Otitis media in Greenlandic Inuit children

Management, intervention and perceptions in a high-risk population

PhD Thesis

Malene Nøhr Demant, MD

Department of Otorhinolaryngology and Maxillofacial Surgery

Zealand University Hospital, Køge, Denmark

Arsarnerit qaatutut unnuami
Qilaap qaarajuttup assuutai
Nusutsisut pulatertaraakka
Ullaalli qaasup minguertaraanga

Pigaarma nuna taatoq isseqisoq
Anorrimik persoriinnaq qaaguk
Pilissavorli aappilliuttoq seqineq
Uisorernertut kissalaartoq aasaq

Når nordlyset synges i dissonans
Hen over nattens store
himmelapsis
Så hvirvles jeg ned i en
bundløs dans
Men genopstår af morgenens
katharsis

Mit store og iskolde land,
jeg er din
Send blæst, send mig sne
og send blot storme
Men skænk mig sommernatten
rød som en rubin
Et kort sekund,
et kys af sol og varme

With northern lights whirling
in dissonance
Projected on night's vaulted
darkness
I unravel in a heedless dance
But rise afresh in morning's
catharsis

Beloved and hoar-frozen land,
I am yours
Send gales, send me snow
and rush the storms forth
Just grant a midsummer's
crimson night that restores
An interlude of light and
sun-kissed warmth

Primary academic advisor

Preben Homøe

Department of Otorhinolaryngology and Maxillofacial Surgery, Zealand University Hospital, Køge

University of Copenhagen, Denmark and University of Greenland, Ilisimatusarfik, Greenland

Academic co-advisors

Ann Hermansson

Departments of Otolaryngology, Oral and Maxillofacial Surgery and Pediatrics, Lund University Hospital

Lund University, Lund, Sweden

Ramon Gordon Jensen

Department of Otolaryngology, Head and Neck Surgery & Audiology, Rigshospitalet

University of Copenhagen, Denmark

External assessor

Jørgen Lous

University of Southern Denmark

Assessment committee

Anders Koch (chairperson)

Associate professor, University of Copenhagen, Denmark, and Professor, University of Greenland, Ilisimatusarfik, Greenland

Peter Morris

Professor, Menzies School of Health Research, Australia

Sten Hellström

Professor, Karolinska University Hospital, Sweden

Preface and acknowledgements

The first time I encountered a patient with chronic suppurative otitis media was on the west coast of Greenland, where I was working as a medical doctor in the small hospital of Aasiaat. I was stunned by the smell and the abundant discharge coming out of the child's little ear. I had never encountered that sort of middle ear infection in Denmark, and I did not know how to handle it properly. Luckily, Greenland is home to some of the most skillful and experienced doctors I have ever met, so I called my senior colleague Jørgen Breinholt and the patient received the best care we could provide. However, I started wondering how and why these middle ear infections were so dominant in the everyday life at the clinic.

When I got back home to Denmark, I met professor Preben Homøe, who led me into the world of Greenlandic health research. Our shared fascination of the magnificent Greenlandic nature and the people living in it, was the beginning of the journey that brought me here. I would like to sincerely thank Preben and Ramon Gordon Jensen for introducing me to the field of otitis media in Greenland as well as for their guidance and optimism throughout this challenging journey. I also thank Ann Hermansson and Jørgen Lous for their thorough supervision and valuable insights.

I am thankful for all the support I have always received at the Queen Ingrid Health Care Centre and Queen Ingrid's Hospital in Nuuk, where especially Gert Mulvad, Michael Lynge Petersen, Jesper Olesen and Jens Fleischer have been invaluable in the process of this research. I have always been received with open arms at all the health care centres and hospitals around Greenland, despite the personnel's limited time and sometimes immense work pressure. For that I am truly grateful.

I thank Janus Jakobsen and Christian Gluud from Copenhagen Trial Unit, for introducing me to the quest for perfectionism of high-quality randomized controlled trials and for their efforts to always strive for the best.

A special thanks to Anne-Marie Ulrik who started out as my senior supervisor in the clinical world in Aasiaat, continued her support as my chief medical officer in Nuuk and finally, as my friend, conducted the ceremony for my wedding last year.

I thank my colleagues at the Greenland section of the National Institute for Public Health where Christina Viskum Lytken Larsen helped me through a challenging time while introducing me to the fascinating world of qualitative research and helped me see the concept of research from a broader perspective.

