential diagnoses, and thus impede an appropriate patient management.

The studies of the present thesis were performed from 2002 to 2004 in the United Republic of Tanzania and more specifically at Haydom, Mbulu district; Wasso, Ngorongoro district and Mahenge, Ulanga district. The prevalence and characteristics of FSs were assessed in three community-based door-to-door studies in the catchment area of the Haydom Lutheran Hospital (HLH), Wasso Hospital and Mahenge Hospital, complemented with retrospectively collected data from main hospitals and Mother and Child Health Centers (MCHs) of the study area by using screening questionnaires.
In a hospital based study (Haydom Lutheran Hospital), we identified patients with meningitis in order to describe their clinical characteristics including laboratory and clinical aspects. Patients with neurological symptoms and/or signs were examined by a neurologist and clinical as well as laboratory data were collected.

Our study found a prevalence rate of 20.5/1,000 (95% CI: 17.5-23.9/1,000) FSs in children between 2 months and 7 years at the time of the interview and is in line with other studies about FSs, however, it does not confirm the assumption of a higher prevalence in low-income countries of sub-Saharan Africa. Reasons for this are varied and include superstitious beliefs, higher mortality rates or inaccurate recollection of events in the past. However, our study confirms a trend of a higher proportion of complex FSs in low-income countries. This is important, as complex FSs have been discussed as possible risk factors for the development of later neurological sequelae like epilepsy.

In patients with meningitis, fever, meningism and impairment of consciousness represented the most important clinical warning symptoms. Our findings show that bacterial pathogens like *Haemophilus influenza (H. influenza), Streptococcus pneumoniae (S. pneumoniae)* and *Neisseria meningitides (N. meningitides)* were, in this order, the most frequent pathogens, especially in pediatric patients. Mycobacterial meningitis prevailed in elderly patients. Compared to other regions, the proportion of patients with meningitis caused by *H. influenzae* in our study population is disproportionally high, which may be due to the lack of appropriate vaccination coverage in rural and remote areas. This is in line with

other study results and demonstrates that the causative pathogens vary a lot regarding the age range, region or pre-existing concomitant diseases.

Our study underlines the importance of access to health services for populations of rural areas of low-income countries where appropriate and adapted diagnostic and treatment facilities are available. Beside the detection of the causative organisms, the diagnosis of concomitant diseases like HIV and the exclusion of differential diagnoses like cerebral malaria are indispensable methods to ensure the best treatment. In addition, childhood vaccination coverage needs to be assured, especially in remote and vulnerable populations.

The current thesis intends to underline prevalence and characteristics of neurological disorders like FSs and meningitis in low-income countries like sub-Saharan Africa, especially with regard to their infectious etiology. In conclusion, further reliable studies are necessary to ascertain the prevalence, burden and mortality rates as well as appropriate treatment strategies of neurological and psychiatric disorders. In fact, in 2015 the United Nations launched the sustainable development goals to which almost all nations agreed and which also draws attention to Global Mental Health. In that sense, the current thesis seems more than timely and underlines the need for further research as well as education for both health care personnel and patients, in Global Mental Health.

5 Zusammenfassung

Neurologische Erkrankungen, insbesondere infektiösen Ursprungs, scheinen häufiger in Entwicklungsländern wie Subsahara-Afrika vorzukommen. Neben der Prävalenz scheint auch die Mortalität in Entwicklungsländern erhöht zu sein. Epileptische Anfälle und Meningitis werden dabei häufig als führende neurologische Erkrankungen in afrikanischen Patienten angegeben. Wie wir in unseren Studien zeigen konnten, äußern sich neurologische Erkrankungen oft mit relativ ähnlichen und unspezifischen Symptomen wie beispielsweise Bewusstseinsverlust. Dies erschwert häufig eine exakte und rasche Diagnosefindung. Verschiedene afrikanische Studien zeigten, dass neurologische Erkrankungen, insbesondere epileptische Anfälle, Fieberkrämpfe und Meningoenzephalitiden, oft Ursache von Bewusstseinsverlust darstellen und häufig mit einer ungünstigen Prognose, wie beispielsweise neurologischen Folgeschäden, einhergehen. Insbesondere infektiöse neurologische Erkrankungen scheinen zu einer höheren Mortalität in Subsahara-Afrika beizutragen. Der Mangel an adäquaten diagnostischen Methoden oder bildgebender Verfahren, unqualifiziertes medizinisches Personal und die oftmals erst späte Vorstellung der Patienten in medizinischen Einrichtungen sowie auch das Fehlen von entsprechendem Impfschutz, insbesondere in abgelegenen Regionen, erschweren die Diagnostik und somit eine angemessene Therapie. Darüber hinaus behindern diese Faktoren auch die Feststellung von relevanten Begleiterkrankungen sowie den Ausschluss anderer wichtiger Differentialdiagnosen.

Die Studien, auf denen die vorliegende Arbeit basiert, wurden von 2002 bis 2004 in der Vereinigten Republik Tansania, genauer in Haydom, Mbulu Distrikt, Wasso, Ngorongoro Distrikt und Mahenge, Ulanga district durchgeführt. Informationen zur Berechnung der Prävalenz und Charakteristika von Fieberkrämpfen wurden mithilfe von Screening-Fragebögen in drei Tür-zu-Tür Studien im Einzugsgebiet des Haydom Lutheran Hospital (HLH), Mahenge Hospital und Wasso Hospital gesammelt und durch retrospektiv gesammelte Daten aus den Hauptkrankenhäusern der entsprechenden Distrikte sowie deren Mutter-und-Kind Gesundheitszentren (MCH) ergänzt.
In einer krankenhausbasierten Studie (Haydom Lutheran Hospital) identifizierten wir Patienten mit Meningitis und sammelten Informationen über die laborchemischen und klinischen Eigenschaften. Patienten, die aufgrund neurologischer Auffälligkeiten im Krankenhaus aufgenommen wurden, wurden durch einen Neurologen untersucht und die klinischen und laborchemischen Untersuchungsergebnisse zusammengetragen.

In unserer Studie ermittelten wir eine Prävalenz von 20.5/1,000 (95% CI: 17.5-23.9/1,000) bei Kindern, die zum Zeitpunkt der Befragung zwischen 2 Monaten und 7 Jahren alt waren. Dieses Ergebnis steht im Einklang mit vielen anderen Studien über Fieberkrämpfe, bestätigt jedoch nicht die Annahme, dass Fieberkrämpfe im Allgemeinen in Entwicklungsländern wie Subsahara Afrika häufiger vorkommen. Aberglaube, eine höhere Mortalität oder Vorfälle, die in der Zwischenzeit in Vergessenheit geraten sind, können Ursachen für die Unterschätzung der Prävalenz in unserer Studie darstellen. Der erhöhte Anteil komplexer Fieberkrämpfe in unserer Studie bestärkt jedoch die Annahme, dass diese häufiger in Entwicklungsländern vorkommen. Dies steht möglicherweise in Verbindung mit einer oftmals ermittelten höheren Prävalenz von Epilepsien in dieser Region, da komplexe

Anfälle unter anderem als Risikofaktoren für spätere neurologische Schäden wie Epilepsie bekannt sind.

Fieber, Meningismus und Bewusstseinsverlust stellen die wichtigsten Warnsymptome bei Patienten mit Meningitis dar. In unserer Studie konnten wir feststellen, dass bakterielle Erreger wie *Haemophilus influenzae (H. influenzae), Streptococcus pneumoniae* (*S. pneumoniae*) und *Neisseria meningitidis (N. meningitidis)*, in absteigender Reihenfolge, die häufigsten Erreger für Meningitis, insbesondere bei pädiatrischen Patienten darstellten. Mykobakterielle Meningitiden traten häufiger in älteren Patienten auf.
Im Vergleich zu anderen Studien zeigt sich der Anteil der Patienten mit *H. influenzae* Meningitiden in unserer Studienpopulation unverhältnismäßig hoch, möglicherweise ist dies das Resultat eines fehlenden Impfschutzes, insbesondere in abgelegenen Regionen. Diese Ergebnisse fanden sich auch in vielen weiteren Studien und zeigen, dass die ursächlichen Erreger je nach Altersgruppe, Region oder Vorerkrankung stark variieren können.

Neben der Feststellung der ursächlichen Erreger sind die Diagnosen von Vorerkrankungen wie HIV sowie der Ausschluss von Differentialdiagnosen, wie die der zerebralen Malaria, unerlässliche Methoden, um eine adäquate Behandlung zu gewährleisten. Zusätzlich muss eine Durchimpfungsrate im Kindesalter gewährleistet sein, insbesondere in schwer erreichbaren, abgelegenen und gefährdeten Populationen.

Die vorliegende Dissertation hebt die Bedeutung der Prävalenz und klinischer Charakteristika neurologischer Erkrankungen wie Fieberkrämpfe und Meningitis in Entwicklungsländern wie Subsahara Afrika hervor. Weitere Forschungsstudien über die Prävalenz und Mortalität neurologischer Erkrankungen sowie den Zusammenhang mit Infektionskrankheiten wie Meningitis, Fieberkrämpfen und die Entwicklung einer späteren Epilepsie in Entwicklungsländern können dazu beitragen, Erkrankungen in diesen Regionen besser zu verstehen und zu verhindern. In der Tat führten im Jahre 2015 die Vereinten Nationen die sogenannten „Sustainable Development Goals“ ein, die u.a. für ein erhöhtes Bewusstsein der globalen mentalen Gesundheit werben.

In diesem Sinne ist die vorliegende Dissertation absolut zeitgemäß, da sie ein höchst aktuelles Thema, die globale mentale Gesundheit, unter unterschiedlichen Gesichtspunkten beleuchtet.

6 Introduction

6.1 General background information

6.1.1 Neurological disorders – a burden of low-income countries?

The burden of neurological disorders looms large, especially in developing countries. The broad range of neurological disorders include, inter alia, seizure disorders, infectious diseases, cardiovascular as well as neurodegenerative disorders. Beside prevalence and mortality rates, the spectrum of neurological disorders in low-income countries differ significantly from those in high-income countries. Prevalence and mortality rates seem to be higher in low-income countries like sub-Saharan Africa, especially those of infectious etiology and convulsive disorders[1-3]. Comparing the global top ten causes of Years of Life Lost, ascertained by the "Global Burden of Disease Study 2013", it becomes apparent that common diseases in high-income countries distinguish clearly from those in low-income countries like Tanzania: human immunodeficiency virus and acquired immune deficiency syndrome (HIV/AIDS), lower respiratory tract infections, malaria, tuberculosis and encephalitis are leading causes in low-income countries whereas ischaemic heart disease, stroke and lung cancer head the table of high-income countries[4]. A study conducted at the Haydom Lutheran Hospital (HLH) in Tanzania determined that about 9% of all hospital admissions fell under neurological diagnoses, mainly seizures or infectious diseases, with an overall mortality rate of 21%[2]. Another study of two Ethiopian teaching hospitals, one with and the other without supervision of neurologists, reviewed medical admissions and showed that 18% and 25%, respectively, suffered from neurological diseases with mortality rates of 22% and 35%[5]. The latter study reflects not only the burden of neurological disorders in low-income countries, but also the underestimation of those diseases and the need of educated and qualified specialists to detect and handle patients appropriately.

Impairment of consciousness is a frequent symptom of neurological patients, particularly associated with febrile illness. An African study documented that neurological emergencies like febrile seizures (FSs), epilepsy, head trauma, cerebral malaria and meningitis represent the leading diseases for impairment of consciousness in patients and thus rendering an exact diagnosis difficult[6].

With regard to the high prevalence of seizure disorders and infectious neurological diseases mentioned above, this thesis focuses on FSs and meningitis with their causes, clinical characteristics, and patient management.

6.1.2 Febrile seizures

Definition of terms

FSs are epileptic seizures associated with febrile illness in early childhood, excluding obvious intracranial pathologies[7-9]. FSs are by far the most common seizure disorders in childhood, with a peak in the second year of life[10]. FSs are often accompanied by impairment of consciousness and tonic-clonic convulsions. Various definitions regarding the age range of FSs exist, but, in most instances, FSs occur within the first two years of life, with a frequency peak at 18 months[8-12]. A higher susceptibility to FSs for male children has been described in

several studies[13-15] however, the exact causes for this phenomenon has not been unequivocally clarified.

FSs can be divided into two main groups: simple and complex FSs.
Complex FSs represent seizures with at least one of the following features[8,9]:

- a duration of more than 15 minutes (a seizure lasting more than 30 minutes is defined as a "status epilepticus");
- an occurrence of more than once within 24 hours;
- an occurrence of focal neurological symptoms during the FS.

Apart from a status epilepticus in FSs, the majority of all FSs are self-limiting (most FSs lasting less than 2 minutes)[16].

Prevalence and mortality rates

Prevalence and incidence rates of FSs are estimated at 2-4% of all children[11,12,17], but those rates vary a lot because of different methods and definitions used. Comparing prevalence between low- and high-income countries, data range from 9.9/1,000 in Germany[18] to 116/1,000 in Nigeria[19] (for more details see Paper 1: Supplementary Table S1). Furthermore, several studies point to a relationship between rural regions with lower socioeconomically standard and education and a higher frequency of neurological disorders, especially epilepsy and FSs, compared to urban regions[19,20]. Another American study found a higher prevalence for FSs in black children in comparison to white children[21].
Beside a higher prevalence, several studies also determined higher mortality rates which can be related to concomitant diseases like lower respiratory tract infections[22,23], a common cause of fever in African children and number one of the top ten causes of Years of Life Lost in developing countries[4,24]. Especially in remote areas of low-income countries, mortality rates in pediatric patients, mostly due to convulsive disorders like FSs, seem to be high[25]. Moreover, Hesdorffer et al. (2015) found an increased number of FSs in children with sudden unexplained death in childhood, assuming that there is a risk of seizure related deaths in those children[26].
In a Tanzanian hospital-based study, 71% of all cases were complex FSs[2], whereas a British survey detected only 20% as complex FSs[17]. Considering the entirety of all these results, we can assume that FSs seem to be more common in low-income countries and it is especially complex FSs that have been observed more often in sub-Saharan Africa.

Additionally, a seasonal distribution can be observed in the prevalence of FS, as for example more cases occurred during raining seasons or winter seasons, which bears the danger of infectious diseases[27,28].

Risk factors for the development of febrile seizures

Genetic susceptibility, environmental triggers like infections and inflammatory as well as metabolic dysregulations in children can cause, inter alia, FSs (Figure 1). Malnutrition and anemia also seem to be possible risk factors for the development of FSs[15]. These factors confirm the assumption that FSs are multifactorial systemic events. Viral infections, particularly respiratory tract infections, represent the most frequent accompanying illness in children with FSs[29,30]. Pathogen agents like influenza A or human herpesvirus 6 constitute the leading causative organisms related to those infections[31,32]. Especially in African regions, malaria plays also a prominent role as fever cause in children with FSs[33]. Malaria with febrile seizures also represents one of the most important differential diagnoses of cerebral malaria

with epileptic seizures which bears a high mortality and necessitates a different approach and management of the patient.

Beside this, pre- and perinatal factors are often discussed as possible risk factors for the development of FSs. Thus, the children of mothers with medical problems during gestation or labor, smoking and alcohol abuse during pregnancy and newborns with decreased birth weight or premature infants showed higher prevalence of FSs during the first years of their lives[29,34,35].

Also, a positive family history of FSs or afebrile epileptic seizures increase the risk of the development of FSs[29]. Frequently, the controversial discussion arises if FSs may occur as a reaction to vaccine against measles, mumps and rubella and a Danish study ascertained a number of gene variants associated with vaccine related FSs[36]. However, some studies determined exclusively a transient higher risk within the first days after the vaccination against measles, mumps and rubella, but the absolute risk remains low and the positive effect of the protection against these agents outweighs the potential occurrence of FSs[36,37].

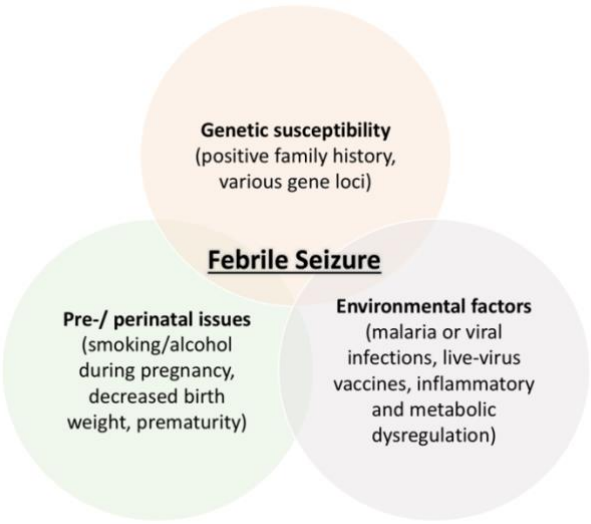

Figure 1. Multifactorial pathogenesis of febrile seizures.

