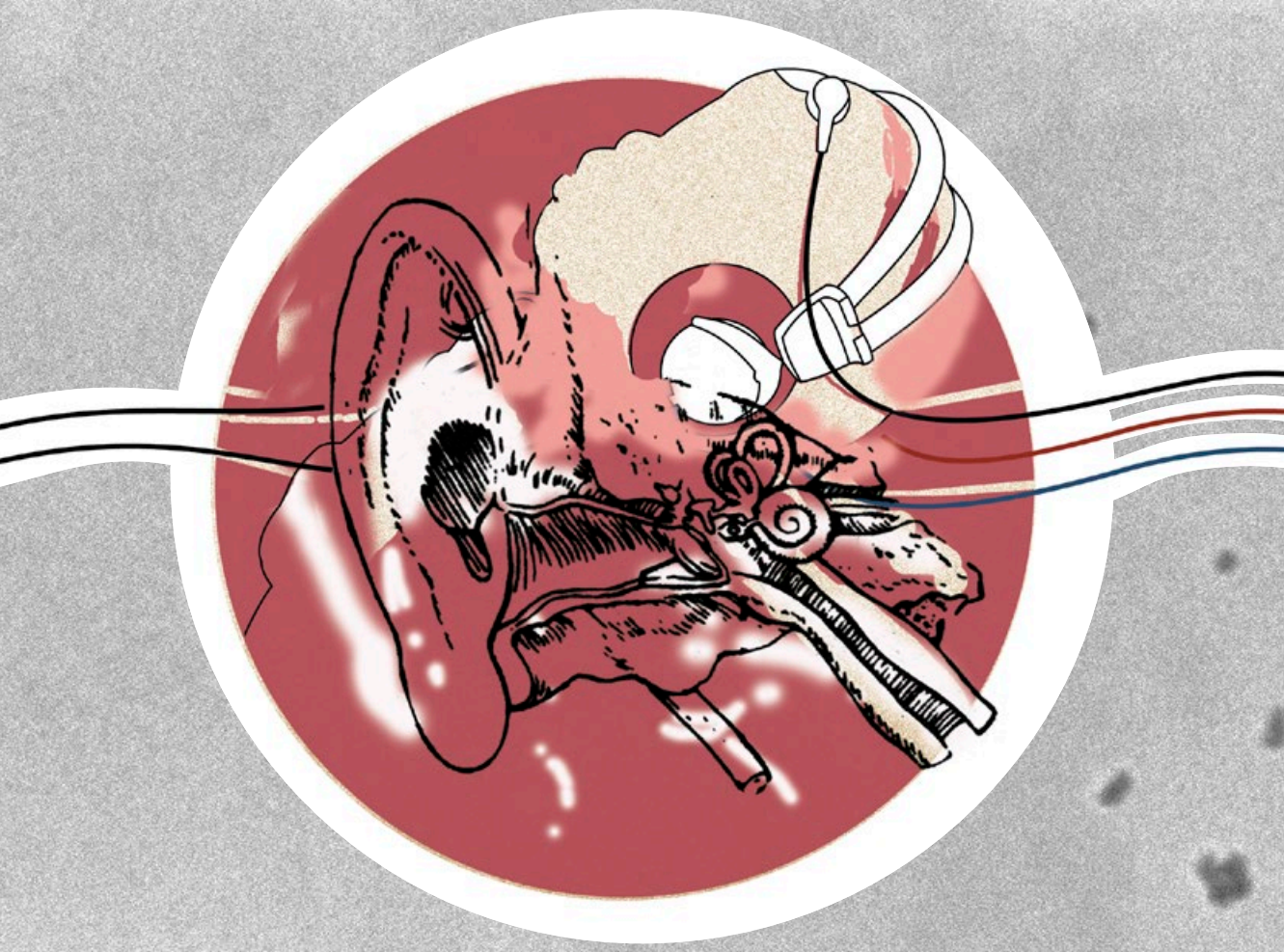
Mariia Karppinen

# Otorrhoea & ear- and auditory-related outcomes of bacterial meningitis

## among children in Angola



University of Helsinki
2019

Department of Otorhinolaryngology
Faculty of Medicine
Doctoral Programme in Clinical Research
University of Helsinki
Helsinki, Finland

# Otorrhoea & ear- and auditory-related outcomes of bacterial meningitis

## among children in Angola

Mariia Karppinen

ACADEMIC DISSERTATION

To be presented and publicly discussed,
with the permission of the Faculty of Medicine,
University of Helsinki,
in the Richard Faltin -lecture hall,
Surgical Hospital, Kasarmikatu 11-13
on March 8th 2019, at 12 noon.

**Supervised by** Professor Anne Pitkäranta, MD, PhD
Department of Otorhinolaryngology
University of Helsinki

Docent Tuula Pelkonen, MD, PhD
Department of Paediatrics
Children's Hospital, Helsinki University Hospital
University of Helsinki

**Reviewed by** Professor Heikki Löppönen, MD, PhD
Department of Otorhinolaryngology
University of Eastern Finland
Kuopio, Finland

Docent Merja Helminen, MD, PhD
Department of Paediatrics
University of Tampere
Tampere, Finland

**Opponent** Professor Malou Hultcrantz, MD, PhD
Department of Otorhinolaryngology
Karolinska Institutet
Stockholm, Sweden

The Faculty of Medicine uses the Urkund system (plagiarism recognition)
to examine all doctoral dissertations.

Cover and layout: Ville Repo

ISBN 978-951-51-4905-3 (paperback)
ISBN 978-951-51-4906-0 (PDF)

Printing: Picaset Oy
Helsinki 2019

To my family

# Table of Contents

# Abstract

**Background:** In resource-poor settings, otorrhoea, otitis media (OM) and bacterial meningitis (BM) cause substantial morbidity and mortality in children. Chronic otorrhoea causes disabling hearing impairment (HI) and may progress into intracranial infections, such as BM. In order to treat middle-ear infections, knowledge of the causative agents is crucial in Africa, where limited data are available. Additionally, little is known about the contribution of OM to BM, the effects of a bacterial aetiology and the prognostic value of an auditory brainstem response (ABR) on disease outcomes in resource-poor settings, where childhood BM often kills or leaves survivors with disabling and severe sequelae.

**Patients and methods:** This thesis includes four different studies. The first study investigated the microbiology of otorrhoea samples from children 0 to 15 years of age between 2008 and 2015 from Luanda, Angola in a laboratory-based retrospective set-up and reviewed the related literature among African children over a two-decade period.

A randomised treatment trial of 723 children with BM in Luanda, Angola, between 2005 and 2008 served as the basis to study ear- and auditory-related outcomes of childhood BM in subsequent observational studies. The second study investigated the frequency and effect of OM on the disease presentation, course and outcomes. The third study examined the relationship between different bacterial aetiologies and the age at hearing outcomes. And, finally, the fourth study examined the predictive value of the auditory brainstem response (ABR) on the adverse outcomes, and analysed the changes of ABR in childhood BM.

**Results:** Otorrhoea in Luanda was caused by 32 different bacteria, the majority being Gram-negative organisms (85%). Current treatment quidelines appear locally applicable, since resistance to quinolones remained rare. However, among *Enterobacteriaceae* and *Staphylococcus aureus*, considerable resistance was noted. Furthermore, the literature review showed a high occurrence of otorrhoea and chronic suppurative otitis media (CSOM) in African children as well as possible gaps in existing knowledge.

Among children with BM, OM occurred in 12%, of which the majority was otorrhoea. OM in Angola served as a marker for a more complex presentation, clinical course and outcome of BM. Multivariate analysis indicated that OM significantly increased the odds of dying or complicated clinical course. Furthermore, otorrhoea was associated with HIV positivity and poor socioeconomic conditions among infants.

HI was a common sequela of BM, given that 12.8% of survivors became deaf, 6% experienced severe HI and 9% moderate HI. The effect of causative agents was significant only when hearing in both ears was analysed. Meningococcal meningitis caused less HI of any degree compared to other aetiologies (22% vs. 45%). In the age-group analysis (children <12 months of age), *Streptococcus pneumoniae* caused more deafness than other infectious agents (31% vs. 12%).

Finally, we found no predictive value using either a single or repeated ABR measurement to predict death or to predict death or severe neurological sequelae. At the group level, the neural conduction time was prolonged in BM compared to controls. However, due to the low specificity and sensitivity in our sample, prolongation does not serve as a prognostic tool.

**Conclusions:** Antimicrobial susceptibility patterns support the current World Health Organization (WHO) guidelines for treating otorrhoea, which, in Africa, appears highly common, clearly implicating public health practises. In Angola, associated OM complicated BM, and otorrhoea served as a potential marker for HIV. The extent of HI appears to depend upon various factors, among which bacterial aetiology seems to play a role. We continue to need prognostic tools for BM, which are appropriate to resource-poor settings.

# Yhteenveto

**Taustaa:** Matalan toimeentulon maissa korvan märkävuoto, välikorvatulehdukset ja märkäinen aivokalvontulehdus aiheuttavat huomattavaa sairastavuutta ja kuolleisuutta lapsilla. Pitkään jatkuva korvavuoto vaurioittaa kuuloa ja voi levitä kallonsisäiseksi tulehdukseksi muun muassa aivokalvoihin. Jotta välikorvatulehduksia voidaan tehokkaasti hoitaa, tieto niiden aiheuttajista on tärkeää – erityisesti Afrikassa, jossa tietoa taudinaiheuttajista ja antibioottiherkkyyksistä lapsilla on vain vähän saatavilla. Lisäksi lasten aivokalvontulehduksen taudinkulkuun ja ennusteeseen vaikuttavista tekijöistä tiedetään vähän, erityisesti köyhimmissä maissa, joissa aivokalvontulehdus johtaa usein kuolemaan tai vammauttaa pysyvästi huomattavan osan henkiin jääneistä.

**Potilaat ja menetelmät:** Tämä tutkimus koostui neljästä osatyöstä, ja selvitti 1) korvan märkävuodon mikrobiologiaa 0–15-vuotiailta lapsilta Luandassa, Angolassa vuosina 2008-2015 otetuista näytteistä retrospektiivisessä tutkimusasetelmassa. Lisäksi kirjallisuuskatsauksessa käytiin läpi afrikkalaislapsilla asiasta tehdyt tutkimukset kahden edeltävän vuosikymmenen ajalta.

Vuosina 2005-2008 toteutettu laaja aivokalvontulehduksen hoitotutkimus 0-13 vuotiailla lapsilla toimi tutkimusaineistona jatkotutkimuksillemme. Näissä tutkimuksissa selvitettiin 2) liitännäisen korvatulehduksen vaikutusta aivokalvontulehdukseen; 3) taudinaiheuttajan ja iän suhdetta aivokalvontulehduksen aiheuttamaan kuulovikaan; sekä 4) kuuloradan herätepotentiaalien muutoksia ja ennustearvoa aivokalvontulehduksen ennusteeseen.

**Tulokset:** Korvan märkävuotoa aiheutti 32 eri bakteeria, joista suurin osa oli Gram-negatiivisia bakteereita (85%). Ajankohtainen hoitosuositus krooniselle vuotavalle korvatulehdukselle on Luandassa edelleen käypä, sillä fluorokinolonien antibioottiresistenssi oli harvinaista. Enterobakteerien sekä *Staphylococcus aureus* – bakteerien osalta todettiin antibioottiresistenssiä. Kirjallisuuskatsauksessa todettiin korvan märkävuodon ja kroonisen märkäisen korvatulehduksen olevan afrikkalaislapsilla hyvin yleisiä. Samalla havaittiin myös, että näistä sairauksista oli vain vähän tietoa afrikkalaislasten keskuudessa.

Aivokalvontulehdukseen sairastuneista lapsista 12%:lla todettiin liitännäinen korvatulehdus, josta suurin osa oli korvan märkävuotoa. Angolassa korvatulehdus liittyi aivokalvontulehduksen hankalampaan taudinkuvaan, taudin kulkuun ja ennusteeseen. Korvatulehdus lisäsi kuoleman tai hankalan taudinkuvan riskiä monimuuttuja-analyysissä. Lisäksi lapsilla, joilla oli korvan märkävuotoa, esiintyi enemmän HIV-infektiota, ja alle vuoden ikäisistä märkävuotoa esiintyi enemmän lapsilla, jotka olivat köyhimmistä olosuhteista.

Kuulovika oli yleinen aivokalvontulehduksen komplikaatio: 12,8% lapsista kuuroutui, 6% sai vakavan ja 9% keskivaikean kuulovian. Taudinaiheuttajan vaikutus kuulovaurioon oli merkitsevä ainoastaan, kun molempien korvien kuulo analysoitiin. Meningokokin aiheuttamassa aivokalvontulehduksessa kuulovikaa esiintyi vähemmän verrattuna muihin taudinaiheuttajiin (22% vs. 45%). Kun iän vaikutus otettiin huomioon, alle vuoden ikäisillä lapsilla *Streptococcus pneumoniae* aiheutti kuuroutta jopa 31%:lla.

Yksittäisen tai toistetun aivorunkoherätevastemittauksen avulla ei pystytty ennustamaan kuolemaa tai vakavaa neurologista vammautumista. Kaiken kaikkiaan aivorungon kuuloradan johtuminen oli hitaampaa potilailla verrattuna terveisiin kontrolleihin. Koska sensitiivisyys ja spesifisyys suhteessa kuolemaan tai vakavaan vammautumiseen olivat matalia, johtumisaikojen pidentyminen potilailla ei soveltunut taudin ennusteen arvioimiseen.

**Johtopäätelmät:** Antibioottiherkkyysanalyysien tulokset tukevat ajankohtaisia Maailman terveysjärjestön hoitosuosituksia kroonisen märkäisen välikorvatulehduksen hoidossa. Korvan märkävuoto on Afrikassa hyvin yleistä ja vaatii kansanterveydellisiä toimia. Angolassa korvatulehdus komplisoi bakteerimeningiittiä, ja korvan märkävuoto voi viitata HIV-infektioon. Kuulovika aivokalvontulehduksessa liittyy moniin tekijöihin, mm. taudinaiheuttajaan ja lapsen ikään. Aivokalvontulehduksen ennusteen arvioimiseksi erityisesti köyhimmissä maissa tarvitaan lisää työkaluja.

# Resumo

**Circunstâncias:** Em condições de baixa-renda, a otorréia, otite média (OM) e meningite bacteriana (MB) causam mortalidade substancial e especialmente em crianças. A otorréia crônica causa perda auditiva desabilitante e pode progredir a infecções intracranianas, como a MB. Para tratar as infecções de ouvido médio, o conhecimento de agentes causais é crucial na África, onde há disponibilidade limitada de dados. Além disto, conhece-se pouco sobre a contribuição da OM à MB, efeitos da etiologia bacteriana e o valor prognóstico da resposta auditiva do tronco cerebral (RATC) às consequências de doenças em condições carentes, onde a MB infantil geralmente mata ou deixa os sobreviventes com sequelas severas e desabilitantes.

**Pacientes e métodos:** Este estudo investiga, em primeiro lugar, amostras microbiológicas da otorréia de crianças de 0 a 15 anos de idade, entre 2008 e 2015 de Luanda, Angola, em condições retrospectivas de laboratório, assim como por uma revisão literária relacionada sobre crianças africanas por um período de duas décadas.

Um estudo randomizado de tratamento de 723 crianças com MB em Luanda, Angola, entre 2005 e 2008, serviu como base para a pesquisa de consequências otológicas e auditivas da MB infantil aos estudos de observação subsequentes. Em Segundo lugar, esta tese investiga adicionalmente a frequência e o efeito da OM no quadro, evolução e consequências da doença. Em terceiro lugar, a tese examina a relação entre diferentes etiologias bacterianas e a idade nas consequências auditivas. E finalmente, examinamos ainda o valor prognóstico da resposta auditiva do tronco cerebral (RATC) às consequências adversas, assim como analisou-se ainda as alterações da RATC no MB infantil.

**Resultados:** A otorréia em Luanda era causada por 32 bactérias diferentes, sendo a maioria organismos Gram-negativos (85%). Os guias de tratamento atuais são aparentemente localmente aplicáveis pela rara resistência às quinolonas. Porém, resistência considerável entre *Enterobacteriaceae e Staphylococcus aureus* foi observada. Além disto, a revisão da literatura mostrou uma alta ocorrência de otorréia e otite media crónica supurativa (OMCS) nas crianças africanas, assim como possíveis lacunas no conhecimento existente.

Entre as crianças com MB, a OM occorreu em 12%, a maioria dos quais com otorréia. A OM em Angola serviu como uma marcadora para um quadro, evolução clínica e consequência mais complexa da MB. A análise multivariada indicou que a OM aumentava significativamente a mortalidade ou uma evolução clínica complicada. Além disto, a otorréia foi associada com a VIH positividade e condição sôcio-econômica vulnerável entre as crianças.

A perda auditiva foi uma sequela comum da MB, sendo que 12.8% dos sobreviventes ensurdeceram, 6% tiveram uma séria perda auditiva e 9% uma perda auditiva moderada. O agente de efeito causal foi significativo apenas quando a audição em ambos os ouvidos foi analisada. A Meningite meningococal causou menos perda auditiva de qualquer grau, comparado a outras etiologias (22% vs. 45%). Na análise de grupo etário (crianças <12 mêses de idade), a *Streptococcus pneumoniae* causou mais surdez do que outros agentes infecciosos (31% vs. 12%).

Finalmente, não encontramos um valor previsível usando a medição unitária ou repetida de RATC para prever a morte ou uma sequela neurológica severa. Ao nível de grupo, o tempo de conducção neural foi prolongada na MB ao comparado com os controles. Entretanto, devido à baixa especificidade e sensibilidade na nossa amostra, o prolongamento não serve como uma ferramenta prognôstica.

**Conclusões:** Os padrões de suscetibilidade antimicrobiana apoiam as diretrizes das guias atuais da Organização Mundial da Saúde (OMS) para o tratamento da otorréia, cuja ocorrência é comum na África, com claras implicaões às práticas de saúde pública. A OM associada complicava a MB e a otorréia serviu com uma marcadora potencial para VIH em Angola. A extensão da perda auditiva parece depender de vários fatores, entre os quais a etiologia bacteriana desempenha um papel aparente. Ainda há necessidade às ferramentas prognósticas da MB mais apropriadas às condições carentes em recursos.

# Original publications

This thesis is based on the following articles, which are referred to in the text by their Roman numerals [studies I–IV].

I. Karppinen M, Bernardino L, dos Anjos E, Pätäri-Sampo A, Pitkäranta A, Peltola H, Pelkonen T. Etiology of Childhood Otorrhea in Luanda, Angola, and a Review of Otitis Media in African Children. Accepted for publication. *Pediatr Infect Dis J* 2018 Dec 3. 10.1097/INF.0000000000002254 [doi].

II. Lempinen L, Karppinen M, Pelkonen T, Laulajainen-Hongisto A, Aarnisalo AA, Sinkkonen S, Bernardino L, Peltola H, Pitkäranta A, Jero J. Otitis Media-Associated Bacterial Meningitis in Children in a Low-Income Country. Submitted to *Pediatr Infect Dis J*.

III. Karppinen M, Pelkonen T, Roine I, Cruzeiro ML, Peltola H, Pitkäranta A. Hearing impairment after childhood bacterial meningitis dependent on etiology in Luanda, Angola. *Int J Pediatr Otorhinolaryngol*. 2015;79(11):1820-1826.

IV. Karppinen M, Sjövall A, Pelkonen T, Bernardino L, Roine I, Pitkäranta A, Aarnisalo AA, Nevalainen P, Lauronen L. Prognostic value and changes of auditory brain stem response in children with bacterial meningitis in Luanda, Angola. *Clin Med Insights Ear Nose Throat*. 2018;11:1179550618758648.

The articles are reprinted here with the permission of the publishers.

# Abbreviations

ABR ..... Auditory brainstem response
AOM ..... Acute otitis media
AUC..... Area under the curve
BM ..... Bacterial meningitis
CI ..... Confidence interval
CNS ..... Central nervous system
CRP ..... C-reactive protein
CSF ..... Cerebrospinal fluid
CSOM ..... Chronic suppurative otitis media
DALY ..... Disability-adjusted life year
EHC ..... Ear and hearing care
ENT ..... Ear, nose and throat
ESBL ..... Extended-spectrum β-lactamase
GBD ..... Global burden of disease
GCS ..... Glascow Coma Scale
HI..... Hearing impairment
Hib ..... *Haemophilus influenzae* type b
HIC..... High-income country
*H. influenzae* ..... *Haemophilus influenzae*
ICC ..... Intracranial complication
ICP ..... Intracranial pressure
IPL ..... Interpeak latency
IQR..... Interquartile range
LMIC ..... Low- and middle-income country
MEE ..... Middle-ear effusion
MRSA ..... Methicillin-resistant *Staphylococcus aureus*
*N. meningitidis* ..... *Neisseria meningitidis*
OM ..... Otitis media
OME..... Otitis media with effusion
OR ..... Odds ratio
PCR ..... Polymerase chain reaction
*P. aeruginosa*..... *Pseudomonas aeruginosa*
*S. pneumoniae* ..... *Streptococcus pneumoniae*
*S. aureus* ..... *Staphylococcus aureus*
SD ..... Standard deviation
SDG ..... Sustainable Development Goal
TM ..... Tympanic membrane
U-5 ..... Children under the age of five years
WHO..... World Health Organization
YLD ..... Years lived with a disability
YLL ..... Years of life lost

# 1. Introduction

Otorrhoea – typically a sign of acute or chronic otitis media (OM) – causes substantial morbidity in children worldwide. In resource-poor settings, it is often indicative of a chronic middle-ear infection leading to disabling hearing impairment (HI) and represents a risk factor for intracranial complications, such as bacterial meningitis (BM).[1] Most of the burden of OM-related complications occurs in children in resource-poor settings.[2]

BM is an infection of early childhood, which in Africa kills up to half of all infected children, while almost one-quarter are left with severe complications.[3,4] While the global incidence of BM is decreasing, children in low- and middle-income countries (LMICs) carry a substantial portion of the global burden of BM.[5]

In order to efficiently treat otorrhoea and middle-ear infections, knowledge of the causative agents and their antimicrobial surveillance remain crucial. Studying BM among children, who represent the majority affected by the disease globally, may improve knowledge related to preventing and treating the disease as well as its complications in the future. Many aspects of BM in resource-limited settings remain poorly understood.

This study sought to assess otorrhoea, and ear- and auditory-related outcomes of childhood BM in Luanda, Angola. We investigated the microbiology of childhood otorrhoea in Luanda and reviewed the related literature among African children over a two-decade period. We further characterised OM-associated BM, and assessed the effect of OM on the course and outcomes of the disease. Furthermore, we sought to analyse the frequency of HI in different bacterial aetiologies of BM and the effect of age on HI. Finally, we assessed the predictive value of and changes to the auditory brainstem response (ABR) on the outcome of BM.

# 2. Review of the literature

## 2.1 Angola country profile and global health perspectives

Angola is a vast country situated in the southwest of Africa belonging to the Central African Region in the World Health Organization's (WHO) categorisation (Figure 1). With its long Atlantic coastline, and its central plateau, Angola is one of the largest countries on the African continent. Angola gained independence from Portugal following a 15-year war in 1975. Subsequently, a 27-year civil war ended in 2002, at which point the country made substantial progress economically, politically and in terms of general welfare. Despite its oil reservoirs, of which the Angolan economy deeply depends, the country remains classified as a lower middle-income economy.

During the post-civil war era, gross domestic product growth has decelerated to 0.7% and Angola continues to face severe development challenges.[6] When examining human development indicators, Angola falls near or behind the averages of most Sub-Saharan African countries on the development continuum (Table 1). Amongst its population, 37% live under the national poverty line. The mortality rate among children under 5 years of age (U-5) climbed to more than 200 per 1000 live births at the end of the civil war, and has remained one of the highest globally during the last decade.


**Figure 1.** Map of Africa showing Angola, the capital Luanda, and the WHO African region.

**Table 1.** Angola country profile in comparison to Sub-Saharan Africa, in 2017.[6-8]

| | Angola | Sub-Saharan Africa |
|---|---|---|
| **Demographics and economy** | | |
| Population, millions | 29.8 | 1 061 |
| Annual population growth, % | 3.3 | 2.7 |
| Population aged under 15 years[a], % | 47 | 42 |
| People living under the extreme poverty line of $1.90 a day[b], % | 30 | 41 |
| People living under the poverty line of $3.20 a day[b], % | 56 | 66 |
| Gross National Income per capita, US$ | 3330 | 1454 |
| Gross domestic product growth, % | 0.7 | 2.6 |
| **Health** | | |
| Life expectancy at birth, years | 62 | 60 |
| Under-5 mortality rate per 1000 live births | 81 | 76 |
| Malnutrition[c] in children aged under-5, % | 19 | 18 |
| Immunisation, measles among children aged 12-23 months, % | 42 | 70 |
| **Education and communication** | | |
| Primary school completion rate[d], % | 40 | 70 |
| People using internet, % | 13 | n/a |
| Mobile use per 100 | 45 | 75 |

[a]World Health Organization (WHO) estimates available from year 2013 for Angola, and from 2008 for Sub-Saharan Africa.
[b]World Bank estimates available based on data from 2008 and 2015.
[c]Diagnosed as weight-for-age <–2 SDs of the WHO reference values.
[d]World Bank data available from 2010 for Angola.
N/a, not available.

The Global Burden of Disease (GBD) study is a standardised approach developed to measure and compare the health status of populations.[9] As such, for a specific condition, it quantifies the impact of premature death and disability on a population. The standard unit, the disability-adjusted life year (DALY), is the sum of years of life lost (YLLs) due to mortality and years lived with a disability (YLDs).

DALYs can be interpreted as gaps between a population's actual and their ideal health status. Annually, 31 million people develop persistent otorrhoea, among whom almost one-quarter are U-5 children. These figures represent a burden of 3.5 million DALYs.[10] A substantial portion is attributed to children living in resource-limited settings, including Africa.[2] Since bacterial meningitis (BM) is often fatal and disabling, its global burden accounts for more than 25 million DALYs. Since BM affects U-5 children, among them BM remains one of the major contributors to DALYs—that is, sixth in children aged 1 to 12 months and seventh in children aged 1 to 4 years.[10] Again, the majority of these children reside in LMICs.

## 2.2 Childhood otorrhoea and otitis media – African perspectives

### 2.2.1 Definitions and symptoms

#### Definitions

Otitis media (OM) represents a spectrum of diseases involving inflammation of the middle ear. In acute OM (AOM) acute signs and symptoms emerge and are detected in the middle ear together with middle-ear effusion (MEE). These include moderate or severe bulging of the tympanic membrane (TM) or milder bulging in combination with either ear pain or intense erythema of the TM.[11] Additionally, a new-onset middle ear–borne otorrhoea is defined as AOM.[11] If the infection fails to recover, a chronic infection results. Chronic suppurative OM (CSOM) refers to inflammation of the middle ear and mastoid air cells with chronic or intermittent suppuration leaking through a perforated TM. Controversy exists on the duration of discharge. WHO defines CSOM as a persistent otorrhoea of at least two weeks' duration, whilst otologists define CSOM as a longer duration of symptoms, lasting, for instance, more than three months.[1,12] Many clinicians consider the frequently associated cholesteatoma, the growth of squamous epithelium, in the definition of CSOM.[13,14] Otitis media with effusion (OME) refers to a condition without signs of acute infection, with effusion in the middle ear, behind an intact TM.