To all my colleagues at the office in Køge, I could not have done this without you. Thank you for sharing ups and downs and friendships.

Last but not least I would like to thank my loving family for their eternal support and for always being there for me with both professional, logistical and emotional aid. Without it, I could not have done this.

And Jakob, my colleague, my tutor, my husband, my best friend. Thank you.

Table of contents

List of papers

The thesis is based on the following papers:

Paper 1

The effects of ventilation tubes versus no ventilation tubes for recurrent acute otitis media or chronic otitis media with effusion in 9 to 36-month-old Greenlandic children, the SIUTIT trial: study protocol for a randomized controlled trial.

Demant MN, Jensen RG, Jakobsen JC, Gluud C, Homøe P.

Trials, 2017

Paper 2

The use of smartphone otoscopy in Greenland: a cross-sectional study

Demant MN, Jensen RG, Bhutta MF, Laier GH, Lous J, Homøe P

[submitted for publication in the International Journal of Pediatric Otorhinolaryngology]

Paper 3

Parental perceptions and management strategies for otitis media in Greenland

Demant MN, Larsen CVL, Homøe P

International Journal of Pediatric Otorhinolaryngology, 2019

Abbreviations

AOM	Acute otitis media
ASA	American Society of Anesthesiologists
CI	Confidence interval
CIQ	Caregiver Impact Questionnaire
COME	Chronic otitis media with effusion
CSOM	Chronic suppurative otitis media
DaPa	Decapascal
ENT	Ear, Nose, and Throat
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HL	Hearing loss
IRA	Interrater agreement
IQR	Interquartile range
MEE	Middle ear effusion
OAE	Otoacoustic emission
OM	Otitis media
OME	Otitis media with effusion
OM-6	Otitis Media-6 questionnaire
rAOM	Recurrent acute otitis media
RCT	Randomized controlled trial
SOM	Secretory otitis media
QoL	Quality of life
VT	Ventilation tubes
WHO	World Health Organization

List of tables, figures and appendix

Tables

Figures

Appendix

1. Background

1.1 Definition of otitis media

The definition of otitis media (OM) is complex, and the term cover several interrelated disease subtypes with different treatment regimens and consequences. For some subtypes, OM can be viewed as a continuum representing different stages of the disease, and as a consequence a clear distinction is difficult [1]. Figure 1 shows the interrelation of the different subtypes.
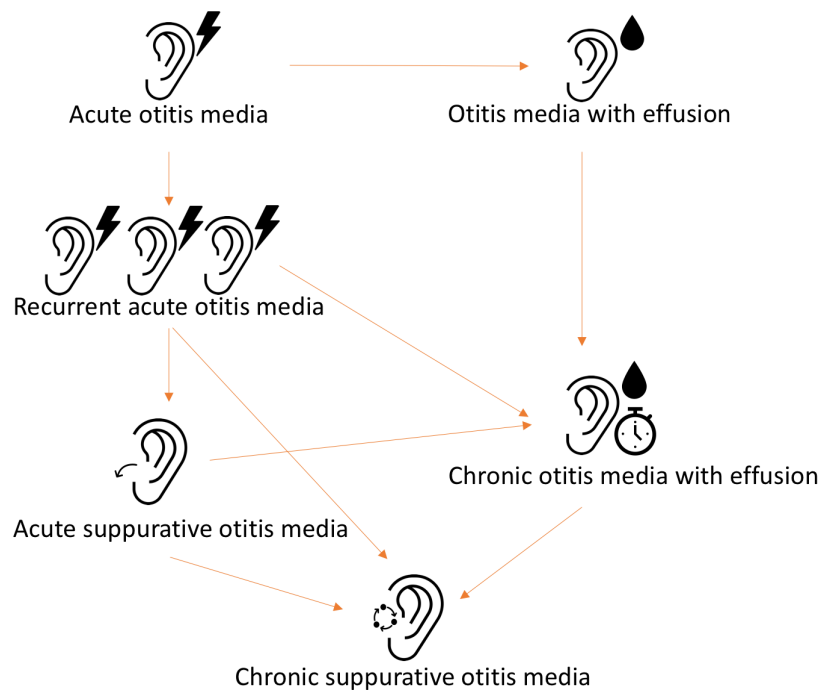
Figure 1. The interrelation of different subtypes of OM.