As complex attributes, such as prolonged or focal seizures, seem to repeat in children with recurrent FS episodes and complex FSs represent a risk factor for recurrent FSs, a strong relation between complex and recurrent FSs is obvious[21,38]. Beside this, an early age of onset and a positive history of afebrile and febrile seizures also represent possible risk factors for the development of recurrent FSs[21,38,39].

The relation between febrile seizures and later epilepsy

The risk of suffering from epilepsy later in life in children with a history of FSs seems to be higher. A positive family history of afebrile epileptic seizures or FSs, complex features and recurrent FSs, represent, inter alia, significant risk factors for the development of later epilepsy in children with previous FSs[21,35,40-42]. For example, Annegers et al. determined a fivefold higher risk for the development of afebrile epileptic seizures in children with FSs. Overall, this represents a risk of developing unprovoked seizures of about 7 % until the age of 25 years[43]. As mentioned above, these findings should be noted in the context of higher prevalence of complex FSs and the possibly related higher prevalence of epilepsy in sub-Saharan Africa[22,44,45].

Considering the frequently discussed positive family history as a risk factor for the development of FSs and later epilepsy, it has to be taken into account that several genetic factors may promote the development of epileptic seizures. For example, gene-loci like SCN1A, GABRG2, IL-1ß, SLC4A3, CHRNA4 or FEB1-4 were detected as causative and/or

contributory factors in this context and some of these genes seem to be involved in the association between hereditary epilepsy and FSs[46,47].

Management and treatment

The guidelines composed by the International League against Epilepsy set out a number of treatment options in case of FSs[48]. The most important element in treating acute FSs is the prevention of a status epilepticus as well as complications which can emerge during the seizure. Thus, the registration of seizure symptoms and the prevention of aspiration or injuries build up the first steps. Furthermore, high fever should be reduced with household remedies like tepid sponging and an adequate fluid intake. In FSs lasting longer than 2-3 minutes the administration of rectal diazepam is indicated. Intravenous benzodiazepines or phenobarbital are indicated in cases of prolonged FSs or status epilepticus. Solely in individual cases a prophylaxis with benzodiazepines or anticonvulsant drugs can be considered[48].

Consultants working in rural Africa often report of traditional attempts to heal FSs or epilepsy, as these disorders are frequently attributed to supernatural powers or evil spirits[49]. Superstitious beliefs and traditional medicine like hot bush tea, cow urine or oil for drinking as an attempt to heal the seizure and to prevent following seizures complicate the management of FSs and can cause severe consequences like severe burns, aspiration and pneumonia[49-51]. Scarifications on the forehead or over other body parts are, at times, also part of traditional treatment and have been regularly observed during the studies which this thesis is based on. These practices seem to be more frequent in families living in rural or peri-urban areas of low-income countries[49,52].

These facts underscore the inevitable necessity of conveying sufficient information about the disease and interactive as well as exhaustive communication with parents and other relatives about the development and correct management of FSs.

6.1.3 Meningitis

Definition of terms

Meningitis is an inflammation of the meninges covering the brain and spinal cord, caused by several viral, bacterial, fungal or parasitic pathogens as well as other factors like drugs or immunoglobulins. An additional infection of the brain itself, a so-called meningoencephalitis, is common and often hard to demarcate precisely. Meningitis can cause life-threatening emergencies and has to be detected and treated as quickly as possible to prevent late sequelae or lethal outcomes.

Prevalence and mortality

The World Health Organization has declared meningitis as one of the twenty most frequent causes of “Years of Life Lost”[53]. Considering the incidence rates of meningitis in different world regions, it becomes apparent that in low-income countries like those of Africa the rates are considerably higher compared to high-income regions: Thigpen et al. (2011) determined an overall incidence rate of 1.4/100,000 for bacterial meningitis in all age groups in the United States between 2002 and 2003[54]. During the same time period, Parent du Châtelet et al. (2005) calculated an overall incidence rate of 43/100,000 for bacterial meningitis cases in all age groups in Burkina Faso[55]. These and many other studies also determined that particularly children under the age of 5 years show the highest incidence rates for meningitis[54-57].

Regarding mortality rates of meningitis, substantially higher rates occur in low-income countries[4,53]. An African study showed that meningitis is one of the top ten leading causes of death in children[58]. Another African study conducted in Swaziland came to the conclusion that meningitis is more common in children, but mortality rates seem to be significantly higher in adult patients[57].

Several vaccine programs led to a decline of incidence rates and epidemical outbreaks of meningitis. In the so-called 'meningitis belt', a region known for its recurring epidemics of meningococcal serogroups in sub-Saharan Africa including Burkina Faso, Mali and Niger, the introduction of a conjugate vaccine against meningococcal serogroup A nearly led to an elimination of these epidemics, but thereupon cases through other meningococcal serogroups and pathogens increased[59]. In contrast to that Watt et al. (2009) determined higher incidence and mortality rates for the actual preventable *Haemophilus influenzae* caused meningitis in low-income countries, such as Africa, pointing to the problem of an adequate implementation of vaccine strategies especially in remote areas[60]. Although incidence and mortality rates decrease over years, the distribution pattern of pathogens varies and an imbalance between low- and high-income countries still exists[1,4,61].

Demographic features

Most of the cases with meningitis occur in children under the age of 15 years, frequently during their first year of life[56,57]. An American study shows, however, a decline in the frequency of children meningitis and an increasing median age in meningitis patients, probably an effect of the introduction of several vaccines[54].

Clinical presentation

Meningitis frequently presents with clinical symptoms/signs like headache, nausea, fever, neck stiffness on flexion, impairment of consciousness, as well as a positive Lasègue, Brudzinski or Kernig signs. 'Meningism' has different meanings and either describes a syndrome of typical symptoms/signs of meningitis like mentioned above, or merely connotates "neck stiffness". However, symptoms/signs especially in infants and small children are often less specific and difficult to diagnose. Berkley et al. (2004) defined several "red flag" symptoms, like a bulging fontanella, neck stiffness, cyanosis and impaired consciousness, to facilitate diagnosis in pediatric patients, which in turn leads to a faster treatment[62]. In several studies, epileptic seizures occurred more often in patients with meningitis caused by *H. influenzae*[63,64]. However, strictly speaking epileptic seizures already point towards involvement of the brain and therefore, once present, the correct diagnosis is no longer that of meninigitis but meningoencephalitis.

Laboratory findings

Beside a careful evaluation and revaluation of the clinical appearance of the patient, laboratory methods play an important role in the diagnostic of meningitis. The examination of the cerebrospinal fluid (CSF) and blood cultures are the most important tests performed. In blood tests, especially in low-income countries, HIV testing and a blood smear for detecting malaria parasites are recommended for the detection of differential diagnoses or recognition of concomitant diseases[65-67]. While blood glucose and white cell count in blood tests can be less specific, it is often necessary for the interpretation of CSF tests[65]. Performing spinal taps enables interpretation of the appearance, cell count and predominant cells, glucose and protein status of the CSF and can be used for microbiological

Gram staining as well as microbiological culture[67]. Table 1 provides an orienting guide for the interpretation of CSF analysis. For example, in case of a bacterial meningitis, the CSF often appears turbid with high cell counts and low glucose levels. Microbiological cultures are also used for the implementation of resistance testing.

Cerebrospinal fluid	Bacterial	Viral	Tuberculous	Normal
Appearance	turbid	clear	fibrin web	clear
Cell count (n/mm³)	1,000 or more	50-1,000	10-1,000	<5 lymphocytes
Predominant cell	polymorphs	mononuclear	mononuclear	
Glucose (mmol/l)	↓ <1/2 plasma	N/↑ >1/2 plasma	↓ <1/2 plasma	1/2 plasma

Table 1. Interpretation of cerebrospinal fluid in patients with meningitis. Adapted from the Oxford Handbook of Clinical Medicine[68].

Nearly all bacterial meningitis can be detected by means of a CSF Gram stain[69] (if the correct technique is applied), in comparison to that, blood cultures only lead to a positive diagnosis of bacterial meningitis in two third of the cases, as determined in Europe[70]. Increased cerebral pressure in patients with meningitis may lead to the complication of a herniation by conducting a spinal tap. Therefore, prior imaging to exclude an increased intracranial pressure should avoid complications like that. In low-income countries, availability of imaging modalities is rare, thus, spinal taps are often not performed, which delays rapid diagnostic and treatment[71].

Distribution pattern of pathogens

Most of the causative pathogens of meningitis are of bacterial origin. *Haemophilus influenza (H. influenza), Streptococcus pneumoniae (S. pneumoniae)* and *Neisseria meningitides (N. meningitides)* represent the most common bacterial agents. However, the order of importance of pathogens differs depending on regional variations, epidemics, vaccination coverage, age distributions and concomitant diseases. In pediatric patients, especially those under 1 year, *H. influenzae*, *S. pneumoniae* and *N. meningitidis* mostly form the main causes of meningitis cases[56,72]. After the first year of life, *N. meningitidis* and *S. pneumoniae* often occur more frequently than *H. influenzae*[54,56]. To the contrary, due to nosocomial outbreaks or in epidemic regions like the so called 'meningitis-belt' where meningococcal epidemics are common, other pathogens like *Salmonella* or several serogroups of *N. meningitidis*, respectively, were found as the most common causative organisms associated with meningitis[73,74]. Cryptococcal and mycobacterial pathogens are often found in HIV positive patients and elderly patients and are often accompanied by high mortality rates[75-79]. Finally, the introduction of various vaccines against common pathogens led to an alteration in the distribution of pathogens causing meningitis. Particularly in epidemic regions, significant declines in *H. influenzae* or *S. pneumoniae* cases have been observed after the vaccination against the abovementioned pathogens, however, this is mainly observed in high-income countries[61,80,81].

Differential diagnoses and concomitant diseases

As mentioned above, HIV positive and elderly patients are more at risk of contracting opportunistic infections. Especially in HIV positive patients, cryptoccal and mycobacterial meningitis are common; listeria caused meningitis, but also common organisms such as *S. pneumoniae* and *H. influenzae*, can be determined more often in elderly patients, all accompanied by higher mortality rates compared to younger patients[75,76,78].

Particularly in African regions, cerebral malaria, inter alia, represents an important and common differential diagnosis. Especially in children, cerebral malaria often resembles meningitis in the clinical presentation with signs such as impairment of consciousness or fever. Considering the possibility of a simultaneous presence of meningitis and cerebral malaria in a patient, blood smears are not sufficient in the diagnosis as the presence of malaria protozoa does not necessarily mean that they are the cause of the disease. In those cases, meningitis should be actively excluded in all possible cases and, at the same time, an overestimation of cerebral malaria should be avoided[66,82].

Management and treatment

A pre-requisite for an appropriate treatment of meningitis patients is an exact diagnosis of the causative organism. An appropriate therapy regime requires a consistent CSF penetration and potent activity against major pathogens. In case of bacterial meningitis, two equivalent and accessible main antibiotic groups are recommended, including third generation cephalosporins (e.g. ceftriaxone, cefotaxime) and conventional antibiotics (e.g. ampicillin, bencylpenicillin, chloramphenicol)[69,83]. Furthermore, an adequate choice of a therapy regime depends also on the kind of the causative organism, as for example some organisms are able to express resistances to beta-lactam antibiotics by beta-lactamase production, which may lead to resistances against penicillin.[84]. Cephalosporins like ceftriaxone are seemingly more effective than penicillin in combination with gentamicin and also better manageable, as it can be given in a single injection per day[85], but particularly in resource-poor settings like Tanzania, they are not widely affordable and, thus, a combination of penicillin and chloramphenicol or gentamicin is still recommended[86] . However, due to the oto- and nephrotoxicity, aminoglycosides should be used very carefully, especially if laboratory possibilities for observing the therapeutic levels are lacking[85]. Nevertheless, the frequency of resistances against common antibiotics in the main causative organisms is rising and should be tested, if possible[65,87].

Moreover, due to misuse and overuse of antibiotics, an increase of antimicrobial resistances has been observed in the past decades and demands for a constantly perennial verification of adequate therapy regimes[88]. For example, treatment failures related to the development of penicillin resistant S*. pneumoniae* during the 1970s and also multi-drug resistances against cefotaxime and meropeneme were increasing rapidly, hampering an adequate treatment which led to an increased number of deaths[89-91]. Additionally, a nationwide survey over time periods between 2000 and 2012 evaluated the changes in antibiotic sensitivity of *H. influenzae* in pediatric patients and found a continuous increase of antibiotic resistance of *H. influenzae* against ampicillin, ceftriaxone or carbapeneme, for example[92]. However, the implication of new conjugate vaccines may offer sufficient projection against most drug-resistant pathogens[60,90].

In case of mycobacterial meningitis, a 4-fold combination of isoniazid, rifampicin, pyrazinamide and ethambutol is recommended as a 12-months therapy, streptomycin may be used as an additional tuberculostatic therapy[86]. Increasing resistances against tuberculostatic therapy is however emerging as a serious problem during the past decades worldwide, thus, an early detection of resistance as well as a tailored treatment with an appropriate second-line regime is of utmost importance in the patient management of mycobacterial menigitis[91,93].

The benefit of an additional therapy with corticosteroids is still controversial. In patients with mycobacterial meningitis, an early treatment with corticosteroids seems to improve survival, especially in adults[94]. In cases with bacterial meningitis, corticosteroids seem to reduce later sequelae, but only if used in high-income countries[95]. In addition, an adequate fluid, nutritional and oxygen management is essential[86].

In the prophylaxis of meningitis, vaccination programs play a pivotal role. New polyvalent vaccines combine protection against several diseases such as pneumococcal disease caused by *S. pneumoniae* or meningococcal disease caused by *N. meningitidis* and may simplify routine vaccination especially in low-income countries. Specifically in epidemic regions like the 'meningitis belt', conjugate vaccines against special serogroups are abundant and already showed great success in the elimination of meningococcal epidemics[59,96,97]. This effect can also be observed for other common causative organisms like *H. influenzae* and *S. pneumoniae* worldwide, but studies in low-income countries are scarce. However, as already mentioned, it becomes apparent that there exists a lack of appropriate vaccination coverage especially in remote areas, as studies demonstrated a decline in the vaccination coverage against *H. influenzae* or only an incomplete immunization for example in Tanzania[98,99].

The usage of traditional medicine in Tanzania is high. Particularly in remote and rural areas, traditional treatment is commonly practiced, mainly for symptomatic diseases, chronic diseases and malaria[100]. Beside superstitious beliefs, an easier accessibility and lower costs are reasons for the use of traditional medicine in resource-poor settings which is often accompanied by higher mortality rates or later sequelae[51,100].

6.1.4 United Republic of Tanzania

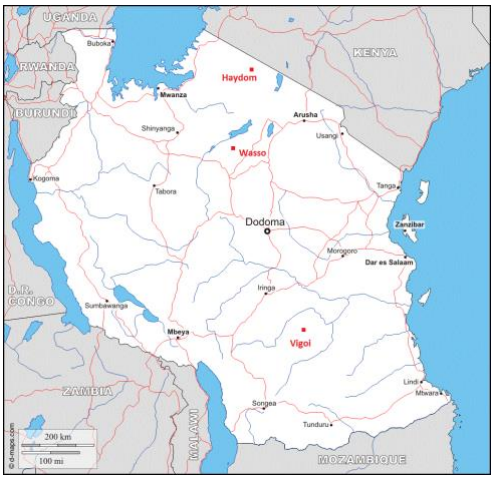

Figure 2. Map of the United Republic of Tanzania with the three study regions Haydom, Wasso and Vigoi. Adapted with permission from d-maps.com[101].

The United Republic of Tanzania is located in east Africa, bordering Uganda, Kenia, Rwanda and Burundi in the north, the Indian Ocean in the east, Mozambique in the South and Malawi, Zambia and the Democratic Republic of the Congo in the west (Figure 2)[102]. In 1961, Tanzania gained its independence of Britain and in 1964, the United Republic of Tanzania has been founded[103]. Nowadays, Dodoma represents the official capital. Dar es Salaam, the former capital, is still the economic capital of Tanzania.
51,015,882 people live in Tanzania, 99% are Africans. 95% of the over 130 tribes existing in Tanzania are of Bantu origin[103]. About 30% of the population are Christians, 35% Muslims (over 99% of the people living in Zanzibar are Muslims) and 35% indigenous beliefs[103].
Kiswahili, English and Arabic are the most spoken languages in Tanzania[103].