Otorrhoea, in comparison, is defined as discharge leaking from the ear. It may originate from the middle ear, the mastoid, the inner ear, the intracranial cavity, the external auditory canal, or from a combination of these sites.[14] But the simplest form in children is typically a sign of acute or recurrent OM with a perforated TM or ventilation tubes. In patient series and cross-sectional screening studies from Africa, otorrhoea is typically indicative of CSOM.[15,16] In epidemiological modelling, OM refers to both AOM and CSOM.[17]

#### Symptoms

Children with OM exhibit a spectrum of symptoms. In AOM, recent-onset symptoms possibly overlap with a preceding viral respiratory tract infection.[11] Respiratory symptoms are common findings; additionally, parents often report excessive crying, restless sleep, irritability, ear pain, poor appetite and a fever.[18] Ear pain is indicated, but does not represent a crucial sign of AOM and the ability to localise the pain varies with the child's age. The American Academy of Paediatrics considers rubbing or holding of the ear, a fever or a change in a child's sleep or behaviour patterns indicative of ear pain.[11] In Africa, parents' awareness of OM remains low and they are unlikely to suspect it.[16]

If TM ruptures, AOM is thought to cause less or no pain, possibly contributing to not seeking care in resource-poor settings, even when otorrhoea persists.[1,16] Patients with chronic otorrhoea may, however, experience discomfort or a milder earache and many found the condition socially challenging.[19] Hearing impairment (HI) is a frequent symptom of CSOM. The term chronic in CSOM is representational. In Africa, in a cohort of young children with a median age <5 years, otorrhoea persisted longer than 18 months in more than two-thirds of affected ears.[20] Subsequently, the disease often persists into adolescence and young adulthood. In Africa, cholestheatoma is a frequent complication of CSOM occurring in up to 20% of chronically discharging ears.[20]

### 2.2.2 Epidemiology, risk factors and aetiology

#### Epidemiology and risk factors

Middle-ear infections are common worldwide caus-

ing significant morbidity in children.[21] Globally, more than 470 million episodes of OM are estimated to occur annually, more than half of which occur in children.[2,22] OM is an infection of early childhood, since the incidence of AOM peaks just before a child's first birthday at around 8 to 13 months of age.[23,24] Recurrent infections commonly occur, and more than 80% of children have had an episode of AOM by 3 years of age.[25] CSOM typically develops during the first years of childhood as a consequence of AOM when treatment is not received or fails.[12,26] Annually, more than 7 million children U-5 develop CSOM.[2] In Africa, many develop chronic otorrhoea as early as before reaching 6 months of age and continue to develop the disease at a high rate during the first 5 years of life.[27,28] Later in childhood and during adolescence, CSOM may develop via OME, as suggested by research from Kenya.[28]

While AOM commonly occurs throughout the world, CSOM prevalence varies greatly between countries. In particular, it affects individuals at a socioeconomic disadvantage. Thus, children living in resource-poor or limited settings carry a higher risk for chronic otorrhoea. This is thought to occur via several mechanisms, including poor access to healthcare, a diminished host immunity and an increased exposure to a high bacterial load for pathological organisms.[29] The common denominator for all of these mechanisms is poverty. Awareness of the disease and possible complications remain poorly understood amongst patients and caregivers.[30] Specific risk factors for persistent otorrhoea in Africa consist of the early onset of disease, malnutrition, bottlefeeding, household smoke, rural residency, a poor socioeconomic status, geographic distance from a health facility and family size.[27,31]

Moreover, CSOM affects certain indigenous populations most often. In particular, prevalence amongst Inuits and Australian aboriginals range from 14% to 30%.[32,33] After the prevalence rates in the Pacific and Southeast Asia, the incidence estimates are highest for Africa.[2] In Africa, the incidence rates for AOM and CSOM range from 14.71 to 43.37 per 100 and 4.79 to 7.56 per 1000, respectively, with the highest rates found in the Central African region, which includes Angola.[2]

## Aetiology

In most parts of the world, the bacteria typically cultured in AOM-related MEE consist of *Streptococcus pneumoniae (S. pneumoniae), Haemophilus influenzae (H. influenzae)* and *Moraxella catarrhalis.* In resource-poor settings *Staphylococcus aureus (S. aureus)* occurs frequently, while in Africa, *Moraxella catarrhalis* is rarely found.[34,35] In a South African study, when samples were taken via tympanocentesis, the main bacterial isolates consisted of *H. influenzae, S. pneumoniae* and *S. aureus*.[34]

In CSOM, the inflammation of the middle ear persists, bacteria from the ear canal colonise in the middle-ear mucosa and the prevalence of Gram-negative bacteria increases. CSOM pathogens may also enter the middle ear via contaminated water.[36] *Pseudomonas* spp. and *S. aureus* represent the most frequent organisms followed by other Gram-negative species.[12,26] In addition, anaerobs such as *Bacteroides* spp. and *Fusobacterium* spp. are frequently detected.[26] The bacterial aetiologies of CSOM were thought to be relatively similar between resource-limited and affluent settings.[29] However, variations between populations and geographic settings appear to play some role. For example, a study among school children and young adults from Kenya found *Proteus* and *Enterococcus* spp. in most of the cases.[37] Furthermore, a young age may predispose an individual to different aetiologies. For instance in Africa *Proteus* is frequently detected in young children.[37,38] Immunosuppression may additionally affect the causative agents of CSOM. For instance, *Proteus mirabilis* associated with anaemia in South Africa.[39] Yet, no significant difference has been found when comparing HIV-positive and HIV-negative children.

### 2.2.3 Diagnosis and management in resource-poor settings

#### Diagnosis

The acute onset of symptoms is a key feature in the diagnosis of AOM.[11] To confirm the diagnosis, pneumatic otoscopy is decisive, revealing signs of middle-ear infection and effusion behind TM: that is, a moderate to severe bulging position, limited or absent motility, or otorrhoea originating from the middle ear.[11] In addition, milder bulging combined with pain or intense erythema on TM indicates AOM.[11] Tympanometry can be used to detect MEE. Other diagnostic measures consist of evidence of otorrhoea on tympanocentesis or myringotomy. In CSOM, otoscopy reveals red and inflamed or thickened mucosa with or without the presence of discharge leaking from the middle ear through a visualised perforation.[1,40] The duration of otorrhoea differentiates the chronic form of OM from acute cases.[1] CSOM may manifest through inactive phases when only middle-ear mucosa is inflamed, and discharge is missing or minimal.[40] Dry perforation with healthy middle-ear mucosa is not suggestive of CSOM.

#### Nonsurgical Treatment

Despite the large number of treatment trials for AOM, optimal treatment — particularly in high-income countries (HICs) — remains somewhat controversial, resulting in a variety of guidelines. Sufficient pain relief represents an important part of treatment. Yet, with regards to antimicrobials, for instance, the Swedish national guidelines recommend watchful waiting for children between 1 and 12 years of age in uncomplicated AOM and antimicrobial treatment for bilateral AOM in children under the age of 2 years old and for all individuals with perforated TM.[41] By contrast, Finnish national guidelines primarily recommend antimicrobial treatment when diagnosis is confirmed. It appears that children under the age of 3 years benefit from antimicrobial treatment.[42] In resource-poor settings, however, prompt antimicrobial therapy for AOM is recommended, since untreated ear infections carry the risk of severe complications, death and disability.[43] No evidence exists on the safety of withholding treatment for AOM using antibiotics in resource-poor settings.[43]

If a persistent otorrhoea develops, the primary therapy consists of aural toileting and topical antimicrobials.[26] Aural toileting refers to ear cleansing with mobbing, dry wicking, flushing or suctioning, all aimed at keeping the ear canal clean and dry.[40] No consensus exists, however, on the interval of ear cleansing in children.[26] WHO recommends antimicrobial use combined with dry wicking, specifically relying on topical quinolone administered three times daily for two weeks.[43] In children, topical quinolones appear effective in clearing up the discharge in the short-term.[44-46] Additionally, quinolones may favourably affect hearing, although evidence on long-term hearing outcomes and on the healing of a TM perforation remains lacking.[47] The effect of topical quinolones has been demonstrated in Africa, specifically in Gambia and in Malawi.[44,48] A review of OM among Australian indigenous populations concluded, that swimming played no role in the treatment or management of CSOM.[33] In Africa, however, no such research exists. With large perforations, preventing contaminated water from entering the ear is recommendable.

In the absence of evidence, WHO recommends avoiding the use of topical antiseptics and steroids to treat chronic otorrhoea in children.[43] The evidence favours the use of topical antimicrobials over antiseptics.[43] Of steroids utility, little is known in children.[43] In addition, first-line oral treatment does not appear to be more efficient than topical treatment.[49] In the absence of any medical treatment modalities, ear cleansing may carry some benefit.[46] Several recent structured review protocols have been published lately, to evaluate the effectiveness of alternatives consisting of nonsurgical treatment of CSOM.[50-53]

Furthermore, systemic antibiotics should be reserved for situations where the first-line treatment of chronic otorrhoea fails.[26] The cultivation of ear

pus and antimicrobial sensitivity analyses should guide the choice of drug.[26] As the option of last resort, parenteral antibiotics can be used since they have successfully treated chronic otorrhoea.[26,47] Ceftazidime has proved effective in treating *P. aeruginosa*.[54] Yet, again, parenteral treatment should be culture-directed. Intravenous treatment is indicated in cases of ICCs.[26]

We must recall, however, that with persistent otorrhoea, in particular, underlying conditions and comorbidities are common. For instance, HIV, tuberculosis, anaemia and malnutrition occur more often in children with otorrhoea in comparison to the general population.[20,55-57] Moreover, HIV prevalence amongst children with persistent otorrhoea appears strikingly high: 54% in South Africa and 64% in Angola.[20,56] Thus, a child with otorrhoea in a resource-poor setting should always be examined thoroughly.

### Surgical treatment

Surgical treatment is warranted in cases where medical treatment persistently fails, if cholesteatoma accompanies CSOM and when complications occur.[26] The objectives of surgery consist of TM repair, the eradication of the infection or both. Tympanoplasty (type 1, myringoplasty), defined, as the closure of the tympanic perforation with a connective tissue graft, is the procedure indicated in noncholesteatomous CSOM and in cases without infectious complications. Furthermore, a combined reconstruction of the ossicular chain may be indicative (tympanoplasty, types 2 and upward).

Mastoidectomy, the opening of the mastoid air cells and the surgical removal of mucosa, granulation tissue and debris, is considered when tympanoplasty fails, in cases with a persistent infection due to antimicrobial resistance and in cases of infectious complications.[58] Procedures in Nigeria include incision and drainage of the subperiosteal mastoid abscess, cortical mastoidectomy, radical mastoidectomy, myringoplasty and aural polypectomy.[59] In 2013 in Nigeria, however, tympanoplasty (type 1) was only available at 18% of the institutions offering ear surgery.[19]

## 2.2.4 **Consequences**

### Hearing impairment

The complications associated with OM are classified as intratemporal (extracranial) and intracranial complications. HI stands as the most common complication and consequence of OM. In AOM, MEE is present, typically resulting in mild, conductive and transient HI. In CSOM, HI can be conductive due to chronic perforation of TM and disruption of ossicles assembly; sensorineural due to hair cell damage because of invaded bacterial infection to inner ear; or a mixture of conductive and sensorineural HI.[1] Childhood CSOM-induced HI is associated with HI in adulthood.[60]

No consensus exists on defining the degree of HI.[61] However, classification into four groups according to the severity of HI in the better-hearing ear is common.[61,62] The degree of HI in the better-hearing ear is defined by calculating the average of the puretone thresholds over a certain frequency range.[61,62] In children, the term disabling hearing impairment can be used in case of average thresholds >30 dB in the better-hearing ear.[61] Table 2 summarises the WHO working group and European Union expert group grading for HI in children.[61-63]

**Table 2.** World Health Organization (WHO) working group and European Union (EU) expert group grading for hearing impairment. Adapted from previously published data.[61-63]

| Grade | dB range[a] | | Description – Performance |
|---|---|---|---|
| | WHO | EU | |
| No hearing impairment | ≤25 | <20 | No or slight problems – Able to hear whispers. |
| Slight / Mild | 26–40 | 20–39 | Trouble in hearing and understanding soft speech, speech from a distance or speech in a noisy environment – Able to hear and repeat words in normal voice at 1 metre. |
| Moderate | 41[b]–60 | 40–69 | Difficulty in hearing normal speech – Able to hear and repeat words in raised voice. |
| Severe | 61–80 | 70–94 | Only able to hear very loud speech / sounds – Able to hear some words shouted into better ear. |
| Profound | ≥81 | ≥95 | Perceives loud sounds as vibrations – Unable to hear a shouted voice. |

[a]Average hearing thresholds for 500, 1000, 2000 and 4000 Hz in the better-hearing ear.
[b]A hearing impairment of >30 dB in the better-hearing ear is classified as moderate or disabling hearing impairment in children <15 years.

In South Africa, 68% of CSOM-affected ears showed a HI of >25 dB, of which 31% was severe to profound.[39] In Sub-Saharan Africa, excluding the southern WHO region, the prevalence of permanent OM-related HI with a hearing level of >25 dB in the better-hearing ear varies from 0.30% to 0.34%.[2] Higher prevalences have been reported only for South Asia and Oceania. Amongst children U-5, permanent OM-related HI affects 1.92 to 2.21 in 1000 children in Sub-Saharan Africa, while in Western Europe only 0.056 in 1000 children are affected.[2]

Recent WHO estimates from 2018 are consistent with these figures although somewhat higher. Disabling HI occurs in 1.9% of children in Sub-Saharan Africa: amongst those affected, 60% result from preventable causes and 31% due to infections.[64] In a review of HI in Africa, 36% was attributable to middle-ear diseases.[65] Furthermore in Africa OM has become the leading cause of acquired, avoidable HI in children.[65] Amongst school-aged children, a median of 7.7% suffered from HI of >25 dB in the better-hearing ear and a median of 6.6% experienced a HI of >30 dB in the better-hearing ear. These figures are much higher than previously presented estimates, suggesting that HI in Africa remains underestimated. In African settings, a history of childhood otorrhoea associates with HI later in school ages, even when the middle-ear infections were successfully healed at the time of evaluation.[28]

## Other extracranial and intracranial complications

TM perforation and CSOM can be classified as complications of AOM. Other complications, limited to the middle and external ear, include adhesive otitis media, atelectasis of the middle ear, cholesteatoma, cholesterol granuloma and external otitis, while other suppurative intratemporal complications of OM include mastoiditis, facial nerve paresis, petrositis and labyrinthitis.[14] In addition, vestibular, balance and motor dysfunctions may follow OM.[13] Other complications occurring outside the temporal bone

consist of a subperiosteal abscess and a Bezold's abscess. Intracranial complications (ICCs) of OM include BM, dural venous sinus thrombosis, epidural abscess, subdural empyema, intracranial abscess and otitic hydrocephalus.[13]

### Mortality

Globally, mortality due to OM is predominantly mediated through CSOM and related to ICCs.1 The ICC rate of 0.47% for CSOM has remained steady, regardless of the decrease in CSOM from a Taiwanese study.[66] Whilst limited data for children are available, this figure is used in the epidemiological modelling of infectious complications associated with OM.[17] In a global review, the OM-related mortality estimates were calculated, which in Africa were highest for the Central African region, where OM is estimated to account for 96.20 annual deaths per 10 million population, with the highest mortality rates found amongst children U-5.[2] In Angola, these projections account for 277 deaths, with a significant proportion occurring amongst children.

### Other consequences

OM represents the primary reason for prescribing antimicrobias to children.[21] The excessive use of antimicrobials leads to antimicrobial resistance.[67] This is also a concern in many LMICs, where uncontrolled or inadequate antibiotic consumption frequently occur.[21]

Few datasets provide insights into the long-term consequences of CSOM. A follow-up cohort from a high-prevalence population — in this case, Greenland — showed that CSOM in childhood associated with a high risk of middle-ear problems later in adulthood.[68] With highly persistent disease, the complication risk accumulates and the need for surgical interventions increases. In LMICs where CSOM incidence remains high, the disease remains long-lasting and the related HI is often disabling, the long-term effects are likely.[1] OM-related HI may cause speech, language and developmental challenges amongst young children. This will possibly later affect their academic performance.[69]

Because OM represents one of the most common childhood bacterial infections, its care should be optimised. Many cost-effectiveness and cost-utility analyses of interventions are available from HICs.[70,71] Yet, similar African data remain scarce.[1] However, different CSOM treatment strategies aimed at preventing OM-related HI have been examined, whereby aural toileting in combination with topical antimicrobials emerged as the most effective intervention.[72]

## 2.2.5 Studies from Africa

A literature search identified prospective studies focusing on or comprehensively presenting findings for different types of OM in children and adolescents between 2008 and 2018 (Tables 3 & 4). Table 3 summarises population-based or large cross-sectional studies[16,28,37,69,73-75] and patient series,[15,57,76-80] while Table 4 displays the aetiological studies.[34,37,39,56,81,82]

**Table 3.** Otitis media in African children and adolescents in prospective studies, 2008 to 2018.

| Reference | Country | Setting | N | Age | Diagnosis (%) | | | | | Hearing evaluated | Data for U-5 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **A. Population based or large cross-sectional studies** | | | | | Otorrhoea | AOM | CSOM | OME | All OM | | |
| Mukara *et al.*, 2017[16] | Rwanda | C | 810 | 6–59 months | 2.0 | n/a | 4.0 | n/a | 5.8 | No | Yes |
| Hunt *et al.*, 2017[73] | Malawi | C | 281 | 4–6 years | n/a | 2.8 | 5.3[a] | 3.6 | 11.7 | Yes | No |
| Simões *et al.*, 2016[28] | Kenya | PS, S | 13109 | 2–15 years | n/a | 0.7 | 1.5–2.4[b] | 1.5 | 3.7 | Yes | Yes[e] |
| Aduda *et al.*, 2013[37] | Kenya | S | 9100 | 6–21 years | n/a | n/a | 3.3[a] | n/a | n/a | No | No |
| Adebola *et al.*, 2013[74] | Adebola | PS | 101 | 3–6 years | 0 | 0 | 0 | 16.8 | 16.8 | Yes | Yes |
| Olatoke *et al.*, 2008[69] | Nigeria | S | 1500 | 6–15 years | 2.0 | n/a | 2.3[b] | n/a | n/a | Yes | No |
| Clark, 2008[75] | Mozambique | S | 2685 | 1–19 years | 1.0 | n/a | n/a | n/a | n/a | Yes | Yes |
| **B. Patients series** | | | | | | | | | | | |
| Ianacone *et al.*, 2017[57] | Ethiopia | HIV+, Orphanage | 112 | 7–20 years | 8.9 | n/a | n/a | n/a | n/a | No | No |
| Biagio *et al.*, 2014[15] | South Africa | PC | 121 | 2–15 years | 5.2 | 1.7 | 6.6[c] | 16.5 | 24.8 | No | Yes |
| Lundberg *et al.*, 2014[76, f] | South Africa | PC | 180 | 2–15 years | n/a | 0 | 5.0[d] | 11.1 | 16.1 | No | No |
| Baggi *et al.*, 2013[77] | Burundi | Ward | 108 | <5 years | 0 | 0 | 0 | 68.5 | 68.5 | No | Yes |
| Taipale *et al.*, 2012[79] | Angola | SCD, HO | 61 | 8 months–15 years | n/a | 3.3 | 0[a] | 1.6 | 4.9 | Yes | No |
| Taipale *et al.*, 2011a[78] | Angola | HIV+, HO | 78 | 9 months–14 years | n/a | 10.3 | 26.9[a] | n/a | 37.2 | Yes | Yes |
| Alabi *et al.*, 2009[80] | Nigeria | ER | 200 | 3 months–14 years | n/a | 32.0 | n/a | n/a | 32.0 | No | Yes |

Literature search from October 2018. Percentages are diagnoses made in children unless otherwise stated. Data for U-5 stands for extractable numerical data from text, figures or tables for children under the age of 5 years. AOM, acute otitis media; CSOM, chronic suppurative otitis media; OME, otitis media with effusion; OM, otitis media. C, community; PS, pre-school; S, school, HIV+, human immunodeficiency virus infection; PC, primary care; HO, Hospital outpatients; SCD, sickle-cell disease; ER, emergency room; N/a, not applicable.
In absence of superscript for CSOM, no diagnostic criteria for CSOM were provided.
[a]WHO definition, discharge for ≥ 2 weeks.
[b]WHO definition and classification to active or inactive CSOM.
[c]Evidence of a perforation or cholesteatoma with or without purulent discharge.
[d]Perforation of tympanic membrane, retraction pocket or cholesteatoma with or without purulent discharge, previous ear surgery and grommets in tympanic membrane.
[e]Data for children aged 2 to 5 years.
[f]Ears.

**Table 4.** Prospective studies on the bacterial aetiology of different types of otitis media in children and adolescents in Africa, 2008 to 2018.

| Reference, Country | N samples/ isolates | Age | Diagnosis | Main isolate, % | Susceptibility tested | Data for U-5 |
|---|---|---|---|---|---|---|
| Hailegiyordis *et al.*, 2018[81] Ethiopia | 196/99 | <5 years | Otorrhoea | *S. aureus* 8<br>*P. aeruginosa* 6<br>*Streptococcus viridans* 5 | Yes | Yes |
| Ilechukwu *et al.*, 2017[82] Nigeria | 100/94 | 1 months–17 years | Otorrhoea | *Proteus* spp. 30<br>*S. aureus* 28<br>*P. aeruginosa* 17 | Yes | Yes |
| Madhi *et al.*, 2015[34] South Africa | 260/142 | 3–59 months | AOM | *H. influenzae* 31<br>*S. pneumonia* 20<br>*S. aureus* 16 | Yes | Yes |
| Aduda *et al.*, 2013[37] Kenya | 261/348 | 6–21 years | CSOM | *Proteus* spp. 42<br>*Enterococcus* 37<br>*S. aureus* 16 | Yes | No |
| Tiedt *et al.*, 2013[39] South Africa | 113/153 | 1–12 years | CSOM | *Proteus* spp. 31<br>*P. aeruginosa* 19<br>*H. influenzae* 19 | Yes | No |
| Taipale *et al.*, 2011b[56] Angola | 18/18 | 1–11 years | CSOM | *Proteus* spp. 44<br>*Pseudomonas* spp. 22<br>Other bacteria 11 | Yes | Yes |

Literature search from October 2018. Percentages are isolates per ears. Data for U-5 stands for extractable numerical data from text, figures or tables for children under the age of 5 years.
AOM, acute otitis media; CSOM, chronic suppurative otitis media.

## 2.3 Childhood bacterial meningitis — African perspectives

### 2.3.1 Definition and symptoms

Bacterial meningitis (BM) is an infection affecting the membranes surrounding the brain and spinal cord, and cerebrospinal fluid (CSF) in the subarachnoid space and ventricles. The infection may manifest in the form of a classic triad of symptoms—that is, fever, neck stiffness and an altered mental status. However, young children often exhibit nonspecific symptoms, sometimes only manifesting as irritability, lethargy or poor eating.[83] The symptoms of increased intracranial pressure (ICP) may appear, as well as focal neurological signs, ataxia and behavioural abnormalities. Seizures are common whereby almost half of the individuals affected by BM exhibit them upon presentation.[84] Sometimes petechial skin lesions develop, but they primarily associate with *Neisseria meningitidis (N. meningitidis)*.[85]

In addition, BM may develop progressively over several days, or it may appear with a quick onset of symptoms leading to sepsis and meningitis within a couple of hours. Associated sepsis is common, although meningitis may also manifest as an isolated

infection. Nevertheless and despite effective antimicrobial treatment and advances in critical care, the disease is life-threatening and often results in disabling sequelae.

## 2.3.2 Epidemiology, risk factors and aetiology

### Epidemiology and risk factors

BM in particular, is an infection of early childhood, with the highest incidence found during the neonatal period, and remaining high until the age of 2 years. Subsequently, the disease affects children U-5 at a higher rate than older children.[86,87] After the age of 5 years, proportional rates for *S. pneumoniae* remain steady, while *N. meningitidis* increases, and *H. influenzae* type b (Hib) meningitis rarely occurs.[87] Childhood conjugate vaccines have contributed to a decreased incidence in recent decades, also in many low-income countries.[88-90] Regardless of this favourable decline, meningitis continues to affect more than 2 million children annually, representing tenth most common cause of mortality amongst U-5 children globally.[5]

Whilst childhood BM is devastating to any child, the incidence, mortality and complication rates remain highest in the poorest regions of the world. Africa faces a disproportionately large burden of global meningitis.[91] This results from the high rate of endemic BM, epidemics of BM and the young age of the population.[92] Furthermore, incidence rates are relatively high across age groups. For instance, in Burkina Faso, *S. pneumoniae* meningitis incidence rates reached 26.9/100 000 for children aged <1 year, 5.4/100 000 for children aged 1 to 4 years and 7.2/100 000 for children aged 5 to 14 years in 2013.[93] n Finland between 2010 and 2014, by contrast, *S. pneumoniae* incidence rates per 100 000 were 2.33 for children under the age of 2 years, 0.33 for children aged 2 to 4 years and 0.05 for children aged 5 to 17 years.[94]

High rates of immunosuppression resulting from various factors add to the risk of BM. Sickle-cell disease is associated with pneumococcal meningitis, while amongst HIV-infected individuals, the odds of acquiring and dying from pneumococcal meningitis increase.[95,96] In addition to a young age and immunosuppression, poor living conditions and exposure to pathogens predispose individuals to BM. With shunts, skull fractures and cochlear implants, the riks of BM is further elevated.[83,97]

### Aetiology

Although a range of bacteria can cause BM, the main causative agents beyond the neonatal period consist of *S. pneumoniae*, Hib and *N. meningitidis.* These bacteria have the potential to invade into the host's blood stream, and resist the host's natural defences, subsequently invading the central nervous system (CNS).[83] *S. pneumoniae,* a Gram-positive diplococci, represents the leading cause of childhood BM globally.[22,90] *S. pneumoniae* is endemic in Africa, and seasonal peaks occur during the dry season.[90]

In comparison, Hib, a Gram-negative coccobacillus with capsular polysaccharide type b, has notably decreased in countries with high vaccination coverage.[88,90,98] In Angola, due to inefficiencies in vaccine implementation, which began in 2006, Hib meningitis continues to occur regularly albeit at a low rate.[99]

Finally, *N. meningitidis,* a Gram-negative diplococci, is endemic in Africa and causes epidemics. In resource-limited settings, Staphylococcus species, Gram-negative enteric basilli, and *Pseudomonas aeruginosa (P. aeruginosa)* also cause BM in children, typically amongst the youngest ones, or amongst those with predisposing comorbidities and conditions.[4,100] Globally, the proportional incidence of BM caused by other pathogens in children U-5 is increasing.[91]

## 2.3.3 Diagnosis and management

A lumbar puncture and laboratory analysis of CSF are crucial for the diagnosis of BM. From the CSF, an analysis of white blood cells (count and differ-

entiation), the glucose and protein concentrations, Gram stain and cultivation should be performed, with the latter serving as the gold standard for diagnosis.[83] Other diagnostic tools include antigen detection with latex agglutination, and polymerase chain reaction (PCR) from CSF, which are especially valuable in cases of treatment preceding lumbar puncture.[83]

Treatment of BM includes systemic broad-spectrum antimicrobials. Beyond the neonatal period, third-generation cephalosporines are recommended.[101] In addition, adjunctive and supportive treatments aim to improve survival and prevent related sequelae.[101] In short, dexamethasone and glycerol have been studied, but are not routinely used in Africa. Furthermore, corticosteroids provide no benefit in low-income countries, while a recent meta-analysis states, that glycerol may carry a beneficial effect on neurological sequelae and deafness.[102,103]

### 2.3.4 Pathogenesis and pathophysiology

Following the neonatal period, the typical meningeal pathogens are acquired from close contacts. These pathogens colonise in the mucosal surfaces of the nasopharynx of carriers and bind to the host epithelial cells. The carriage rates depend on host-related and socioeconomic conditions. For instance, up to 63% of children U-5 in Africa carry *S. pneumoniae*.[104] Viral infection typically preceeds invasion across the host's epithelial structures, facilitated by different adhesion molecules, and in the case of *S. pneumoniae*, the phase variation of the capsule molecules.[105] Once in the blood stream, the complement cascade is activated. The capsulated bacteria causing BM pose innate resistance to antibody-mediated opsonisation and may further penetrate into CNS.[83] Additionally, the bacteria may enter CNS from local infectious foci through contiguous spread.[106]

Bacteria are capable of crossing the blood–brain barrier by interacting with the host receptors in a complex process via inter- and intracellular transcytosis.[107] In CSF space, limited host defence mechanisms allow bacteria to rapidly multiply. In CNS, after pattern recognition receptors, such as Toll-like receptors in microglia and other antigen presenting cells, recognize the bacterial cell wall components, the host inflammatory response is initiated.[105] These cells release proinflammatory cytokines such as tumor necrosis factor-alpha and interleukines. The cytokines further induce the adhesion molecules on the local vascular endothelial cells supporting leukocyte migration into CSF.[107] Both the invaded neutrophils and endothelial cells produce reactive oxygen and nitrogen species, and matrix metalloproteinases causing blood–brain barrier permeability, further leukocyte recruitment and tissue damage.[105,108] Antibiotics cause bacterial lysis, which further increases the inflammation. Subsequently, ICP increases. The cerebral blood flow is further disturbed due to the dysfunction in the brain vessel autoregulation and decrease in systemic perfusion.[107] Consequently, neuronal injury and apoptosis occur.

### 2.3.5 Studies from Africa

A literature search identified prospective studies focusing on or summarizing the outcomes of childhood BM in Africa between 2008 and 2018 (Table 5).[109-116]

Only a limited number of studies were identified, a minority of which consisted of randomised controlled trials.[112,114] Half of the studies focused on diagnostics, the prevalence of causative agents, their serotype distribution and antimicrobial susceptibility patterns.[109,110,113,116] The effect of Hib vaccinations is clearly documented in these studies, with a decreasing prevalence of Hib meningitis over time. Many of the studies lack any reporting of the neurological sequelae and HI; when reported, the use of differing methods to diagnose and classify sequelae hampered comparisons across studies.