Acute otitis media

Acute otitis media (AOM) is characterized by acute onset of symptoms of inflammation of the middle ear i.e. fluid in the middle ear, a red, bulging tympanic membrane and non-specific signs such as ear rubbing, fever, irritability, excessive crying and changes in sleep pattern, depending on the child's age

[1-3]. In their 2013 guidelines, the American Academy of Pediatrics recommended that AOM should not be diagnosed in children without the presence of middle ear effusion (MEE) [1]. Recurrent AOM (rAOM) is defined as three or more episodes of AOM in 6 months or four or more episodes of AOM in 12 months [1, 2].

Otitis media with effusion

Otitis media with effusion (OME) (synonymous with secretory otitis media (SOM)) is defined by fluid in the middle ear cavity, but with absence of acute symptoms of inflammation [3, 4]. Measurement of tympanic membrane mobility is crucial in the diagnosis, as clinical symptoms may be sparse, with decreased level of hearing as the only sign of effusion. OME often occurs in relation to AOM, both before and after an acute infection, which can make the distinction difficult [5].
Chronic OME (COME) is defined as OME lasting for 3 months or longer [1, 2].

Chronic suppurative otitis media

Chronic suppurative otitis media (CSOM) (synonymous with chronic active mucosal otitis media and chronic tympanomastoiditis) is characterized as chronic inflammation of the middle ear cavity, the eustachian tube and mastoid cavity with recurrent or persistent discharge from a perforation in the tympanic membrane [3, 6, 7]. The exact definition of CSOM has been widely debated and the nomenclature inconsistently used, reflecting that the development from one disease entity to another is not fully understood [8]. Criteria for the duration of ear discharge varies among different definitions. The World Health Organization (WHO) has defined CSOM as ear discharge lasting for 14 days or more, however other definitions are based on the ear discharge lasting for 3 months [6, 7, 9]. The duration of the existence of the perforation has not been specified in the WHO-definition. The inclusion of a dry perforation in the definition is also debated, since the dry perforation can be seen as the disease at an inactive stage [7].
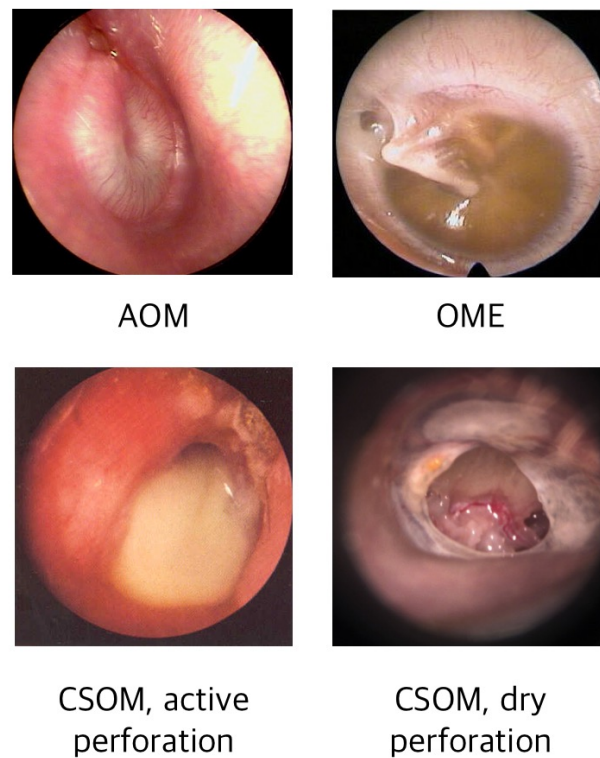
Figure 2. Images of tympanic membranes showing AOM, OME and CSOM.

Photos: Ramon Gordon Jensen.

1.2 Diagnosis of otitis media

There is no generally applied "golden standard" for diagnosis of OM, although the need for stringent and uniform criteria is frequently discussed and considered essential for correct and timely treatment [1, 2, 10]. Otoscopy or otomicroscopy and subsequent OM diagnosis has proven difficult, especially among small children [11, 12]. There is a general consensus that diagnosis should preferably also include testing of the tympanic membrane mobility (i.e. pneumatic otoscopy or tympanometry) which will give a much higher validity to the diagnose. The American Association of Pediatrics recommend that pneumatic otoscopy is always implemented in the diagnostic process [1, 2, 10, 13].