Administrative and health care system

Figure 3 gives an overview of the well-structured hierarchy of the administrative system and the corresponding health care system in Tanzania. The administrative system is built up in different levels starting with a 'region' and ending in the so-called 'ten-cells', representing a number of about 10 households that come under a ten-cell leader. Corresponding to that, the health care system is divided into various levels. The lowest health care level is provided by 'Village Health Centers' ascending to 'Referral or Consultant Hospitals', representing the highest level of medical care. According to the different periods of training, 'village health workers' are, after a short training, responsible for the 'Village Health Services', 'assistant clinical officers' are caring for the patients at 'Dispensary Services' after attending a medical school for about two years, and nurses, midwifes as well as 'clinical officers' with a medical training of at least three years are working in 'Health Center Services'. In district, regional and referral hospitals, medical doctors and professionals are treating the patients.

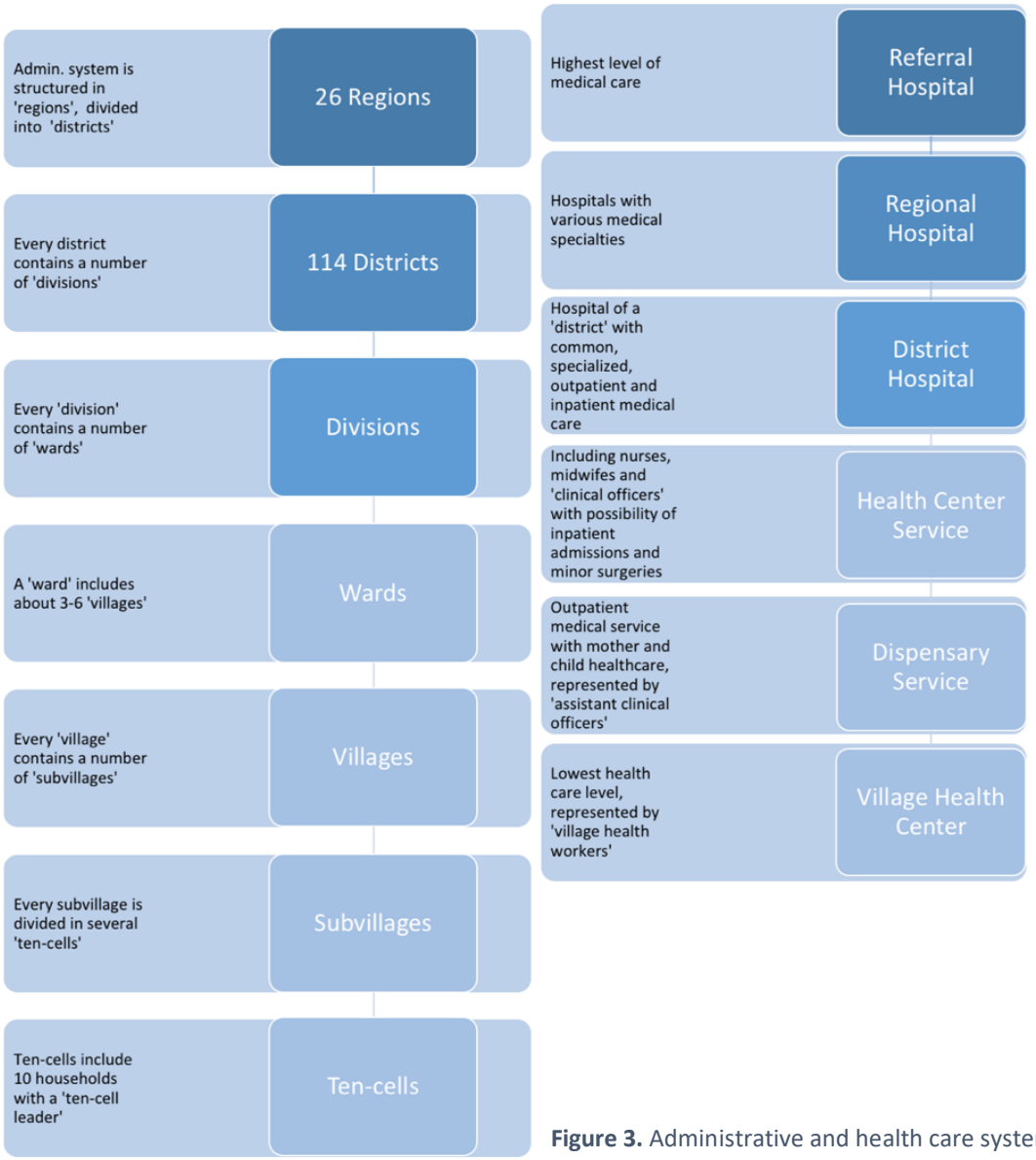

Figure 3. Administrative and health care system in Tanzania.

According to the 'Global Burden of Diseases Study 2013', HIV/AIDS and infectious diseases are the top leading causes of Years of Life Lost[4]. In adult population, the estimated HIV/AIDS prevalence rate is about 5.3%.

Study areas

Figure 2 gives an overview of our study areas in the United Republic of Tanzania. Haydom is situated in the northern highlands of Tanzania and is part of Mbulu district within Manyara region. In 2002, there was a population of 237,280 in this district[104]. Main ethnic groups living in this region are the Iraqw, subsistence farmers, and the Datoga, nomadic pastoralists. The HLH is located in the heart of the village of Haydom and comprises 429 beds[105]. The HLH, opened in 1954, includes, amongst others, surgical, pediatric, medical and maternity wards as well as an intensive care unit and an outpatient department with an HIV treatment unit. The catchment area of the HLH comprises 8 districts, which demonstrates the long distances, patients have to accept for receiving medical treatment at the hospital.

Mahenge (Vigoi) is situated in southern Tanzania and belongs to the Ulanga district in the Morogoro region. In 2000, Ulanga district had a population of approximately 193,280[104]. Most of the people living in Mahenge belong to Wapogoro ethnic group, which is of Bantu origin. Mahenge Hospital includes general medicine, surgery, pediatric, obstetrics and gynecological wards and comprises 120 beds.

Wasso belongs to the Ngorongoro district in the Arusha region in northern Tanzania near to the Kenyan border. The Wasso Hospital comprises approximately 70 beds.

6.2 Specific main aims of the thesis

The two studies included in the current thesis aimed at collecting information about infectious diseases in low-income countries in sub-Saharan Africa, exemplified by FSs and meningitis. The thesis is based on two original articles published in internationally peer-reviewed journals, dealing with FSs and meningitis as common neurological diseases in Tanzania.

Regarding FSs, we concentrated on the following questions:

- Is there a higher prevalence of FSs in rural Tanzania, representing a typical low-income country, compared to high-income countries?
- How far do clinical characteristics of FSs in rural Tanzania differ from those in high-income countries, regarding demographical information, triggering events, symptoms and type of FSs?
- How are FSs managed in rural Tanzania?

Regarding meningitis, we concentrated on the following questions:

- Do demographical details in our study of rural Tanzania differ from those determined in other studies from low-income and high-income countries?
- What are specific symptoms/ signs of patients with meningitis, especially in different age groups or in relation to different pathogens in a typical low-income setting?
- Which laboratory methods are valuable especially in resource-poor setting like Tanzania and what are the laboratory findings?
- What are the pathogens causing meningitis in rural Tanzania and how do they differ within different regions and circumstances?
- What are the symptoms/ characteristically signs and laboratory findings in patients with *H. influenza* meningitis?
- How effective is the treatment and management of patients with meningitis in rural Tanzania with emphasis on *H. influenza* meningitis?

7 Methods and material

7.1 Study design for the collection of information about febrile seizures

The study about FSs took place during a period between 2002 and 2004, collecting information within three defined study regions in rural Tanzania, i.e. Haydom, Wasso and Mahenge[102]. Three door-to-door surveys formed the basis, complemented with supplementary retrospectively collected data from three hospitals and MCHs of the respective study areas for the purpose of prevalence calculation (Table 2). Children younger than 15 years at the time of the study were included into the study population. All subjects with known gender and age between 2 months and 7 years at the time of the interview were included for the calculation of prevalence of FSs. Information on the clinical characteristics of FSs was only assessed within the door-to-door surveys in all interviewed children, irrespective of age. Children with obvious intracranial pathologies, known neurological disorders before the first FS as well as children with at least one event of an unprovoked seizure before the firs FS were excluded from the study population.

	Haydom	Wasso	Mahenge	Overall
Villages (n)	12	4	11	27
Households (n)	1.458	452	4.209	6.119
Supplementary information	Haydom MCH	Wasso hospital	Mahenge MCH and hospital	All supplementary information
All children under 15 years (n)	4.286	967	9.330	14.583
Children between 2 months and 7 years (n)	2.497	623	4.670	7.790

Table 2. Structure and origin of the febrile seizures study population within the three study regions. MCH=Mother and Child Health Center.

A team of three last-year medical students and translators interviewed the parents or relatives of the children of the three study regions with the help of a screening questionnaire (see Paper 1: Supplementary Table S2. Screening Questionnaire). The questionnaire consisted of a case confirmation part, to identify children with FSs, and an in-depth part with more detailed questions about the clinical characteristics of the FSs itself. Regardless of the age of the children, FSs were defined as seizures occurring with a fever in early childhood[7-10]. Complex FSs were FSs i) lasting more than 15 minutes, ii) occurring more than once within 24h and/or iii) appearing with focal features [8,9]. A status epilepticus, a complex feature, is defined as a FS duration of more than 30 minutes [9,10] (see Introduction, 6.1.2 Febrile Seizures).

For a more accurate calculation of prevalence, supplementary retrospectively collected information was used from the respective MCHs and main hospitals of Haydom and Wasso (more detailed information see Paper 1, Methods). Table 2 represents an overview of the study population within the three catchment areas.

Members of 12 villages with 1,458 households were interviewed in Haydom. Additionally, all children attending the MCHs at the HLH during the study period were surveyed. Members of four villages with 452 households were interviewed in Wasso and all admissions of the Wasso hospital between 2002 and 2004 were screened, additionally. In Mahenge, members of 4,209 households of 11 villages were interviewed. All in all, 14,583 children under the age of 15 years – at the time of the interview – were recruited and formed the overall study population. Of these, 9,330 belonged to the Vigoi, 4,286 to Haydom and 976 to Wasso catchment area.
For the calculation of the point prevalence of FSs, the age range between 2 months and 7 years at the time of the interview was chosen, hence 7,790 children were included.
The information of the clinical characteristics of FSs is based on the interviewed children within the door-to-door surveys, irrespective of age.

Excel spreadsheets (Microsoft Inc., Redmond, Washington) were used for entering and calculating the collected data. Prevalence was calculated by dividing the number of cases with FSs by the number of individuals examined in our study population. F-distribution and Fisher's exact test were used to construct 95% CI estimates of the prevalence.

7.2 Study design for the collection of information about patients with meningitis

Between 2002 and 2004, a cross-sectional hospital-based study identified all patients with meningitis admitted at the HLH, a hospital with about 429 beds with several departments like surgery, internal medicine, pediatrics, maternity and gynaecology[105,106]. A neurologist (Andrea Sylvia Winkler) recorded the patients' history, physical and laboratory findings, treatment as well as response to it and divided all admissions into defined diagnostic groups[2]. Meningitis and causative organisms were defined as mentioned above (Introduction, 6.1.3 Meningitis). For the purpose of a more detailed diagnosis, spinal taps were performed in patients with suspected inflammatory neurological diseases, if they were rousable at any time. Imaging modalities were not available at the time of the study. Blood smears were used to detect malaria.

Excel spreadsheets (Microsoft Inc., Redmond, Washington) were used for the assessment and calculation of data. Descriptive methods were used only.

7.3 Ethic approval of the FSs and the meningitis studies

Ethical approval was granted by the National Institute of Medical Research and the Commission of Science and Technology in Dar es Salaam, Tanzania. Informed consent was given by all participants.

8 Results

8.1 Main findings of the febrile seizure study

The following paragraphs summarize the main findings of the febrile seizure study[102].

Age range	Study methods	Overall (n)	Cases (n)	Prevalence Rate
2 months - 7 years	door-to-door surveys	7.790	147	18.9/1,000 (95% CI: 16.0-22.1/1,000)
2 months - 7 years	door-to-door surveys and supplementary methods	7.790	160	20.5/1,000 (95% CI: 17.5-23.9/1,000)
< 15 years	door-to-door surveys	14.583	221	15.2/1,000 (95% CI: 13.2-17.3/1,000)
7 - 14 years	door-to-door surveys	6.021	69	11.5/1,000 (95% CI: 8.9-14.5/1,000)

Table 3. Overview of the different calculated prevalence rates of febrile seizures. FS=febrile seizure, CI=confidence interval.

Table 3 gives an overview of the different calculated prevalence rates of FSs. Within the door-to-door surveys and additional supplementary hospital-based methods, we assessed 160 cases of FSs in children between 2 months and 7 years, resulting in a prevalence rate of 20.5/1,000 (95% CI: 17.5-23.9/1,000). Solely within the door-to-door study, the prevalence of FSs in children between 2 months and 7 years was 18.9/1,000 (95% CI: 16.0-22.1/1,000). In the overall population (children under 15 years), the prevalence was 11.5/1,000 (95% CI: 8.9-14.5/1,000).

Overall, 221 children with FSs were identified in the door-to-door studies in the age group below 15 years. The average of the age at onset of FSs was 2.2 (SD: 1.8) years. In the majority of children, the first FS occurred within the first 2 years of life (67%). The median number of FS episodes was 1, ranging from 1 to 14 episodes and 38% of those had more than one FS episode. More than half of the affected children had their FSs during the first half of the year, including the big raining season from February to

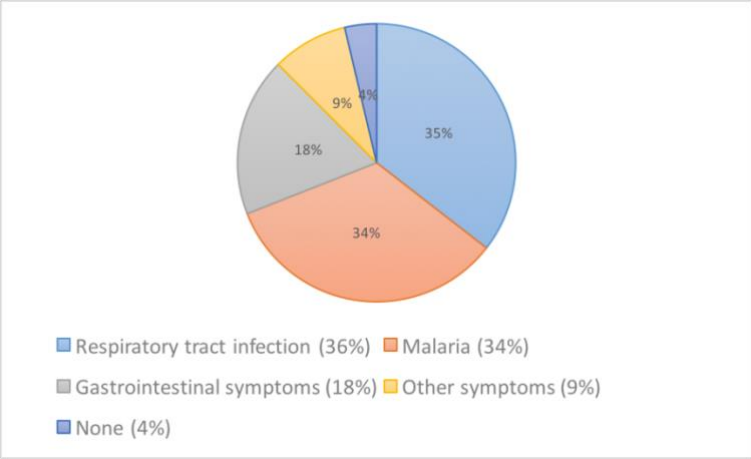

Figure 4. Causes of febrile illness in children with febrile seizures.

April (57%). Most of the children had their seizures outside of medical facilities (85%). Of 145 children with FSs, 61 reported about FSs with at least one complex feature (42%). Figure 4 represents the various causes of the febrile illness with respiratory tract infections and malaria being the most frequent. A positive family history was found in 32% of the children and 54% had a first degree relative affected. In 9% of the cases, traditional medicine was applied, whereas household remedies like tepid sponging and acetaminophen were used frequently to lower the fever (40% and 43%, respectively).

8.2 Main findings of the meningitis study

The following paragraphs summarize the main findings of the meningitis study[106]. A total of 136 patients with meningitis were identified at the HLH. The median age of the patients with meningitis was 4 years (ranging from 7 days to 90 years), with nearly 70% under the age of 16 years. The most common complaints were fever (85%) as well as generalized (57%) and focal (25%) neurological signs. Meningism, a typical syndrome of meningitis (see Introduction, 6.1.3 Meningitis), occurred frequently in 63%. A bulging fontanella was diagnosed in nearly 40% of children under 1 year. Seizures, mostly generalized, occurred in 8%. Seventy-five percent of the cases were acute meningitis cases.