**Table 5.** Bacterial meningitis amongst African children and adolescents in prospective studies, 2008 to 2018.

| Reference Country | Country | Study setting | N | Age | Main causative agent | Death, % | Severe neurological sequelae, % | Hearing impairment,% |
|---|---|---|---|---|---|---|---|---|
| Bercion *et al.*, 2008[109] | Central African Republic | E | 417 | 1 day–16 years | *S. pneumoniae* | 39 | n/a | n/a |
| Lagunju *et al.*, 2008[110] | Nigeria | CS | 97 | 2 months–12 years | Hib | 26 | 68[a] | n/a |
| Edmond *et al.*, 2010[111] | Senegal | CS, Survivors | 66 | 1 month–4 years | Hib | n/a | 64[b] | 52[c] |
| Pelkonen *et al.*, 2011[112] | Angola | RCT | 723 | 2 months–13 years | Hib | 38 | 15 | 27[d] |
| Gervaix *et al.*, 2012[113] | Cameroon | CS | 170 | 2 months–12 years | *S. pneumoniae* | 22 | n/a | n/a |
| McCormick *et al.*, 2013[114] | Malawi | Data from 3 RCTs | 1762 | 2 months–5 years | *S. pneumoniae* | 29 | 26 | n/a |
| Karanja *et al.*, 2014[115] | Kenya | CS, Survivors | 83 | 5 months–10 years | *S. pneumoniae* | n/a | n/a | 43[e] |
| Tadesse *et al.*, 2017[116] | Ethiopia | CS | 99 | 0–18 years | n/a | 16 | n/a | n/a |

Literature search performed in October 2018. E, epidemiological study;
RCT, randomised controlled trial; CS, cross-sectional study; N/a, not available.
[a]Defined as significant neurological sequelae
[b]Includes hearing impairment.
[c]>25 dB in the better-hearing ear.
[d]>40 dB in the better-hearing ear.
[e]Mild-to-moderate or severe-to-profound bilateral hearing impairment, no thresholds provided.

## 2.4 Otitis media–associated childhood bacterial meningitis

Bacterial meningitis (BM) normally results from the spread of bacteria from the bloodstream. BM may also directly result from invasion from adjacent sites, such as the middle ear and the mastoid cavity.[106,117] In high-income settings, OM occurs in approximately 25% of *S. pneumoniae* meningitis cases in children and up to 45% of all-cause childhood BM.[117,118] Additionally, OM may co-exist or follow BM.[119]

From OM, bacteria are thought to enter the CSF space via direct extension through dehiscences—either those already existing or acquired dehiscences (e.g., weakened mastoid bone or fractures) via labyrinthitis, or blood circulation.[120] In congenital malformations, openings between the inner ear and the middle ear facilitate pathogen entry from the middle ear to the labyrinth and, subsequently, to the CSF space.[97] Some temporal bones from young children who died due to BM, indicate an otitis aetiology.[121,122] In early childhood, temporal bone studies illustrate that the middle ear exhibits mesenchymal connections that associate with a high rate of OM and open up a possible route for the haematogenous spread from OM to the subarachnoidal space.[120] Figure 2 provides an illustration of the anatomical structures of the middle ear in proximity to CNS.

In the antimicrobial era, OM-related complications have become rare. Thus epidemiological calculations are based on retrospective series. In resource-limited settings BM was estimated to occur in 0.1%–0.2% of otitis media, of which majority is chronic.[123-125] More recently, an incidence of 0.47% has been established for all ICCs.[66] However, children represent a minority in these studies and the values may not be comparable for poorest countries. In a recent retrospective study from India over a 15-year period in a tertiary centre, researchers traced a declining number of ICCs due to CSOM, where BM accounted for one-quarter of all ICCs in children.[126] Cholesteatoma is a typical comorbidity in patients with ICCs.[127]

In Malawi, 46% of children with pneumococcal meningitis presented with concomitant OM.[128] However, to our knowledge, no detailed analysis with concomitant OM on the presentation, course and outcome of BM is available from resource-limited settings. As certain predisposing conditions are important riskfactors for the disease outcomes, a concomitant or predisposing focus of infection may additionally affect illness outcomes.[117,129]

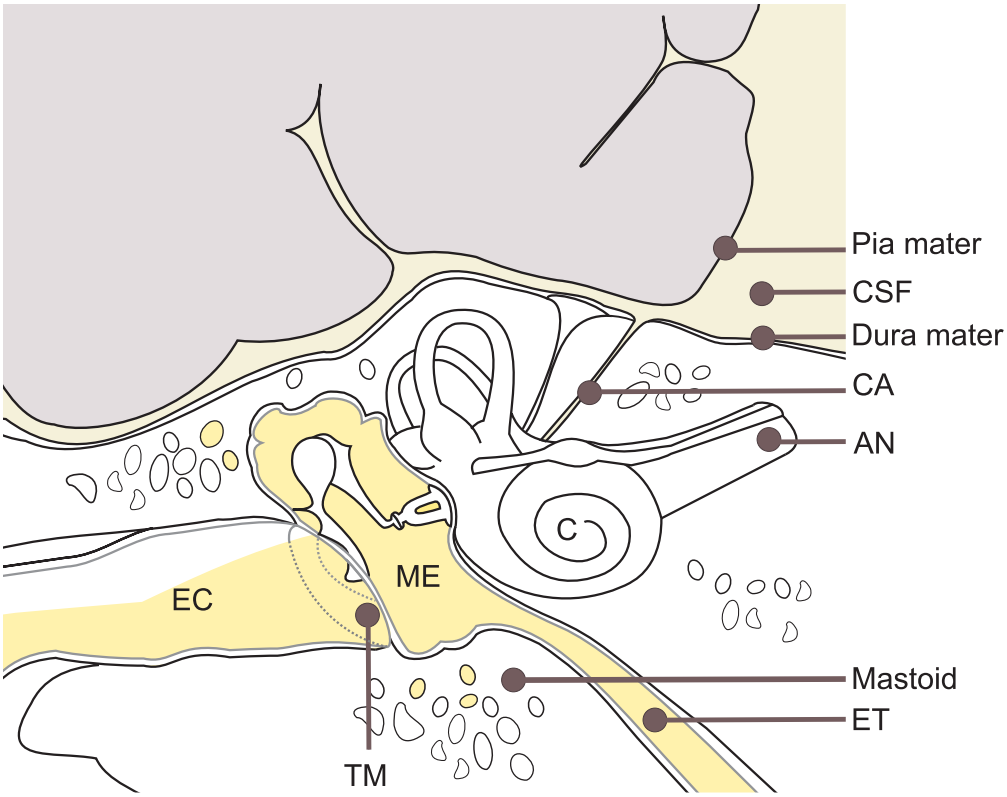
## 2.5 The consequences of childhood bacterial meningitis

A spectrum of sequelae may follow childhood BM. The sequelae can be classified as severe, thus producing significant disability or less severe, resulting in difficulty completing everyday activities and impairing one's quality of life.[132] In a global and regional meta-analysis of BM, HI emerged as the most common severe sequelae reported in up to 34% of cases.[132] Other severe sequelae consisted of seizures (13%), motor deficits (12%), cognitive impairment (9%), hydrocephalus (7%) and visual disturbances (6%).[132] In addition, a mixture of sequelae are common and may present as complex syndromes (see Figure 3).[111]

### 2.5.1 Hearing impairment

Amongst survivors of childhood BM, 10% to 34% develop some degree of HI.[132] BM remains an important cause of acquired HI in children since 31% of all childhood HI result from BM and other infectious related causes.[133] The risk of HI is a consequence of illness-, host- and treatment-related factors.[134] However, all underlying mechanisms and risk factors are not fully understood.

Furthermore, BM is associated with partial or complete, unilateral or bilateral sensorineural HI,



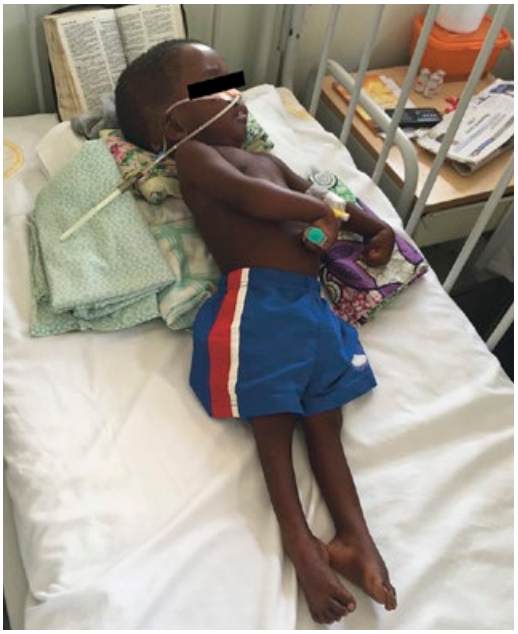



**Figure 2.** Infection of the middle ear (ME) with otorrhoea draining through a perforated tympanic membrane (TM) to the ear canal (EC). The cerebrospinal fluid (CSF) appears turbid, indicating bacterial meningitis.v C, cochlea; CA, cochlear aqueduct; AN, auditory nerve; ET, eustachian tube. Adapted from previously published data.[130,131]

**Figure 3.** An 18-month-old survivor of pneumococcal meningitis in Luanda, Angola diagnosed with tetraparesis, facial nerve paresis, blindness, hearing impairment, seizures and severe mental retardation. Photo: Mariia Karppinen

typically occurring early in the disease.[135] Since HI can occur as an isolated event, independent of neurological sequelae, the underlying mechanisms of HI and neurological sequelae are thought to differ somewhat.[136,137]

#### 2.5.1.1 The pathophysiology and aetiology of hearing impairment

Labyrinthitis and associated HI following BM are well-documented, beginning from research in the nineteenth century.[138] During the early twentieth century, the routes of spread of infection from the meninges to the inner ear via the cochlear aqueduct, the internal auditory canal and the vasculature were established.[138] Histopathological studies show cochlear damage, bacteria and leukocyte infiltration in the cochlea and vestibular organs. Based on a meta-analysis, the median risk of bilateral HI at the >26 dB level is highest for *S. pneumoniae* with a 9.9%, followed by Hib with a 4.5% and *N. meningitidis* with a 4.1%.[132]

In animal studies, the patent cochlear aqueduct represents the primary pathway for infection to enter to the labyrinth. The inflammatory infiltrates fill the perilymphatic space of the scala tympani in the basal turn of the cochlea, and result in gradual damage along the base to the apex axis.[139] Oxidative stress disrupts the blood–labyrinth barrier, which, in the acute phase, correlates with the severity of HI.[119,140] At the cochlear level, bacterial toxins and inflammatory reaction products, such as reactive oxygen species and cytokines, specifically tumor necrosis factor-alpha, damage the hair cells.[141] The outer hair cells show an increased vulnerability.[142] Spiral ganglion neuron loss subsequently occurs in the following weeks.[119] Both the severity of infection and inflammation correlate with the level of HI.[142] After infection, the connective tissue obliterates the perilymphatic spaces, and fibrosis and ossification may follow. Long-term HI is likely caused by hair cell and spiral ganglion neuronal damage as well as labyrinthitis ossificans.[119,143] To a small degree, retrocochlear HI following BM has been decribed in children.[144]

### 2.5.2 Neurological sequelae

Neurological sequelae typically develop during the acute illness phase, but may present as transient (85%) or persistent (15%) deficits following discharge.[137]

Symptoms likely to relieve during the first year post-discharge include ataxia, cranial-nerve deficits, extensor plantar reflexes and brisk reflexes, while persistent symptoms consist of severe mental retardation, tetraparesis, and blindness.[137] Hemiparesis often, although not always, improves.[137] Severe cognitive impairment, defined as a score of <70 intelligent quotient, is frequently unreported upon hospital discharge and may be underestimated in clinical trials.[132] In Bangladesh, significant impairment in mental development was diagnosed in 41% of those followed for 6 to 24 months post-discharge.[145] The risk of at least one severe sequela is highest amongst children U-5 and in the African region compared to other parts of the world.[132] In Africa, about one fifth of BM survivors develop sequelae prior to discharge.[4]

#### 2.5.2.1 The pathophysiology and aetiology of neurological injury

The substances released and immune-mediated host reactions ultimately contribute to the breakdown of the blood–brain barrier, oedema, increased ICP, altered homeostasis and physiology of the brain, finally resulting in neuronal damage, cellular apoptosis and variety of brain injury. Pus-filled ventricles and gross lesions in the brain and meninges represent frequent autopsy findings.[146] Histopathological examinations in humans reveal intravascular coagulation, vasculitis, perivascular infiltrates, ischemic, hemorrhagic and necrotic lesions, axonal injury, apoptosis in the hippocampus, and synaptic loss in the neocortex.[105,107,147] Imaging shows ischemic changes in children left with permanent neurological sequelae[137,148] In the presence of infarctions, multiple lesions commonly occur in the hemispheres, thalamus, basal ganglia and pontine, and associate

with hydrocephalus.[148] Clinically diagnosed focal neurological deficits are commonly reported from large clinical trials and in Malawi they most often associated with pneumococcal aetiology.[84]

Animal studies reveal a proportional correlation between CSF inflammation, mortality and morbidity.[105] Bacterial toxins and excessive host inlammation, specifically the neutrophil activity with secreted proteases, as well as nitric and oxygen species, are thought to contribute to tissue damage. Furthermore, an impaired consciousness is concidered an indicator of neuronal damage.[114]

### 2.5.3 Mortality

In Africa, case-fatality rates remain high, whereby 30% to 50% of children die before hospital discharge.[3,4,93] In addition, 10% of survivors die in the few months and years following discharge.[92] Amongst all BM-related deaths in Africa, the majority occur in children.[92] In the African region, death due to meningitis or encephalitis in children aged 1 to 59 months has slowly decreased from 4.4% to 3.2% between 2006 and 2016.[149] In Angola, 1.1 out of 1000 live births die from meningitis or encephalitis.[150] However, in Africa, these rates likely remain underestimated since many deaths go unrecorded or are interpreted as cerebral malaria. The case-fatality rate – that is, the proportion of individuals dying from the disease – is highest for pneumococcal meningitis (35%) followed by Hib meningitis (23%) and menincococcal meningitis (4%).[132] However, recent estimates from 2016 state that in children U-5, *N. meningitidis* and meningitis caused by other pathogens were responsible for most BM deaths globally..[91]

### 2.5.4 Other consequences

Neuropsychological performance and executive functions represent domains often underevaluated following BM in resource-poor settings. Difficulties in these functions may substantially impact behaviour, education, social relationships and the quality of life amongst survivors. In Senegal, survivors of BM required more additional assistance from parents with toileting, dressing and other activities of daily living in comparison to controls.[111] In Kenya, school-aged survivors of *S. pneumoniae* meningitis experienced problems completing tasks requiring visual and auditory attention.[151] Acute disease creates great financial burdens to families, since the mean discounted lifetime costs due to BM sequelae in Senegal reached approximately US$ 35 000 per child.[152] At the time of the study, none of the families could pay for treatment and rehabilitations for the sequelae.[152]

## 2.6 Predictors of adverse disease outcomes in childhood bacterial meningitis

Predicting BM-associated outcomes may help in allocating resources and planning rehabilitation for those most in need of care. The severity of the infection is closely related to its adverse outcomes. Several models have been developed to predict the prognosis of childhood BM in terms of death, severe neurological sequelae and auditory outcomes. However, since the circumstances, conditions upon presentation and outcomes largely differ between low- and high-income countries, generalisability depends upon the specific setting. From Africa, studies are scarce.[153]

### 2.6.1 Predictors of hearing impairment

A systematic review identified a history of symptoms >48 hours, a low CSF glucose, male gender,

the absence of petechiae and *S. pneumoniae* aetiology as risk factors for HI.[154] However, only one out of four studies originated in resource-poor settings, where the risk factors somewhat differed from those in high-income settings. In Africa, HI associated with a high fever >38.7°C, coma, convulsions, associated cranial nerve neuropathy or neurological sequelae, a low blood leukocyte count, positive CSF Gram-stain or culture and a high CSF protein level.[115,155] In Angola amongst a subset of a BM cohort, predictors of post-discharge HI were evaluated.[156] However, due to a loss of follow-up, only 124 children were studied. Amongst these survivors, focal seizures emerged as the strongest predictor of HI.[156]

The power of these former studies from low-income settings may have been limited to analysing the role of bacterial aetiology in further detail. In addition, the aetiology may play a role if milder HI were taken into account.

### 2.6.2 Predictors of severe neurological sequelae

Symptoms indicating severe disease correspond to neurological sequelae, which in Africa are the following: a history of symptoms lasting more than three days, impaired consciousness or coma and convulsions during hospitalisation.[114,157] In addition, a young age of less than 24 months, focal nerve deficits, abnormal posturing and muscle tone have been associated with neurological sequelae.[114,158] *Salmonella* spp. and *S. pneumoniae* increased, while *N. meningitidis* decreased the odds of permanent sequelae in Malawi.[114] In other parts of the world, malnutrition, low blood leukocytosis, a high CSF protein level and symptoms lasting more than two days carry a risk for adverse neurological outcome.[159,160]

### 2.6.3 Predictors of death

Factors relating to the severity of disease also appear to predict death.[154] These include coma or impaired consciousness, convulsions, peripheral circulatory failure and severe respiratory distress.[154] In addition to these factors, in Africa persistent convulsions during hospitalization, the appearance of purulent or turbid CSF, a positive CSF culture, a high CSF protein level and a low CSF glucose level associate with mortality.[116,157,161] In Malawi, HIV positivity, severe malnutrition and *Salmonella* spp. aetiology have also been identified.[114] In univariate analyses, *S. pneumoniae* carried a higher and *N. meningitidis* lower odds of death.[114] Data from elsewhere suggest malnutrition increases the odds of dying.[160]

## 2.7 Auditory brainstem response

Auditory brainstem responses (ABRs) are electric potentials resulting from the summated activity of a large population of neurons in the auditory pathway firing in synchrony after introducing sound to the ear. ABR is used to estimate hearing sensitivity and the integrity of the ascending auditory system.[162] In addition, ABR serves to study the neural development of infants in conditions that are affecting the auditory pathway in brain stem.[163] ABR test is non-invasive, objective, and unaffected by anaesthetics or anticonvulsants, and thus particularly suitable for young or sick children.

The potentials are recorded using electrodes placed on the scalp. Background noise and biological electric activity such as EEG-waves are filtered out using amplification and averaging techniques. By averaging more than one-thousand recordings, the small electric potentials occurring during 10 ms after stimuli can be distinguished. The waveform components are labelled I to VII, of which the most

reproducible and detectable are waves I, III and V (Figure 4).[164]

The waveforms reflect the neural activity at different levels of the auditory pathway from the auditory nerve to the brain stem (Figure 5). The dendritic cells in the VIII cranial nerve innervating the inner and outer hair cells of the cochlea, generate the wave I.[165] Wave II is generated proximally in the VIII cranial nerve. Wave III originates from the cochlear nuclei in the brain stem, while wave IV is generated in the superior olivary complex.[165] Wave V originates in the lateral lemniscus and inferior colliculus.[165] Subsequent waves VI and VII likely originate in the inferior colliculus.[165] Waves II, VI and VII are typically too variable, while wave IV may merge with wave V. The maturation of a child during early life is reflected in the ABR. The latencies and interpeak latencies (IPLs) lengthen during the early life and reach adult values at approximately 18 to 24 months of age. Subsequently ABR changes very little.[166]

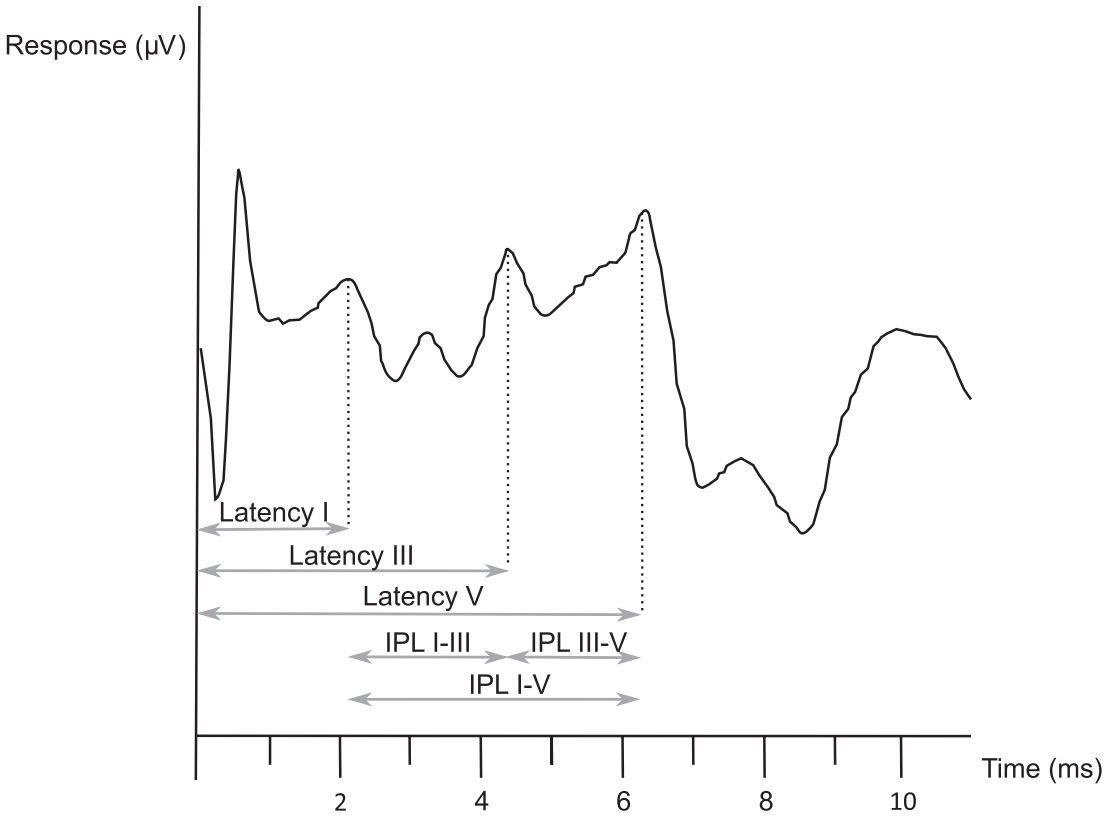



**Figure 4.** A standard auditory brainstem response of a normal-hearing individual (at 63-dB stimulation level) to click-stimulus. Latencies I, III and V and interpeak latencies I–III, III–V and I–V are marked. Adapted from previously published data.[167]

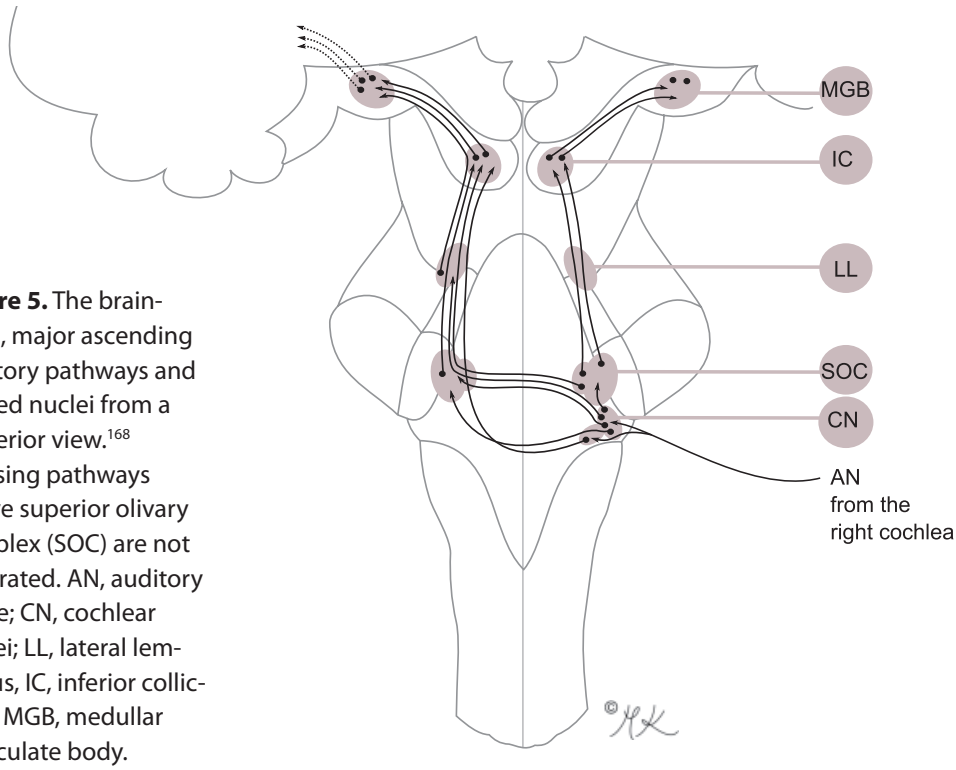



**Figure 5.** The brainstem, major ascending auditory pathways and related nuclei from a posterior view.[168] Crossing pathways above superior olivary complex (SOC) are not illustrated. AN, auditory nerve; CN, cochlear nuclei; LL, lateral lemniscus, IC, inferior colliculus; MGB, medullar geniculate body.

### 2.7.1 Auditory brainstem response in hearing evaluation

In audiology, ABR serves as an important tool in neonatal hearing screening and in assessing hearing amongst those unable to participate in traditional hearing evaluations, such as young and disabled patients. ABR provides an estimation of the hearing threshold that correlates to behavioural thresholds.[169] Patients are tested in a comfortable position, with their neck muscles relaxed since muscle activity causes biological noise producing an unfavourable signal-to-noise ratio. Natural sleep is encouraged.

In click ABR, the click stimulus is a sound pulse comprised of many frequencies, typically 2000 to 4000 Hz. The rate of clicks varies from 10 to 50 clicks per second. In the recording, 1000 to 2000 signals are averaged. Whilst stimulating one ear, the other is masked with a lower intensity. The stimulus intensity is decreased until wave V disappears; the lowest intensity level producing a repeatable wave V indicates the estimated hearing level.

### 2.7.2 Other applications of auditory brainstem response and findings from central nervous system infections

ABRs may provide prognostic information amongst comatosed patients. The stability of the recording associates with survival[170] and the absence of typical waveforms provides a relatively high prognostic accuracy of an unfavorable outcome.[171] The clinical use of ABRs nevertheless remains low and limited to special circumstances in high-income settings.[172,173]

In newborns with hypoxic-ischemic encephalopathy, a severely abnormal ABR with distorted or abolished patterns predicts an ominous outcome.[174,175] In small series examining CNS infections, ABR alterations correlated with death[176] and brainstem lesions.[177] Since ABR is noninvasive, relatively easy to perform, and successfully introduced in Luanda,[178] we rationalised analysing the usefulness of ABR in relation to clinical outcomes.

Changes to ABR during CNS infections have been described in the literature. These changes include prolongation of latencies and IPLs in comparison to normative data or healthy controls in bacterial and tuberculous meningitis.[176,179-181] A study on viral encephalitis noted a decerase in the V/I ratio of latencies.[177] A delay of latencies was also described in the absence of a concomitant ABR-threshold elevation.[179]

# 3. Aims of the study

The specific aims of this study were as follows:

I To describe the aetiological agents, their change over time and the antibiotic susceptibility patterns of otorrhoea and to compare the findings with data obtained from a literature review on otorrhoea and chronic suppurative otitis media in Africa.

II To assess the occurrence and effect of associated otorrhoea and otitis media on the presentation, progression and outcome of bacterial meningitis.

III To assess the effect of the bacterial aetiology and patient age on hearing impairment in bacterial meningitis.

IV To assess the prognostic value and changes in auditory brainstem response in relation to the mortality and severe neurological complications in bacterial meningitis.

This study primarily focused on data collected amongst children in Angola.

# 4. Patients, materials and methods

## 4.1 Study location

This study consists of patients from the Children's Hospital of Luanda, Angola. The hospital is a public university teaching hospital and tertiary referral centre providing services for children ≤15 years of age in the Angolan capital city Luanda. The estimated catchment population is 1.3 million children based on WHO population estimates.[8] Each day, the families of approximately 300 children seek consultation at the emergency department, most without a referral. Since there is only one public ear, nose and throat (ENT) unit in Luanda, most children with ear-related problems are initially evaluated and treated at the Children's Hospital. The neuro-infectious disease ward cares for patients suffering from BM and other CNS infections.

## 4.2 Patients and study design

In this doctoral thesis study, we included children who had an episode of otorrhoea and who were sampled for ear discharge between 2008 and 2015 (n = 654), who were treated for bacterial meningitis between 2005 and 2008 (a subset of n = 723) (Figure 6),[112] and who participated as voluntary controls for ABR recording during the same study period (n = 101) at the Children's Hospital of Luanda.

We collected data in the otorrhoea and review study (study I) retrospectively, whilst the meningitis studies (studies II–IV) consisted of prospective data collection. Study I included a literature review on OM in African children between 1997 and 2017.