Pneumatic otoscopy consists of a pneumatic bulb and a speculum. Changing the pressure around the tympanic membrane will trigger the tympanic membrane to move when pressure is applied if the middle ear cavity is aeriated while a fluid-filled middle ear will decrease tympanic membrane mobility and often easily detectable air-bubbles in the middle ear.

A tympanometer consists of a speaker, a microphone and a manometer. A soundwave is produced and sent towards the tympanic membrane while the pressure around the tympanic membrane changes. The sound is reflected and recorded by the microphone, and, based on the reflection, a measure of compliance of the tympanic membrane as well as a volume estimate is provided [11]. Figure 3 shows examples of tymanometry curves.

Pneumatic otoscopy requires that the tympanic membrane is properly visualized as opposed to tympanometry, which may make the tympanometry easier to use, although the ability of tympanometry to distinguish between diagnostic subgroups without visualization of the tympanic membrane is uncertain, since the result does not depend on the type of fluid behind the tympanic membrane [14, 15].
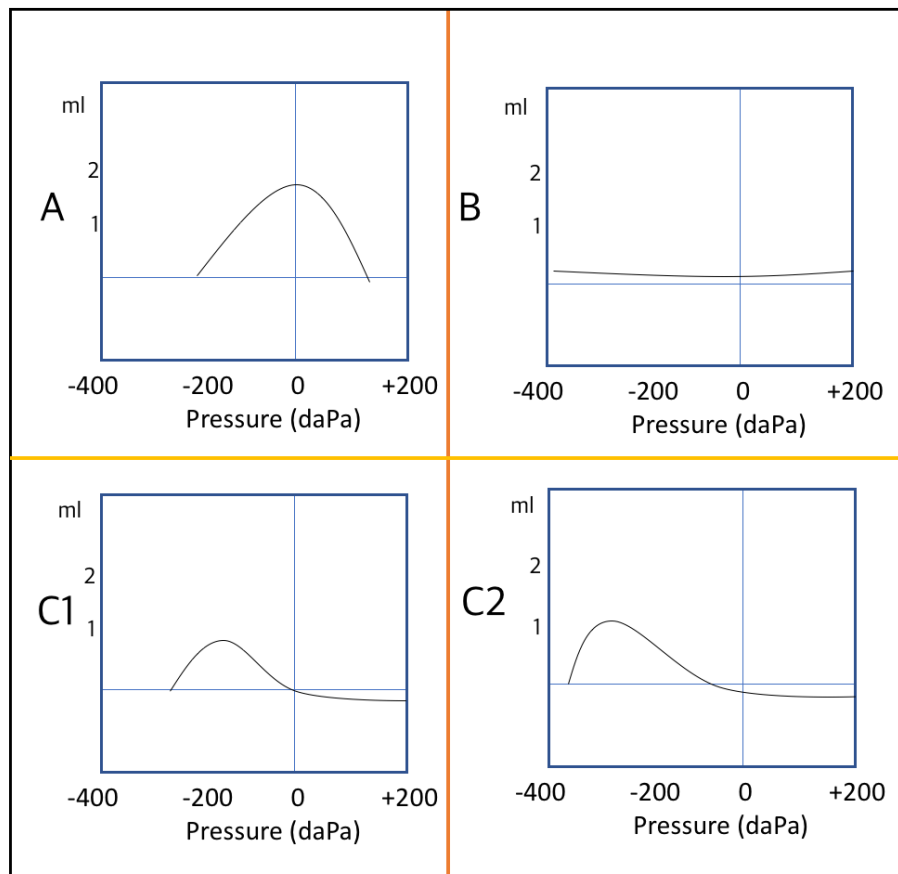
DaPa = deca pascal, ml = millilitre (volume)

Type A is considered normal, illustrating an air-filled middle ear. Type B (flat curve) is indicating fluid in the middle ear, i.e. effusion. Type C is borderline; C1 is defined as pressure between –99 and –199 daPa, C2 as pressure below –200 daPa.

Figure 3. Tympanometry curves.

1.3 Microorganisms involved in otitis media

The most common microorganisms found in relation to AOM are *Streptococchus pneumoniae (S. pneumoniae), Haemophilus influenzae (H. influenzae), Moraxella catarrhalis* (*M. catarrhalis*) and Group A Streptococci [16]. Previously, the general assumption was that the difference between OME and AOM was the absence of bacteria in the middle ear fluid associated with OME. New research implies that OME is not sterile and that the microbiological profile of AOM and OME is somewhat similar [17]. The most common microorganisms found in relation to CSOM are *Pseudomonas aeruginosa* and *Staphylococcus aureus*, although a Greenlandic study also found high levels of H. influenzae in CSOM among Greenlandic Inuit [16, 18]. The formation of biofilm may further complicate effective treatment and necessitate prolonged antibiotic treatment [18].