In 128 of 136 patients with meningitis, spinal taps were performed with the aim of analyzing the CSF. No side effects appeared after spinal taps in all of those 128 patients. Concerning laboratory findings, CSF appeared mainly cloudy and turbid (73%) and the average CSF cell count amounted to 931 (SD: 1,867) cells/μL. Granulocytes and lymphocytes

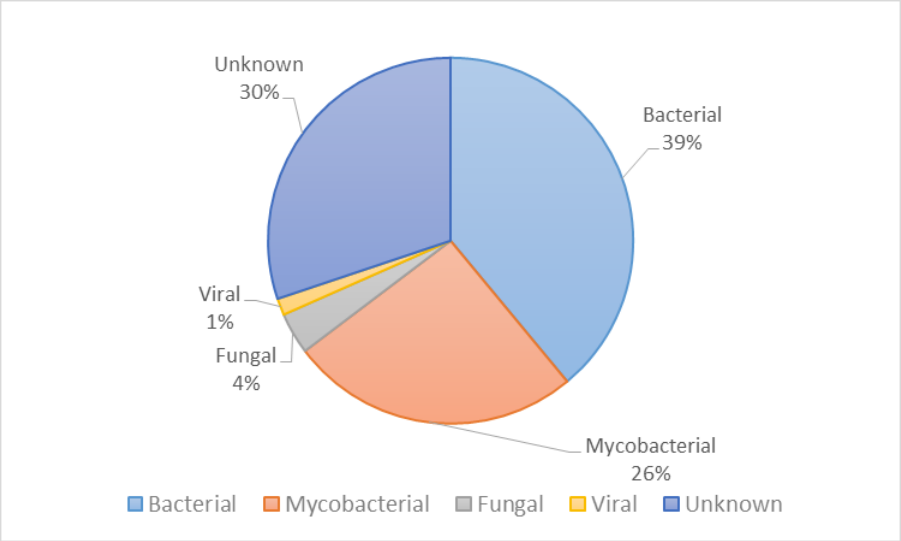

Figure 5. Distribution of causative pathogens in all 136 patients with meningitis.

were found frequently as predominant cells in CSF samples (60% and 27%, respectively).

In 10% of the performed blood smears malaria parasites were detected. Figure 5 gives an overview of the causative organisms in all 136 patients with meningitis. The leading pathogens in patients with meningitis were bacterial and mycobacterial organisms. Bacterial meningitis mostly occurred in the age groups under 15 years, whereas mycobacterial meningitis frequently occurred in patients aged 45 years and older. Figure 6 shows the distribution of pathogens in pediatric patients with bacterial meningitis. Most of the cases occurred in children under 1 year with *H. influenzae* as major pathogen.

Antibiotics like benzylpenicillin and chloramphenicol were frequently used in our patients (85% and 82%, respectively). Data of treatment outcome was only available for the

H. influenza group (see below). Although only 10% were tested positive for malaria parasites on blood smear, 72% received antimalarial drugs like quinine.

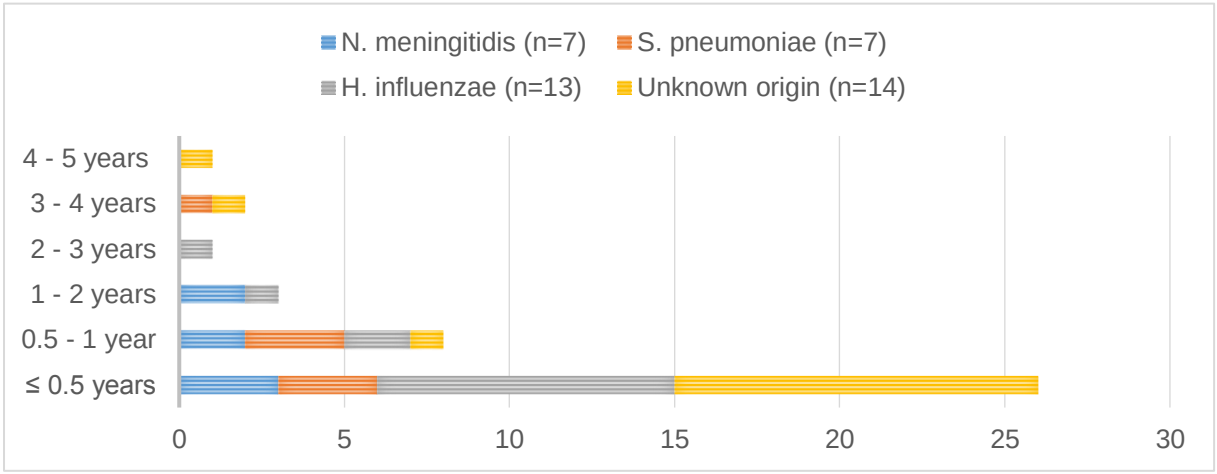

Figure 6. Distribution of causative pathogens in children under 6 years with diagnosed bacterial meningitis.

Taking a detailed look at our patients with meningitis caused by *H.* influenzae (14/53 or 26% of all bacterial meningitis), the average age in those patients was 1.6 (SD: 3.6) years, with a male to female ratio of 1.33 (57% men). The most frequent complaints on admission in cases with *H. influenza*e meningitis was fever in 93%, impairment of consciousness in 79% and seizures in 57%. All CSF samples, performed in 14 patients with *H. influenzae*, appeared turbid and lymphocytes represented the predominant cell type in all CSF samples. Malaria parasites were only detected in one case of the 13 performed blood smears.
Most of the patients with meningitis caused by *H. influenza* were treated with benzylpenicillin, chloramphenicol and additional antibiotics, e.g. gentamicin (11/14), whereas 3/14 were treated with benzylpenicillin and chloramphenicol only. Two thirds (2/3) of patients with *H. influenza* meningitis treated with a combination of benzylpenicillin and chloramphenicol recovered during hospitalization. Almost 73% of those treated with benzylpenicillin, chloramphenicol and additional antibiotics (e.g. gentamicin) died and nearly 2% recovered during hospitalization.

9 Discussion

9.1 Febrile seizures in rural Tanzania

Comparing the different study results concerning prevalence and incidence rates of FSs worldwide, a trend toward higher rates in low-income countries becomes apparent[12,19]. This assumption has been supported by various studies, which determined a higher frequency of FSs in rural regions with low socioeconomically standards compared to urban regions as well as in black populations compared to white populations[19-21]. Our study result, with an overall point prevalence of 20.5/1,000 within the three study regions, is in accordance with other studies about FSs, but does not confirm the trend of a higher prevalence in sub-Saharan Africa. To the contrary, another population-based study conducted in an urban region of Brazil determined an astonishing low prevalence of 6/1,000 compared to other studies in Brazil[107,108]. Taking into account, that mortality rates of FSs in low-income countries may also be higher, this may constitute a crucial factor of our lower than expected prevalence[22,23]. On the other hand, population-based studies about FSs in sub-Saharan Africa are very scarce and a comparison of prevalence estimates ascertained only in hospitals based on different methods should be considered with caution. In our community-based study we interviewed a large study population outside of medical services and also included information of hospital and MCH admissions. Thus, the methodology used in our study may have led to a more realistic prevalence estimate of FSs of 20.5/1,000 and may disprove the assumption of higher rates in low-income countries. However, superstitious beliefs of African tribes, especially the Maasai, and the association of evil spirits or spiritual forces with seizure disorders may have led to an underreporting of FSs in our study population[49,51].

Our results concerning the age range of FSs are in alignment with other studies[8-12]. The average age at onset was 2.2 (SD: 1.8) years and the majority of our study population had their first FS within the first 2 years of life. Several studies showed a gender imbalance with the assumption of a higher susceptibility for male children[13-15], but this fact can also be the result of social and cultural factors, especially in low-income countries.

Our study results also present a seasonal distribution, since more than half of the FSs occurred during the first half of the year and the big raining season. This time of the year entails a higher risk especially for malaria and respiratory tract infections which were found as the main causes of the febrile illnesses in our patients.

Furthermore, malaria and respiratory tract infections represent common severe diseases in low-income countries which are accompanied by high mortality rates[4] and thus may contribute substantially to the higher mortality rates ascertained in FSs in low-income countries compared to high-income countries. Due to incomplete information about the outcome of patients with FSs in our study population, we cannot comment on the mortality of children with FS in our study.

In our study, 42% of the children and/or their parents reported criteria of complex FSs. A percentage of 71% of complex FSs determined in another survey in Tanzania at the HLH[22] in contrast to a percentage of about 20% of complex FSs in a British study[17] may result in the

assumption that complex FSs are more common in Africa. However, it should be noted that complex attributes represent more impressive events and thus may remembered better by the parents than simple seizures. Taking into consideration that several studies found higher prevalence estimates of epilepsy in sub-Saharan Africa compared to high-income countries[44,45,109] and that complex features have been suspected as risk factors for the development of epilepsy[21,40,43] a causative relationship seems plausible.

In about one third of our children with FSs we found a positive family history or recurrent FS episodes each. Complex characteristics have been reported to repeat in children with recurrent FSs and a positive family history and recurrent FSs, amongst others, represent risk factors for subsequent epilepsy[35,41,43,110]. This relationship underlines the importance of a rapid diagnosis and an appropriate treatment to prevent complex and recurrent FSs und thus later sequelae.

Surprisingly, most of the affected patients sought medical aid at hospitals or other medical services and traditional medicine was only used in 9%. The usage of household remedies like tepid sponging or antipyretic drugs to lower the body temperature and thus reduce the risk of FSs is common in such a rural population. Traditional medicine like hot bush tea or cows urine, commonly used in African tribes, can lead to aspiration and oral burn and aggravate the course of FSs[50].

Qualified workers at medical services and well-trained nurses are important, especially in case of the first seizure episode, as a study demonstrated a high rate of misdiagnosis in children with a first event[111]. Detailed information about the recognition of FSs symptoms/signs and the appropriate behavior of parents or relatives of children with seizure disorders would be of great importance and could potentially reduce mortality and later sequelae.

9.2 Meningitis in rural Tanzania

Although prevalence and mortality of meningitis seem to decline worldwide, they are often reported to be higher in low-income countries[4,53-55,58]. This may be based on sporadic epidemic outbreaks, for example in the so-called 'meningitis belt'. It is those outbreaks that together with, vaccination programs and other factors like age and concomitant diseases like HIV/AIDS have led to an alteration of the distribution pattern of pathogens.

In our study, nearly 70% of the examined patients were under the age of 16 years. This finding is in line with other African studies[56,57]. In high-income countries like the United States, a trend towards a higher median age can be observed, possibly a resulting fact of the introduction of several vaccines during childhood[54]. *H. influenzae*, *S. pneumoniae* and *N. meningitidis* formed the main causative organisms in our study. Due to the lack of data about meningitis cases during the last years at the HLH, an alteration of this pathogen pattern, for example by the introduction of new vaccines, cannot be excluded. Vaccines against several causative organisms like various serogroups of *N. meningitidis* or *H. influenzae* have led to a dramatic decline of meningitis cases especially in epidemic regions[80,97,112]. However, another African study found a similar pattern compared to our results with *H. influenzae* as the leading causative organism in children under 1 year[56]. It needs to be considered that Tanzania, where our study was conducted, belongs to those countries where meningitis is endemic (and not epidemic) and additionally due to the poor infrastructure and accessibility of rural and remote areas, vaccines often do not reach areas in need. This was also shown by other African studies which reviewed the vaccination coverage for several pathogens, with the result of a decline in full coverage and the lack of relevant vaccination for example against *H. influenzae* or *S. pneumoniae*[98,99]. However, studies about vaccination coverage in remote areas are scare as most of the studies were conducted in accessible and urban regions. Our findings point to the necessity of further studies about the vaccination coverage in remote rural areas of sub-Saharan Africa, a revision of recommended vaccinations and an improvement in the provision of vaccines to remote areas in order to decrease prevalence and mortality rates of meningitis in low-income countries.

Taking a detailed look at the distribution pattern of causative pathogens between the different age groups in our study population, it becomes apparent that bacterial organisms are mainly responsible for meningitis cases in children, which is in line with many other studies[65,72]. In the age groups above 45 years, mycobacterial meningitis prevailed. Several studies determined the accompanying mortality rates, which seem to be especially high in pediatric and late-stage HIV/AIDS patients[57,113,114]. Referring to the aforementioned, it is obvious that meningitis shows a different pattern in high-compared to low-income countries, which should be taken into consideration especially in planning of patient management and the delivery of vaccine programs.

Unspecific symptoms like fever, neck stiffness and impairment of consciousness were the leading symptoms in our patients. The clinical presentation of meningitis patients can be rather unspecific or symptoms/signs can occur late, especially in very young and very old patients[62,115]. A bulging fontanella, that was present in nearly 40% of our children under 1

year, neck stiffness and epileptic seizures should be interpreted as 'red-flag-signs' in pediatric patients with meningitis and indicate the necessity of fast and appropriate management[62,116,117]. Seizures occurred more often in our patients with meningitis caused by *H. influenzae* (57%), which is in line with findings from other studies representing seizures in *H. influenzae* infection as an alert sign[63,64]. Impairment of consciousness renders an exact diagnosis difficult as this is a common symptom in neurological disorders, especially in Africa[6,117]. Cerebral malaria, which presents often with impairment of consciousness and epileptic seizures is an important differential diagnosis and accompanied by high mortality and/or frequent later sequelae[70,118]. In these cases, blood smears are insufficient for the exact diagnosis and stringent as well as locally adapted management guidelines for meningitis and cerebral malaria are required[66].

Particularly in resource-poor settings, modern laboratory methods or imaging modalities as well as qualified skilled workers are rare and this lack may hamper an exact diagnosis and prompt management of patients with meningitis. CSF analysis, which is an easy-to-use method for most laboratories, can facilitate an exact diagnosis, especially with regard to bacterial meningitis, but spinal taps in patients with increased cerebral pressure can lead to life-threatening herniation and in the absence of imaging modalities, spinal taps are often not performed in resource-poor settings[71]. However, in most of our patients with meningitis spinal taps without side effects were performed to analyze the CSF. A study conducted in sub-Saharan Africa determined that, due to the lack of adequate laboratory and diagnostic methods, a third of meningitis cases in children is missed in district hospitals[119]. Furthermore, in patients without physical signs of an increased cerebral pressure (e.g. papilloedema and/or bradycardia occurring with hypertension and/or unrousable coma), an avoidance of a preceding imaging diagnostic seems to be permitted and enables a faster diagnostic and patient management in patients with meningitis[120].Thus, the diagnostic benefit of spinal tap in patients with meningitis without obvious symptoms of increased cerebral pressure seem to outweigh the risk of life-threatening uncal or tonsillar herniation.

Furthermore, regarding the treatment of patients with meningitis, cephalosporines, which demonstrated a higher sensitivity in meningitis isolates compared to conventional antibiotics like penicillin and gentamicin[85], are not widely available and pricey in sub-Saharan Africa. In our patients with meningitis due to *H. influenzae*, two thirds of the patients treated with bezylpenicillin and chloramphenicol recovered during hospitalization. However, we found a poorer outcome for patients with *H. influenzae* treated with benzylpenicillins and gentamicin add-on therapy overall, as 73% treated with the indicated antibiotics died. This fact may be related to the narrow therapeutic window and high level of side effects such as oto- and nephrotoxicity of aminoglycosides[85]. However, it may also reflect a selection bias as patients treated with gentamicin as an add-on therapy were usually those worse off. Although a combination of chloramphenicol and ampicillin or benzylpenicillin is still recommended in low-income countries[83,86]; this recommendation may change in future with regard to increasing antimicrobial resistances [85,87,121].

9.3 Neurological disorders in rural Tanzania

As already stated above, prevalence and mortality rates of neurological disorders seem to be higher in low-income countries, especially in remote rural areas, with convulsive disorders and central nervous system infections representing the largest part[1-3]. The considerable proportion of concomitant diseases, like HIV/AIDS, tuberculosis or malaria, in low-income countries like those of sub-Saharan Africa as well as aggravating circumstances particularly in remote and rural areas may lead to highly unfavourable health outcomes in those regions, especially in children and vulnerable groups of patients[3,114,122].

Febrile illnesses may lead to FSs, especially in sub-Saharan Africa, and are often accompanied by complex attributes[123]. There is, however, a clear distinction between classical FSs, where there is no intracranial pathology and epileptic seizures in the context of an intracranial pathology such as meningitis that can also present with a fever. Febrile epileptic seizures seem to occur more often in pediatric patients with meningitis under the age of 18 months[117] and complex attributes like prolonged duration or postictal impairment of consciousness as well as neurological deficits were shown as predicting factors for meningitis in patients with febrile epileptic seizures[64,116]. Additionally, complex features, first seizure episodes and impairment of consciousness, as mentioned above, are common symptoms in pediatric patients with meningitis[117]. A connected occurrence of febrile epileptic seizures and meningitis seem to induce higher mortality and morbidity compared to FSs in the classical sense[64]. Thus, a clear distinction of febrile epileptic seizures due to possible intracranial pathologies and febrile seizures without the presence of intracranial pathologies is of utmost importance, especially in the often similar initial stages to enable an earliest possible detection of intracranial pathologies and thus to initiate an appropriate and tailored patient management.

Our studies underline the burden of neurological disorders in low-income countries, especially those of sub-Saharan Africa and in particular with regards to infectious diseases. Concerning FSs, a higher prevalence when compared to high income countries could not be determined, but a higher proportion of complex attributes is obvious and may be related to the reported higher epilepsy prevalence in this region. As meningitis cases represent common and major emergencies in low-income countries, especially in children, the population needs to be made aware, health personnel has to be trained and appropriate laboratory facilities with basic equipment need to be in place. The high proportion of actually preventable *H. influenzae* cases in our study population shows major deficiencies in preventing infectious diseases especially in remote low-income countries.