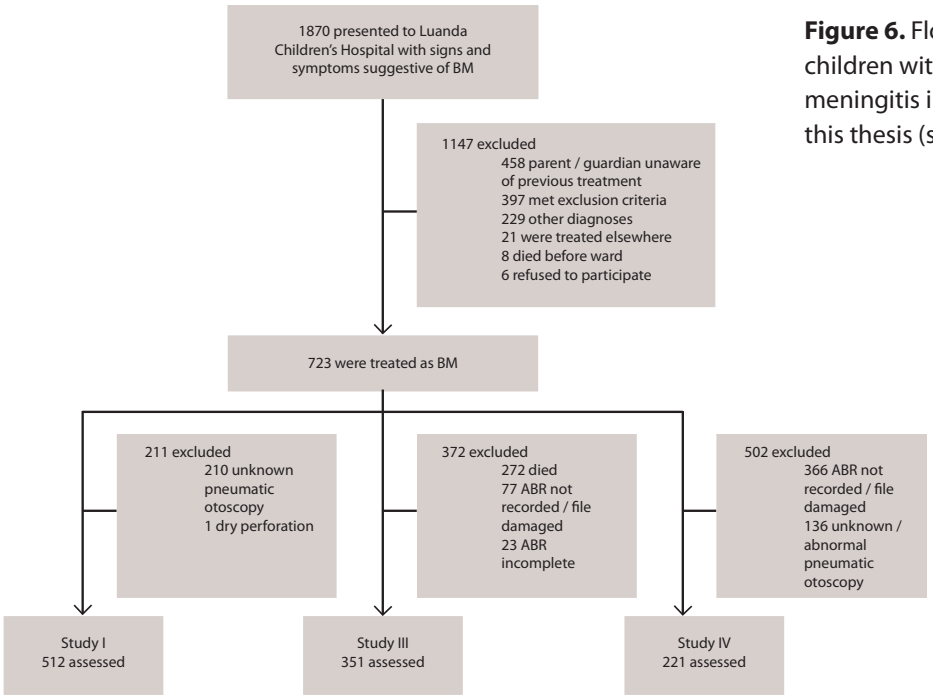



**Figure 6.** Flow of children with bacterial meningitis included in this thesis (studies II–IV).

### 4.2.1 Study and literature review of otorrhoea (study I)

This descriptive, observational, laboratory-based study combines a literature review. The study consisted of 654 children, all under the age of 15 years, of whom 678 otorrhoea samples were taken between 2008 and 2015. The children were both in- and outpatients of the hospital. The causative agents, their change over time and the antimicrobial susceptibility were described.

We also conducted a literature review of OM studies carried out amongst African children between 1997 and July of 2017. We searched Medline, African Journals OnLine, African Index Medicus and Cochrane databases for otitis media studies consisting of at least 30 patients. In addition, published papers and reviews were manually searched for citations. We included studies describing the prevalence or aetiological agents or both in children ≤15 years with CSOM or otorrhoea, regardless of language of publication. In addition, we included publications evaluating the burden of paediatric OM in different healthcare settings.

### 4.2.2 Meningitis studies (studies II–IV)

The three meningitis studies (studies II–IV) are observational, descriptive studies. Study IV further includes a comparative component. Each study consists of a subgroup of 723 children, aged 2 months to 13 years, with presumptive BM treated in Children's Hospital of Luanda as part of a prospective BM treatment trial that took place between 18 July 2005, and 26 June 2008 (Figure 6).[112] The original trial compared different methods of antibiotic delivery with and without adjuvant therapy, which lies beyond the scope of this thesis study. The data collected served as a basis for secondary analyses and study questions.

## 4.3 Clinical and laboratory procedures

### 4.3.1 Study of otorrhoea (study I)

An attending physician referred children with otorrhoea for laboratory sampling. Laboratory technicians from the hospital microbiology laboratory swabbed a sample from the child's draining ear. Ear pus was cultured on blood and chocolate agar plates and incubated in a 3% to 4% $CO_2$ atmosphere at a suitable temperature for 24 to 48 hours. The bacteria were then identified using Gram staining and standard phenotypic bacteriological methods. Antimicrobial susceptibility was tested with commercially available discs using standards from The Clinical & Laboratory Standards Institute.[182] The main isolate and its susceptibility were noted in the laboratory request forms and registered in the laboratory database. Discharging ears were treated according to the hospital guidelines.

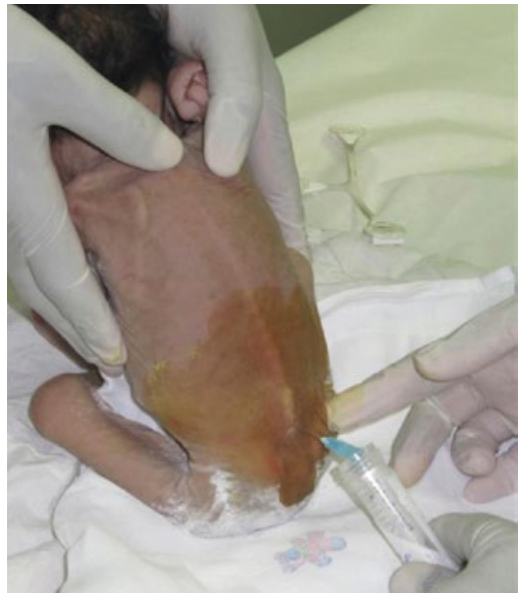


**Figure 7.** Performing a spinal tap in Luanda, Angola, for a child with sauspected bacterial meningitis. Photo: Tuula Pelkonen.

### 4.3.2 Meningitis studies (studies II–IV)

Consecutive children presenting with impaired consciousness, seizures and meningeal signs had a lumbar puncture collected by the attending physician in the hospital's emergency room (Figure 7). When CSF appeared cloudy, proved positive in Gram-stain or latex agglutination test, or resulted in ≥50 x $10^6$/L leukocytes, the child was assessed for eligibility in the study. Those with trauma, an intracranial shunt, previous neurological abnormality, immunosuppression not resulting from HIV or sickle-cell disease, active tuberculosis, a previous known HI or who received > 1 parenteral dose of antimicrobials were excluded from the study.

After obtaining a signed informed consent from a parent or guardian, data collection began. An interview detailing demographic characteristics and previous symptoms was carried out. On the ward, children were monitored by study nurses, who collected data daily using separate study forms. Study physicians working on the ward examined each patient daily. A hearing evaluation and neurological evaluation were carried out at predefined timepoints. The principal investigator, a paediatrician, monitored and supervised the study throughout the project.

All children were treated following the WHO guidelines,[183] with cefotaxime 250 mg/kg per 24 hours for at least 7 days with difference in antibiotic delivery during the first 24 hours: either continuous infusion or boluses and adjuvant paracetamol or a placebo for 48 hours. All children received glycerol and, if needed, ibuprofen, correction for hypovolemia and treatment for anaemia, hypoglycaemia, seizures, and malaria.

#### 4.3.2.1 Case definitions

BM was confirmed in a child presenting with compatible symptoms and signs when the CSF culture or PCR proved positive; a blood culture proved positive; or at least two of the following were fulfilled: CSF leukocytes ≥100 x $10^6$/L, positive Gram stain, positive latex agglutination test, or serum CRP ≥40 mg/L.

An OM diagnosis was based on pneumatic otoscopy revealing either a suppurative secretion originating from the middle ear (otorrhoea) or middle-ear effusion combined with at least two of the following signs: decreased or absent mobility, bulging position, or an abnormal color or opacity of the TM.

#### 4.3.2.2 Laboratory analyses

Following a spinal tap, CSF leukocyte and erythrocyte counts were measured, and CSF was Gram stained and cultured in the hospital laboratory. Upon a negative result, latex agglutination tests were used to detect antigens of Hib, *S. pneumoniae* and *N. meningitidis*. Remaining CSF was stored in tubes and placed in a freezer (-70°C) before transportation for real-time PCR to Portugal or Finland.

Basic laboratory samples were drawn upon admission and in the ward. Those used to characterise or compare patients in the studies II–IV consisted of the following: CSF leukocyte and glucose counts, blood haemoglobin, leukocytes, sedimentation rate, CRP, malaria thick film, HIV serology and Mantoux positivity. These analyses were performed locally following standard laboratory procedures.

#### 4.3.2.3 Neurological evaluation

Neurology was examined upon admission, on the ward, at discharge and during scheduled follow-up visits by study physicians.

#### 4.3.2.4 Auditory brainstem response protocol

A 1-channel ABR recording (Bera MADSEN Octavus® system v.2.001, Windows XP/2000 compatible; GN Otometrics, Taastrup, Denmark) was performed on patients within 24 h of admission, again on day 7, and during scheduled follow-up visits.

Before initiating the trial, study nurses received detailed training on how to perform the ABR recording. No medical sedation was used, but ABR was performed bedside during coma or natural sleep (Figure 8) or in a comfortable position, with child lying in his or her parent's lap. If children were

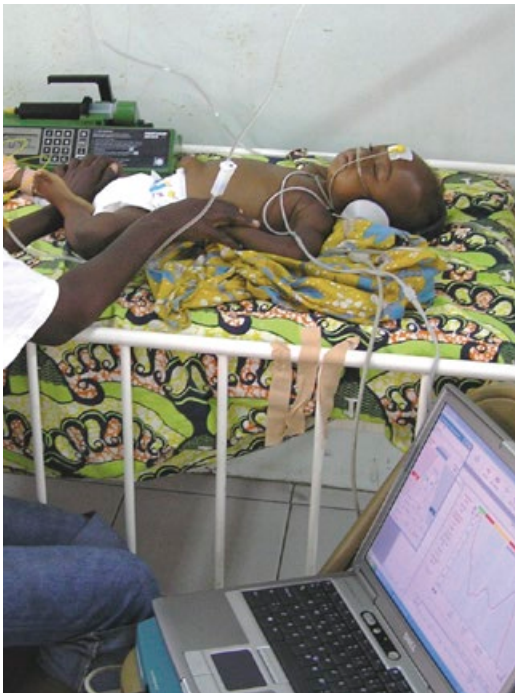


**Figure 8.** Recording an auditory brainstem response from an unconscious child being treated for childhood bacterial meningitis. Photo: Tuula Pelkonen.

conscious prior to the recording, they were encouraged to close their eyes, while young children were soothed by breastfeeding them, thus allowing them to calm down and fall asleep.

After cleaning the skin, electrodes were positioned on the mastoids and high forehead. Broadband click stimuli were delivered to the ear examined using headphones and intensities of 80, 60 and 40 dB, while the contralateral side received masking with a 20-dB lower stimuli. The potential difference between the mastoid of stimulated ear and vertex was recorded (Figure 9).

In all ABR evaluations, evaluators were blinded to the individual outcome of each patient. Expert ENT physician from the Audiology Centre of Helsinki interpreted the ABRs in Finland in terms of the ABR thresholds (study III). The authors of study IV further categorised the responses using visual analysis after training for ABR evaluation (study IV). We used a simple and pragmatic categorisation based on robust changes applicable in clinical settings—that is, those with a bilateral absence and those with wave forms present from at least either side. Expert audiologist and neurophysiologists were consulted if

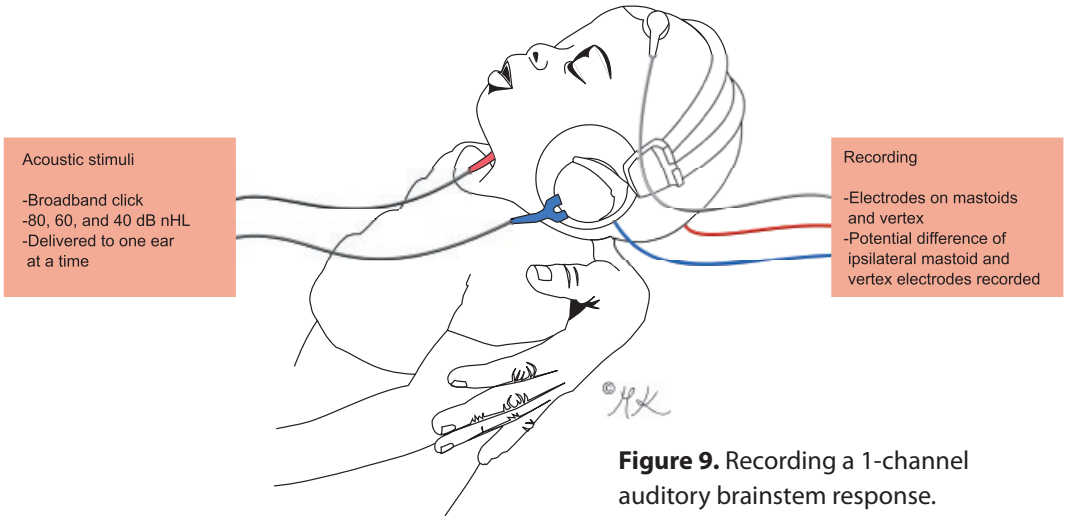



**Figure 9.** Recording a 1-channel auditory brainstem response.

necessary. The peak latencies of waves I, III, and V were measured when they were identifiable from the traces of 80-dB clicks and IPLs I to III (I–III), III to V (III–V) and I to V (I–V) were calculated. In the case of asymmetries in latencies and estimated hearing levels, the better ear (lower estimated threshold, fewer delayed latencies) was chosen for analysis.

Voluntary children (n = 101), most outpatients of the hospital and some accompanying family members participated as controls undergoing ABR recording. Those with abnormal findings in pneumatic otoscopy, history of HI or BM were excluded. ABR was successfully recorded for 64 children, for whom latency and IPL parameters were obtained.

## 4.4 Description of variables and outcome measures (studies II–IV)

The variables used to describe the BM patients in each study consisted of measures of demographic characteristics, antibiotic use prior to admission, symptoms and signs of acute illness before and during admission, on the ward, at discharge, and during follow-up visits as well as clinical parameters and additional treatments and diagnosis.

A lack of home telephone indicated a low socioeconomic position of the families. Those children who upon admission had a weight-for-age <–2 SDs of the WHO reference values and additionally showed severe dyspnea, were defined as presenting in a poor general condition. The Glascow Coma Scale (GCS) served to quantify consciousness—that is, scores below 15 were considered altered and a score of less than 7 was defined as a coma. Seizures and focal neurological signs were also recorded. Furthermore, additional infectious focus, other than BM and OM such as pneumonia were diagnosed during a hospital stay. Second-line antimicrobials and treatment for malaria and tuberculosis were also noted. In ABR, the absence of a response was defined as no replicable V wave in superimposed tracings at an 80-dB stimulus level bilaterally. The delay of latencies and IPLs of ABR were defined as a deviation of > +2 standard deviations (SDs) of age-appropriate control at an 80-dB stimulus level.[176,181]

The primary outcome measures used in the meningitis studies (studies II–IV) consisted of the following: death and death combined with complicated clinical course (study II); hearing impairment in the better hearing ear or either ear amongst survivors, and a hearing impairment of all ears pooled together, prior to the discharge (study III); death and death combined to severe neurological sequelae, referred in the text also as a poor outcome (study IV). Table 6 summarises the main variables and outcome measures.

**Death** rates were based on mortality during a hospital stay after inclusion in the study and before hospital discharge.

**A complicated clinical course** was defined as having focal convulsions or focal neurological symptoms, prolonged convulsions after the third day of the treatment or an additional infection other than OM.

**Severe neurological sequelae** consisted of blindness, tetraplegia, severe psychomotor retardation or hydrocephalus upon discharge. Any neurological sequelae also involved hemiparesis, monoparesis, any psychomotor retardation or ataxia.

**Hearing impairment** was defined as an elevated ABR threshold (>40 dB) in the better-hearing ear or either ear in children, or in a group of all ears. The estimated hearing threshold of each ear was defined as the lowest stimulus level producing a detectable ABR (V wave). We differentiated between four ABR thresholds: 40 dB, 60 dB, 80 dB and >80 dB. Thus, the estimated hearing thresholds indicated normal hearing, a moderate-to-severe HI, and severe HI, respectively. An absent response at all three stimulus levels was considered as an ABR-threshold >80 dB, indicating profound HI or, more precisely, deafness.

**Table 6.** Main characteristics of the studies of bacterial meningitis included in the thesis.

| | Study II | Study III | Study IV |
|---|---|---|---|
| **Study patients** | Patients with ear status determined upon admission | Survivors with ABR[a] before discharge | Patients with ABR from admission day and a normal ear examination |
| **Main variables/ Subgroups of interest** | Otitis media<br><br>Otorrhoea<br><br>Age (cut-off at 12 months) | *S. pneumoniae*<br><br>Hib<br><br>*N. meningitidis*<br><br>Other bacteria<br><br>Age (cut-off at 12 months) | Absence or presence of latencies<br><br>Delay of latencies and interpeak latencies<br><br>GCS[b] (altered, coma) |
| **Outcome variables** | Death<br><br>Death or complicated clinical course | Hearing impairment in better ear<br><br>Hearing impairment in either ear<br><br>Hearing impairment in all ears | Death<br><br>Death or severe neurological sequelae |

[a]ABR, auditory brainstem response
[b]GCS, Glascow Coma Scale

## 4.5 Statistical analyses

Dichotomous categorical variables were compared using chi-squared test or when not applicable, the Fisher's exact test. With continuous variables, normality of the data was tested with visual inspection. Non-parametric tests were used in case of skewness. We used nonparametric Mann–Whitney *U* test to compare medians, and the parametric Student's t-test to test means. When comparing differences across several groups, contingency tables larger than two-by-two were applied for dichotomous categorical variables and the nonparametric Kruskall–Wallis test for continuous variables. In addition, univariate logistic regression analysis was used to study the association between variables. For a multiple logistic regression analysis, selected variables with a sufficient number of patients and $p < 0.1$ were selected. Confidence intervals (CIs) of 95% were calculated for odds ratios (OR). We considered $p < 0.05$ as statistically significant. Statistical analyses were performed using StatView version 5 for Windows and IBM SPSS statistics 22.0 and 23.0 for MacOS. In addition, we used NCSS 12 (NCSS, LLC, Kaysville, UT, USA).

## 4.6 Ethical considerations

During our January 2017 research visit, we confirmed the institutional ethical approval for study I. The ethics committee approved the original BM study (ISRCTN62824827) after rejecting the use

of corticosteroids as an adjunctive therapy.[112] An amendment covering subsequent studies (studies II–IV) was approved on 21 December 2007. Data collection began after a child's parent or guardian provided their informed consent. An external monitoring board oversaw the prospective trial, whereby all data were sent to the board during the ongoing trial. If the outcomes amongst children had differed significantly, the study would have ceased.

# 5. Results

## 5.1 Characteristics of study patients (studies I–IV)

Table 7 summarises the main characteristics of patients included in the studies I–IV. Study III consists of survivors from BM. The subsets of BM patiens in studies II–IV are presented in Table 8.

**Table 7.** Main characteristics of children included in the studies I–IV

| | Study I | Study II | Study III | Study IV |
|---|---|---|---|---|
| **Diagnosis** | Otorrhoea | Otitis media and bacterial meningitis | Bacterial meningitis | Bacterial meningitis |
| **Patients, n** | 654 | 512 | 351 | 221 |
| **Age in months, median (IQR)** | n/a | 13 (33) | 13 (34) | 20 (42) |
| **Female, %** | 44 | 45 | 48 | 41 |
| **Number of children living in the household, median (IQR)** | n/a | 3 (2) | 3 (2) | 3 (2) |
| **No telephone at home, %** | n/a | 42 | 43 | 45 |

N/a, not available.

**Table 8.** Underlining comorbidities, history of acute illness, and clinical and laboratory findings upon admission in children having bacterial meningitis, included in the studies II–IV.

| | Study II n = 512 | Study III n = 351 | Study IV n = 221 |
|---|---|---|---|
| **Comorbidities** | | | |
| Malnutrition[a], % | 32 | 27 | 33 |
| HIV test positive, n/n (%) | 34/427 (8) | 21/319 (7) | 8/185 (4) |
| SCD screening test positive, n/n (%) | 117/345 (34) | 82/271 (30) | 51/164 (31) |
| Malaria parasites, n/n (%) | 160/498 (32) | 103/341 (30) | 68/214 (32) |
| Mantoux test >10 mm, n/n (%) | 41/338 (12) | 41/287 (14) | 22/150 (15) |
| **History of acute illness** | | | |
| Duration of symptoms before admission in days, median (IQR) | 4 (5) | 4 (4) | 5 (4) |
| Duration of symptoms > 7 days, % | 22 | 19 | 24 |
| Convulsions prior to admission, % | 68 | 62 | 67 |
| Antibiotic use prior to admission, % | 41 | 39 | 35 |
| **Findings on admission** | | | |
| Poor general condition, % | 46 | 42 | 44 |
| Altered consciousness, % | 64 | 54 | 63 |
| Coma, % | 18 | 15 | 19 |
| Focal neurological signs, % | 20 | 21 | 18 |
| Dehydration, % | 16 | 13 | 15 |
| Dyspnoea, % | 43 | 40 | 45 |
| **Laboratory** | | | |
| Blood leukocytes, median /µL (IQR) | 15 (12) | 14 (11) | 14 (10) |
| CRP, median mg/L (IQR) | 149 (94) | 153 (110) | 31 (104) |
| Blood haemoglobin, mean mg/L (SD) | 7.6 (2) | 7.7 (2) | 7.8 (3) |
| CSF leukocytes, median x$10^6$/L (IQR) | 645 (1830) | 790 (2840) | 1033 (2280) |
| CSF glucose, median mg/dL (IQR) | 14 (26) | 14 (29) | 19 (34) |
| Causative agent identified in CSF, n (%)<br>Hib<br>*S. pneumoniae*<br>*N. meningitidis*<br>Other bacteria<br>No causative agent identified in CSF | <br>137 (27)<br>119 (23)<br>33 (6)<br>22 (4)<br>201 (39) | <br>99 (28)<br>82 (23)<br>31 (9)<br>12 (3)<br>127 (36) | <br>54 (24)<br>46 (21)<br>22 (10)<br>8 (4)<br>91 (41) |

CRP, C-reactive protein; CSF, cerebrospinal fluid; SCD, sickle-cell disease.
[a]Diagnosed as weight-for-age <–2 SDs of the WHO reference values.

## 5.2 Discharging ear infections in children in Luanda and Africa (study I)

### 5.2.1 The microbiology of otorrhoea in Luanda

A sample was taken from 678 draining ears. In total, bacteria were isolated from 542 (80%) ears representing 32 different bacteria (Figure 10). The majority of isolates consisted of Gram-negative bacteria (n = 459, 85%), more specifically enteric rods (n = 284, 52%). *Pseudomonas* spp. was the most frequent isolate (n = 158, 29%) followed by *Proteus* spp. (n = 134, 25%) and *Klebsiella* spp. (n = 36, 7%). *S. aureus* emerged as the most common Gram-positive agent (n = 54, 10%) followed by *S. pneumoniae* (n = 21, 4%). Several pathogens, including *Salmonella* spp. (14 children, 3% of isolates), *Shigella* (7 children, 1% of isolates), *Yersinia* spp. (4 children, 1% of isolates) and zoonotic *Edwardsiella tarda* (3 children, 1% of isolates), were identified. The annual isolation rates of bacteria appear in Figure 11.

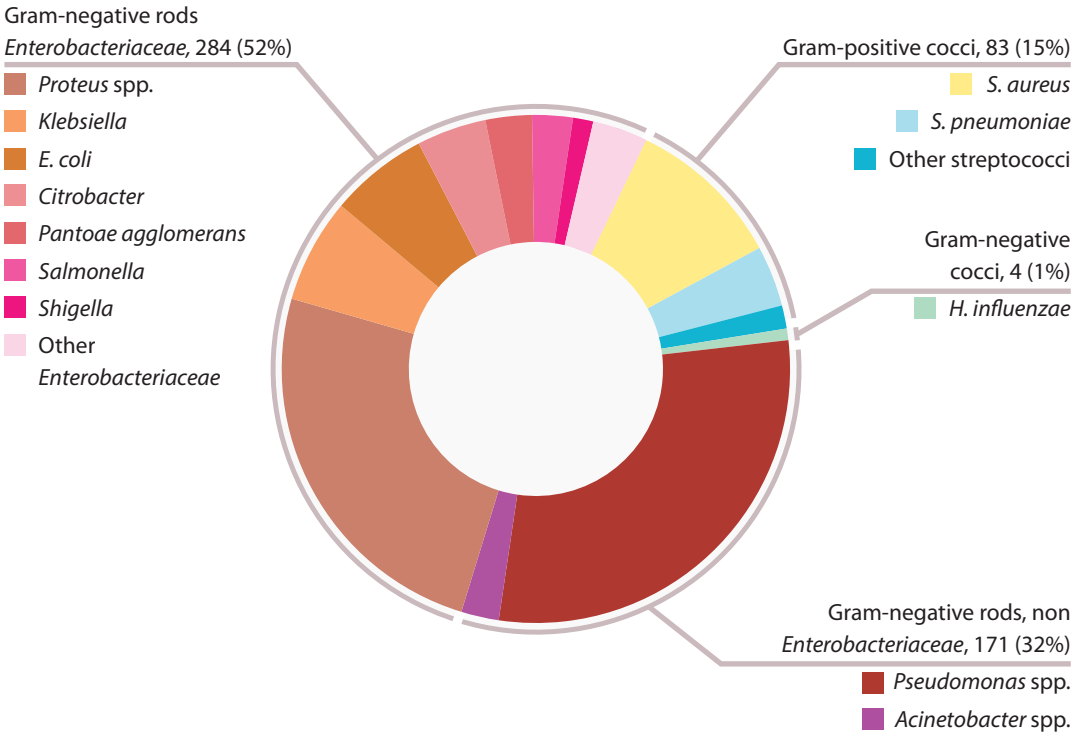
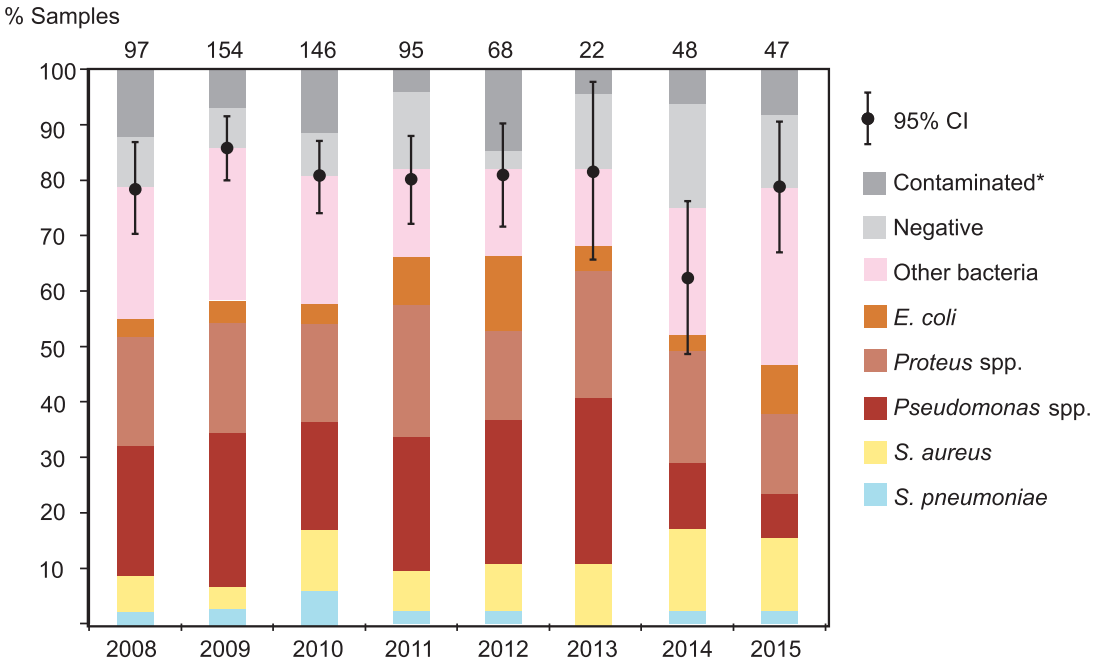



**Figure 10**. Distribution of 542 bacterial isolates cultivated from 678 draining ears from children, Luanda, Angola, 2008–2015.

**Figure 11**. Annual isolation rates of bacteria from 678 otorrhoea samples from children from Luanda, Angola, shown as proportions. The numbers at the top of the columns represent all of the samples drawn. For positive cultivation rates, the 95% CI are shown. *Represents the contaminated growth detected on the cultivation plates, no results.




Susceptibility analyses revealed a 93% quinolone sensitivity to the four most common isolates. However, resistance was noted for *S. aureus*; amongst the isolates tested, 69% (n = 18/26) were Methicillin-resistant *S. aureus (*MRSA). Isolates producing extended-spectrum β-lactamase (ESBL) constituted 14% (n = 16/110) of all *Enterobacteriaceae*.