1.4 Burden of otitis media in indigenous populations - epidemiology and risk factors

OM is among the most frequent reasons for children contacting health clinics worldwide as well as the most common reason for antibiotic prescriptions in the United States (US) and many other Western countries [3, 10, 19]. A systematic review addressing global estimates on the burden of OM found that incidence rates for AOM ranged from 3.64 new episodes per 100 people per year in Central Europe to 43.37 new episodes per 100 people per year in Western Sub-Saharan Africa [20]. Estimates for incidence rates for CSOM showed a range from 1.70 new episodes per 1000 people per year in Latin America to 9.37 in Oceania [20]. However, these estimates are not all based on field studies but in many instances extrapolated from existing data, resulting in some uncertainties.

The difference of OM burden is not only evident among different parts of the world, it is also seen among different populations within the same country, especially when comparing indigenous populations to non-indigenous populations [6, 10, 21]. The Greenlandic Inuit, Alaskan Inuit, Native Americans and the Australian Aboriginals have all been found to have overall higher rates of OM than their non-indigenous peers, and indigenous children seem to experience the disease earlier in life and in more severe forms than non-indigenous children [21-25].

The prevalence of CSOM ranges from being a rare condition (<1%) in high-income countries, to moderate prevalence (< 2%) in some low- or middle-income countries, and to higher than 4% in some indigenous populations such as the Greenlandic Inuit, Alaskan Inuit, Native Americans and the Australian Aboriginals [6, 10, 21]. According to the WHO, if the prevalence of CSOM is higher than 4%, the population is dealing with a massive health problem requiring urgent attention [6]. Among

Greenlandic Inuit the prevalence of CSOM is 9-14%, which is one of the highest in the world [22, 26, 27].

The risk factors known for OM show that it is a multifactorial disease, and the complex and not fully understood causal pathway of the disease is caused by environmental, anatomical and genetic factors [3, 7, 28, 29]. Passive tobacco smoking, attending day care, male gender, number of upper respiratory tract infections (URTI), lack of breast feeding and adenoid hypertrophy are all risk factors consistently associated with higher risk of AOM [3, 10]. The development of CSOM is closely related to episodes of AOM, and therefore some risk factors are shared [16, 21]. However, CSOM is a disease more prevalent in low-income countries and indigenous populations and is further correlated with low socioeconomic status and ethnicity [9, 30, 31].

It is currently not known what causes the higher rates of OM among indigenous populations, but it is most likely multifactorial, including factors such as inadequate housing and crowding, early bacterial colonization, passive tobacco smoking and general poverty [6, 21, 32-35]. A population-based study from Greenland found that being Inuit caused a five-fold increase in the risk of developing CSOM [26]. Other risk factors were number of siblings, attending day-care, mothers reporting ear discharge and short duration of mothers' school education. Greenlandic Inuit children have been found to carry a massive load of potentially pathogenic bacteria such as *S. pneumoniae* and *H. influenzae* and a study among Australian Aboriginal children showed earlier colonization with *S. pneumoniae*, *M. catarrhalis* and *H. influenzae* as compared to non-indigenous children [34, 36].

1.5 Treatment of otitis media

Antibiotics

Treatment guidelines on the prescription of oral antibiotics for AOM varies among countries [1, 13, 37]. A Cochrane review from 2015 based on 13 randomized controlled trials (RCTs) including 3401 children from high-income countries found that treatment with oral antibiotics had no effect on early pain and only a small effect on pain 4 to 7 days after initial treatment (number needed to treat = 16) [38]. The children most likely to benefit from antibiotic treatment were children below the age of 2 with bilateral infection and children with concomitant otorrhea [38]. This indicates that correct, stringent diagnosis and selection of children may decrease the numbers needed to treat to avoid serious infections. Both the Cochrane review as well as another review from 2014, conclude that overall, the use of oral antibiotics for AOM *does* reduce pain faster than a placebo, but disadvantages such as vomiting and diarrhea need to be weighed against the relatively small benefit [38].