More reliable studies about prevalence and mortality rates as well as appropriate management of neurological disorders are necessary in low-income countries. Lumbar puncture with the aim to examine the CSF for infection related parameters should be advocated for and medical personnel needs to be trained accordingly. Management guidelines for neurological disorders, in our case especially FSs and meningitis, need to be re-visited according to latest knowledge and adapted to the local circumstances of a resource-poor setting. Additionally, an exact mapping of immunization coverage, especially

in remote areas of low-income countries, may provide important information about the distribution pattern of responsible pathogens and, in this way, can contribute to an improvement of the prophylaxis and treatment of neurological and infectious diseases in sub-Saharan Africa.

10 Original Publications

10.1 Community-based prevalence and clinical characteristics of febrile seizures in Tanzania

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Population Study | **Articles**

Community-based prevalence and clinical characteristics of febrile seizures in Tanzania

Corinna Storz[1], Michael Meindl[2], William Matuja[3], Erich Schmutzhard[2] and Andrea S. Winkler[1,4]

BACKGROUND: The prevalence of febrile seizures (FSs) and epilepsy are often reported to be higher in sub-Saharan Africa. Furthermore, several studies describe complex features of FSs as risk factors for the development of subsequent epilepsy.

METHODS: During the period from 2002 to 2004 door-to-door studies with supplementary data collection were conducted in three different areas of Tanzania, examining the prevalence of FSs in 7,790 children between the age of 2 mo and 7 y at the time of the interview. The information on the presence of FSs of 14,583 children, who at the time of the interview were younger than 15 y, was collected in order to describe reported seizures, if any.

RESULTS: Overall, 160 children between 2 mo and 7 y with a prevalence rate of 20.5/1,000 (95% confidence interval: 17.5–23.9/1,000) met the criteria for FSs. The average age at onset was 2.2 (SD: 1.8) y and ~42% had complex FSs. Respiratory tract infections and malaria were the most frequent concomitant diseases.

CONCLUSION: Our findings do not confirm the assumption of an increased prevalence of FSs in sub-Saharan Africa. However, the elevated number of complex FSs emphasizes the necessity of more reliable studies about FSs and its consequences.

Febrile seizures (FSs) in children seem to occur frequently and often cause anxiety in parents. Prevalence rates from hospital- and community-based studies conducted up to now vary a lot according to the methods used, age definition and the country in which these studies were conducted (**Supplementary Table S1** online). The majority of the studies estimate a prevalence of FSs in about 2–4% of all children (1–3). However, prevalence rates range from 9.9/1,000 ascertained in Germany (4) to 116.1/1,000 determined in a rural population in Nigeria (5).

Prevalence and incidence rates of FSs may be higher in regions of Asia and Africa, but epidemiological studies of low-income countries are scarce. Complex FSs have been reported to be more frequent in children in sub-Saharan Africa (6), and it is especially complex features, such as prolonged or focal seizures, that have been described as risk factors for the development of epilepsy (7–9) and may be related to the reported higher prevalence of epilepsy in sub-Saharan Africa (10,11). Furthermore, FS associated infectious diseases seems to be different in children with FSs in sub-Saharan Africa compared to the disease spectrum in the western world and management of those diseases such as malaria has to be taken into account when dealing with FSs in low-income countries (12).

This door-to-door study in combination with complementary multisource data collection at hospitals and Mother and Child Health Centres (MCHs) was designed to ascertain the community-based prevalence of FSs, to describe the various clinical attributes and to assess special features of FSs in Tanzania.

RESULTS

Prevalence of Febrile Seizures

The number of cases with FSs found via the different methods and the resulting prevalence rates referring to the children between 2 mo and 7 y at the time of interview have been summarized in Table 1. In this age category, 7,790 children consisting of 3,857 boys and 3,933 girls who belong to the study region are divided up as follows: 2,497 of Haydom, 623 of Wasso, and 4,670 children of the Vigoi Ward.

Overall, 147 children fulfilled the given criteria for FSs within the door-to-door surveys. In summary, 147 children of 7,790 between 2 mo and 7 y had at least one FS, resulting in a point prevalence rate of 18.9/1,000 (95% confidence interval (CI): 16.0–22.1/1,000) and a male to female ratio of 1.04:1.

With the help of the additional methods, 14 children with FSs were identified via the MCH Haydom and the Hospital of Wasso (Table 1).

After deducting one child listed twice, 160 children made up of 82 boys and 78 girls met the criteria for FSs in its entirety. Combining the data ascertained by the different methods, the overall prevalence rate is 20.5/1,000 (95% CI: 17.5–23.9/1,000, with a male to female ratio of 1.05:1 (Table 1).

The FS prevalence of the children under the age of 15 y solely within the door-to-door studies is 15.2/1,000 (95% CI: 13.2–17.3; 221/14,583 children under the age of 15 y). Taking into account only the children whose ages lie above the cut-off age

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Table 1. Prevalence rates ascertained through door-to-door studies and additional methods within the study region[a]

Study design		Haydom (n = 2,497)	Wasso (n = 623)	Vigoi (n = 4,670)	Overall (n = 7,790)
Door-to-door studies	Cases with FS, (n)	57	14	76	147
	Male/female ratio	0.90:1	1.00:1	1.17:1	1.04:1
	Prevalence, n/1,000 (95% CI)	22.8 (17.3–29.5)	22.5 (12.3–37.4)	16.3 (12.8–20.3)	18.9 (16.0–22.1)
Additional methods	Cases with FS, (n)	4[b]	10[c]	n/a	14
Combined[d]	Cases with FS, (n)	61	23[e]	76	160
	Male/female ratio	0.91:1	1.09:1	1.17:1	1.05:1
	Prevalence, n/1,000 (95% CI)	24.4 (18.7–31.3)	36.9 (23.5–54.9)	16.3 (12.8–20.3)	20.5 (17.5–23.9)

FS, febrile seizure; n/a, not applicable.
[a]Prevalence rates refer to children between 2 mo and 7 y at the time of interview. [b]Cases recruited at Mother and Child Health Center Haydom. [c]Cases recruited at Wasso Hospital.
[d]All cases of FS in total, collected by the three door-to-door surveys, Mother and Child Health Center as well as the hospital in Wasso. [e]One child was listed twice.

for FSs within the door-to-door surveys, the prevalence of FSs is 11.5/1,000 (95% CI: 8.9–14.5; 69/6,021 children between 7 and 14 y of age).

Features of Febrile Seizures

Overall, 221 children with FSs were identified through the three door-to-door studies when referring to the study population of below 15 y at the time of the interview. Of those 221 children, 157 children (Haydom 102, Wasso 22, Vigoi 33) or their respective parents consented to an interview with a specific in-depth questionnaire (Tables 2–4).

Reliable information about the age at onset was available from 151 children. The arithmetic average of the age at onset was 2.2 (SD: 1.8) y. In approximately two thirds of the cases, the first FS occurred within the first 2 y of life. Referring to the information of 129 children, more than half of the cases (57%) had their FSs in the first half of the year and 29% during the heavy raining seasons from February to April. Details concerning the place of where the FS happened were known from 261 seizures. Almost 85% of these FSs happened outside medical facilities, for example at home or on the road.

The number of FS episodes, known from 151 children, ranged from 1 to 14 episodes with a median at 1 episode. Fifty-seven of those (38%) had more than one FS episode. The median duration of a FS, referring to 221 seizures, was 10 min, ranging from 1 min to a maximum of 360 min. Information about the length of fever before the FS was available from 144 episodes, resulting in an average of 2.5 (SD: 2.9) d. Eighty-six percent of 264 seizures were self-limiting (Table 2).

Sixty-one of 145 children (42%) with FSs had at least one complex feature. Thus, 3 children had focal seizures, 41 children had prolonged seizures and 1 of the children had a recurrent seizure. Five children had prolonged focal seizures and 11 had prolonged recurrent FSs. Detailed information about the complex FSs and its features is listed in Table 3.

Thirty-two percent of them had a history of seizure disorders within their family, of which 54% affected first degree relatives.

Causes of the febrile illness were mainly respiratory tract infections (36%) and malaria (34%), followed by gastrointestinal symptoms in 19%. Malaria at time of the fever was ascertained in 64% of 163 performed blood smears. In 181 of 199 FSs episodes (91%), medical attention was sought at hospitals or medical dispensaries. Household remedies like tepid sponging (40%) and acetaminophen (43%) often were used to reduce the fever and traditional medicine was applied in 9% of the cases. In 37 (25%) of 146 cases, the children received no treatment (Table 4).

Table 2. Features of febrile seizures within the door-to-door studies[a]

Age at onset (n = children)	151
Arithmetic average (SD), y	2.2 (1.8)
Within first 2 y of life, % (n)	67 (101)
Seasonal distribution (n = seizures)	129
Within the first half of the year, % (n)	57 (73)
While big rain period (February–April), % (n)	29 (37)
Place of incidence (n = seizures)	261
Outside of medical facilities, % (n)	84.9 (220)
Number of FS episodes (n = children)	151
Median (min–max), episodes	1 (1–14)
Recurrent FS episodes, % (n)	38% (57)
Duration of FS (n = seizures)	221
Median (min–max), min	10.0 (1.0–360.0)
Length of fever before FS (n = episodes)	144
Arithmetic average (SD), d	2.5 (2.9)
End of FS (n = seizures)	264
Self-limiting, % (n)	85.8 (211)
Characteristics of FS (n = children)	145
Simple FS, % (n)	58 (84)
Complex FS, % (n)	42 (61)

FS, febrile seizure.
[a]Characteristics refer to a varying number of children, episodes, seizures, and symptoms as appropriate for the extracted information.

DISCUSSION

The overall point prevalence of 20.5/1,000 within the three study regions is in accordance with other studies conducted in sub-Saharan Africa. **Supplementary Table S1** online provides an overview of published studies concerning the frequency of FSs: a hospital-based study from the Haydom Lutheran Hospital in Tanzania, which is part of the region of the present study, estimated a hospital incidence of 37.9/1,000 for children

below the age of 10 y (6). In further African studies listed in the table, the higher prevalence rates range from 26.5/1,000 (13) to 116.1/1,000 (5), based on different methods. Comparing the highest indicated rates of 51/1,000 (14) in Europe, 48/1,000 (15) in America, and 83/1,000 (2) ascertained in Asia, there seems to be trend to higher prevalence of FSs in Asia and Africa which was not confirmed by our study. The low FS point prevalence of 18.9/1,000 (when children up to 7 y from door-to-door studies only were considered) was confirmed by a low prevalence of 11.5/1,000 of children aged between 7 and 14 y at the time of the interview, i.e., those who are above the cut-off age for the occurrence of FSs. In a large Danish population study, Vestergaard *et al.* did not detect an increased long-term mortality in children with FSs, only a small exceed in the first 2 y after complex FSs was apparent (16). In comparison, several studies conducted in developing countries determined a higher mortality rate in patients with FSs and the authors attribute this fact mainly to the concomitant diseases of FSs, for example bronchopneumonia infections (6,17). Assuming that the mortality in children with FSs is higher in developing countries, this fact may explain the lower than expected prevalence in our study; however, studies about mortality in FSs are scarce. The superstitious beliefs of several African tribes, for example the association of seizure disorders and FSs with demonic possession or spiritual forces, may have led to underreporting (18). And in fact especially among the Maasai tribe in the Arusha region, the willingness to give details on the occurrence of FSs was very limited in this study. It also has to be taken into account that some information, especially that of FSs from many years ago, may not have been accurately reflected.

Table 3. Characteristics of complex febrile seizures[a]

Complex FS, % (*n* = children)	42 (61/145)
Distribution of complex features (*n* = children)	61
Prolonged, % (*n*)	93 (57)
Focal/unilateral, % (*n*)	13 (8)
Recurrent[b], % (*n*)	20 (12)
Distribution of complex features in children with complex FS (*n* = children)	61
Prolonged, % (*n*)	67 (41)
Focal/unilateral, % (*n*)	5 (3)
Recurrent[b], % (*n*)	2 (1)
Prolonged focal/unilateral, % (*n*)	8 (5)
Prolonged recurrent[b], % (*n*)	18 (11)
Distribution of complex features (*n* = seizures)	110
Prolonged, % (*n*)	76 (83)
>15–30 min, % (*n*)	45 (37/83)
>30 min (Status Epilepticus), % (*n*)	55 (46/83)
Focal/unilateral, % (*n*)	14 (15)
Recurrent[b], % (*n*)	11 (12)

FS, febrile seizure.
[a]Characteristics refer either to 61 children with complex FSs or 110 complex FSs as appropriate for the extracted information. [b]>1 seizure within 24 h.

Table 4. Family history, associated symptoms, and treatment of children with febrile seizures within the door-to-door studies

Family history (*n* = children)	151
Seizure disorders, % (*n*)	32 (48)
First degree relatives, % (*n*)	54 (26/48)
Associated symptoms (*n* = symptoms)	352
Respiratory tract infection, % (*n*)	35.5 (125)
Malaria, % (*n*)	33.5 (118)
Gastrointestinal symptoms, % (*n*)	18.5 (65)
Other symptoms, % (*n*)	8.8 (31)
No symptoms, % (*n*)	3.7 (13)
Malaria at time of fever, % (*n* = children)	64 (104/163)
Prehospital medical treatment (*n* = children)	*n* varies
Tepid sponging, % (*n*)	40 (58/146)
Acetaminophen, % (*n*)	43 (49/113)
Traditional medicine, % (*n*)	9 (13/147)
No treatment, % (*n*)	25 (37/146)
Antiepileptic drugs, % (*n*)	4 (2/52)
Consulting medical facilities (*n* = episodes)	199
At hospital, % (*n*)	76 (152/199)
At dispensaries, % (*n*)	15 (29/199)
No consulting, % (*n*)	9 (18/199)

As shown in **Supplementary Table S1** online, the male to female ratios range from 1:1 (19) to 3.75:1 (20), indicating that male children may be more susceptible to FSs. Our balanced male to female ratio of 1.05:1 does not confirm this phenomenon. About two thirds of the children had their first FS within the first 2 y of life. This is in accordance with other studies, reporting an age peak in the second year of life (1,2). In this study, more than half of the cases occurred during the first half of the year, which includes the heavy raining seasons from February till May and thus entails a higher risk of malaria infection. Two studies from Japan (21) and Italy (22) also observed such a seasonal distribution for FSs in correlation with seasonal diseases.

A history of complex FSs was ascertained in 42% of our cases. In a British survey, Verity *et al.* determined complex convulsions in 20% of all cases (23). On the contrary, Winkler *et al.* found a high preponderance of complex FSs of 71% in a hospital-based study at Haydom Lutheran Hospital (6). These figures suggest that complex FSs may occur more frequently in sub-Saharan Africa. However, there is a possibility that the higher proportion of complex FSs in our community-based study may be due to recall bias and the fact that parents tend to remember grave seizures more readily compared to simple ones. In the current study, 38% of the children suffered from recurrent FS episodes. Overall, young age at onset, epilepsy or FSs in relatives and complex FSs seem to be significant risk factors for the occurrence of recurrent FS episodes (7,24). As complex attributes seem to repeat in children with recurrent FS episodes (25) and recurrences, amongst others, may

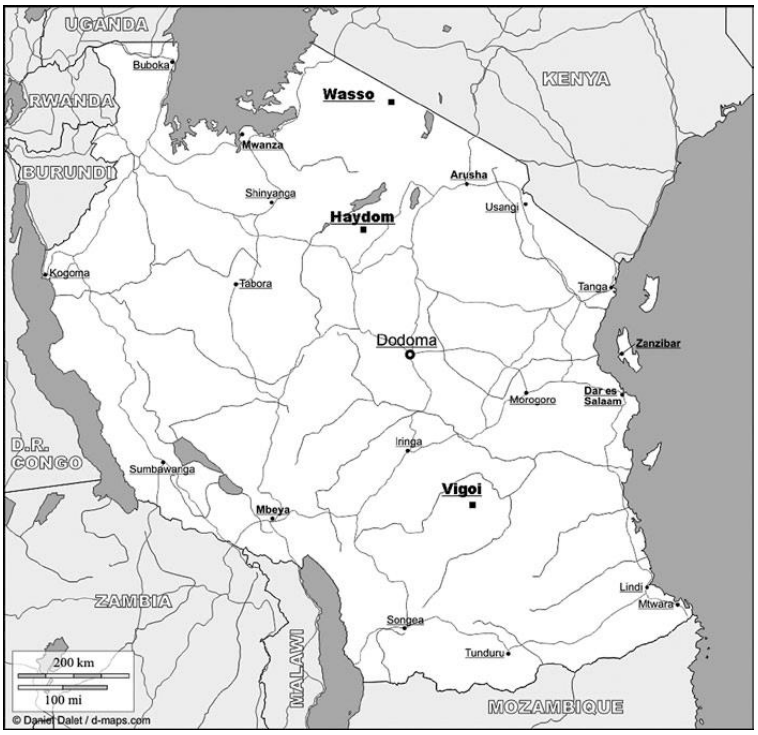

Figure 1. Map of Tanzania with the three study locations. Adapted with permission from d-maps.com (41).

conceivably implicate subsequent epilepsy (8,26), the need of preventing these recurrent FSs becomes apparent.