### 5.2.2 A review of discharging ear infections in African children

Our literature search yielded 160 citations, of which we included 20 in our review. From these, 12 publications provided data on the prevalence and the burden of otorrhoea or CSOM, while 8 publications included microbiological data. Figure 12 shows the studies reporting prevalence and occurrence of CSOM and otorrhoea. These studies are listed in Table 2 of the original publication (study I).[15,28,55,69,76,78,79,184-186] Table 9 presents the aetiological findings reported.[38,39,187-192] In addition, 2 publications evaluated the burden of OM, which accounted for 45% of all new paediatric ENT cases and 5% of all paediatric visits.[193,194] Most studies consisted of hospital-based samples, whereas few population-based studies provided data amongst children. The review revealed a high prevalence for CSOM and otorrhoea amongst African children. Furthermore, an uneven distribution of the origin of studies was noted.

**Figure 12**. Prevalence and occurrence of CSOM and otorrhoea among children ≤15 years of age in Africa, 1997–2017.
The numbers in the map correspond to the references.
*Prevalence classification by WHO[1].

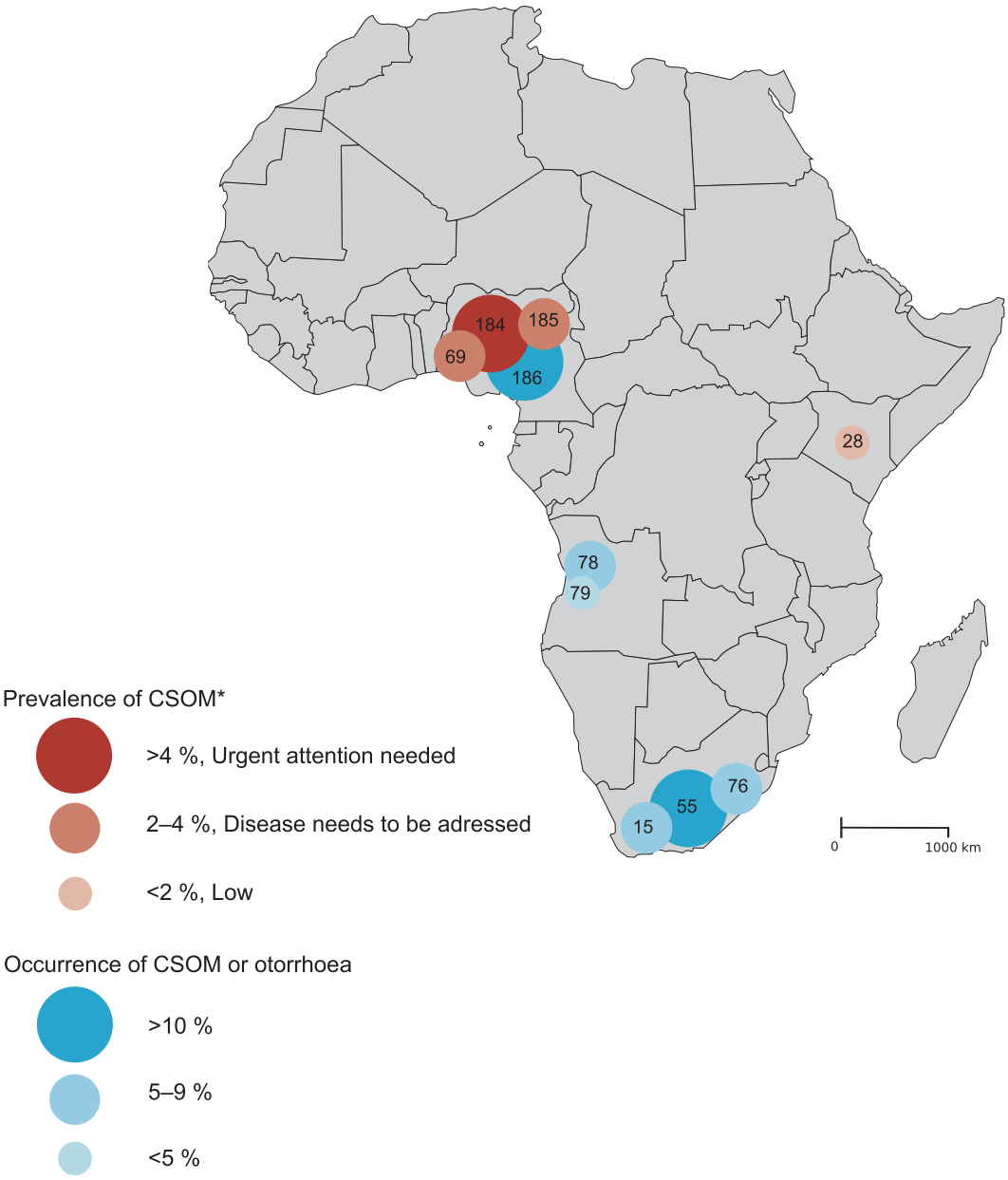


**Table 9.** Primary pathogens in ear pus samples taken from children ≤15 years of age diagnosed with otorrhoea and CSOM in Africa, 1997–2017.

| Reference | Country | N isolates | Main pathogens, of isolates, % |
|---|---|---|---|
| **Otorrhoea** | | | |
| **Abera and Biadeglegne, 2009**[38] | Ethiopia | 256 | *Proteus* spp. 47<br>*S. aureus* 36 |
| **Abera and Kibret, 2011**[187] | Ethiopia | 331 | *Proteus* spp. 31<br>*S. aureus* 23<br>*Pseudomonas* spp. 19 |
| **Bello *et al.*, 2011**[188] | Nigeria | 289[a] | *S. aureus* 40<br>*Proteus* spp. 28<br>*E. coli* 11 |
| **Nnebe-agumadu *et al.*, 2011**[189] | Nigeria | 61 | *Pseudomonas* spp. 57<br>*Klebsiella* 16<br>*Proteus* spp. 11 |
| **Motayo *et al.*, 2012**[190] | Nigeria | 59 | *Pseudomonas* spp. 49<br>*S. aureus* 24<br>*Proteus* spp. 24 |
| **CSOM** | | | |
| **Muleta *et al.*, 2004**[191] | Ethiopia | 99 | *Proteus* spp. 43<br>*S. aureus* 14<br>*P. aeruginosa* 13 |
| **Tiedt *et al.*, 2013**[39] | South Africa | 153 | *Proteus* spp. 22<br>*P. aeruginosa* 14<br>*H. influenzae* 14 |
| **Matundwelo and Mwansasu 2016**[192] | Zambia | 60 | *Staphylococcus* spp. 37<br>*Proteus* spp. 35<br>*Pseudomonas* spp. 15 |

[a]Aetiologies reported among those with antimicrobial susceptibility tested (289 of 301 isolates).

## 5.3 Otorrhoea and otitis media in childhood bacterial meningitis (study II)

In total, 62 from 512 children (12.1%) had OM, diagnosed as either discharge originating from the middle ear (n = 39) or middle-ear effusion as well as the symptoms and signs of an infected middle ear (n = 23).

Our analysis revealed that those with OM or otorrhoea were sicker upon arrival and more often exhibited a complicated or a fatal course of BM (Tables 10 & 11). In children with OM, multiple infectious foci (32%) and dehydration (26%) upon admission were common. Furthermore, otorrhoea associated with being HIV-positive (19% vs. 7%, p = 0.026). OM patients were older compared to non-OM patients, and those with otorrhoea were even older in comparison to non-OM patients (median age of 24 months and 45 months vs. 12 months, respectively, $p < 0.001$).

**Table 10.** Clinical and laboratory findings of children with bacterial meningitis and otitis media (OM) or otorrhoea compared to those with normal middle-ear status (non-OM) in Luanda, Angola.

| | OM n = 62 | Otorrhoea[a] n = 39 | Non-OM n = 450 |
|---|---|---|---|
| **Comorbidities** | | | |
| Malnutrition[b], n (%) | 23 (37) | 15 (38) | 142 (32) |
| HIV test positive, n/n (%) | 6/50 (12) | 6/32 (19)$^{0.026}$ | 28/377 (7) |
| SCD screening test positive, n/n (%) | 12/36 (33) | 8/26 (31) | 105/309 (34) |
| Malaria parasites, n (%) | 20 (32) | 14 (36) | 141 (31) |
| Mantoux test positive (>10 mm), n/n (%) | 8/41 (20) | 6/27 (22) | 33/297 (11) |
| **Findings upon admission** | | | |
| Poor general condition, n (%) | 35 (56) | 23 (59) | 198/449 (44) |
| Dehydration, n (%) | 16 (26)$^{0.040}$ | 8 (21) | 66 (15) |
| Altered level of consciousness, n (%) | 46 (74) | 28 (72) | 281 (62) |
| Focal neurological signs, n (%) | 12 (19) | 6 (15) | 90 (20) |
| Ptosis, oculomotorius paresis, n (%) | 2 (3) | 2 (5)$^{0.020}$ | 4 (1) |
| Additional focus of infection, n (%)<br>Pneumonia, n (%) | 20 (32)$^{0.016}$<br>15 (24)$^{0.048}$ | 14 (36)$^{0.008}$<br>11 (28)$^{0.020}$ | 82 (18)<br>65 (14) |
| **Laboratory** | | | |
| Blood leukocytes, median /µL (IQR) | 14 (12) | 13 (9) | 15 (12) |
| CRP, median mg/L (IQR) | 144 (108) | 130 (92) | 149 (94) |
| Blood haemoglobin, median mg/L (IQR) | 8 (4) | 8 (4) | 8 (2) |
| CSF leukocytes, median x$10^6$/L (IQR) | 450 (1668) | 400 (1500) | 683 (1880) |
| CSF glucose, median mg/dL (IQR) | 13.4 (28) | 13.1 (18) | 15.7 (26) |
| **Causative agent identified in CSF, n (%)** | | | |
| Hib | 14 (23) | 6 (15) | 123 (27) |
| *S. pneumoniae* | 18 (29) | 12 (31) | 101 (22) |
| *N. meningitidis* | 6 (10) | 3 (8) | 27 (6) |
| Other bacteria | 1 (2) | 1 (3) | 21 (5) |
| No causative agent identified in CSF | 23 (37) | 17 (44) | 178 (40) |

Statistical significance ($p < 0.05$) in the superscript. Statistical tests performed included the Mann–Whitney *U* test, the chi-squared test and the Fischer's exact test. CRP, C-reactive protein; CSF, cerebrospinal fluid; SCD, sickle-cell disease.
[a]Otorrhoea group is included in the OM group
[b]Diagnosed as weight-for-age <–2 SDs of the WHO reference values.

**Table 11.** Clinical outcome of children with bacterial meningitis and otitis media (OM) or otorrhoea compared to those with normal middle-ear status (non-OM) in Luanda, Angola.

| Outcome at discharge | OM n = 62 | Otorrhoea[a] n = 39 | Non-OM n = 450 |
|---|---|---|---|
| Death, n (%) | 19 (31) | 13 (33) | 121 (27) |
| Fatal or complicated clinical course, n (%) | 55 (89)$^{0.046}$ | 34 (87) | 349 (78) |
| Days hospitalized before death, median (IQR) | 6 (7) | 6 (7)$^{0.029}$ | 4 (4) |
| Death or severe neurological sequelae, n (%) | 27 (44) | 17 (44) | 164 (36) |
| Severe neurological sequelae, n/n (%) | 9/43 (21) | 4/26 (15) | 43/329 (13) |
| Any neurological sequelae[b], n/n (%) | 23/43 (53) | 14/26 (54) | 168/329 (51) |
| Ataxia, n/n (%) | 21/43 (49) | 13/26 (50) | 159/329 (48) |

Statistical significance ($p < 0.05$) in the superscript. Statistical tests performed included the Mann–Whitney *U* test, the chi-squared test and the Fischer's exact test.
[a]Otorrhoea group is included in the OM group
[b]Other than ataxia.

OM increased the likelihood of death or a complicated clinical course to 2.27 (95% CI 1.004–5.15) in our univariate logistic regression analysis (Table 12), remaining significant in the multivariate analysis [odds ratio (OR) 3.44, 95% CI 1.29–9.16]. Other significant risk factors in our multivariate analyses consisted of an age under 12 months (OR 2.07, 95% CI 1.17–3.67), malnutrition (OR 2.26, 95% CI 1.22–4.19), pre-admission convulsions (OR 2.40, 95% CI 1.41–4.07) and an altered state of consciousness upon admission (OR 1.97, 95% CI 1.17–3.34). *N. meningitidis* associated with fewer fatalities or a less complicated clinical course (OR 0.31, 95% CI 0.13–0.74).

We conducted further analyses in infants (≤12 months, n = 249) and in those older than 12 months (n = 263). Infants presenting with concomitant otorrhoea (n = 8) more frequently lived in families without telephones (88% vs. 48%), had no previous antimicrobials administered (0% vs. 48%), were malnourished (50% vs. 17%), showed lower median blood leukocyte counts (median 4/µL vs. 15/µL) compared to infants with non-OM (n = 229). The OM-infants (n = 20) died later (median day 6 vs. day 3) than non-OM infants.

Amongst children older than 12 months, those with otorrhoea (n = 31) were admitted to hospital later (after 7 days in 33% vs. 16%), required second-line antibiotics (39% vs. 19%) and malaria treatment (84% vs. 66%) more often whilst hospitalised compared to non-OM children (n = 221). Their hospital stays were longer (median 15 days vs. 9 days) and the clinical course was more often fatal or complicated (87% vs. 70%) compared to those without OM.

**Table 12.** Risk factors for death or a complicated clinical course in univariate logistic regression analysis.

| Risk factor | Univariate analysis<br>OR (95% CI)<br>n = 512 | p-value |
|---|---|---|
| **Demographics** | | |
| Age under 12 months | 2.23 (1.43–3.48) | <0.001 |
| No telephone at home | 1.62 (1.04–2.54) | 0.033 |
| **Comorbidities** | | |
| Malnutrition[a] | 1.76 (1.08–2.88) | 0.02 |
| HIV test positive[b] | 1.80 (0.67–4.78) | ns |
| SCD screening test positive[c] | 1.37 (0.79–2.39) | ns |
| **History of acute illness** | | |
| Duration of symptoms >7 days[d] | 2.73 (1.44–5.18) | 0.002 |
| Convulsions prior to admission | 3.70 (2.38–5.75) | <0.001 |
| Antibiotic use prior to admission | 1.88 (1.18–3.02) | 0.009 |
| **Findings on admission** | | |
| Altered level of consciousness | 2.68 (1.73–4.15) | <0.001 |
| Dehydration | 2.80 (1.31–6.01) | 0.008 |
| Dyspnoea | 2.91 (1.80–4.72) | <0.001 |
| Otitis media | 2.27 (1.004–5.15) | 0.049 |
| Otorrhoea | 1.97 (0.75–5.16) | ns |
| **Causative agent in CSF**<br>Hib<br>*S. pneumoniae*<br>*N. meningitidis*<br>Other bacteria<br>No causative agent identified in CSF | <br>1.79 (1.06–3.05)<br>1.67 (0.96–2.90)<br>0.17 (0.08–0.35)<br>2.91 (0.67–12.59)<br>1.21 (0.57–2.58) | <br>0.031<br>ns<br><0.001<br>ns<br>ns |

OR, odds ratio in univariate logistig regression analysis; CI, confidence interval; Ns, not significant; CSF, cerebrospinal fluid; SCD, sickle-cell disease.
[a]Diagnosed as weight-for-age <–2 SDs of the WHO reference values.
[b]n = 427, [c]n = 345, [d]n = 509.

## 5.4 Hearing impairment in childhood bacterial meningitis (study III)

Prior to hospital discharge, a hearing examination was successfully completed on 351 of 451 (78%) survivors and 685 of 902 (76%) ears. A bacterial aetiology was identified in 224 (64%) of these children, consisting of 99 Hib cases (28%), 82 *S. pneumoniae* cases (23%), 31 *N. meningitidis* cases (9%) and 12 other bacteria (3%). In 51 (11%) children, BM was confirmed based on our diagnostic criteria, whilst 76 (17%) children remained classified as suspected BM.

Severe or profound HI was common amongst survivors [65 of 351 (19%)], given that 45 (12.8%) became deaf (ABR threshold >80 dB) and 20 (6%) exhibited an ABR threshold of 80 dB in the better-hearing ear. Furthermore, 30 children (9%) exhibited an ABR threshold of 60 dB. The plots of the ABR thresholds in the better-hearing ear appear in Figure 13. No clear association between HI and any of the aetiological groups emerged. HI of any degree (ABR threshold >40 dB) in reached 34% with Hib, 30% with *S. pneumoniae*, 19% with *N. meningitidis* and 33% with other bacteria.

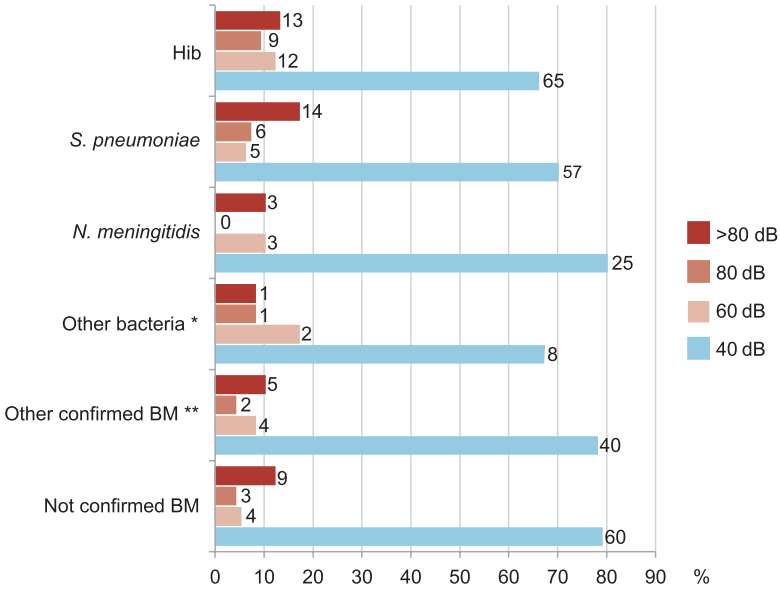



**Figure 13.** Percentages for the better-hearing ear's estimated threshold from 351 survivors of bacterial meningitis (BM) from auditory brainstem response recordings prior to hospital discharge in Luanda, Angola. The absolute numbers of children are shown at the end of each bar.
**Proteus mirabilis* (3), *Salmonella* spp. (3), other streptococcal species (2), *Staphylococcus aureus* (2), *Klebsiella* (1) and unidentified bacteria (1).
**Symptoms and signs of BM with a positive blood culture, leukocyte concentrations in cerebrospinl fluid exceeding 100 x$10^6$/L, a C-reactive protein concentration higher than 381 mmol/L (40 mg/L) or a positive Gram-stain.

When any degree of HI (ABR threshold >40 dB) in either ear in children was analysed, *N. meningitidis* caused less (28% vs. 55%, p = 0.006) and Hib more (59% vs. 45%, p = 0.038) HI compared to other identified aetiologies. When looking at the ears only, we found a significant difference. With a known bacterial aetiology, meningococcal meningitis caused significantly less HI of any degree in comparison to other causative organisms (22% vs. 45%, p = 0.001) (Figure 14).

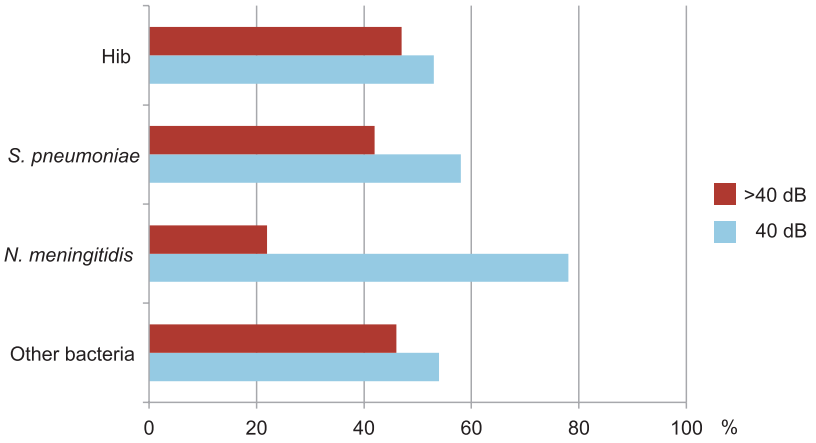



**Figure 14.** Percentage of hearing impaired and unimpaired ears with known bacterial aetiology (n = 383) in children surviving bacterial meningitis from auditory brainstem response recordings prior to hospital discharge, Luanda, Angola.

The majority of survivors, consisting of those tested for hearing and with a confirmed bacterial aetiology, were under 12 months of age. HI in the better-hearing ear was detected more often in children under 12 months compared to older children at the cut-offs of >40 dB and >60 dB [38% (n = 46 of 120) vs. 22% (n = 23 of 104), p = 0.0087 and 27% (32 of 120) vs. 14% (n = 15 of 104), p = 0.025, respectively]. If the bacterial aetiology was known, more HI in either ear (>40 dB) was detected in infants less than 12 months of age than in older ones [63% (n = 74 of 117) vs. 38% (n = 39 of 103), p = 0.0002].

In children under 12 months of age, *S. pneumoniae* was harmful and caused deafness more often than other identified organisms (31% vs. 12%, p = 0.025) as well as a HI at the ABR threshold >60 dB (41% vs. 21%, p = 0.017). In children at least 12 months old, Hib caused more HI at an ABR threshold >60 dB than other causative organisms (26% vs. 10%, p = 0.031).

## 5.5 Prognostic value and changes to the auditory brainstem response (study IV)

Overall, 55 of 221 (25%) children died, whilst 22 of 221 (10%) experienced severe neurological sequelae at discharge. The absence of a typical ABR waveform on the first-day recording bilaterally was common (48%) and was not associated with mortality or mortality combined with severe neurological injury upon hospital discharge ($p > 0.05$ for both cross tabulations, Table 13). Furthermore, no association emerged comparing those with an altered consciousness or comatose patients ($p > 0.05$ for both cross tabulations). Repeating ABR on day 7 ($n = 166$) added no value, since the outcome did not differ between those whose response was present versus those for whom a response was absent in the repeated measurement in relation to death (5% vs. 11%, $p > 0.05$), in relation to death combined with a severe neurological injury (17% vs. 23%, $p > 0.05$) or in an univariate logistic regression analysis ($p > 0.05$).

The latencies and IPLs measured in the better-hearing ear of the remaining children ($n = 114$) emerged as longer in those patients who died or developed severe neurological injury, although these differencies were not statistically significant ($p > 0.05$ in all comparisons based on age groups). In further analyses, we examined the association between delayed ABR parameters on poor outcome. We found no statistically significant differences in the delay between those who died or survived, both amongst all patients or amongst those with an altered consciousness ($p > 0.05$ for all cross tabulations). However, a delay occurred more commonly in children who died or who developed neurological sequelae in comparison to those who survived: amongst all patients (43% vs. 22%, $p = 0.024$) and amongst those with an altered consciousness (44% vs. 22%, $p = 0.043$).

**Table 13.** ABR characterisation versus outcomes in cross tabulations

| ABR characterisation | Death or severe neurological sequelae | Survived without severe neurological sequelae | p-value |
|---|---|---|---|
| **Bilateral absence** | | | |
| All | 35/76 (46) | 72/145 (50) | ns |
| Altered consciousness | 33/68 (49) | 35/72 (49) | ns |
| Coma | 12/21 (62) | 12/20 (60) | ns |
| **Delay of absolute or interpeak latencies[a]** | | | |
| All | 17/40 (43) | 16/72 (22) | 0.024 |
| Altered consciousness | 15/34 (44) | 8/37 (22) | 0.043 |
| Coma | n/a | n/a | - |

Data are numbers and proportions (%) used in cross-tabulations.
Ns, not significant; N/a, not applicable due to insufficient number of patients.
[a]A delay of latencies of waves III, V or interpeak latencies of I–III, III–V or I–V.

Additionally, we observed a significant difference between BM patients and the control children. These differences consisted of the following: amongst infants and young children (<24 months) in the latency of wave V ($p = 0.001$) and IPLs of III–V ($p = 0.005$) and I–V ($p = 0.003$) and amongst children older than 24 months for wave I ($p = 0.041$), III ($p = 0.003$) and V ($p = 0.001$) and IPLs for I–III ($p = 0.04$) and I–V ($p = 0.019$). These latencies were delayed in patients (Figure 15 for selected parameters).

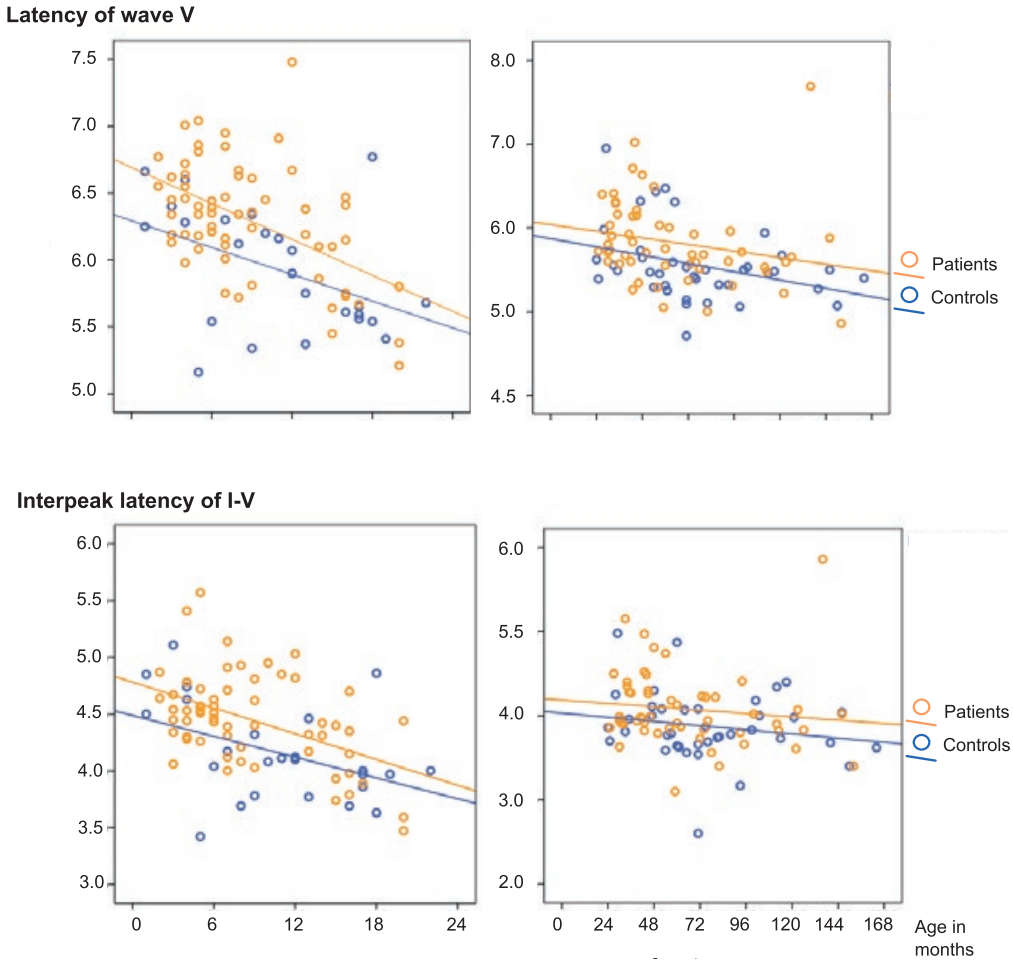



**Figure 15**. The latency of wave V and interpeak latencies I–V in the auditory brainstem responses at an 80-dB stimulation level in patients with bacterial meningitis (n = 114) and controls (n = 64) from Luanda, Angola. Children <24 months of age are shown on the left side while children ≥24 months of age are plotted on the right side. The nonparametric Mann–Whitney *U* test was used for all comparisons.

# 6. Discussion

## 6.1 Otorrhoea and neglected middle-ear infections

Study I sought to analyse the findings from otorrhoea samples: the bacterial aetiology, their change over time and their antimicrobial patterns. Our findings show that the predominant bacterial isolates in ear discharge were numerous and versatile, also containing bacteria atypical for ear discharge found amongst children in high-income settings.[12] The data support our hypothesis that otorrhoea in children in low-income settings show specific characteristics. The observational study design and a lack of more specific data do not allow us to draw more precise conclusions, however. In addition, some of the isolates may represent normal flora. Therefore, the bacteria that maintain infections in the middle ear in chronic otorrhoea remain uncharacterised.[26]

The high prevalence of Gram-negative rods (84%) parallels other studies from lesser developed parts of the world.[35] Moreover, results finding *Pseudomonas* spp. in 29% and *Proteus* in 25% of cases agree with the findings from other laboratory-based series from Africa, which reported prevalences of 19% to 57% for *Pseudomonas* spp.[187,190] and 11% to 47% for *Proteus,*[38,189] respectively. The detection rate of 10% for *S. aureus* is close to the rate of 12% found in a prospective study of CSOM from Kenya, although that study extended to adulthood.[37] The prevalence of *S. aureus* in Africa remains high in all-cause otorrhoea, and was the most common isolate in a recent report from Ethiopia. [81] Some studies, however, detected notably more *Proteus* – an organism that was the most common isolate in Kenya (32%)[37] and in Ethiopia (31–47%)[38,187] in children.