The included studies were all done on children from high-income countries and results should therefore be extrapolated with caution to high-risk populations such as the Greenlandic Inuit.

Antibiotics used for the prevention of AOM have been found effective in a Cochrane review from 2011 [39]. Here, the authors concluded that the administration of oral antibiotics once or twice daily reduced the risk of AOM episodes, during the treatment period. This effect increased among at-risk otitis-prone children and may increase further if administered among children in high-risk populations [39]. In Australia, where the indigenous population suffers from overall OM in a degree comparable to the Greenlandic Inuit, Leach et al. conducted an RCT comparing long-term (24 weeks or until tympanometry verified normal middle ear status) treatment with amoxicillin or placebo [40]. The trial found that long-term treatment with amoxicillin improved overall ear-health, i.e. decreased the number of children with perforated tympanic membranes as well as decreased the load of pneumococcal carriage [40].

The use of antibiotics is generally not recommended as the standard treatment for OME [41]. A recent Cochrane review based on 23 trials including 3258 children found that even though antibiotics were associated with the complete resolution of OME, no effect was found on hearing levels or ventilation tube insertions [42]. No data was found on outcomes such as speech development and quality of life (QoL) [42].

Topical antibiotics are used for treatment of CSOM combined with aural toilette [43].

Surgical interventions

Ventilation tubes (VT) (also called tympanostomy tubes or grommets) are small tubes, that, when inserted into the tympanic membrane, create ventilation of the middle ear and equalizes the oxygen tension, bypassing the problems created by a dysfunctional eustachian tube as well as allowing fluid to exit. Generally, the two main indications for treatment with VT are COME with associated hearing impairment and rAOM [1, 2, 4, 44, 45]. It is the most frequent ambulant surgery performed on children in the US. The frequency of VT treatment around the world varies greatly [44, 46]. Denmark has one of the highest frequencies of VT treatments in the world, with 250 in 10.000 children receiving VT [47].

The most recent Cochrane review by Browning et al., updated in 2010, on VT for hearing loss (HL) associated with OME included 10 trials with a total of 1728 children [48]. The authors found a benefit of 4 dB at 6 to 9 months after surgery among the children treated with VT. However, after 12 and 18 months, this benefit was no longer present. Among the included trials, no effect was seen on QoL, language- or speech development [48]. Another review from 2011 by Hellström et al. found similar results with improved hearing levels at 9 months after surgery and no conclusive evidence on the

effect on language development. However, based on one RCT and two prospective cohort studies, the authors found that VT improved QoL of the treated children within the first 2 to 9 months after surgery. The review excluded studies that included children with OME for a shorter duration than 3 months, thereby not fulfilling the consensus criteria for COME [49].

A recent Cochrane review by Venekamp et al. from 2018 investigated the current available evidence supporting treatment of children with rAOM [50]. The review included five RCTs, based on VT treatment on 805 children in total, all in high or unclear risk of bias. Overall, the review concluded that the treatment of rAOM with VT decreases the number of AOM episodes, but in the magnitude of one episode during the first 6 months and may be lower within 12 months [50]. One review by Hellström et al. from 2011 and one meta-analysis by Steele et al. from 2017, including both RCTs and non-RCTs, found insufficient evidence that VT treatment for rAOM reduces the number of episodes with AOM [49, 51]. None of the reviews found studies reporting on QoL after VT among children suffering from rAOM. Finally, one review by Lous et at. from 2011 concluded that even though the authors found a small benefit of VT treatment, the supporting evidence was very limited and that high-quality RCTs including outcomes such as QoL for both the children and their caregivers, are needed [52].

There are currently no national guidelines in Greenland on the treatment of OM [53]. The evidence to support the use of ventilation tubes in high risk populations such as the Greenlandic Inuit does not exist and, as elaborated above, even in low-risk developed parts of the world the effects of ventilation tubes are still somewhat questionable and guidelines generally based on low-quality evidence [48-50, 54].

Adenoidectomy is found to have a modest impact on rAOM among children below the age of 2 and on children above the age of 4 suffering from COME [55]. A Cochrane review found a significant effect on the resolution of OME, but not on hearing levels, and no effect on AOM [56]. Myringotomy only is not considered effective in the treatment of OM [3].

Overall, current recommendations for the treatment of OM worldwide are primarily based on RCTs and observational studies conducted among low-risk populations.