Since complex features, especially the prolonged types, seem to be associated with the development of epilepsy (7–9,27), this high percentage of complex features may be related to the reported higher prevalence of epilepsy in sub-Saharan Africa (10,11) in comparison to high-income nations (28). Beside complex attributes, the number of FS episodes, a positive family history of unprovoked seizures and neurological abnormality represent, inter alia, risk factors for subsequent epilepsy (3,8,29). In our study, we found a positive family history of seizures in nearly one third of the cases and also recurrent FS episodes occurred in more than one third of the children. However, the discussion as to whether FSs may favor the development of epilepsy is still controversial.

Detailed studies indicate that decreased birth weight, pre- and perinatal problems, prematurity as well as lower socioeconomic status, smoking and alcohol abuse during pregnancy represent possible risk factors for the emergence of FSs (29–32).

The cause and severity of the febrile illness loom large in the development of FSs, and it has to be taken into account that associated diseases in sub-Saharan Africa differ from those in high-income countries. Malaria, tuberculosis, influenza, and measles for instance, represent the common infectious and parasitic diseases in Africa region (33). A frequent appearance of FSs and febrile illnesses caused by influenza A virus (34), human herpes virus 6 (35), and respiratory tract infections (32) were determined in several studies. A study conducted at Haydom Lutheran Hospital in Tanzania identified malaria as one of the most frequent accompanying illness in children with FSs (36). This also applies to the current study, as we found respiratory tract infections and malaria as the leading presenting symptoms of the febrile illnesses, which is compatible with the aforementioned seasonal distribution.

According to our results, most of the seizures happened outside medical facilities. Lack of means of transportations and aggravating factors during the journey to the often distant healthcare facilities in this region emphasize that it is often impossible to receive appropriate medical help timely. Therefore, help is often sought by traditional healers instead of medical facilities (18). However, our study shows that in case of a FS, most of the parents attended medical facilities like hospitals or dispensaries. We also came to the conclusion that household remedies like tepid sponging and acetaminophen were, in the meanwhile, often used to reduce the fever and limit the seizure. Antipyretic drugs may lower the body temperature in febrile children, but several studies ascertained that there is no benefit of antipyretic drugs in preventing recurrent FSs (37,38). The guidelines composed by the International League against Epilepsy strongly recommend an acute therapy to prevent a febrile status epilepticus. This includes the registration of symptoms, prevention of aspiration or injuries and reduction

of fever by the parents or other attendees. Furthermore, diazepam rectal in FSs with duration longer than 2–3 min and benzodiazepines or phenobarbital intravenous in case of prolonged FSs or status epilepticus (39).

Conclusion

In conclusion, our study supports findings that the prevalence of FSs in sub-Saharan Africa may not be higher compared to high-income countries. However, the comparatively large share of complex FSs has implications and emphasizes the necessity of further studies into FSs in countries of sub-Saharan Africa. It is deemed important to expand the knowledge on FSs and its risk factors, and to improve medical care in low-income regions in order to prevent potential adverse neurological outcome such as epilepsy later in life.

METHODS

The study took place during the period from 2002 to 2004 in the catchment area of Haydom Lutheran Hospital, Manyara region; Wasso Hospital, Arusha region; and Mahenge Hospital, Morogoro region, Tanzania. Three door-to-door surveys form the basis of this study and for the purpose of prevalence calculation two of those surveys (Haydom and Wasso) were complemented with supplementary retrospectively collected data from the study areas' main hospitals and respective MCHs of the study region with the aim to achieve a near 100% case recruitment. For Mahenge hospital, no reliable supplementary data collection method could be identified so that prevalence calculation relies on data from the door-to-door study only.

Information Retrieval and Definitions

Within the door-to-door surveys, a team of three last-year medical students and translators interviewed the parents or relatives of the children from the three study regions by using a screening questionnaire. This questionnaire consisted of a case confirmation part for identifying children with FSs and a more specific part with detailed questions about the characteristics of the FSs (see **Supplementary Table S2** online) and had already been validated in a previous hospital-based study (6). Cases of other seizure disorders (e.g., epilepsy) except FSs were excluded. With the help of translators the information was written down manually and was transcribed into Excel spreadsheets later. Double listed information between the door-to-door surveys and the additional methods were detected with the assistance of the parents and ten-cell-leaders (community leaders) as well as by comparing names and area of origin using Excel spreadsheets.

The following definitions were adhered to: FSs are defined as seizures occurring with a fever without obvious intracranial pathology in early childhood and are subdivided into simple and complex FSs, the latter being represented by seizures (i) lasting more than 15 min, (ii) occurring more than once within 24 h, and (iii) appearing with focal features (7,25). A FS duration of more than 30 min is defined as a status epilepticus and belongs to the category of complex FSs (40).

Setting and Recruitment

The data collection was conducted in three areas of Tanzania. The performance of the community-based studies depended largely on Tanzania's administrative system that is subdivided into 26 regions consisting of various districts and divisions with subordinated wards, which in turn combine several villages. So-called "Ten-cells" represent the smallest administrative units within the village. Figure 1 shows a map of Tanzania with the three study locations: Haydom in northern Tanzania, Wasso near to the Kenyan border, and Vigoi (Mahenge) in southern Tanzania.

Only children that were younger than 15 y at the time of the study were included into the study population. All subjects with known gender and exact age between 2 mo and 7 y at the time of interview were listed to assess the point prevalence of FSs in order to keep the recall bias for age to a minimum. For the prevalence calculation, the information of the door-to-door surveys was supplemented with that from other data sources, as described below. However, in-depth information on clinical characteristics of FSs was only ascertained within the door-to-door surveys and for that purpose data of all interviewed children of the study population irrespective of age was included.

For the door-to-door studies the nearer catchment area (closest villages within a radius of 5–10 km) of the three chosen hospitals (Figure 1) was tackled. Hospitals were selected according to previously established working relationships between the principal investigator of the study (A.S.W.) and the hospital directors. The sampling unit was represented by the ten-cell, the smallest administrative unit in Tanzania. The ten-cell is overseen by a ten-cell leader who assured access to the study population. All households in one ten-cell were seen.

In Haydom, 12 villages belong to the nearer catchment area. Members of 1,458 households of randomly selected ten-cells (villages were widespread) were interviewed. In addition, all children attending the well-structured MCHs at Haydom Lutheran Hospital during that period were also surveyed.

In Wasso, four villages belong to the nearer catchment area of Wasso hospital. Members of 452 households of all ten-cells of these villages were seen. In addition, Wasso Hospital had a very good archiving system and all admissions between 2002 and 2004 were screened for febrile seizures.

In Mahenge, 11 villages belong to the nearer catchment area of Mahenge hospital. Members of 4,209 households of all ten-cells of these villages were seen. No additional methods of data acquisition such as MCH or hospital archive was deemed appropriate.

In the course of the overall door-to-door survey of all three sites, 81 individuals refused to give information or were absent, hence 14,583 children under the age of 15 y in 27 villages were included into the overall study population. Of these, 4,286 children belonged to Haydom, 967 to Wasso, and 9,330 to Vigoi catchment area. For the purpose of calculating the point prevalence of FSs, the information of 7,790 children in the age category between 2 mo and 7 y, which belong to the defined study region, was collected.

Statistical Analysis

The collected data were entered and calculated within Excel spreadsheets. The 95% CI of the prevalence rates were calculated by using Fisher's exact test. Most of the collected information about the clinical features relates to the summary of all FS episodes of one subject.

Ethics

Ethics approval was granted by the National Institute of Medical Research and the Commission of Science and Technology in Dar es Salaam, Tanzania. Informed consent was obtained from the parents of all included children.

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at http://www.nature.com/pr

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Supplementary Table S1. Overview of Studies Concerning Prevalence- and Incidence Rates of Febrile Seizures

Region	Reference	Town/ Country	Collection period	Study Design	Defined Age of FS	Sample Size, No.	Cases with FS, No.	Male:Female Ratio	Incidence (n/1,000)[a]	Prevalence (n/1,000)[b]
Europe										
	(42)	Bradford, United Kingdom	1999-2000	retrospective hospital-based	1 m-15 y[g]	328[h]	203	1.23:1	1 (AI)	n/a
		South-Asian immigrants				148[h]	104	n/k	2 (AI)	n/a
		Non-South Asians				180[h]	99	n/k	1 (AI)	n/a
	(43)	Rasina, Serbia	1986-1995	prospective longitudinal population-based	6 m-5 y	19,000	570	1.01:1	3 (AI)	n/a
	(44)	northern Sweden	1973-1974	prospective longitudinal hospital based	<5 y	15,284	107	1.28:1	7 (AI)	n/a
	(1)	Västerbotten, Sweden	1985-1987	prospective cohort study	<5 y	15,420	128	1.72:1	5 (AI) 41 (CI)	n/a
	(45)	Turku, Finland	1986	prospective cohort study	<5 y	1,033	70	1.19:1	14 (AI)	n/a

	(4)	Altenburg, Germany	1982-1985	prospective population-based	<6 y	n/k	n/k	n/k	2 (AI)	10
	(46)	Valladolid, Spain	1986-1987	retrospective population-based	<7 y	53,242	93	1.21:1	n/a	23
	(23)	Bristol, United Kingdom	1970-1975	retrospective cohort study[c]	<6 y	13,038	303	n/k	n/a	23
	(19)	Alexandroupolis, Greece	n/k	retrospective cohort study	n/k	1,708	56	1:1	n/a	33
	(47)	Rotterdam, Denmark	n/k	retrospective hospital-based	<7 y	3,570	140	n/k	n/a	39
	(48)	Aarhus, Denmark	2001	retrospective[d] population-based	3 m-5 y	6,624	323	n/k	n/a	49
	(14)	Reykjavik, Iceland	1996	retrospective cohort study	n/k	9,679	494	1.08:1	n/a	51
America										
	(49)	Oakland, California	1960-1967	prospective cohort study	<6 y	18,500	246	1.14:1	19 (CI)	13
	(50)	Rochester, Minnesota	1935-1967	retrospective hospital-based	no age limit[g]	n/k	472	1.23:1	n/a	4
	(51)	Passo Fundo, Brazil	2003-2007	prospective cohort study	<5 y	1,687	27	n/k	n/a	17

	(52)	rural Kentucky	1975	retrospective cohort study	6 y-15 y[g]	3,822	68	n/k	n/a	17
	(53)	Tecumseh, Michigan	1959-1960	retrospective longitudinal population-based[e]	<20 y[g]	3,953	142	1.68:1	n/a	36
	(7)	Bethesda, Maryland	1959-1966	prospective cohort study[f]	<8 y	n/k	1,706	n/k	n/a	n/a
		White Children				n/k	732	1.12:1	n/a	35
		Black Children				n/k	883		n/a	42
	(15)	Washington County, Maryland	1969	retrospective cohort study	<10 y[g]	2,042	98	n/k	n/a	48
Asia										
	(54)	Hong Kong, China	1998-2003	retrospective longitudinal hospital-based	<6 y	1,113	565	1.41:1	4 (AI)	n/a
	(55)	Taiwan, China	n/k	retrospective population-based	<4 y	10,460	256	n/k	24 (CI)	n/a
	(56)	Karala, India	n/k	retrospective population-based	6 m-6 y	1,192	120	n/k	101 (CI)	n/a
	(57)	Ranbir Singh Pura, India	2009	retrospective door-to-door	6 m-5 y	3,966	5	n/k	n/a	1
	(58)	Bangalore, India	1993-1995	retrospective population-based	n/k	102,557	338	n/k	n/a	3

	(20)	Thugbah, Saudi Arabia	1989	retrospective door-to-door	<6 y	5,353	19	3.75:1	n/a	4
	(59)	Kolkata Municipal Area, India	2003-2004	retrospective door-to-door	6 m-5 y	16,979	189	1.86:1	n/a	11
		Slum Area			6 m-5 y	4,020	13	n/k	n/a	3
		Non-Slum Area			6 m-5 y	12,959	176	n/k	n/a	14
	(60)	Kolkata, India	2003-2004	retrospective door-to-door	<7 y	52,377	56	n/k	n/a	12
	(61)	Bombay, India	n/k	retrospective door-to-door	<14 y[g]	1,581	28	2.1:1	n/a	17
	(62)	Wenzhou, China	n/k	retrospective cohort study	n/k	6,406	235	n/k	n/a	37
	(2)	Fuchu City Tokyo, Japan	1974-1980	prospective longitudinal population-based	n/k	17,044	1,406	1.3:1	n/a	83
Africa										
	(36)	Haydom Lutheran Hospital, Tanzania	2002-2003	prospective hospital-based	3 m-5 y	8,676	82	1.1:1	n/a	10
	(63)	Nigeria	1986	retrospective door-to-door	<8 y	2,925	7	n/k	n/a	11
	(13)	Zambia	1998	prospective hospital-based	5 m-5 y	1,886	50	n/k	n/a	27
	(64)	Kaduna, Nigeria	2008-2010	retrospective hospital-based	9 m-5 y	635	17	1.8:1	n/a	27

(6)	Haydom Lutheran Hospital, Tanzania	2002-2004	prospective hospital-based	1 m-7 y	5,200	197	1.3:1	n/a	38
(5)	Nigeria:	1984	retrospective door-to-door						
	Enugu (urban)			6 m-6 y	2,135	172	1.15:1	n/a	81
	Amokwe (rural)			6 m-6 y	620	72	1.32:1	n/a	116

Abbreviations: AI, annual incidence; CI, cumulative incidence; FS, Febrile Seizure; n/a, not applicable; n/k, not known

[a] Defined as the number of new cases found in a population within a given age range (usually < 5 years)

[b] Defined as the number of all cases found in a population within a given age range (usually < 5 years)

[c] Within the scope of the Child Health and Education Study

[d] Within the scope of the Danish National Hospital Register

[e] Within the scope of the Tecumseh Community Health Study

[f] Within the scope of the Neurological and Communicative Disorders and Stroke Collaborative Perinatal Project

[g] Within these studies, febrile seizures are defined as any seizures associated with febrile illnesses, due to the wide age range.

[h] Sample size represents children presenting with seizures within the defined period, rates were calculated using estimated mid-year population.

References for Supplementary Table S1

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Supplementary Table S2. Screening Questionnaire

Screening part of the questionnaire: case ascertainment of febrile seizures

Date: Village: District:

TCL: Head of household (H.H.): Household ID Code:

Name patient: Name informant: Name enumerator:

We would like to know about your health and the questions below all refer to your lifetime experience. For children substitute "have you ever" by "has your child ever":

A) For all individuals:

1. Have you ever lost consciousness or have you ever fallen and lost consciousness?

2. Loss of consciousness

a) When you lost consciousness what were your arms and legs doing?

b) When you lost consciousness was this associated with jerking or extensions of arms and/or legs? (Ask witness, demonstration; if there is no witness account go to question 3).

3. Seizure event

a) Were these attacks associated with:

Tongue or Lip bite/ Urinary incontinence/ Faecal incontinence/ Injury/ Burn?

b) After regaining consciousness, was this associated with:

Being very tired/ Sleeping a lot/ Being confused/ Doing strange things?

B) For children between 2 months and 7 years of age who have screened positive under section A) question 1-3:

1. Is there fever associated with attacks:

a) Always?

b) At times?

c) Never?

If the answer is a) and the child regularly regains consciousness within six hours of having had the seizure the patient is screened positive for febrile seizures. In that case please refer to the questions for febrile seizures below.

In-depth part of the questionnaire: Febrile seizures

If the above case ascertainment part was positive for febrile seizures, ask the below questions.

1. First and last seizure ever?

Date (first seizure): Date (last seizure):

2. About last episode:

a) How many febrile seizure(s) did the child have during this episode (give dates and hours when they occurred)?

1st seizure: 2nd seizure:

3rd seizure: 4th seizure:

5th seizure: 6th seizure:

b) How long did each of the seizure(s) last for?

1st seizure: 2nd seizure:

3rd seizure: 4th seizure:

5th seizure: 6th seizure:

c) State for each of the seizure(s) whether convulsions were unilateral (state side) or bilateral:

1st seizure: 2nd seizure:

3rd seizure: 4th seizure:

5th seizure: 6th seizure:

d) Did the child retain any neurological sequelae after any of the seizure(s)?