The true meaning of finding unexpected pathogenic bacteria such as *Shigella* and *Salmonella* detected in our sample remains elusive, since we do not yet know if they represented the actual causes of otorrhoea. Nor could we trace whether these pathogens associated with severe immunodeficiencies. A previous study from the same laboratory identified *Shigella* in an otorrhoea sample.[56] However, the detection of unexpected bacteria frequently occurs in Africa, where traditional treatment practices using animal and plant extracts administered directly into the ear remain common even amongst children.16 Briefly, *Alcaligenes faecaelis*, which is typically found in pigeon faeces, an ingredient used in traditional ear medicine, was isolated in CSOM in Angola, and otogenic tetanus is not rare in Africa.[37,195]

Whilst speculative, it is possible if not likely that these findings are affected by poverty. For instance, lack of clean water, close contact to soil, human and animal faeces, prevailing malnutrition and immunosuppression due to various reasons all relate to poverty. Several studies have confirmed the association between poverty and chronic otorrhoea.[27,31]

Our findings on antimicrobial susceptibility favour the current WHO recommendations for treating CSOM and persistent otorrhoea[43] in Angolan children since the sensibility to quinolones reached 93% for the four most common isolates. This finding agrees with observations from South Africa, where 95% of Gram-negative and 93% of Gram-positive bacteria in ear discharge showed susceptibility to quinolones.[34,39] Similarly, in Zambia and Nigeria, otorrhoea isolates were susceptible to quinolones albeit at lower susceptibility rates.[188,189,192] A recent study from Angola amongst children and adults diagnosed with CSOM found

susceptibility to ciprofloxacin in 92% of *Pseudomonas* and 85% of *Proteus* cases.[196]

Knowledge regarding current susceptibility trends is particularly valuable for situations when cultivation is not readily available. The high prevalence of MRSA raises concerns and should caution clinicians when choosing antimicrobials beyond ear-related conditions. The ESBL strain prevalence of 14% in *Enterobacteriachae* is consistent albeit lower than a reported prevalence of 23% from Africa.[197] Taking into account the variety of bacteria and the possibility of resistance, our data support sampling and cultivation whenever resources permit.

Our literature review aimed to systematise knowledge on prevalence, occurrence and burden of disease and allow comparison across microbiological findings amongst African children. Our literature search revealed possible gaps in knowledge on paediatric otorrhoea and CSOM during the past two decades. Population-based studies reporting on children remained scarce, whilst even less was identified for children U-5. Notably, few studies exist on OM burden from emergency and paediatric units. Our literature review, however, showed high prevalence for CSOM, similar or occasionally higher than those presented in 2004 by WHO.[1]

The high number of children with otorrhoea reported in African studies suggests that AOM is not well recognised in Africa. Most children are brought in late when the TM(s) have already perforated.[80] Care is primarily sought solely due to accompanying symptoms such as fever.[80] Furthermore, access to care appears limited. For instance, a multiple indicator and health survey covering more than 16 000 households in Angola found out that only half of U-5 children with symtoms of potential pneumonia were taken to a health facility or health provider – an indicator from UNICEF indicating failure in seeking treatment and accessing care.[198,199] In Rwanda, only one-third of parents to children U-5 with active otorrhoea sought care via prescription medications, whilst another one-third relied on traditional medications and one-third sought no care at all.[16] In South Africa, half of the patients had received no treatment at all for a draining ear during the previous three months.[39] Late presentations are common, allowing complications to occur (Figure 16). These findings call for intensified counselling regarding potential complications and the importance of seeking treatment early as part of disease prevention.

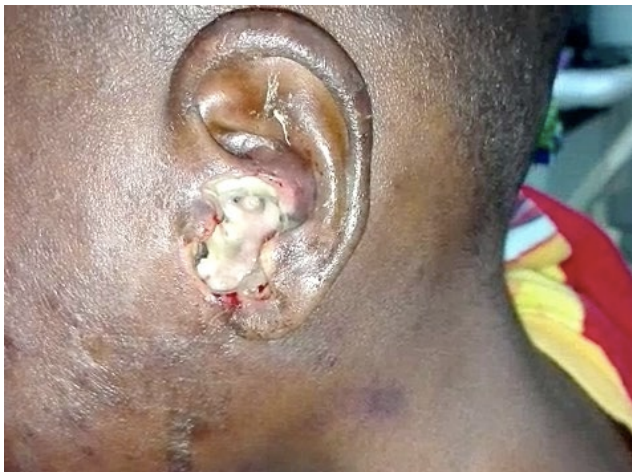


**Figure 16**. A teenage boy from the Children's Hospital of Luanda, Angola, presenting with chronic otorrhoea, and a necrotic ear canal and surrounding tissue. Photo: Dr. Manuel Leite Cruzeiro.

## 6.2 Concomitant otitis media in bacterial meningitis

Our observation that 12.1% of BM associated with OM agrees with the findings of Molyneux *et al.*, who reported a similar percentage (12.4%) amongst ear infections in paediatric BM.[96] Our result, however, differs from reported series from high-income settings: Dodge *et al.,* for instance, found accompanying OM in 35% of cases, whilst Pedersen *et al.* found a prevalence of 45%.[118,136]

Our finding that OM associated with a complicated clinical course or fatality disagrees with findings from Østergaad *et al.*, who demonstrated that the case-fatality rate was lowest amongst those categorised as having otogenic BM.[117] The differences in the underlying type of OM and illnesses predisposing the individual to chronic otorrhoea likely explain these differences. CSOM may damage the middle ear, mastoid mucosa and connective tissue, and facilitate bacteria entering directly into CSF or via haemoatogenic spread. Acquired deshiscencies are established risk factors for BM.[200] Furthermore, we found that OM predicted a complicated clinical course or mortality. This is similar to a meningitis study by van de Beek *et al.,* who found that the presence of OM increased the odds 1.8-fold of an unfavourable outcome (1–4 on Glascow Outcome Scale.[129]

This study contributes to the existing body of evidence on the association of otorrhoea and HIV.[20,55-57] Compared with the reported frequencies of 54% to 62% of HIV in otorrhoea, HIV in our BM patients with otorrhoea was less prevalent at 19%. The difference was, however, significant compared to BM patients without OM comorbidity, and even more than children from the general population in Angola. These findings outline the importance of HIV-testing amongst patients with otorrhoea in Africa. HIV may represent a significant underlying factor leading to a more complicated clinical course or fatal outcome in our study patients with OM; however, due to insufficient number of HIV-test results available we did not include it as a variable in our multivariate logistic regression analyses.

Furthermore, discharging ears often associate with poverty, a likely underlying factor that may affect disease outcomes in multiple ways. Despite our attempts, we could not control for all possible confounders. Practically speaking, otorrhoea in Africa may be an indicator of underlying illnesses, and when associated with BM, may be indicative of a more complex clinical course. Longer antibiotic treatment is likely necessary with concomitant OM. In other words, typical short-course (5 days) antimicrobial treatments for BM in Africa are inadequate. In addition, atypical causative organisms of BM should be considered in cases of CSOM. Some of our cases may represent BM with an otogenic origin, which often manifests as multiple ICCs. Therefore, careful evaluation is warranted and an ENT intervention may be required.

The finding that *N. meningitidis* less often associated with adverse outcomes is similar to a previous study in which McCormick *et al.* found a similar association between *N. meningitdis* and fewer deaths amongst children with BM.[114]

## 6.3 Bacterial aetiology, age and hearing impairment in bacterial meningitis

Study III of this thesis investigated how different bacterial aetiologies and age associated with auditory outcomes. We paid particular interest to bacterial aetiology. The overall rate of deafness at 12.8% agrees with findings from Malawi and Kenya, where prevalences of 12% to 17% for severe to profound HI have been reported.[84,115]

Our results mostly confirmed and agreed with a meta-analysis from 1993 and a later analysis of pooled data from Africa.[132,201] These studies found

similar aetiology-related auditory outcomes associated with *N. meningitidis,* which posed the least potent to inducing any HI.[132,201] Similar to our finding, Peltola *et al.* found that *N. meningitidis* causes less HI.[202]

In our sample when including all ears in the analysis, however, Hib associated more frequently with HI when compared to other agents (59% vs. 45%, p = 0.038). These findings agree with a review of BM sequelae from Africa, in which the highest risk of HI associated with Hib.[92] Similarly, a study from Latin America found that Hib aetiology associated with all of the elevated ABR thresholds studied.[202] In our sample, Hib represented the most common isolated bacteria and may explain some of our results.

In two meta-analyses, *S. pneumonia* associated with the highest risk for HI.[132,201] In our series, the detrimental effect of *S. pneumoniae* was evident amongst the youngest children, amongst whom we observed an association with deafness. Young age was, however, independently associated with HI. This agrees with previous findings.[156,202] Because many of earlier studies vary with regards to the diagnosis of BM, testing methods, thresholds used and timing of testing, comparisons remain difficult.

The potential of *S. pneumoniae* to damage hearing is well-documented in animal models.[105-107] As such, *S. pneumonia* may induce more inflammation and its toxins —such as pneumolysin — possess direct ototoxic properties.[141] In humans, the serotypes appear to play a role: 12F is more frequently and 6B less frequently associates with HI.[203] Furthermore, *S. pneumoniae* leads to a higher rate of cochlear implantation and produces moderate and severe ossification of the cochlea more than other bacterial agents.[204] Moreover, compared to other agents, *S. pneumoniae* more often induces coma[114] a risk factor for HI identified in previous studies.[115,155,156]

In resource-poor settings, the body of evidence points towards the severity of illness — that is, a deep or prolonged impaired consciousness — typically overriding the effect of other factors, such as disease aetiology. However, the effect of the aetiology may play a more important role in future if children with BM are admitted earlier and the severity of the disease is better controlled with advanced care.

## 6.4 Auditory brainstem response in bacterial meningitis

Study IV evaluated whether the simple and robust categorisation of ABR upon admission and repeatedly in hospital carries any prognostic value and feasibility in resource-poor settings. The role of more subtle changes in patient ABRs on different outcomes and compared to healthy controls were also studied. Thus, the study questions were: Do changes in ABR associate with mortality or with mortality and severe neurological sequelae upon discharge?

This study showed that in our study setting robust changes to ABR carry no predictive value on survival compared to death, or on survival compared to death or severe neurological injury on the first day of admission. This finding applied to all patients and subsequently amongst those with an altered consciousness or coma. Repeating the ABR later in hospital did not differentiate between patients, whereby adverse outcomes occurred regardless of the pragmatic categorisation based on repeated recordings. These findings agree with a study of coma,[170] wherein adverse outcomes occurred even with normal, late ABR recordings. However, the results differ from a small series on tuberculous meningitis, in which an abnormal ABR correlating with death.[176]

Since the elongation of IPLs following an increase in ICP typically indicates an evolving brain death,[170] we studied other ABR parameters in relation to poor outcomes. Furthermore, amongst our patients who developed poor outcomes, we noted a trend towards a longer latency and IPL time. This difference was, however, not statistically significant.

We identified those patients whose conduction time was most affected in comparison to age-matched controls. The low number of youngest children in the control group may have biased our results. The delay was more common amongst those with an unfavourable outcome (43% vs. 22%). In other words, a poor outcome occurred in 52% of children with a marked delay compared with 29% without a delay, yielding a low specificity and sensitivity on disease prognosis. This differs from other studies of survival, where ABR showed high prognostic accuracy of an unfavourable outcome.[171]

To better discuss the significance of our findings, the areas under the curve (AUCs) were also calculated for ABR delay and GCS from plotted receiver operating characteristic curves (data not shown). AUC for delay remained low at 0.60 indicating a poor accuracy and poor clinical applicability. GCS showed superior AUC values of 0.71, yet still providing only a fair accuracy for the prognosis.

ABR does not provide direct information related to the cerebral hemispheric function. The gross changes to ABR amongst our series with a bilateral absence of response may stem from a severe increase in ICP, indicating imminent brain death or following ischaemia producing brainstem lesions involving the central auditory pathway. In our series, a significant proportion of children developed severe handicaps, which in other series has correlated with changes in the brainstem level.[148] A high ICP and rostrocaudal deterioration of the brainstem and imminent brain death cause an absence of wave V, since wave V associates with brainstem compression.[205] An increasing ICP alone may cause a reduction in the wave V amplitude.[177,205] Since we found no correlation between an absent response and outcomes, we assume that the cochlear-level pathologies influenced our findings.

BM-induced HI at the cochlear level may have influenced the delay of absolute latencies, although the ear with a lower ABR threshold was chosen for latency and IPL analyses and a delay of latency I alone was not considered a genuine delay. Click stimuli activates a high-frequency portion of the cochlea first, which dominates the generated synchronous neural activity.[167] If BM damages the high-frequency portion of the cochlea, the neural activity may have been generated more in the apical regions of the cochlea resulting in prolonged latencies.[167] IPLs, by contrast, are generally thought to measure the CNS conduction time and reflect retrocochlear pathologies.[167] The observation that IPLs were largely affected on the first-day recording suggests that the infection process affects conduction at the brainstem level via other mechanisms.

Our findings regarding the delay of latencies or IPLs comparing patients and controls agree with previous studies on CNS infections.[176,180,181] Those with a longer central conduction time suffered from significant changes to ICP and the cerebral perfusion pressure in previous studies,[170,205] thus we may have indirectly measured elevated ICPs. In addition to ICP, vascular dysfunctions and ischaemia, demyelination represents another retrocochlear pathology possibly affecting ABRs.[167] Finally, hydrocephalus, a complication associated with BM, can cause alterations to ABR.[176,181] All these mechanisms may have impacted our recordings.

## 6.5 Strengths and limitations of the study

Observational studies are prone to certain limitations and warrant a cautious interpretation of the results. Subgroup analyses carry the risk of false-positive findings.[206] In this study, the extensive prospectively collected data in studies II–IV served as the basis for secondary analyses, to test hypotheses that were carefully thought-out, clinically relevant and thus justified. We stated the hypotheses prior to conducting our analyses.

When applicable, we applied logistic regression analysis to strengthen the associations examined. The study samples across studies I–IV were relatively large or larger in comparison to studies in similar settings. In addition, the outcome measures were carefully planned and likely hold an impressive validity. Generalisation of the results remains limited to similar settings, however, whereby our results apply best to children in similar socioeconomic conditions and with comparable comorbidities.

Furthermore, a selection bias may result in some limitations. In study I, for instance, only children referred to the Luanda laboratory for ear discharge sample collection were included in our study. In comparison to the prevalence estimates for the region, this represents only a fraction of all admissions. The sampling activity diminished during the data collection. Clinical evaluation may have influenced those cases for which a sample was obtained.

In BM studies II–IV, we included subgroups based on our eligibility criteria. Thus, study II included 71% of all patients based on otoscopic examination. Study III included 78% of all survivors based on an available ABR examination. A portion of the analyses, however, only included children or ears with a confirmed bacterial aetiology. Study IV included only 62% of those with ABR available based on an otoscopic examination. We argue that those children not fulfilling our inclusion criteria did not differ significantly from those included in the study. One exception, here, however, is death. Because many of the children died during the first 24 hours, the case-fatality rate after the first ABR recording reamined lower than across the entire cohort albeit it still remained very high at 24%, thereby permitting analyses.

Many of the limitations of the present study stem from the lack of resources characteristics of low-income country settings. In study I, a lack of advanced patient data management systems prevented us from conducting more in-depth analyses.[207] We could not definitively differentiate chronic otorrhoea from AOM with a perforation. In addition, in some cases otorrhoea may have developed from external otitis with an intact TM. Several pathogenic bacteria were isolated in otorrhea samples. Identification did not rely on PCR or other more sophisticated methods.

In BM studies, latex agglutination and PCR were performed only for a minority of patients. The high number of cases with an unknown causative agent in CSF likely stems from the high use of preadmission antimicrobials in Angola. Recently in Finland, some of the frozen CSF samples without a known causative agent underwent PCR analysis. In 40 of 55 (73%) samples, PCR revealed a causative bacterial agent. However, a portion of the children may have suffered from a different disease, including cerebral malaria, virus encephalitis, tuberculous meningitis and, in a few cases, trypanosoma infection.

In relation to ear and auditory examinations, tympanometry, otomicroscopy and otoacoustic emissions would have supplemented the pneumatic otoscopy and ABR. Thus, we could not distinguish between conductive and sensorineural HI.[208] The hearing threshold estimation may have been biased by other causes of HI including quinine treatment and ototoxic antimicrobials prior to hospital admission that we could not control.

Audiology experts conducted the ABR-threshold evaluation in study III. Findings from the pre-discharge hearing evaluations correlated with later hearing evaluations at follow-up.[209] ABR may yield false-positive findings (no detectable latency for wave V at any stimulus level). In complete absence of latencies, deafness was always clinically validated (the child did not respond to speech and claps amongst other stimuli).

The cut-off of HI was set to a fairly high level—40 dB, a level beyond the WHO-defined hearing threshold of a disabling HI in children.[61] This serves as a strength of this study by eliminating some possible confounding due to conductive HI, but may underestimate the true degree of HI. A more precise examination of hearing requires frequency-specific evaluation permitting reliable categorisation based on WHO-defined hearing grades.[61] Amongst in-

fants, frequency-specific tone burst and auditory steady-state response would have provided additional information; amongst older children, pure-tone audiometry would have yielded further details on hearing. Variations in ABR, such as chirp-stimuli that elicit improved synchronous activity of auditory nerve fibres, produces better-defined amplitudes. Such methods could prove more practical when testing hearing.[210] Yet, a lack of resources and facilities prevented more comprehensive evaluations.

We interpreted ABRs in study IV following detailed training, and in cooperation with audiology and neurophysiology consultations. Blinding the clinical status of the patient may serve as a strength in our study; however, identification of wave V near the true threshold level can be challenging and examining only ABR tracing without validation from a clinical examination may cause some bias. Finally, at times, the signal-to-noise ratio may have overcome averaging, resulting in a false-positive rating for the absence of wave forms. Performing CT scans and MRIs would have served to further examine the neurological sequelae and permitted a more detailed analysis of changes to the ABR central latency.

The results from study IV should be interpreted with caution since cochlear-level HI may have affected the findings. To minimise the bias arising from HI, the side that showed the lowest ABR-threshold was chosen for our analyses and only the highest stimulus level was used. Within this study, we did not intend to control for other factors related to a patient's dismal outcome and which have been previously intensely analysed; [157,211] instead our aim was to study specifically whether ABR would serve in prognostication of BM in settings where any tools for disease outcome are highly needed.

## 6.6 Future prospects

The Sustainable Development Goals (SDGs) included in the 2030 Agenda for Sustainable Development aim to amongst other objectives ensure healthy lives and promote well-being for all, ensure inclusive and equitable quality education and promote lifelong learning opportunities for all. Under these goals, achieving universal health coverage and education for individuals with disabilities guide strategies towards preventing OM, BM and their complications and managing disabling sequelae associated with these diseases.

### 6.6.1 Prevention of otitis media and bacterial meningitis in resource-poor settings

High vaccination coverage significantly prevents OM and BM episodes.[99] Improved hygiene and sanitation could prevent some episodes of OM and BM. Improving health education amongst parents may result in earlier care-seeking behaviour allowing early identification and more efficient OM and BM treatment. In African settings, almost one-quarter of all children receiving a BM diagnosis initially sought care from traditional healers.[152] At the community-level, healthcare workers may aid in raising awarness and promoting care seeking in relevant situations.[212] Greater effort should be given to enabling access to health services.

### 6.6.2 Managing hearing impairment and neurological sequelae in resource-poor settings

As stated in the 2015 GBD study, the rising average YLD rates carry implications for health systems. With BM, the global YLDs have been increasing.[22] With a higher survival rate, more survivors will require specialised ear and hearing care (EHC), rehabilitation and education. Amongst survivors of BM,

the complex sequelae require a multi-disciplinary approach. This is particularly challenging in low- and middle-income countries, since their services already do not necessarily meet the population needs.

An alarming shortage of ENT services and training opportunities persist in Africa.[213,214] Whilst in Europe, one ENT specialist serves a population of 20 000;[215] by comparison, in Africa, one ENT surgeon and one audiologist typically exist per 1 million inhabitants.[213] Subsequently, few advances have been reported.[214] Some regions or countries continue to lack any of these services. In addition, families face several challenges accessing available services.[216] In Angola, surgical treatment is limited; currently, the public ENT unit of Luanda only offers tympanoplasty (type 1). A lack of equipment prevents mastoidectomy at the moment. ENT surgery in the private sector is expanding; however, most patients suffering from CSOM can only afford treatment in the public sector.

Similarly, rehabilitation services for cerebral palsy in Africa remain minimal.[218] As such, community-based rehabilitation programmes may carry a beneficial effect, although we continue to lack studies from children.[219] Amongst cerebral palsy patients in Ghana, caregiver empowerment benefitted the affected families.[220] Sustainable and accessible EHC services succeed when developed within an established local healthcare delivery system.[212] Outreach clinics may improve access to care and outcomes, particularly when integrated at the primary level allowing for efficient on-site management.[221] One possible means to reach remote communities may rely on advances in mobile diagnostics.[76] For instance, a smartphone-based hearing screening technology proved equally efficient when compared to conventional screening audiometry in terms of sensitivity and specificity, referral rate and time used in testing amongst school-aged children from underserved regions in South Africa.[222]

With SDGs in mind, WHO launched an initiative aimed at preventing deafness and HI in 2017 resolution, with calls to address EHC in several ways. The strategies outlined included, amongst others, integrating EHC strategies in primary health care; developing, implementing and monitoring screening programmes for the early identification of ear diseases such as CSOM in high-risk populations; improving access to affordable and cost-effective assistive hearing technologies; establishing training programmes in EHC; and promoting alternative communication methods.[223]

### 6.6.3 Research prospects

WHO's 2017 resolution on the prevention of deafness and hearing also carries implications for the academy. High-quality population-based data on ear diseases remain needed, in addition to developing evidence-based strategies and policies. The possible gaps in knowledge of childhood OM and HI in Africa are widely acknowledged.[73] Recommendations for population-based studies on HI are available and should be taken into account when planning new epidemiological studies to enable comparisons between studies and populations as well as included in GBD evaluations. Children U-5 should be included in such studies. In addition, prevention and intervention strategies specifically designed for resource-limited settings should be objectively planned and validated.

With a deeper understanding of the interplay between different risk factors and pathological processes, CSOM could be more efficiently prevented or treated in future. In BM, host–pathogen interactions, host–inflammatory reactions and brain and cochlear injury have all been intensely researched. In future, neuroregeneration may provide therapeutic interventions.[106] Meanwhile, studies on adjuvant and optimized therapies, for instance with nonbacteriolytic antibiotics, are still needed, to enhance the outcome of this very detrimental disease of childhood.[224] In resource-poor settings, protocols for optimised supportive therapies could also improve outcomes. The majority of children with BM in resource-poor

settings continue to receive treatment beyond intensive-care facilities.

The broader spectrum of outcomes in BM, including the quality of life, the effects on an individual's psychosocial life and education, deserve further documentation. Data on cognitive delay, speech or language problems and behavioural issues are particularly lacking in low-income countries.[92] Reporting of sequelae should follow uniform classifications. Strategies and standardised follow-up plans adjusted for low- and middle-income settings should be established. In Senegal, for instance, no BM survivors received any follow-up care for 12 months following hospital discharge.[111]

### 6.6.4 Ethical prospects

To improve the health and development status of LMICs, research on the causes of the greatest disease burden remains necessary and justified. The present study addressed problems highly prevalent in Angola. Although ethical standards of research are universal, and in our study were locally evaluated, complexities of research of this kind specific to resource-poor settings may arise. For instance, in the absence of appropriate rehabilitation services, researchers must ask to what extent is diagnostic testing ethically appropriate. However, gaps in knowledge can be considered obstacles to global health improvements. Understanding the burden of diseases, both at the individual and population levels, remains crucial when attempting to develop interventions and improve health systems capable of responding to population needs.

Sustainable solutions call for equal partnerships in and investments on local research in order for LMICs to become true producers and users of research. Local research may more likely stem from locally defined problems, produce culturally appropriate interventions and provide evidence-based strategies to tackle barriers preventing access to care in the population in question. Because systems providing research capacities often remain scarce, coordinated interventions and strategies to build them are necessary.[225]

# 7. Conclusions

Based on the studies I–IV, we may draw the following conclusions:

I A versatile range of bacterial species, in most cases Gram-negative rods (*Pseudomonas* spp., *Proteus* spp. and *Klebsiella* spp.), cause otorrhoea in Angola. *S. aureus* remains the most common Gram-positive agent with a 69% representation of MRSA. Major aetiological shifts did not occur during the study period. Susceptibility to fluoroquinolone remains high.

Data on otorrhoea and CSOM amongst children in Africa is limited. The common bacterial agents in our study are similar to those from other African studies. The prevalence of persistent otorrhoea across studies appears sufficiently high to reach the magnitude of a public health concern.

II Concomitant OM in BM is relatively common (12%) in Angola, displaying a complex presentation and clinical course. These children exhibit a higher risk of complicated disease or death. Those with otorrhoea likely originate from poor conditions, often have underlying illnesses and should be tested for HIV.

III Hearing impairment occurs frequently amongst BM survivors in Angola with a differing association between the bacterial aetiologies and the extent of hearing impairment. Age remains an important factor contributing to the auditory outcome. Furthermore, *S. pneumoniae* seems particularly damaging to young children, whilst *N. meningitidis* associates with milder hearing impairment.

IV A single or repeated ABR did not predict poor outcomes in Angola. Delayed latencies of waves III or V or IPLs associated with a higher rate of mortality or severe neurological sequelae, but were not relevant as a practical prognostic tool. Childhood BM affects the neural conduction time in the auditory pathway in the brain stem.

Based on this thesis, in future population-based studies on OM amongst African children including children U-5 are warranted. Longitudinal cohort studies of BM from low-income countries would serve to clarify the interplay amongst various risk factors, the course and prognosis of disease and the true long-term effects of BM. Furthermore, we need reliable and useful diagnostic tools for HI in resource-poor settings in order to plan and adjust rehabilitation services. Moreover, clinically relevant tools for prognostics are still needed in resource-poor settings.

Based on a broader perspective, future actions should focus on preventive strategies for OM and BM, including amongst others optimal childhood immunisations, improvements in hygiene, sanitation and living conditions and parental education; developing public health strategies to reach populations at the community level and allow for early identification of diseases; improving access to care, hearing aids and hearing technologies; and supporting the rehabilitation and education of disabled children.

# Conclusões

Baseado nos estudos I a IV, podemos traçar as seguintes conclusões:

I. Uma gama versátil de espécies de bacterias, na maioria das vezes Gram-negativas (*Pseudomonas* spp., *Proteus* spp., *Klebsiella* spp.), ocasiona otorréia em Angola. *S. aureus* permanece como o agente Gram-positivo mais comum, com 69% de representação da *S. aureus* resitente à meticilina (SARM). Não houve maiores mudanças etiológicas durante este período de pesquisa. A susceptibilidade a fluoroquinolonas permanecere alta.

Os dados sobre a otorréia e otite média crónica supurativa (OMCS) são limitados entre as crianças na África. Os agentes bacterianos comuns no nosso estudo são similares àqueles de outros estudos na África. A prevalência da otorréia persistente nos estudos aparece suficientemente alta a atingir a magnitude de uma preocupação de saúde pública.

II. A OM concomitante no MB é relativamente comum (12%) em Angola, apresentando um quadro e evolução clínica complexa. Estas crianças apresentam um grande risco para doença complicada ou morte. Aquelas com otorréia são provavelmente provenientes de condições precárias, havendo comumente enfermidades ocultas e devem ser testados para VIH.

III. A perda auditiva ocorre frequentemente entre os sobreviventes da MB em Angola, com uma associação diferenciada entre as etiologias bacterianas e a extensão da perda auditiva. A idade ressalta como um factor importante, contribuindo à consequência auditiva. Além disso, a *S. pneumoniae* parece particularmente destrutivo às crianças jovens, enquanto a *N. meningitidis* é associada com perda auditiva mais suave.

IV. Uma RATC única ou repetitiva não prevê consequencias negativas em Angola. Latências tardias de ondas III ou V ou latências intervalos interpicos associadas com uma maior taxa de mortalidade ou sequela neurológica severa, mas não foram relevantes como ferramenta prática prognóstica. A MB infantil afecta o tempo de conducção neural no caminho do tronco cerebral.

Baseado neste estudo, recomenda-se inclusão de crianças menores de 5 anos nas pesquisas populacionais futuras sobre a OM entre crianças africanas. Estudos longitudinais de MB de grupo de países pobres servirá para esclarecer a interacção entre os vários factores de risco, a evolução e prognose de doenças e os verdadeiros efeitos de longo prazo da OMCS. Além disto, necessita-se de ferramentas diagnósticas confiáveis e utilizáveis para perda auditiva em condições carentes para planejar e ajustar os serviços de rehabilitação. Ademais, necessita-se ainda ferramentas clínicamente relevantes para prognósticas às condições carentes.