1.6 Complications and consequences of otitis media

Acute complications

Although rare, there are serious acute complications related to AOM, both intra- and extracranial. It is estimated that 21-28 thousand people die every year due to AOM complications, with the risk of death

being high among children aged 0-4 years, lowest in the 25-34-year age group and highest among people above the age of 75 [6, 20].

The middle ear cavity's close relation to intracranial structures provides the risk of developing intracranial complications such as brain abscess, meningitis, sinus thrombosis and encephalitis [9, 57]. Extracranial complications include affection of the facial nerve, leading to facial paralysis, mastoiditis and labyrinthitis [9, 57]

Despite the high rates of AOM in Greenland, the incidence of mastoiditis is relatively low [58].

Hearing

OM is the most prevalent cause for temporary hearing loss among children worldwide [59]. Adequate hearing levels are crucial for small children in the midst of developing cognitive and social skills including speech [60]. Even mild hearing loss may affect educational and socio-emotional capabilities resulting in long-term cognitive and behavioural disadvantages [61-63] .

The WHO estimates that 50% of the 60 to 330 million people worldwide suffering from CSOM have hearing impairment and state that it may lead to impaired educational skills as well as other cognitive challenges, thereby having potential deleterious impact on social development and progression [6]. Previous studies on hearing levels among Greenlandic Inuit have consistently shown high levels of hearing loss. In a study from 1995 of children aged 5-14 years, the authors found that 43% of the participating children had hearing loss of more than 20 dB on one or both ears [64]. A cohort study from 2013 found that 50% of the participants, aged 11-24 years had hearing loss ≥15 dB and 10% had hearing loss ≥40 dB [65]. Furthermore, individuals who had suffered from CSOM during childhood had a 91% risk of developing hearing loss later in life [65]. The prevalence of hearing loss among Greenlandic adolescents is thereby three times higher than in the US [27, 65].

Eighty percent of all hearing disabled people in the world live in resource-constrained areas, which are also often where ear and hearing programs are least developed [66]. In a survey conducted by the WHO in 2013, only 40% of all low- to middle-income countries had a designated ear and hearing strategy [67].

1.7 Quality of life among affected families

Several studies have shown that even though OM in the developed part of the world is considered a somewhat mild disease, caregivers to children affected by OM have significantly decreased quality of life (QoL), when compared to families not affected by OM [68-71]. Brouwer et al. found that having a

child with rAOM provided the same decrease in QoL as having a child with mild to moderately severe chronic illness [68].

Different questionnaires have been developed to measure the impact of QoL. The questionnaire OM-6 addresses the impact on the child, whereas the questionnaire Caregiver Impact Questionnaire focuses on the parental aspects of the disease [72, 73]. However, these questionnaires have not been developed to investigate the impact in indigenous populations, which are the ones who are mostly affected. Perceptions and management strategies of disease have previously been found to differ from Western parts of the world when compared to indigenous populations [74, 75].

1.8 Greenland at a glance

Geography and demographics of Greenland

Greenland, Kalaallit Nunaat (the Land of the Kalaallit i.e. Greenlanders/Inuit/humans) is part of the Arctic region, geographically part of North America but politically part of the Kingdom of Denmark [76, 77]. The definition of the Artic region is not fully agreed upon, hence the term "circumpolar region" is often used. The circumpolar region consists of populations from eight different countries (The Arctic Eight): Canada, Russia, Finland, Sweden, Norway, USA, Iceland and Denmark, represented by Greenland and the Faroe Islands [77]. The Inuit population, counting approximately 167,000 individuals in total, live in different parts of the region, with the majority of Inuit living in USA (57,000), followed by Canada (50,000) and Greenland (50,000), and finally Denmark (8,000) and Russia (1,300) [78]. The Inuit populations in all countries share many challenges both environmentally and socially. While parts of the circumpolar region include some of the most developed countries in the world, the Inuit population continues to have health disparities compared to the non-indigenous populations [78, 79]. The countries in the region are collaborating on different levels, including the Arctic Council and International Union for Circumpolar Health [80, 81].