1st seizure: 2nd seizure:

3rd seizure: 4th seizure:

5th seizure: 6th seizure:

e) How long did the patient have fever before the first seizure started?

f) What physical symptoms were associated with this episode (coughing, diarrhea, vomiting, ear ache, sore throat, common cold)?

g) Was a blood smear taken (if yes, what was the result)?

3. About previous episodes:

a) How many previous episodes of febrile seizures were there (give dates)?

1st episode: 2nd episode:

3rd episode: 4th episode:

b) How many seizure(s) were there per episode (give number and specify when they occurred)?

1st episode: 2nd episode:

3rd episode: 4th episode:

c) How long did each of the seizure(s) last for?

1st episode: 2nd episode:

3rd episode: 4th episode:

d) State for each of the seizure(s) whether convulsions were unilateral (state side) or bilateral:

1st episode: 2nd episode:

3rd episode: 4th episode:

e) Did the child retain any neurological sequelae after any of the seizure(s)?

1st episode: 2nd episode:

3rd episode: 4th episode:

f) How long did the patient have fever before the first seizure started?

1st episode: 2nd episode:

3rd episode: 4th episode:

g) What physical symptoms were associated with this episode (coughing, diarrhea, vomiting, ear ache, sore throat, common cold)?

1st episode: 2nd episode:

3rd episode: 4th episode:

e) Was a blood smear taken (if yes, what was the result)?

1st episode: 2nd episode:

3rd episode: 4th episode:

4. Any previous medical problems?

Meningitis/ Tb/ Cerebral malaria/ Head trauma/ Other:

5. Family history of neurological illness (febrile seizures, epilepsy, other)?

If yes, state which disease:

6. Mother's health during pregnancy?

If problems, specify:

7. Delivery?

At home/ At hospital/ At health center:

On term/ Preterm:

8. Problems during delivery?

Prolonged/ Precipitated/ Crying well/ Sucking well/ Blue or yellow skin/ Neonatal seizures:

9. Delayed milestones?

If yes, give the highest achieved motor and language skill:

Present prior to first febrile seizure?

10. Developmental arrest?

If yes, at what age?

Preceded by specific illness (meningitis etc.?):

Present prior to first febrile seizures?

11. Is there mental handicap or intellectual decline?

If yes, how dependent is the child on the carer?

Totally/ > 50% of the time/ <50% of the time:

Not at all:

Who is the carer?

Present prior to first febrile seizure?

12. Health care:

Was medical attention sought for febrile seizures?

If yes, how often/ Where?

13. Drug treatment:

a) Do/did they use tepid sponging during fever at home?

b) Do/did they use paracetamol or ibuprofen during fever at home?

c) Is patient taking anti-epileptic drugs?

If yes, which drug/ Dose/ Since when/ Response/ Side effects?

d) Has patient previously been taking anti-epileptic drugs?

If yes, which drug/ Dose/ For how long/ Response/ Side effects/ Reason why stopped?

e) Has the patient ever tried herbal treatment?

If yes, what/ When/ Duration/ Response/ Side effects/ Ask especially for scarification?

A short clinical examination will be performed.

10.2 Clinical findings and management of patients with meningitis with an emphasis on *Haemophilus influenzae* meningitis in rural Tanzania

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Clinical findings and management of patients with meningitis with an emphasis on *Haemophilus influenzae* meningitis in rural Tanzania

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ABSTRACT

Introduction: The spectrum of meningitis pathogens differs depending on the age of patients and the geographic region, amongst other. Although meningitis vaccination programs have led to the reduction of incidence rates, an imbalance between low- and high-income countries still exists.
Methods: In a hospital-based study in rural northern Tanzania, we consecutively recruited patients with confirmed meningitis and described their clinical and laboratory characteristics.
Results: A total of 136 patients with meningitis were included. Fever (85%), meningism (63%) and impairment of consciousness (33%) were the most frequent clinical symptoms/signs. Nearly 10% of all patients tested were positive for malaria. The majority of the patients with bacterial meningitis (39%), especially those under 5 years of age, were confirmed to be infected with *Haemophilus influenzae* (26%), *Streptococcus pneumoniae* (19%) and *Neisseria meningitidis* (15%). *Haemophilus influenzae* represented the dominant causative organism in children under 2 years of age.
Conclusion: Our study emphasizes the importance of recognizing warning symptoms like fever, meningism and impairment of consciousness, implementing laboratory tests to determine responsible pathogens and evaluating differential diagnoses in patients with meningitis in sub-Saharan Africa. It also shows that *Haemophilus influenza* meningitis is still an important cause for meningitis in the young, most probabaly due to lack of appropriate vaccination coverage.

1. Introduction

Infectious neurological diseases such as meningitis often represent major emergencies, which have to be diagnosed and medicated immediately to prevent serious sequelae or lethal outcomes. Several studies ascertained that neurological disorders have a high prevalence in low-income countries, especially those of infectious etiology, and that they are often accompanied with high mortality rates [1–3]. In general, according to the World Health Organisation, meningitis is among the twenty most frequent causes of "Years of Life Lost" [4]. When considering the incidence rates of meningitis between different countries, substantially higher rates are calculated in Africa [5] and Asia [6] compared to the United States [7]. Epidemic meningitis in the so-called "meningitis belt", due to the high incidence rates of meningococcal disease, contributes substantially to the burden of disease [8]. After the introduction of several meningitis vaccines, such as the conjugate vaccine against *Haemophilus influenzae* type B in The Gambia in 1997, incidence rates of *H. influenzae* type B disease decreased significantly, provided that at least two doses were given to ensure adequate protection [9,10]. This is supported by a study from Senegal that demonstrates a sharp decline of meningitis caused by *H. influenzae* after the implementation of *H. influenzae* type B vaccination in paediatric patients [11]. The introduction of vaccines has also an effect on the pathogen spectrum, as a study that took place in Burkina Faso and Togo, which are both part of the meningitis belt, shows now *Streptococcus pneumoniae* to be the most common pathogen followed by *Neisseria meningitidis* and *H. influenzae* [12].

However, in spite of this development, an imbalance between low- and high-income countries continues to exist and in remote areas of low-income countries, *H. influenzae* still seems to contribute to the main causative pathogens in children with meningitis, accompanied

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by high mortality rates [13–15]. Although meningitis caused by *H. influenzae* represents an actually preventable disease, significant higher incidence and mortality rates occur in low-income countries like Africa [15]. This fact underlines the importance of insuring sufficient vaccination coverage especially in remote areas, where treatment and management of those life-threatening diseases are already complicated.

This seemingly changing picture of meningitis calls for accurate clinical and laboratory-based diagnosis especially in remote areas of low-income countries like sub-Saharan Africa, where studies in patients with meningitis are particularly rare. In this study we therefore describe the causes, clinical and laboratory characteristics of 136 patients with meningitis at the Haydom Lutheran Hospital (HLH) in northern Tanzania with a focus on meningitis caused by *H. influenzae*.

2. Materials and methods

2.1. Patients and setting

This cross-sectional study attempted to identify all cases of meningitis occurring between August 2002 and September 2004 at the HLH in rural northern Tanzania, Manyara region, Mbulu district. The HLH serves a catchment area of seven districts in four regions and has approximately 400 beds [16].

All patients with neurological symptoms and/or signs including impairment of consciousness admitted to the HLH were consecutively enrolled and examined by a neurologist (ASW) who recorded the patients' history, physical- and laboratory findings. Patients who developed neurological abnormalities in the course of their hospitalization were also included. All admissions recorded during the study were divided into defined diagnostic groups, whereby each patient was assigned to only one group, depending on its predominant neurological symptom/sign [1]. The following definitions, terms and methods were used to make appropriate and replicable medical diagnoses.

2.2. Clinical case definitions

Meningism describes a clinical syndrome with at least one of the following signs: positive Lasègue's sign, positive Kernig's sign, positive Brudzinski's sign and neck stiffness. If the latter was just on maximum flexion, an additional meningism sign would be needed for a positive diagnosis.

Meningitis was diagnosed when at least one of the following criteria was fulfilled: a) clinical meningism and increased cell count in CSF (>4 cells/μl), b) symptoms/signs of meningeal irritation like headache, neck pain, nausea or vomiting and increased number of cells in CSF, c) symptoms/signs of meningeal irritation without increased cell count in CSF but exclusion of subarachnoid haemorrhage, space occupying lesions or increased intracranial pressure due to other reasons and d) failure of exclusion of other causes but good therapeutic response.

The course of the disease as defined by the duration of symptoms was divided in acute (under 1 week), subacute (1–2 weeks) and chronic (>2 weeks).

The origin of meningitis was defined as follows: 1) Bacterial origin: acute meningitis and a cell count of >1000/μl CSF or a microbiological identification of bacterial pathogens without clinical evidence for a non-bacterial cause. 2) Mycobacterial origin: subacute or chronic meningitis or any meningitis with clinical signs of a generalized tuberculosis as well as effective treatment with tuberculostatics and a cell count of normally <1000/μl CSF. 3) Viral and fungal origin: any clinical course of meningitis with clinical signs of viral infection such as zoster oticus or fungal cells in CSF, respectively, and a cell count of <1000/μl CSF. 4) Patients with meningism but <1000 cells/μl CSF, a lack of clinical signs of viral, mycobacterial or fungal meningitis as well as a failure of microbiological identification had, by definition, a meningitis of unknown origin.

There were no imaging modalities available at the time of the study.

2.3. Laboratory methods

Spinal taps were performed in patients with suspected inflammatory neurological diseases if they were rousable at any time. Each CSF of patients undergoing spinal taps was analysed for appearance (turbidity and coloration) and cell count was determined by using counting chambers. Protein concentration of CSF was measured using test strips, test strips to measure glucose concentration were not available at the time of the study. A microbiological identification of organisms was performed by Gram stains or latex agglutination tests to distinguish between *N. meningitidis*, *H. influenzae*, *S. pneumoniae* and *Escherichia coli*. In addition, cultures were obtained for confirmation. Blood smears were used to detect and classify malaria pathogens. Human immunodeficiency virus (HIV) testing was not widely available.

2.4. Statistical methods

Data were entered and analysed with Microsoft Excel spreadsheets. Descriptive methods were used only.

2.5. Ethics

Ethical approval was granted by the National Institute of Medical Research and the Commission of Science and Technology in Dar es Salaam, Tanzania. Informed consent was obtained from all participants. In case of children or mentally incapacitated patients, informed consent was given by parents and caregivers, respectively.

3. Results

3.1. Demographic details

A total of 136 patients with meningitis were studied at the HLH. For comparison purposes, Winkler et al. determined a hospital-based prevalence rate of approximately 85/1000 for patients with neurological disorders and about 9/1000 for patients with meningitis over a period of eight months [1]. The median age of the patients with meningitis in this study was 4 years ranging from 7 days to 90 years, whereby 68% of all patients were under the age of 16 years. The male to female ratio was 1.7:1.

The average distance of the patients' homes to the HLH was 44 (SD: 57) km and the undertaken journey lasted approximately 3 (SD: 6) h. The average length of stay in the hospital was 25 (SD: 31) days with average costs of 25,430 (SD: 25,908) Tanzanian Shilling (TZS) (Table 1). The per capita income in the United Republic of Tanzania was about 440,000 TZS (375 USD) per year in 2005 [17].

3.2. Complaints on admission and clinical characteristics

Table 2 shows the most common complaints and clinical characteristics. The leading complaints were fever in 85% (115/136), generalized neurological signs like impaired consciousness, generalized muscle hypertonia and a bilateral positive Babinski sign in 57% (78/136) as well as focal neurological signs like cranial nerve lesions, unilateral positive Babinski sign, lateral deviation of gaze and hemiparesis in 25% (34/136) of the patients. Furthermore, meningism occurred frequently with 63% (85/136). In more than one third of the cases, the Lasègue's or the Kernig's sign was positive. Neck stiffness occurred in nearly 60% (81/136). In 39% (20/52) of the children under 1 year, a bulging fontanella was diagnosed. Respiratory symptoms like cough and rales on auscultation were found in about 22% (32 and 30/136) of all patients. Seizures, especially generalized types, occurred in nearly 8% (11/136).

According to the duration of symptoms 75% (102/136) represented acute, 12% (16/136) subacute and 13% (18/136) chronic cases of meningitis.

Table 1
Demographic information about patients with meningitis at Haydom Lutheran Hospital (n = 136).

Characteristics	Number of patients (n)
Age in years	n = 136
Average (±SD)	14.14 (±19.10)
Median (MIN-MAX)	4 (0.02–90)
Gender in n (%)	n = 136
Male in n (%)	85 (61)
Female in n (%)	51 (38)
Male:female ratio	1.7:1
Distance for travelling to HLH in kilometers	n = 65
Average (±SD)	44 (±57)
Median (MIN-MAX)	30 (4–350)
Duration of the journey to HLH in hours	n = 65
Average (±SD)	3.0 (±6.0)
Median (MIN-MAX)	2 (0.3–48)
Length of stay at HLH in days	n = 136
Average (±SD)	25 (±31)
Median (MIN-MAX)	14 (1–136)
Costs in TZS	n = 131
Average (±SD)	25,430 (±25,908)
Median (MIN-MAX)	15,950 (800–123,625)

Abbreviations: HLH, Haydom Lutheran Hospital; SD, standard deviation; TZS, Tanzanian Shilling.

3.3. Laboratory findings

All laboratory findings are summarized in Table 3. CSF was analysed in 128 patients. It mainly appeared cloudy and turbid (73%). In 126 CSF samples the cell count could be determined. In approximately 93% (117/126) of the analyses, a cell count of >4 cells/μl was found, a high cell count of >1000 cells/μl was still seen in 29% (37/126). The average CSF cell count amounted to 931 (SD: 1867) cells/μl. The most predominant cells found in 128 CSF samples were granulocytes (60%) and lymphocytes (27%). In 10% (12/126) of the blood smears malaria parasites were detected.

Table 2
Frequent complaints on admission of patients with meningitis at Haydom Lutheran Hospital (n = 136).

Symptom/sign	Number of patients (%)
Fever	115 (84.6)
Neurological signs	85 (62.5)
Generalized signs	78 (57.4)
Impairment of consciousness	45 (33.1)
Generalized muscle hypertonia	34 (25.0)
Positive Babinski sign	9 (6.6)
Generalized hyperreflexia	14 (10.3)
Generalized seizures	7 (5.1)
Focal neurological signs	34 (25.0)
Cranial nerve lesions	14 (10.3)
Unilateral positive Babinski sign	8 (5.9)
Lateral deviation of gaze	8 (5.9)
Hemiparesis	7 (5.1)
Focal seizures	4 (2.9)
Focal weakness	2 (1.5)
Meningism	85 (62.5)
Neck stiffness	81 (59.6)
Kernig's sign	54 (39.7)
Lasègue's sign	51 (37.5)
Brudzinski's sign	1 (0.7)
Bulging fontanella (≤1 year)	20 (38.5)[a]
Photophobia	18 (13.2)
Seizures	11 (8.1)
Generalized[b]	*7 (63.6)*
Focal[b]	*4 (36.4)*
Cough	32 (23.5)
Rales (on chest examination)	30 (22.1)

[a] Percentage refers to n = 52 children ≤1 year.
[b] Mentioned above in 'generalized and focal neurological signs' row.

Table 3
Laboratory findings in patients with meningitis.

Investigation	
CSF appearance in n (%)	n = 128
Turbid	94 (73)
Clear	25 (20)
Bloody	8 (6)
Unknown	1 (1)
CSF cell count	n = 126[a]
Average (±SD) in cell count/μl	931 (±1867)
Median (MIN-MAX) in cell count/μl	112 (0–14,000)
≤4 cell count/μl in n (%)	9 (7)
>4 cell count/μl in n (%)	117 (93)
Average (±SD) in cell count/μl	*1002 (±1919)*
Median (MIN-MAX) in cell count/μl	*136 (5–14,000)*
>1000 cell count/μl in n (%)	37 (29)
Average (±SD) in cell count/μl	*2905 (±2522)*
Median (MIN-MAX) in cell count/μl	*1865 (1128–14,000)*
CSF predominant cells in n (%)	n = 128
Granulocytes	77 (60)
Lymphocytes	34 (27)
Mixed cell counts	1 (1)
Yeast cells	1 (1)
Unknown	15 (12)
Malaria detection in n (%)	n = 126
Negative	114 (91)
Positive	12 (10)

Abbreviations: CSF, cerebrospinal fluid, SD, standard deviation.
[a] Cell count of two patients was missing.