Baseado em perspectivas mais amplas, as acções futuras devem focar nas estratégias preventivas da OM e MB, incluindo, entre outros, a imunizações infantís otimizadas, melhoramentos higiênicos, de saneamento, condições de vida e educação dos pais; desenvolvimento de estratégias de saúde pública ao alcance da população à nível de communidade e permitir a identificação prévia de doenças; melhorando-se o acesso ao tratamento, suportes e tecnologias auditivas; e apoiando-se a reabilitação e educação de crianças desabilitados.

# Acknowledgements

This thesis was conducted at the Children's Hospital of Luanda, Angola, and within the Doctoral Programme in Clinical Research at the University of Helsinki. The studies were carried out in cooperation with the Helsinki University Hospital — specifically with the Departments of Paediatrics, Otorhinolaryngology, Microbiology and Clinical Neurophysiology. This study received financial support from the Ear Research Foundation, the Päivikki and Sakari Sohlberg Foundation, the Paediatric Research Foundation, the Finnish Cultural Foundation, the Paediatric Research Centre and Finland's State Funding for University-level Health Research. I am grateful for the excellent courses, statistics classes and support I received from the Doctoral Programme at the University of Helsinki.

I am deeply grateful to my supervisors, Professor Anne Pitkäranta and Docent Tuula Pelkonen, a pair that perfectly complemented one another throughout this process. Anne, you are a real visionary and a coach, always ready to take on new challenges, and turn new pages in the book called life. Your optimism and leadership inspired and encouraged me to continue further, and you are always steps ahead. Tuula, you are a truly careful and caring guide. You are incredibly brave, and have created a huge international collaborative research network benefiting the children of Angola and the whole of Africa. You led us to Luanda, took care of us and supported me especially during moments of doubt. I admire you both so much — you are incredible researchers, physicians and women with bold hearts.

I warmly thank the reviewers of this thesis, Professor Heikki Löppönen and Docent Merja Helminen. Your thoughtful comments and constructive criticism improved my work significantly. I would also like to thank Professor Harri Saxén, Docent Petri Mattila and Docent Tarja Heiskanen-Kosma for your support as part of my follow-up committee. I also wish to thank Professor Malou Hultcrantz for accepting the invitation to be my opponent.

I am sincerely grateful to the grand old sirs and designers of the first Luanda BM study: Professor Emeritus Heikki Peltola and Dr Luis Bernardino. Heikki, your enthusiastic guidance, exceptional writing skills and hospitality in Helsinki and Kuusamo have illuminated my path. Dr Bernardino, the former head of the Paediatric Hospital of Luanda, I thank you for your work on the BM study, for your kind hospitality in Luanda and for inviting us to your home.

I wish to praise all of my co-authors in Luanda who welcomed us to the hospital. I extend my special thanks to Dr Manuel Leite Cruzeiro, for guiding us in the neuro-infectious ward and the emergency department and as well as for collaborating with us despite his incredibly busy schedule and heavy workload. Thanks also go to Elizabete dos Anjos, Lic Psych, for laboratory assistance. I appreciate the hard and valuable work you do every day for the best of Luanda's children. I hope from the bottom of my heart that local research will be strengthened and will continue to improve in response to local needs.

Agradeço ao Dr. Bernardino, o ex-Director do Hospital Pediátrico de Luanda, pelo seu trabalho no estudo da BM e pela sua hospitalidade gentil em Luanda e por ter convidado-nos à sua casa e apresentado-nos à sua família. Quero agradecer a todos os meus co-autores em Luanda que nos desejaram bemvindas ao hospital. Extendo os meus agradeci-

mentos especiais ao Dr. Leite Cruzeiro por guiar-nos na enfermaria neuro-infecciosa e no departamento de emergência, assim como pela colaboração conosco apesar de horário apressado e pesada carga de trabalho. Agredecimento também ao Lic. Psiq. dos Anjos pela assistência laboratorial. Fazem um trabalho muito valioso e pesado para o bem das crianças de Luanda. Um grande agredecimento para vocês por isto. Desejo, do fundo do meu coração, que a pesquisa local se fortaleça e que no futuro esta corresponda cada vez melhor às necessidades locais.

I would also like to express my gratitude to my associates from the various departments at the Helsinki University Hospital, without whom the individual studies forming this thesis would not have been possible. In particular, I thank Docent Antti Aarnisalo for his valuable expertise in audiology; Professor Leena Lauronen and Docent Päivi Nevalainen for all of their careful and thorough input related to clinical neurophysiology; and Anu Pätäri-Sampo, MD, PhD, for her know-how in clinical microbiology. I owe my gratitude to Irmeli Roine, MD, PhD, for all of her valuable input on the research process. Thanks go as well to Laura Lempinen, MD, for the truly cooperative work in our joint study. I also thank my other co-authors: Professor Jussi Jero, Anu Laulajainen-Hongisto, MD, PhD, Saku Sinkkonen, MD, PhD, and Atte Sjövall, MD. I am also thankful to Timo Pessi, MSc, Matti Kataja, PhD, and all of the statistics instructors at the University of Helsinki for their advice. I also warmly acknowledge Vanessa L Fuller for the English-language revision of this thesis.

I am immensely grateful to my dear research group members, Okko and Emilie, for sharing numerous adventures in Luanda, and trips to several conferences around Europe. I wish I could run as fast as you.

I thank my entire childhood family, specifically my mother Pirjo and father Jari and grandparents Maija-Liisa and Seppo for all of their support and for encouraging me to venture out into the world. Thank you, dear Riikka, Kosti (it's time to return the computer to you) and Markus for being there for me. I also thank my in-laws, especially Sinikka, for letting me use your flat to write this thesis, Henriikka, for taking care of Uno, and all who have been there for me during truly the busiest time in my life.

I am immensely grateful for having my friends Liisa, Sini, Henni and Tia in my life; I owe special thanks Liisa – sincerely, what would I do without you? I also extend my thanks to my medical school friends Riina, Reetta and Minttu, and my medical school clinical group 'klinikkaryhmä' with whom I grew up to become a doctor. I am also thankful to all of my inspiring colleagues from Physicians for Social Responsibility. The active years in the organisation with you taught me so much about global health and development cooperation projects. I extend my thanks to Niina, Sebastian and Paula for showing me the path, and to Raija, Helena and Kisu for walking that path with me – at times in the muddy Peruvian Amazon.

This has been a journey of learning and challenge; however, you learn nothing with your hands stuck in your pockets.

Finally, my chauffer, babysitter and handyman, the love of my life, Harri — your love carries me everywhere. I love you. And to my dear boys Maxi, Felix and Uno — I love you so much, this book is dedicated to you.

Mariia Karppinen
Helsinki, February 2019

# References


1. World Health Organization. Chronic suppurative otitis media: burden of illness and management options. Geneve: World Health Organization; 2004.
2. Monasta L, Ronfani L, Marchetti F, Montico M, Brumatti LV, Bavcar A, et al. Burden of disease caused by otitis media: systematic review and global estimates. PloS one 2012;7(4):e36226.
3. Bernardino L, Magalhaes J, Simoes MJ, Monteiro L. Bacterial meningitis in Angola. Lancet 2003 May 3;361(9368):1564-1565.
4. Pelkonen T, Roine I, Monteiro L, Joao Simoes M, Anjos E, Pelerito A, et al. Acute childhood bacterial meningitis in Luanda, Angola. Scand J Infect Dis 2008;40(11-12):859-866.
5. GBD 2016 Mortality Collaborators. Global, regional, and national under-5 mortality, adult mortality, age-specific mortality, and life expectancy, 1970-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet 2017 Sep 16;390(10100):1084-1150.
6. The World Bank. Country Profile, Angola. 2018; Available at: *http://databank.worldbank.org/data/views/reports/reportwidget.aspx?Report_Name=CountryProfile&Id=b450fd57&tbar=y&dd=y&inf=n&zm=n&country=AGO.* Accessed October 20th, 2018.
7. The World Bank. World Development Indicators, Sub-Saharan Africa. 2018; Available at: *http://databank.worldbank.org/data/reports.aspx?source=2&country=SSF#.* Accessed October 20th, 2018.
8. World Health Organization. Angola: WHO Statistical profile. 2015; Available at: *http://www.who.int/gho/countries/ago.pdf?ua=1.* Accessed November 7th, 2018.
9. Murray CJ, Lopez AD. Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study. Lancet 1997 May 17;349(9063):1436-1442.
10. GBD 2015 DALYs and HALE Collaborators. Global, regional, and national disability-adjusted life-years (DALYs) for 315 diseases and injuries and healthy life expectancy (HALE), 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016 Oct 8;388(10053):1603-1658.
11. Lieberthal AS, Carroll AE, Chonmaitree T, Ganiats TG, Hoberman A, Jackson MA, et al. The diagnosis and management of acute otitis media. Pediatrics 2013 Mar;131(3):e964-99.
12. Verhoeff M, van der Veen EL, Rovers MM, Sanders EA, Schilder AG. Chronic suppurative otitis media: a review. Int J Pediatr Otorhinolaryngol 2006 Jan;70(1):1-12.
13. Bluestone CD. Clinical course, complications and sequelae of acute otitis media. Pediatr Infect Dis J 2000 May;19(5 Suppl):S37-46.
14. Gates GA, Klein JO, Lim DJ, Mogi G, Ogra PL, Pararella MM, et al. Recent advances in otitis media. 1. Definitions, terminology, and classification of otitis media. Ann Otol Rhinol Laryngol Suppl 2002 Mar;188:8-18.
15. Biagio L, Swanepoel DW, Laurent C, Lundberg T. Paediatric otitis media at a primary healthcare clinic in South Africa. South African Medical Journal.Suid-Afrikaanse Tydskrif Vir Geneeskunde 2014;104(6):431-435.
16. Mukara KB, Lilford RJ, Tucci DL, Waiswa P. Prevalence of Middle Ear Infections and Associated Risk Factors in Children under 5 Years in Gasabo District of Kigali City, Rwanda. Int J Pediatr 2017;2017:4280583.
17. GBD 2015 Disease and Injury Incidence and Prev-

alence Collaborators. Suplementary appendix to: Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016 Oct 8;388(10053):1545-1602.

18. Tahtinen PA, Laine MK, Ruuskanen O, Ruohola A. Delayed versus immediate antimicrobial treatment for acute otitis media. Pediatr Infect Dis J 2012 Dec;31(12):1227-1232.
19. Orji F. A survey of the burden of management of chronic suppurative otitis media in a developing country. Ann Med Health Sci Res 2013 Oct;3(4):598-601.
20. Hallbauer UM, Atkins MD, Tiedt NJ, Butler IR, Pieters M, Elliott E, et al. Co-morbidities in children presenting with chronic suppurative otitis media--a South African study. J Trop Pediatr 2014 Jun;60(3):198-202.
21. Vergison A, Dagan R, Arguedas A, Bonhoeffer J, Cohen R, Dhooge I, et al. Otitis media and its consequences: beyond the earache. Lancet Infect Dis 2010 Mar;10(3):195-203.
22. GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016 Oct 8;388(10053):1545-1602.
23. Fireman B, Black SB, Shinefield HR, Lee J, Lewis E, Ray P. Impact of the pneumococcal conjugate vaccine on otitis media. Pediatr Infect Dis J 2003 Jan;22(1):10-16.
24. Sigurdsson S, Eythorsson E, Hrafnkelsson B, Erlendsdottir H, Kristinsson KG, Haraldsson A. Reduction in All-Cause Acute Otitis Media in Children <3 Years of Age in Primary Care Following Vaccination With 10-Valent Pneumococcal Haemophilus influenzae Protein-D Conjugate Vaccine: A Whole-Population Study. Clin Infect Dis 2018 Sep 28;67(8):1213-1219.
25. Teele DW, Klein JO, Rosner B. Epidemiology of otitis media during the first seven years of life in children in greater Boston: a prospective, cohort study. J Infect Dis 1989 Jul;160(1):83-94.
26. Mittal R, Lisi CV, Gerring R, Mittal J, Mathee K, Narasimhan G, et al. Current concepts in the pathogenesis and treatment of chronic suppurative otitis media. J Med Microbiol 2015 Oct;64(10):1103-1116.
27. Lasisi AO, Olaniyan FA, Muibi SA, Azeez IA, Abdulwasiu KG, Lasisi TJ, et al. Clinical and demographic risk factors associated with chronic suppurative otitis media. Int J Pediatr Otorhinolaryngol 2007 Oct;71(10):1549-1554.
28. Simoes EA, Kiio F, Carosone-Link PJ, Ndegwa SN, Ayugi J, Macharia IM. Otitis Media and Its Sequelae in Kenyan Schoolchildren. J Pediatric Infect Dis Soc 2016 Dec;5(4):375-384.
29. Berman S. Otitis media in developing countries. Pediatrics 1995 Jul;96(1 Pt 1):126-131.
30. Chandrashekharayya SH, Kavitha MM, Handi P, Khavasi P, Doddmani SS, Riyas M. To Study the Level of Awareness About Complications of Chronic Suppurative Otitis Media (CSOM) in CSOM Patients. J Clin Diagn Res 2014 Feb;8(2):59-61.
31. Orji FT, Dike BO, Oji O. Determinants of non-healing ear discharge in chronic suppurative otitis media in a developing country. Eur Arch Otorhinolaryngol 2015 Oct;272(10):2713-2718.
32. Koch A, Homoe P, Pipper C, Hjuler T, Melbye M. Chronic suppurative otitis media in a birth cohort of children in Greenland: population-based study of incidence and risk factors. Pediatr Infect Dis J 2011 Jan;30(1):25-29.
33. Jervis-Bardy J, Sanchez L, Carney AS. Otitis media in Indigenous Australian children: review of epidemiology and risk factors. J Laryngol Otol 2014 Jan;128 Suppl 1:S16-27.
34. Madhi SA, Govender N, Dayal K, Devadiga R, Van Dyke MK, van Niekerk N, et al. Bacterial and Respiratory Viral Interactions in the Etiology of Acute Otitis Media in HIV-infected and HIV-uninfected South African Children. Pediatr Infect Dis J 2015 Jul;34(7):753-760.

35. Mahadevan M, Navarro-Locsin G, Tan HK, Yamanaka N, Sonsuwan N, Wang PC, et al. A review of the burden of disease due to otitis media in the Asia-Pacific. Int J Pediatr Otorhinolaryngol 2012 May;76(5):623-635.
36. Sabella C. Management of otorrhea in infants and children. Pediatr Infect Dis J 2000 Oct;19(10):1007-1008.
37. Aduda DSO, Macharia IM, Mugwe P, Oburra H, Farragher B, Brabin B, et al. Bacteriology of chronic suppurative otitis media (CSOM) in children in Garissa district, Kenya: a point prevalence study. Int J Pediatr Otorhinolaryngol 2013 Jul;77(7):1107-1111.
38. Abera B, Biadeglegne F. Antimicrobial resistance patterns of Staphylococcus aureus and Proteus spp. isolated from otitis media at Bahir Dar Regional Laboratory, North West Ethiopia. Ethiop Med J 2009 Oct;47(4):271-276.
39. Tiedt NJ, Butler IRT, Hallbauer UM, Atkins MD, Elliott E, Pieters M, et al. Paediatric chronic suppurative otitis media in the Free State Province: clinical and audiological features. South African Medical Journal.Suid-Afrikaanse Tydskrif Vir Geneeskunde 2013;103(7):467-470.
40. Acuin J. Chronic suppurative otitis media. BMJ Clin Evid 2007 Feb 1;2007:0507.
41. Diagnostik, behandling och uppföljning av akut mediaotit (AOM) – ny rekommendation (Avsnittet rörotit uppdaterat 2018). Information från Läkemedelsverket 2010(5):13-24.
42. Tahtinen PA, Laine MK, Huovinen P, Jalava J, Ruuskanen O, Ruohola A. A placebo-controlled trial of antimicrobial treatment for acute otitis media. N Engl J Med 2011 Jan 13;364(2):116-126.
43. World Health Organization. Recommendations for management of common childhood conditions: evidence for technical update of pocket book recommendations: newborn conditions, dysentery, pneumonia, oxygen use and delivery, common causes of fever, severe acute malnutrition and supportive care. Geneva: World Health Organization; 2012.
44. Macfadyen C, Gamble C, Garner P, Macharia I, Mackenzie I, Mugwe P, et al. Topical quinolone vs. antiseptic for treating chronic suppurative otitis media: a randomized controlled trial. Trop Med Int Health 2005 Feb;10(2):190-197.
45. Macfadyen CA, Acuin JM, Gamble C. Systemic antibiotics versus topical treatments for chronically discharging ears with underlying eardrum perforations. Cochrane Database Syst Rev 2006 Jan 25;(1):CD005608. doi(1):CD005608.
46. Morris P. Chronic suppurative otitis media. BMJ Clin Evid 2012 Aug 6;2012:0507.
47. Woodfield G, Dugdale A. Evidence behind the WHO guidelines: hospital care for children: what is the most effective antibiotic regime for chronic suppurative otitis media in children? J Trop Pediatr 2008 Jun;54(3):151-156.
48. van Hasselt P, van Kregten E. Treatment of chronic suppurative otitis media with ofloxacin in hydroxypropyl methylcellulose ear drops: a clinical/bacteriological study in a rural area of Malawi. Int J Pediatr Otorhinolaryngol 2002 Mar 15;63(1):49-56.
49. Minja BM, Moshi NH, Ingvarsson L, Bastos I, Grenner J. Chronic suppurative otitis media in Tanzanian school children and its effects on hearing. East Afr Med J 2006 Jun;83(6):322-325.
50. Brennan-Jones C, Chong LY, Head K, Tu N, Burton MJ, Schilder A, et al. Topical antibiotics with steroids for chronic suppurative otitis media. Cochrane Database of Systematic Reviews 2018(6).
51. Brennan-Jones C, Head K, Chong LY, Tu N, Burton MJ, Schilder A, et al. Topical antibiotics for chronic suppurative otitis media. Cochrane Database of Systematic Reviews 2018(6).
52. Chong LY, Head K, Richmond P, Snelling T, Schilder A, Burton MJ, et al. Systemic antibiotics for chronic suppurative otitis media. Cochrane Database of Systematic Reviews 2018(6).
53. Chong LY, Head K, Richmond P, Snelling T, Schilder A, Burton MJ, et al. Topical versus systemic antibiotics for chronic suppurative otitis media. Cochrane Database of Systematic Reviews 2018(6).
54. Somekh E, Cordova Z. Ceftazidime versus aztre-

onam in the treatment of pseudomonal chronic suppurative otitis media in children. Scand J Infect Dis 2000;32(2):197-199.

55. Karpakis J, Rabie H, Howard J, van Rensburg AJ, Cotton M. Otorrhoea is a marker for symptomatic disease in HIVinfected children. South African Medical Journal 2007;97(12):1292-1294.
56. Taipale A, Pelkonen T, Taipale M, Bernardino L, Peltola H, Pitkaranta A. Chronic suppurative otitis media in children of Luanda, Angola. Acta Paediatr 2011 Aug;100(8):e84-8.
57. Ianacone DC, Smith AF, Casselbrant ML, Ensink RJH, Buchinsky F, Melaku A, et al. Prevalence of chronic ear disease among HIV+ children in Sub-Saharan Africa. Int J Pediatr Otorhinolaryngol 2017 Dec;103:133-136.
58. Trinidade A, Page JC, Dornhoffer JL. Therapeutic Mastoidectomy in the Management of Noncholesteatomatous Chronic Otitis Media: Literature Review and Cost Analysis. Otolaryngol Head Neck Surg 2016 Dec;155(6):914-922.
59. Akinpelu OV, Amusa YB, Komolafe EO, Adeolu AA, Oladele AO, Ameye SA. Challenges in management of chronic suppurative otitis media in a developing country. Journal of Laryngology & Otology 2008 Jan;122(1):16-20.
60. Aarhus L, Tambs K, Kvestad E, Engdahl B. Childhood Otitis Media: A Cohort Study With 30-Year Follow-Up of Hearing (The HUNT Study). Ear Hear 2015 May-Jun;36(3):302-308.
61. Pascolini D, Smith A. Hearing Impairment in 2008: a compilation of available epidemiological studies. Int J Audiol 2009;48(7):473-485.
62. Stephens D. Study Group on Terminology, Definitions and Hearing Assessment. In: Martini A (ed) European Work Group on Genetics of Hearing Impairment. European Commission Directorate, Biomedical and Health Research Program (HEAR) Info Letter 2 1996(EU: European Commission Directorate.).
63. World Health Organization. Prevention of blindness and deafness, Grades of hearing impairment. Available at: *http://www.who.int/deafness/hearing_impairment_grades/en/*. Accessed October 20th, 2018.
64. World Health Organization. Deafness prevention, Estimates. 2018; Available at: *http://www.who.int/deafness/estimates/en/*. Accessed October 20th, 2018.
65. Mulwafu W, Kuper H, Ensink RJ. Prevalence and causes of hearing impairment in Africa. Trop Med Int Health 2016 Feb;21(2):158-165.
66. Lin YS, Lin LC, Lee FP, Lee KJ. The prevalence of chronic otitis media and its complication rates in teenagers and adult patients. Otolaryngol Head Neck Surg 2009 Feb;140(2):165-170.
67. Costelloe C, Metcalfe C, Lovering A, Mant D, Hay AD. Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. BMJ 2010 May 18;340:c2096.
68. Jensen RG, Koch A, Homoe P. Long-term tympanic membrane pathology dynamics and spontaneous healing in chronic suppurative otitis media. Pediatr Infect Dis J 2012 Feb;31(2):139-144.
69. Olatoke F, Ologe FE, Nwawolo CC, Saka MJ. The prevalence of hearing loss among schoolchildren with chronic suppurative otitis media in Nigeria, and its effect on academic performance. Ear Nose Throat J 2008 Dec;87(12):E19.
70. Harrison CJ. Amoxicillin Is the Most Cost-Effective Therapy for Acute Otitis Media: The Culmination of 40 Years of Research. J Pediatr 2017 Oct;189:5-8. e1.
71. Shaikh N, Dando EE, Dunleavy ML, Curran DL, Martin JM, Hoberman A, et al. A Cost-Utility Analysis of 5 Strategies for the Management of Acute Otitis Media in Children. J Pediatr 2017 Oct;189:54-60.e3.
72. Baltussen R, Smith A. Cost-effectiveness of selected interventions for hearing impairment in Africa and Asia: a mathematical modelling approach. Int J Audiol 2009 Mar;48(3):144-158.
73. Hunt L, Mulwafu W, Knott V, Ndamala CB, Naunje AW, Dewhurst S, et al. Prevalence of paediatric chronic suppurative otitis media and hearing im-

pairment in rural Malawi: A cross-sectional survey. PLoS One 2017 Dec 21;12(12):e0188950.
74. Adebola SO, Ayodele SO, Oyelakin OA, Babarinde JA, Adebola OE. Pre-school hearing screening: profile of children from Ogbomoso, Nigeria. Int J Pediatr Otorhinolaryngol 2013 Dec;77(12):1987-1991.
75. Clark JL. Hearing loss in Mozambique: current data from Inhambane Province. Int J Audiol 2008;47 Suppl 1:S49-56.
76. Lundberg T, Biagio L, Laurent C, Sandstrom H, Swanepoel DW. Remote evaluation of video-otoscopy recordings in an unselected pediatric population with an otitis media scale. Int J Pediatr Otorhinolaryngol 2014 Sep;78(9):1489-1495.
77. Baggi E, Semino M, Bianchini S, Fattizzo M, Rosazza C, Esposito S, et al. Middle ear problems in children hospitalised because of lower respiratory tract infections: a comparison between two cohorts in Burundi and Italy. Int J Pediatr Otorhinolaryngol 2013 Dec;77(12):1984-1986.
78. Taipale A, Pelkonen T, Taipale M, Roine I, Bernardino L, Peltola H, et al. Otorhinolaryngological findings and hearing in HIV-positive and HIV-negative children in a developing country. European Archives of Oto-Rhino-Laryngology 2011;268(10):1527-1532.
79. Taipale A, Pelkonen T, Bernardino L, Peltola H, Pitkäranta A. Hearing loss in Angolan children with sickle-cell disease. Pediatrics International 2012;54(6):854-857.
80. Alabi BS, Abdulkarim AA, Fatai O, Abdulmajeed SO. Prevalence of acute otitis media among children with pyrexia in a Nigerian hospital. Auris Nasus Larynx 2009;36(5):532-535.
81. Hailegiyorgis TT, Sarhie WD, Workie HM. Isolation and antimicrobial drug susceptibility pattern of bacterial pathogens from pediatric patients with otitis media in selected health institutions, Addis Ababa, Ethiopia: a prospective cross-sectional study. BMC Ear Nose Throat Disord 2018 May 24;18:8-018-0056-1. eCollection 2018.
82. Ilechukwu GC, Ilechukwu CA, Ubesie AC, Okoroafor I, Ezeanolue BC, Ojinnaka NC. Bacterial agents of the discharging middle ear among children seen at the University of Nigeria Teaching Hospital, Enugu. The Pan African medical journal 2017;26:87.
83. Kim KS. Acute bacterial meningitis in infants and children. Lancet Infect Dis 2010 Jan;10(1):32-42.
84. Molyneux EM, Walsh AL, Forsyth H, Tembo M, Mwenechanya J, Kayira K, et al. Dexamethasone treatment in childhood bacterial meningitis in Malawi: a randomised controlled trial. Lancet 2002 Jul 20;360(9328):211-218.
85. Saez-Llorens X, McCracken GH,Jr. Bacterial meningitis in children. Lancet 2003 Jun 21;361(9375):2139-2148.
86. Tsai CJ, Griffin MR, Nuorti JP, Grijalva CG. Changing epidemiology of pneumococcal meningitis after the introduction of pneumococcal conjugate vaccine in the United States. Clin Infect Dis 2008 Jun 1;46(11):1664-1672.
87. Thigpen MC, Whitney CG, Messonnier NE, Zell ER, Lynfield R, Hadler JL, et al. Bacterial meningitis in the United States, 1998-2007. N Engl J Med 2011 May 26;364(21):2016-2025.
88. Castelblanco RL, Lee M, Hasbun R. Epidemiology of bacterial meningitis in the USA from 1997 to 2010: a population-based observational study. Lancet Infect Dis 2014 Sep;14(9):813-819.
89. Brouwer MC, van de Beek D. Epidemiology of community-acquired bacterial meningitis. Curr Opin Infect Dis 2018 Feb;31(1):78-84.
90. Wall EC, Everett DB, Mukaka M, Bar-Zeev N, Feasey N, Jahn A, et al. Bacterial meningitis in Malawian adults, adolescents, and children during the era of antiretroviral scale-up and Haemophilus influenzae type b vaccination, 2000-2012. Clin Infect Dis 2014 May;58(10):e137-45.
91. GBD 2016 Meningitis Collaborators. Global, regional, and national burden of meningitis, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol 2018 Dec;17(12):1061-1082.
92. Ramakrishnan M, Ulland AJ, Steinhardt LC, Moisi

JC, Were F, Levine OS. Sequelae due to bacterial meningitis among African children: a systematic literature review. BMC Med 2009;7:47.