3.4. Distribution of pathogens

Across all age groups, approximately 39% (53/136) suffered from bacterial meningitis. *H. influenzae* (26% or 14/53) and *S. pneumoniae* (19% or 10/53) were the most common organisms found, followed by *N. meningitidis* (15% or 8/53). Fourty percent (21/53) of those cases were of unknown bacterial origin. Twenty-six percent (35/136) had mycobacterial, 4% (5/136) fungal and only 2% (2/136) viral meningitis according to the clinical case definition, as detailed in the method section. Overall, in 30% (41/136) the origin remained unknown (Table 4). Fig. 1 gives an overview of the age distribution of bacterial and mycobacterial meningitis: approximately 77% (41/53) of bacterial and 23% (8/35) of mycobacterial origin fell into the under 5-year age group, where bacterial meningitis clearly prevailed. In those aged 45 years and above, meningitis of mycobacterial origin occurred almost exclusively.

3.5. Therapeutic management

Antibiotics, especially benzylpenicillin (84.6% or 115/136) and chloramphenicol (81.6% or 111/136) represented the largest therapeutic proportion, closely followed by tuberculostatics. Antimalarial drugs like quinine were given to 72% (98/136) of patients despite only 10% of them being positive for malaria parasites on blood smear. Chloramphenicol and benzylpenicillin (often combined) as well as gentamicin

Table 4
Pathogen spectrum in patients with meningitis (n = 136).

Infectious agent	
Bacterial in n (%)	53 (39)
Haemophilus influenzae	14 (26)
Streptococcus pneumoniae	10 (19)
Neisseria meningitidis	8 (15)
Unknown	21 (40)
Mycobacterial	35 (26)
Fungal	5 (4)
Viral	2 (2)
Unknown	41 (30)

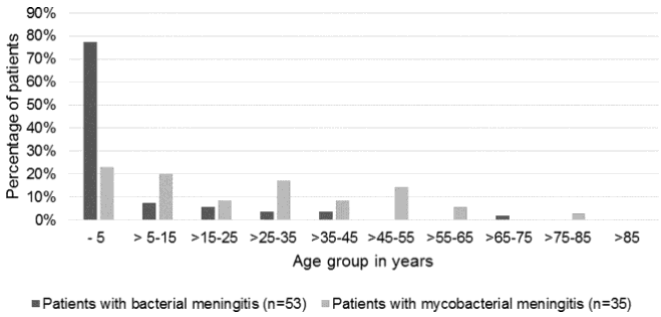

Fig. 1. Age distribution of 88 patients with bacterial and mycobacterial meningitis.

were used routinely for meningococcal, pneumococcal or *H. influenzae* meningitis. Treatment against tuberculous meningitis consisted of a combination of 3, 4, or 5 different tuberculostatics including isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin.

3.6. Details of patients with meningitis caused by H. influenzae

All details about patients with meningitis caused by *H. influenzae* are listed in Table 5. Fourteen of the 136 patients (10%) suffered from meningitis caused by *H. influenzae*, thus *H. influenzae* was the most common pathogen found in bacterial meningitis (14/53 or 26%). The average age was 1.6 (SD: 3.6) years with a male to female ratio of 1.3. The average length of stay in the hospital was 9 (SD: 9) days with average costs of 7749 (SD: 5780) TZS. The frequent complaints on admission of the 14 patients with *H. influenzae* meningitis was fever in 93% (13/14), impairment of consciousness in 79% (11/14), cough in 72% (10/14) and meningism with 64% (9/14), mostly represented through neck stiffness in 71% (10/14). Seizures occurred in 57% (8/14) of the patients with *H. influenzae*, of which 63% (5/14) were generalized seizures.

Within laboratory findings, all CSF samples of patients with *H. influenzae* appeared turbid (14/14). Cell count within the CSF could be determined in 13 patients, resulting in a medium cell count of 1240 cells/µl ranging from 18 to 9600 cells/µl. The predominant cell type found in all 14 CSF samples was lymphocytes. Malaria detection was performed in 13 patients with *H. influenzae* meningitis, 92% were negative (12/13).

Patients with meningitis caused by *H. influenzae* were treated with benzylpenicillin and chloramphenicol without (3/14) or with (11/14) additional antibiotics such as gentamicin. Sixty-seven percent (2/3) oft the patients treated with benzylpenicillin and chloramphenicol recovered during hospitalization. In those treated with benzyplpenicillin, chloramphenicol and additional antibiotics, 73% (8/11) of the patients died,18% (2/11) recovered during hospitalization and one patient was still improving at the time of the study.

4. Discussion

In our study a large part of meningitis was caused by bacterial pathogens, followed by mycobacterial agents. Within bacterial meningitis, *H. influenzae*, *S. pneumoniae* and *N. meningitidis* formed the main part. Taking a detailed look at the age distribution within the pathogen spectrum, it is noticeable that bacterial meningitis was predominant in the age group under 5 years. In the age groups above 45 years mycobacterial meningitis prevailed, but it has to be taken into account that the percentage of mycobacterial origin did not substantially differ within the different age groups (Fig. 1). This phenomenon was also demonstrated in other African studies, determining the highest incidences of bacterial meningitis in children under 15 years, with those aged under 1 year representing the largest part of paediatric patients [12,18]. In comparison to that, a study in the United States observed an increasing median age at diagnosis with the majority of patients being adults, owed to the introduction of several vaccines [7].

Table 5
Detailed information about patients with *H. influenzae* (n = 14).

Demographic information	
Age in years	n = 14
Average (±SD)	1.55 (±3.63)
Median (MIN-MAX)	0.5 (0.06–14)
Gender in n (%)	n = 14
Male	8 (57)
Female	6 (43)
Male:female ratio	1.33
Frequent complaints on admission	
Symptom/sign in n (%)	14
Fever	13 (93)
Impairment of consciousness	11 (79)
Generalized muscle hypertonia	8 (57)
Lateral deviation of gaze	2 (14)
Meningism	9 (64)
Neck stiffness	10 (71)
Kernig's sign	9 (64)
Lasègue's sign	9 (64)
Bulging fontanella (≤1 year)	3 (27)[a]
Photophobia	5 (36)
Seizures	8 (57)
Generalized	5 (63)
Focal	3 (38)
Cough	10 (72)
Rales (on chest examination)	5 (36)
Nausea and vomitting	9 (64)
Laboratory findings	
CSF appearance in n (%)	14
Turbid	14 (100)
Clear	0 (0)
CSF cell count	n = 13
Average (±SD) in cell count/µl	1793.23 (±2650.71)
Median (MIN-MAX) in cell count/µl	1240 (18–9600)
≤4 cell count/µl in n (%)	0 (0)
>1000 cell count/µl in n (%)	7 (54)
Average (±SD) in cell count/µl	3118.57 (±3087.01)
Median (MIN-MAX) in cell count/µl	1860 (1240–9600)
CSF predominant cells in n (%)	n = 14
Lymphocytes	14 (100)
Malaria detection in n (%)	n = 13
Negative	12 (92)
Positive	1 (8)

Abbreviations: SD, standard deviation.
[a] Percentage refers to n = 11 children ≤1 year.

A study conducted in Israel as well as studies from Burkina Faso and Togo showed, that *H. influenzae*, *S. pneumoniae* and *N. meningitidis* – in this order – form the main organisms responsible for meningitis cases in paediatric patients, confirming our results determining *H. influenzae* as the most common pathogen causing bacterial meningitis in our study population [12,19]. To the contrary, a study that took place in Romania ascertained *N. meningitidis* as the most common pathogen causing meningitis in children under 5 years [20]. These different results are possibly subject to regional pathogenic variations and disease outbreaks on the one hand and to the different vaccination programs on the other hand. Introduction of vaccines against certain meningococcal serogroups or *H. influenzae* types led to dramatic decline of meningitis cases in epidemic regions, for instance, and therefore to an alteration of the distribution pattern of pathogens [10,11,21]. However, studies about the immunization coverage against pathogens causing meningitis in Tanzania, where our study took place, are scarce.

A clear drawback of our study is the time period in which it was conducted and the lack of data about patients with meningitis during the last years. The WHO recommended vaccination schedule for the United Republic of Tanzania contains, amongst other, *H. influenzae* and *S. pneumoniae* [22], immunization against meningococcal serogroups are not part of that routine vaccination program but recommended in some high-risk populations only [23]. Although the WHO global summary determined an immunization coverage for example against *H. influenzae* type B increasing from 85% to 97% within the last five years after the comprehensive introduction of the vaccine against *H. influenzae* type B in Tanzania 2009 [24], a recent investigation at the same hospital where our study took place showed that vaccination programs reach children in rural areas only very slowly and, in fact, do not include meningitis relevant vaccination for example against *H. influenzae* or *S. pneumoniae* [25]. The mentioned study even registered a decline in the coverage of full vaccination against tuberculosis, poliomyelitis, diphtheria, pertussis, tetanus and measles from 72% in 1998 to 57% in 2007 [25]. This has also been shown in another study which reviewed the vaccination coverage for poliomyelitis, measles, tuberculosis and DTwPHibHep (a vaccine against diphtheria and tetanus toxoid, pertussis, *H. influenzae* type B and hepatitis B) in children between 12 and 13 months in east African regions, with the result that, referring to Tanzania, only 39% received the full dose of the recommended vaccines and 52% received only an incomplete vaccination [26]. The delivery of these indispensable vaccines to remote rural areas is often hampered by the lack of appropriate infrastructure and therefore, despite recommended, vaccination programs often do not reach areas in need. In addition, once on site, the vaccination programs may not be accessed by the local population due to a variety of reasons. In this context, various factors seem to be important to increase vaccination coverage: cost-effectiveness of the vaccine and thereby affordability by local health systems, functional logistic and transport services guaranteeing intact cooling chains, provision of health services especially for rural communities and nomadic groups and last but not least information and education of the local population as to the necessity of their children taking part in vaccination programs. The influence of vaccination programs on the distribution of pathogens was most likely low in our study population, as indicated by our high proportion of patients with *H. influenzae*, and the same may apply to other remote rural regions in Africa. The lack of appropriate vaccination coverage against common pathogens like *H. influenzae* may still lead to a difference in incidence and mortality rates between high- and low-income countries as *H. influenzae* meningitis occur significantly more often in low-income countries, especially after the implementation of vaccines against this pathogen [15,27]. Africa and Asia are part of the ten countries with the highest number of deaths worldwide caused by infections by *H. influenzae*, emphasizing the burden of this actually preventable disease in low-income countries [15].

In addition to prophylaxis, the improvement of meningitis case management in rural African settings is key and includes scaling up of neurological training of health care providers and improvement of diagnostic facilities, amongst other, thereby preventing severe clinical courses or even death [27].

Taking a detailed look at age distribution of our patients with bacterial meningitis, it also becomes apparent that *H. influenzae* occurs mainly in patients with meningitis under the age of 2 years. This is confirmed by other studies, ascertaining the highest incidence rates of *H. influenzae* in children under 2 years, most of them being under 1 year [12,19]. Neck stiffness, impairment of consciousness, cough and seizures are reported to be common symptoms in *H. influenzae* and are in line with our study results, but these symptoms do not represent specific symptoms for *H. influenzae*, as they frequently occur in bacterial meningitis [28]. Evaluating the clinical presentation of all our patients with meningitis with fever in >84%, neck stiffness in 60% and impairment of consciousness in 33%, our study results are in line with findings of other studies. Fever, headache, altered mental state as well as neck stiffness are often found as one of the leading symptoms/signs in patients with meningitis [29,30]. Although only a few patients had the classical meningitis triad of fever, neck stiffness and an altered mental state, van de Beek et al. state that at least two of those symptoms are warning signals in the diagnosis of meningitis, as well as an absence of all three symptoms can nearly exclude the diagnosis [29]. Another important factor in paediatric patients is the presentation of epileptic seizures associated with a fever (as opposed to febrile seizures), accompanied by impairment of consciousness or neurological deficits, as these symptoms may be indicators of bacterial meningitis [31,32]. Our study determined a higher occurrence of seizures in the patients with meningitis caused by *H. influenza* compared to all patients, a phenomenon which was already observed in earlier studies and may be used as an alert 'red flag' symptom for a *H. influenzae* infection [28,33]. As clinical symptoms in paediatric patients are far less specific and more difficult to examine, Berkley et al. found a bulging fontanella, neck stiffness, cyanosis, impaired consciousness or seizures as one of the "red flag"-symptoms in paediatric patients with meningitis, which indicates the necessity of a spinal tap and appropriate treatment [34]. This also applies to our study, as nearly 40% of the children with meningitis under 1 year presented with a bulging fontanella.

In our study, 73% of the spinal taps carried out, appeared turbid and in 60% there were granulocytes as predominant cells, which supports the diagnosis of bacterial meningitis in our patient sample and facilitates rapid therapy [35]. In our cases with diagnosed *H. influenzae* meningitis, even all CSF samples appeared turbid and showed an increased cell count per µl with lymphocytes as predominant cells. This suggests a potential pre-treatment before reaching the hospital. When considering that only 29% of all CSF samples in general had >1000 cells per µl, antibiotics use prior to hospital admission, leucocyte underestimation due to poorly trained personnel or a viral cause of the meningitis, which is difficult to ascertain with little diagnostic means at hand such as in low-income countries, seems likely. Spinal taps in patients with increased cerebral pressure can be unsafe in the absence of prior imaging and are therefore often not performed in low-income settings, which prevents fast and reliable diagnoses as well as appropriate treatment [36]. However, a study conducted in a district hospital in Kenya, sub-Saharan Africa, showed that despite the implementation of leucocyte counting in CSF samples a sixth of the meningitis cases were not detected, which emphasizes the urgent need of skilled laboratory workers and other diagnostic methods like culture facilities [37].

Increasing bacterial resistances against ampicillin and chloramphenicol, especially with the main causative pathogens like *H. influenzae*, *S. pneumoniae* and *N. meningitidis*, show the need for an alternative antibiotic treatment against meningitis nowadays [38–40]. However, in low-income countries, where cephalosporins are not widely available and pricey, a combination of chloramphenicol and ampicillin or benzylpenicillin is still recommended [41,42]. Although an add-on therapy with gentamicin promises an increased bactericidal effect of β-lactam antibiotics [43], our study shows a poorer outcome for patients

with *H. influenzae* treated with benzylpenicillins and gentamicin add-on therapy overall, which may be related to the narrow therapeutic window and the risk of oto- and nephrotoxicity of aminoglycosides [38]. In view of these results, we recommend gentamicin to be used carefully in the absence of possibilities to observe therapeutic levels. However, the worse outcome in patients with add-on gentamicin therapy may also be due to the fact that gentamicin was often reserved for the more severe cases, which may have introduced a selection bias. Furthermore, the frequent use of quinine in our patients, irrespective of their blood smear result, shows, the uncertainties and lack of guidance regarding the diagnosis of neurological disorders and their associated laboratory results. In summary, drug treatment of neuroinfections, be it for bacterial or parasitic pathogens, on the one hand, is hampered by lack of access to appropriate medication, and on the other hand, by over-treatment with antibiotics and/or antiparasitic drugs. Consequently, many challenges seem to exist to improving antibiotic/antiparasitic use in low-income countries, calling for strict surveillance, antimicrobial stewardship and development of new bedside diagnostic tools for bacterial/parasitic infections and antimicrobial susceptibility [44].

5. Conclusion

The distribution pattern of pathogens varies a lot according to the area, season and vaccination coverage. While, on the one hand, meningitis due to *H. influenzae* or *N. meningitidis* are almost entirely eliminated especially in high-income countries, there exist, on the other hand, still high incidence and mortality rates in remote areas of low-income countries. Our results support this fact, showing that bacterial meningitis, with *H. influenzae* as leading pathogen, is a common burden in low-income regions, especially in the young. This has to be taken into consideration to guarantee appropriate diagnosis and treatment. Recognition of the rather unspecific warning signs in patients with meningitis like fever, neck stiffness, impairment of consciousness and a bulging fontanella in children under 1 year seems crucial and, if present, treatment needs to be initiated without further delay. The additional presence of epileptic seizures should point to a possible *H. influenzae* meningitis, as this symptom was significantly more frequent in our patients with *H. influenzae* compared to other the pathogens. Furthermore, it is of utmost importance to evaluate relevant differential diagnoses like cerebral malaria to be able to adjust treatment to these conditions. Analysis of CSF remains the diagnostic mainstay for meningitis in general and the cornerstone of pathogenic evaluation. The high prevalence of *H. influenzae* in our study population was most likely due to the non-deliverance of vaccination programs in the rural and remote area in which our study took place. Prophylaxis of meningitis through an appropriate vaccination coverage especially in remote areas, plays a key role in preventing death and neurological sequelae, particularly in children. In addition, appropriate antibiotic use in low-income countries needs to be advocated for and, in this context, antimicrobial stewardship adapted to local circumstances has to be established.

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Conflicts of interest

None.

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