93. Kambire D, Soeters HM, Ouedraogo-Traore R, Medah I, Sangare L, Yameogo I, et al. Nationwide Trends in Bacterial Meningitis before the Introduction of 13-Valent Pneumococcal Conjugate Vaccine-Burkina Faso, 2011-2013. PLoS One 2016 Nov 10;11(11):e0166384.
94. Polkowska A, Toropainen M, Ollgren J, Lyytikainen O, Nuorti JP. Bacterial meningitis in Finland, 1995-2014: a population-based observational study. BMJ Open 2017 Jun 6;7(5):e015080-2016-015080.
95. Ramakrishnan M, Moisi JC, Klugman KP, Iglesias JM, Grant LR, Mpoudi-Etame M, et al. Increased risk of invasive bacterial infections in African people with sickle-cell disease: a systematic review and meta-analysis. Lancet Infect Dis 2010 May;10(5):329-337.
96. Molyneux EM, Tembo M, Kayira K, Bwanaisa L, Mweneychanya J, Njobvu A, et al. The effect of HIV infection on paediatric bacterial meningitis in Blantyre, Malawi. Arch Dis Child 2003 Dec;88(12):1112-1118.
97. Bluestone CD. Prevention of meningitis: cochlear implants and inner ear abnormalities. Arch Otolaryngol Head Neck Surg 2003 Mar;129(3):279-281.
98. Peltola H. Worldwide Haemophilus influenzae type b disease at the beginning of the 21st century: global analysis of the disease burden 25 years after the use of the polysaccharide vaccine and a decade after the advent of conjugates. Clin Microbiol Rev 2000 Apr;13(2):302-317.
99. Peltola H, Pelkonen T, Bernardino L, Monteiro L, Silvestre Sda C, Anjos E, et al. Vaccine-induced waning of Haemophilus influenzae empyema and meningitis, Angola. Emerg Infect Dis 2014 Nov;20(11):1887-1890.
100. Owusu M, Nguah SB, Boaitey YA, Badu-Boateng E, Abubakr AR, Lartey RA, et al. Aetiological agents of cerebrospinal meningitis: a retrospective study from a teaching hospital in Ghana. Ann Clin Microbiol Antimicrob 2012 Oct 4;11:28-0711-11-28.
101. van de Beek D, Brouwer MC, Thwaites GE, Tunkel AR. Advances in treatment of bacterial meningitis. Lancet 2012 Nov 10;380(9854):1693-1702.
102. Brouwer MC, McIntyre P, Prasad K, van de Beek D. Corticosteroids for acute bacterial meningitis. Cochrane Database Syst Rev 2015 Sep 12;(9):CD004405. doi(9):CD004405.
103. Wall EC, Ajdukiewicz KM, Bergman H, Heyderman RS, Garner P. Osmotic therapies added to antibiotics for acute bacterial meningitis. Cochrane Database Syst Rev 2018 Feb 6;2:CD008806.
104. Mueller JE, Yaro S, Ouedraogo MS, Levina N, Njanpop-Lafourcade BM, Tall H, et al. Pneumococci in the African meningitis belt: meningitis incidence and carriage prevalence in children and adults. PLoS One 2012;7(12):e52464.
105. Mook-Kanamori BB, Geldhoff M, van der Poll T, van de Beek D. Pathogenesis and pathophysiology of pneumococcal meningitis. Clin Microbiol Rev 2011 Jul;24(3):557-591.
106. Liechti FD, Grandgirard D, Leib SL. Bacterial meningitis: insights into pathogenesis and evaluation of new treatment options: a perspective from experimental studies. Future Microbiol 2015;10(7):1195-1213.
107. Doran KS, Fulde M, Gratz N, Kim BJ, Nau R, Prasadarao N, et al. Host-pathogen interactions in bacterial meningitis. Acta Neuropathol 2016 Feb;131(2):185-209.
108. Leib SL, Leppert D, Clements J, Tauber MG. Matrix metalloproteinases contribute to brain damage in experimental pneumococcal meningitis. Infect Immun 2000 Feb;68(2):615-620.
109. Bercion R, Bobossi-Serengbe G, Gody JC, Beyam EN, Manirakiza A, Le Faou A. Acute bacterial meningitis at the 'Complexe Pediatrique' of Bangui, Central African Republic. J Trop Pediatr 2008 Apr;54(2):125-128.
110. Lagunju IA, Falade AG, Akinbami FO, Adegbola R, Bakare RA. Childhood bacterial meningitis in Ibadan, Nigeria--antibiotic sensitivity pattern of pathogens, prognostic indices and outcome. Afr J

Med Med Sci 2008 Jun;37(2):185-191.
111. Edmond K, Dieye Y, Griffiths UK, Fleming J, Ba O, Diallo N, et al. Prospective cohort study of disabling sequelae and quality of life in children with bacterial meningitis in urban Senegal. Pediatr Infect Dis J 2010 Nov;29(11):1023-1029.
112. Pelkonen T, Roine I, Cruzeiro ML, Pitkaranta A, Kataja M, Peltola H. Slow initial -lactam infusion and oral paracetamol to treat childhood bacterial meningitis: a randomised, controlled trial. Lancet Infect Dis 2011 Aug;11(8):613-621.
113. Gervaix A, Taguebue J, Bescher BN, Corbeil J, Raymond F, Alcoba G, et al. Bacterial meningitis and pneumococcal serotype distribution in children in cameroon. Pediatr Infect Dis J 2012 Oct;31(10):1084-1087.
114. McCormick DW, Wilson ML, Mankhambo L, Phiri A, Chimalizeni Y, Kawaza K, et al. Risk factors for death and severe sequelae in Malawian children with bacterial meningitis, 1997-2010. Pediatr Infect Dis J 2013 Feb;32(2):e54-61.
115. Karanja BW, Oburra HO, Masinde P, Wamalwa D. Risk Factors for Hearing Loss in Children following Bacterial Meningitis in a Tertiary Referral Hospital. Int J Otolaryngol 2013;2013:354725.
116. Tadesse BT, Foster BA, Shibeshi MS, Dangiso HT. Empiric Treatment of Acute Meningitis Syndrome in a Resource-Limited Setting: Clinical Outcomes and Predictors of Survival or Death. Ethiop J Health Sci 2017 Nov;27(6):581-588.
117. Ostergaard C, Konradsen HB, Samuelsson S. Clinical presentation and prognostic factors of Streptococcus pneumoniae meningitis according to the focus of infection. BMC Infect Dis 2005 Oct 27;5:93-2334-5-93.
118. Pedersen TI, Howitz M, Ostergaard C. Clinical characteristics of Haemophilus influenzae meningitis in Denmark in the post-vaccination era. Clin Microbiol Infect 2010 May;16(5):439-446.
119. Klein M, Koedel U, Pfister HW, Kastenbauer S. Morphological correlates of acute and permanent hearing loss during experimental pneumococcal meningitis. Brain Pathol 2003 Apr;13(2):123-132.
120. Terao K, Cureoglu S, Schachern PA, Paparella MM, Morita N, Sato T, et al. Marrow-middle ear connections: a potential cause of otogenic meningitis. Otol Neurotol 2011 Jan;32(1):77-80.
121. Djeric DR, Schachern PA, Paparella MM, Jaramillo M, Haruna S, Bassioni M. Otitis media (silent): a potential cause of childhood meningitis. Laryngoscope 1994 Dec;104(12):1453-1460.
122. Yildirim-Baylan M, Schachern P, Tsuprun V, Shiabata D, Paparella MM, Cureoglu S. The pathology of silent otitis media: a predecessor to tympanogenic meningitis in infants. Int J Pediatr Otorhinolaryngol 2014 Mar;78(3):451-454.
123. Kangsanarak J, Fooanant S, Ruckphaopunt K, Navacharoen N, Teotrakul S. Extracranial and intracranial complications of suppurative otitis media. Report of 102 cases. J Laryngol Otol 1993 Nov;107(11):999-1004.
124. Kangsanarak J, Navacharoen N, Fooanant S, Ruckphaopunt K. Intracranial complications of suppurative otitis media: 13 years' experience. Am J Otol 1995 Jan;16(1):104-109.
125. Dubey SP, Larawin V, Molumi CP. Intracranial spread of chronic middle ear suppuration. Am J Otolaryngol 2010 Mar-Apr;31(2):73-77.
126. Jain A, Arora N, Meher R, Passey JC, Bansal R. Intracranial complications of CSOM in pediatric patients: A persisting problem in developing countries. Int J Pediatr Otorhinolaryngol 2017 Sep;100:128-131.
127. Yorgancilar E, Yildirim M, Gun R, Bakir S, Tekin R, Gocmez C, et al. Complications of chronic suppurative otitis media: a retrospective review. Eur Arch Otorhinolaryngol 2013 Jan;270(1):69-76.
128. Molyneux EM, Tembo M, Kayira K, Bwanaisa L, Mweneychanya J, Njobvu A, et al. The effect of HIV infection on paediatric bacterial meningitis in Blantyre, Malawi. Arch Dis Child 2003 Dec;88(12):1112-1118.
129. van de Beek D, de Gans J, Spanjaard L, Weisfelt M, Reitsma JB, Vermeulen M. Clinical features and prognostic factors in adults with bacterial meningitis. N Engl J Med 2004 Oct 28;351(18):1849-1859.

130. Stone JH, Francis HW. Immune-mediated inner ear disease. Curr Opin Rheumatol 2000 Jan;12(1):32-40.
131. Runge MS, Greganti MA, Netter FH. Vertigo. Netter's internal medicine. 2 nd ed. Philadelphia: Saunders/Elsevier; 2009. p. 891.
132. Edmond K, Clark A, Korczak VS, Sanderson C, Griffiths UK, Rudan I. Global and regional risk of disabling sequelae from bacterial meningitis: a systematic review and meta-analysis. Lancet Infect Dis 2010 May;10(5):317-328.
133. World Health Organization. Childhood hearing loss: strategies for prevention and care. Geneva: World Health Organization; 2016.
134. Fortnum HM. Hearing impairment after bacterial meningitis: a review. Arch Dis Child 1992 Sep;67(9):1128-1133.
135. Rodenburg-Vlot MB, Ruytjens L, Oostenbrink R, Goedegebure A, van der Schroeff MP. Systematic Review: Incidence and Course of Hearing Loss Caused by Bacterial Meningitis: In Search of an Optimal Timed Audiological Follow-up. Otol Neurotol 2016 Jan;37(1):1-8.
136. Dodge PR, Davis H, Feigin RD, Holmes SJ, Kaplan SL, Jubelirer DP, et al. Prospective evaluation of hearing impairment as a sequela of acute bacterial meningitis. N Engl J Med 1984 Oct 4;311(14):869-874.
137. Pomeroy SL, Holmes SJ, Dodge PR, Feigin RD. Seizures and other neurologic sequelae of bacterial meningitis in children. N Engl J Med 1990 Dec 13;323(24):1651-1657.
138. Ruben R. Bacterial meningitic deafness: historical development of epidemiology and cellular pathology. Acta Otolaryngol 2008 Apr;128(4):388-392.
139. Bhatt SM, Lauretano A, Cabellos C, Halpin C, Levine RA, Xu WZ, et al. Progression of hearing loss in experimental pneumococcal meningitis: correlation with cerebrospinal fluid cytochemistry. J Infect Dis 1993 Mar;167(3):675-683.
140. Kastenbauer S, Klein M, Koedel U, Pfister HW. Reactive nitrogen species contribute to blood-labyrinth barrier disruption in suppurative labyrinthitis complicating experimental pneumococcal meningitis in the rat. Brain Res 2001 Jun 22;904(2):208-217.
141. Perny M, Solyga M, Grandgirard D, Roccio M, Leib SL, Senn P. Streptococcus pneumoniae-induced ototoxicity in organ of Corti explant cultures. Hear Res 2017 Jul;350:100-109.
142. Perny M, Roccio M, Grandgirard D, Solyga M, Senn P, Leib SL. The Severity of Infection Determines the Localization of Damage and Extent of Sensorineural Hearing Loss in Experimental Pneumococcal Meningitis. J Neurosci 2016 Jul 20;36(29):7740-7749.
143. Klein M, Koedel U, Pfister HW, Kastenbauer S. Meningitis-associated hearing loss: protection by adjunctive antioxidant therapy. Ann Neurol 2003 Oct;54(4):451-458.
144. Borkowski WJ,Jr, Goldgar DE, Gorga MP, Brookhouser PE, Worthington DW. Cerebrospinal fluid parameters and auditory brainstem responses following meningitis. Pediatr Neurol 1985 May-Jun;1(3):134-139.
145. Saha SK, Khan NZ, Ahmed AS, Amin MR, Hanif M, Mahbub M, et al. Neurodevelopmental sequelae in pneumococcal meningitis cases in Bangladesh: a comprehensive follow-up study. Clin Infect Dis 2009 Mar 1;48(Suppl 2):S90-6.
146. Quaade F, Kristensen KP. Purulent meningitis. A review of 658 cases. Acta Med Scand 1962 May;171:543-550.
147. Wippel C, Maurer J, Fortsch C, Hupp S, Bohl A, Ma J, et al. Bacterial cytolysin during meningitis disrupts the regulation of glutamate in the brain, leading to synaptic damage. PLoS Pathog 2013;9(6):e1003380.
148. Chang CJ, Chang WN, Huang LT, Chang YC, Huang SC, Hung PL, et al. Cerebral infarction in perinatal and childhood bacterial meningitis. QJM 2003 Oct;96(10):755-762.
149. World Health Organization. Global Health Observatory data repository, WHO LMIC Regions, Meningitis/encephalitis. 2018; Available at: *http://apps.who.int/gho/data/view.main.CM-*

*3002015REG7-CH7?lang=en*. Accessed October 20th, 2018.

150. World Health Organization. Global Health Observatory data repository. 2018; Available at: *http://apps.who.int/gho/data/view.main.ghe2002015-CH7?lang=en*. Accessed October 20th, 2018.
151. Kihara M, de Haan M, Were EO, Garrashi HH, Neville BG, Newton CR. Cognitive deficits following exposure to pneumococcal meningitis: an event-related potential study. BMC Infect Dis 2012 Mar 31;12:79-2334-12-79.
152. Griffiths UK, Dieye Y, Fleming J, Hajjeh R, Edmond K. Costs of meningitis sequelae in children in Dakar, Senegal. Pediatr Infect Dis J 2012 Nov;31(11):e189-95.
153. Pelkonen T, Roine I, Monteiro L, Cruzeiro ML, Pitkaranta A, Kataja M, et al. Prognostic accuracy of five simple scales in childhood bacterial meningitis. Scand J Infect Dis 2012 Aug;44(8):557-565.
154. de Jonge RC, van Furth AM, Wassenaar M, Gemke RJ, Terwee CB. Predicting sequelae and death after bacterial meningitis in childhood: a systematic review of prognostic studies. BMC Infect Dis 2010 Aug 5;10:232-2334-10-232.
155. Forsyth H, Kalumbi F, Mphaka E, Tembo M, Mwenechanya J, Kayira K, et al. Hearing loss in Malawian children after bacterial meningitis: incidence and risk factors. Audiological Medicine 2004 01/01;2(2):100-107.
156. Roine I, Pelkonen T, Cruzeiro ML, Kataja M, Peltola H, Pitkaranta A. Hearing impairment and its predictors in childhood bacterial meningitis in Angola. Pediatr Infect Dis J 2013 May;32(5):563-565.
157. Pelkonen T, Roine I, Monteiro L, Correia M, Pitkaranta A, Bernardino L, et al. Risk factors for death and severe neurological sequelae in childhood bacterial meningitis in sub-Saharan Africa. Clin Infect Dis 2009 Apr 15;48(8):1107-1110.
158. Akpede GO, Akuhwa RT, Ogiji EO, Ambe JP. Risk factors for an adverse outcome in bacterial meningitis in the tropics: a reappraisal with focus on the significance and risk of seizures. Ann Trop Paediatr 1999 Jun;19(2):151-159.
159. Roine I, Peltola H, Fernandez J, Zavala I, Gonzalez Mata A, Gonzalez Ayala S, et al. Influence of admission findings on death and neurological outcome from childhood bacterial meningitis. Clin Infect Dis 2008 Apr 15;46(8):1248-1252.
160. Roine I, Weisstaub G, Peltola H, LatAm Bacterial Meningitis Study G. Influence of malnutrition on the course of childhood bacterial meningitis. Pediatr Infect Dis J 2010 Feb;29(2):122-125.
161. Johnson AW, Adedoyin OT, Abdul-Karim AA, Olanrewaju AW. Childhood pyogenic meningitis: clinical and investigative indicators of etiology and outcome. J Natl Med Assoc 2007 Aug;99(8):937-947.
162. Hecox K, Galambos R. Brain stem auditory evoked responses in human infants and adults. Arch Otolaryngol 1974 Jan;99(1):30-33.
163. Wilkinson AR, Jiang ZD. Brainstem auditory evoked response in neonatal neurology. Semin Fetal Neonatal Med 2006 Dec;11(6):444-451.
164. Jewett DL, Williston JS. Auditory-evoked far fields averaged from the scalp of humans. Brain 1971;94(4):681-696.
165. Burkand R, McNerney K. Chapter II, Introduction to Auditory Evoked Potentials. In: Katz J, editor. Handbook of Clinical Audiology . 6th ed. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins; 2009.
166. Hecox K, Galambos R. Brain stem auditory evoked responses in human infants and adults. Arch Otolaryngol 1974 Jan;99(1):30-33.
167. Don M, Kwong B. Chapter XIII, Auditory Brainsem Response: Differential Diagnosis. In: Katz J, editor. Handbook of Clinical Audiology. 6th ed. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins; 2009.
168. Runge-Samuelson C, Friedland D. Chapter 128, Anatomy of the Auditory System. In: Flint PW, Cummings CW, editors. Cummings otolaryngology--head & neck surgery. 5th ed. Philadelphia, PA: Mosby/Elsevier; 2010.
169. Sininger YS, Abdala C, Cone-Wesson B. Auditory

threshold sensitivity of the human neonate as measured by the auditory brainstem response. Hear Res 1997 Feb;104(1-2):27-38.

170. Garcia-Larrea L, Artru F, Bertrand O, Pernier J, Mauguiere F. The combined monitoring of brain stem auditory evoked potentials and intracranial pressure in coma. A study of 57 patients. J Neurol Neurosurg Psychiatry 1992 Sep;55(9):792-798.
171. Su YY, Xiao SY, Haupt WF, Zhang Y, Zhao H, Pang Y, et al. Parameters and grading of evoked potentials: prediction of unfavorable outcome in patients with severe stroke. J Clin Neurophysiol 2010 Feb;27(1):25-29.
172. Nuwer MR. Fundamentals of evoked potentials and common clinical applications today. Electroencephalogr Clin Neurophysiol 1998 Feb;106(2):142-148.
173. Guerit JM, Amantini A, Amodio P, Andersen KV, Butler S, de Weerd A, et al. Consensus on the use of neurophysiological tests in the intensive care unit (ICU): electroencephalogram (EEG), evoked potentials (EP), and electroneuromyography (ENMG). Neurophysiol Clin 2009 Apr;39(2):71-83.
174. Scalais E, Francois-Adant A, Nuttin C, Bachy A, Guerit JM. Multimodality evoked potentials as a prognostic tool in term asphyxiated newborns. Electroencephalogr Clin Neurophysiol 1998 Mar;108(2):199-207.
175. Guerit JM. Neurophysiological testing in neurocritical care. Curr Opin Crit Care 2010 Apr;16(2):98-104.
176. Arulprakash S, Verma SP, Bhardwaj VK, Mishra SS, Chansori M. Brain Stem Auditory Evoked Responses and Visual Evoked Responses in Children with Tubercular Meningitis. Indian Pediatrics 2006;43(7):631-634.
177. Kalita J, Misra UK. Brainstem auditory evoked potential in Japanese encephalitis. J Neurol Sci 1999 May 1;165(1):24-27.
178. Pitkaranta A, Pelkonen T, de Sousa E Silva MO, Bernardino L, Roine I, Peltola H. Setting up hearing screening in meningitis children in Luanda, Angola. Int J Pediatr Otorhinolaryngol 2007 Dec;71(12):1929-1931.
179. Bao X, Wong V. Brainstem auditory-evoked potential evaluation in children with meningitis. Pediatr Neurol 1998 Aug;19(2):109-112.
180. Kapoor RK, Makharia A, Shukla R, Misra PK, Sharma B. Brainstem auditory evoked response in tuberculous meningitis. Indian J Pediatr 1997 May-Jun;64(3):399-407.
181. Topcu I, Cureoglu S, Yaramis A, Tekin M, Oktay F, Osma U, et al. Evaluation of brainstem auditory evoked response audiometry findings in children with tuberculous meningitis at admission. Auris Nasus Larynx 2002 Jan;29(1):11-14.
182. Clinical and Laboratory Standards Institute. Performance Standards for Antimicrobial Susceptibility Testing; Seventeenth Informational Supplement. CLSI document M100-S17. Wayne, Pennsylvania, USA: Clinical and Laboratory Standards Institute; 2007.
183. World Health Organization. Standardized treatment of bacterial meningitis in Africa in epidemic and non epidemic situations . Geneva: World Health Organization; 2007.
184. Ologe FE, Nwawolo CC. Chronic suppurative otitis media in school pupils in Nigeria. East Afr Med J 2003 Mar;80(3):130-134.
185. Amusa YB, Ijadunola IKT, Onayade OO. Epidemiology of otitis media in a local tropical African population. West Afr J Med 2005 Jul-Sep;24(3):227-230.
186. Ugochukwu EF, Ezechukwu CC, Undie N, Akujobi C. Pattern of pathogens in ear discharge of HIV-infected children in Nnewi, Southeast Nigeria. Nigerian Journal of Clinical Practice 2007 Jun;10(2):130-136.
187. Abera B, Kibret M. Bacteriology and antimicrobial susceptibility of otitis media at dessie regional health research laboratory, Ethiopia. Ethiopian Journal of Health Development 2011;25(2):161-167.
188. Bello R, Agbo E, Olabode H. Antibiogram of Bacterial and Fungal Isolates Associated with Otitis

Media amongst Children in Bauchi State, Nigeria. International Journal of Pharmacy and Bioscience 2011;2:200-207.

189. Nnebe-agumadu U, Okike O, Orji I, Ibekwe RC. Childhood suppurative otitis media in Abakaliki: isolated microbes and in vitro antibiotic sensitivity pattern. Nigerian Journal of Clinical Practice 2011 Apr-Jun;14(2):159-162.
190. Motayo B, Ojiogwa I, Adeniji F, Nwanze J, Onoh C, Okerentugba P, et al. Bacteria isolates and antibiotic susceptibility of Ear infections in Abeokuta, Nigeria. Report and Opinion 2012;4(4):23-26.
191. Muleta D, Gebre-Selassie S, Nida H. Isolation and antimicrobial susceptibility patterns of bacterial pathogens causing otitis media in children in Jimma Hospital Southern Ethiopia. Ethiop J Health Dev 2004;14(2):89-100.
192. Matundwelo N, Mwansasu C. Bacteriology of Chronic Suppurative Otitis Media among Children at the Arthur Davidson Children's Hospital, Ndola, Zambia. Med J Zambia 2016;43(1).
193. Fasunla AJ, Samdi M, Nwaorgu OG. An audit of ear, nose and throat diseases in a tertiary health institution in South-western Nigeria. The Pan African medical journal 2013;14:1.
194. Ilechukwu GC, Ilechukwu C, Ezeanolue BC, Okoroafor IJ, Ojinnaka NC, Ubesie AC, et al. Ear-related problems among children attending the paediatric and otorhinolaryngology out-patients clinics of the University of Nigeria Teaching Hospital, Enugu. Afr Health Sci 2016 Jun;16(2):363-366.
195. Filipe M, Reimer A, Matuschek E, Paul M, Pelkonen T, Riesbeck K. Fluoroquinolone-Resistant Alcaligenes faecalis Related to Chronic Suppurative Otitis Media, Angola. Emerg Infect Dis 2017 Oct;23(10):1740-1742.
196. Udden F, Filipe M, Reimer A, Paul M, Matuschek E, Thegerstrom J, et al. Aerobic bacteria associated with chronic suppurative otitis media in Angola. Infect Dis Poverty 2018 May 3;7(1):42-018-0422-7.
197. Tansarli GS, Poulikakos P, Kapaskelis A, Falagas ME. Proportion of extended-spectrum beta-lactamase (ESBL)-producing isolates among Enterobacteriaceae in Africa: evaluation of the evidence--systematic review. J Antimicrob Chemother 2014 May;69(5):1177-1184.
198. Instituto Nacional de Estatística (INE) Ministério da Saúde (MINSA), Ministério da Planeamento e do Desenvolvimento Territorial (MPDT), ICF. Key findings of the 2015-16 Angola IIMS. Luanda, Angola. Rockville, Maryland, USA: INE, MINSA, MPDT and ICF; 2017.
199. Unicef Data. Monitoring the situation of children and woman. 2018; Available at: *https://data.unicef.org/topic/child-health/pneumonia/*. Accessed October 20, 2018.
200. Reefhuis J, Honein MA, Whitney CG, Chamany S, Mann EA, Biernath KR, et al. Risk of bacterial meningitis in children with cochlear implants. N Engl J Med 2003 Jul 31;349(5):435-445.
201. Baraff LJ, Lee SI, Schriger DL. Outcomes of bacterial meningitis in children: a meta-analysis. Pediatr Infect Dis J 1993 May;12(5):389-394.
202. Peltola H, Roine I, Fernandez J, Gonzalez Mata A, Zavala I, Gonzalez Ayala S, et al. Hearing impairment in childhood bacterial meningitis is little relieved by dexamethasone or glycerol. Pediatrics 2010 Jan;125(1):e1-8.
203. Worsoe L, Caye-Thomasen P, Brandt CT, Thomsen J, Ostergaard C. Factors associated with the occurrence of hearing loss after pneumococcal meningitis. Clin Infect Dis 2010 Oct 15;51(8):917-924.
204. Douglas SA, Sanli H, Gibson WP. Meningitis resulting in hearing loss and labyrinthitis ossificans - does the causative organism matter?. Cochlear implants int 2008 Jun;9(2):90-96.
205. Kawahara N, Sasaki M, Mii K, Tsuzuki M, Takakura K. Sequential changes of auditory brain stem responses in relation to intracranial and cerebral perfusion pressure and initiation of secondary brain stem damage. Acta Neurochir (Wien) 1989;100(3-4):142-149.
206. Rothwell PM. Treating individuals 2. Subgroup analysis in randomised controlled trials: importance, indications, and interpretation. Lancet 2005 Jan 8-14;365(9454):176-186.

207. Connor C, Averburg D, Miralles M. Angola Health System Assessment 2010. : Bethesda, MD, Health Systems 20/20, Abt Associates Inc; 2010.
208. Diedendorf A. Chapter XXIII, Assessment of Hearing Loss in Children. In: Katz J, editor. Handbook of Clinical Audiology. 6th ed. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins; 2009.
209. Roine I, Pelkonen T, Cruzeiro ML, Kataja M, Aarnisalo A, Peltola H, et al. Fluctuation in hearing thresholds during recovery from childhood bacterial meningitis. Pediatr Infect Dis J 2014 Mar;33(3):253-257.
210. Bargen GA. Chirp-Evoked Auditory Brainstem Response in Children: A Review. Am J Audiol 2015 Dec;24(4):573-583.
211. Roine I, Pelkonen T, Bernardino L, Leite M, Kataja M, Pitkaranta A, et al. Factors affecting time to death from start of treatment among children succumbing to bacterial meningitis. Pediatr Infect Dis J 2014 Aug;33(8):789-792.
212. Mulwafu W, Nyirenda TE, Fagan JJ, Bem C, Mlumbe K, Chitule J. Initiating and developing clinical services, training and research in a low resource setting: the Malawi ENT experience. Trop Doct 2014 Jul;44(3):135-139.
213. Fagan J, Jacobs M. Survey of ENT services in Africa: need for a comprehensive intervention. Global Health Action 2009 11/11;2(1):1932.
214. Mulwafu W, Ensink R, Kuper H, Fagan J. Survey of ENT services in sub-Saharan Africa: little progress between 2009 and 2015. Global Health Action 2017 01/01;10(1):1289736.
215. UEMS ORL section. Manpower 2017. 2019; Available at: *http://orluems.com/index.asp?seccion=7&apartado=27&registro=58*. Accessed January 26th, 2019.
216. Bright T, Mulwafu W, Thindwa R, Zuurmond M, Polack S. Reasons for low uptake of referrals to ear and hearing services for children in Malawi. PLoS One 2017 Dec 19;12(12):e0188703.
217. Dr Matuba Filipe. Personal communication. 2019.
218. Donald KA, Kakooza AM, Wammanda RD, Mallewa M, Samia P, Babakir H, et al. Pediatric Cerebral Palsy in Africa: Where Are We? J Child Neurol 2015 Jul;30(8):963-971.
219. Iemmi V, Gibson L, Blanchet K, Suresh Kumar K, Rath S, Hartley S, et al. Community-based Rehabilitation for People With Disabilities in Low- and Middle-income Countries: A Systematic Review. Campbell Systematic Reviews 2015 2015;15.
220. Zuurmond M, O'Banion D, Gladstone M, Carsamar S, Kerac M, Baltussen M, et al. Evaluating the impact of a community-based parent training programme for children with cerebral palsy in Ghana. PLoS One 2018 Sep 4;13(9):e0202096.
221. John M, Parsons A, Abraham S. The value of an ENT specialist outreach service in a Family Medicine Unit for the urban poor in India. J Family Med Prim Care 2016 Jan-Mar;5(1):67-72.
222. Mahomed-Asmail F, Swanepoel de W, Eikelboom RH, Myburgh HC, Hall J,3rd. Clinical Validity of hearScreen Smartphone Hearing Screening for School Children. Ear Hear 2016 Jan-Feb;37(1):e11-7.
223. World Health Organization, Seventieth World Health Assembly. Prevention of deafness and hearing loss 2017; Available at: *http://apps.who.int/gb/ebwha/pdf_files/WHA70/A70_R13-en.pdf?ua=1*. Accessed October 20th, 2018.
224. Uppal L, Singhi S, Singhi P, Aggarwal R. Role of Rifampin in Reducing Inflammation and Neuronal Damage in Childhood Bacterial Meningitis: A Pilot Randomized Controlled Trial. Pediatr Infect Dis J 2017 Jun;36(6):556-559.
225. Franzen SRP, Chandler C, Siribaddana S, Atashili J, Angus B, Lang T. Strategies for developing sustainable health research capacity in low and middle-income countries: a prospective, qualitative study investigating the barriers and enablers to locally led clinical trial conduct in Ethiopia, Cameroon and Sri Lanka. BMJ Open 2017 Oct 13;7(10):e017246-2017-017246.