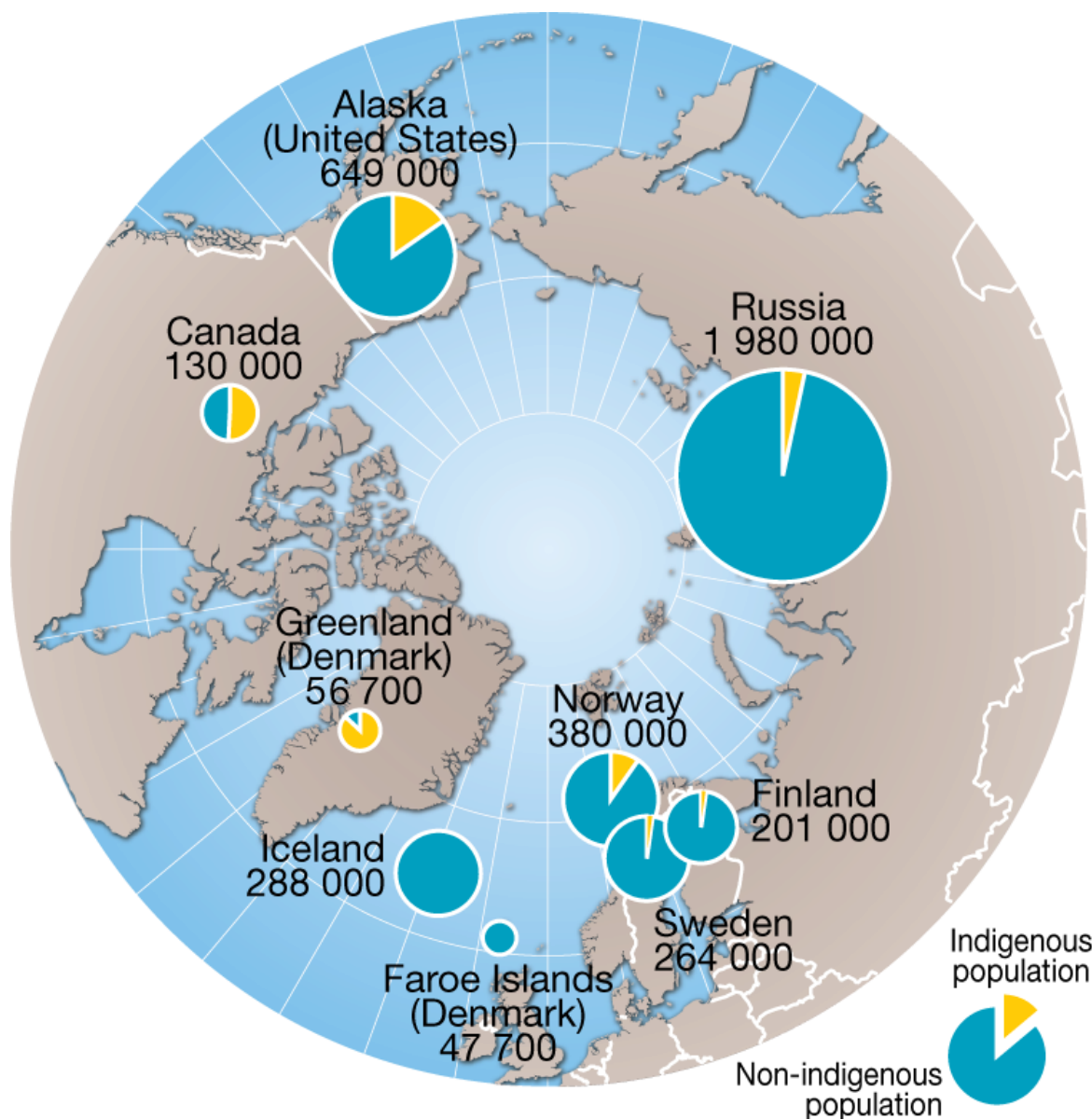Figure 4 provides an overview of "the Arctic Eight".

Figure 4. Map showing "the Arctic Eigth" including estimates of indigenous vs. non-indigenous populations.

Arctic region based on Arctic boundaries defined by Arctic Human Development Report, a working group within the Arctic Council [82].

Source: United Nations Environment Programme/GRID-Arendal, Hugo Ahlenius, http://www.grida.no/polar/ipy/2840.aspx

Greenland is the largest island in the world, covering 2.2 million square kilometres with 90% of the island covered in ice [76]. It is inhabited by approximately 56,000 people, scattered over 17 towns and 60 settlements based primarily on the narrow ice-free coastal lines [76].

The majority of the population live on the south-western part of the coast, a few towns exist on the east and north-west coasts. The northern part of the country, as well as the main land covered by the ice cap, is in every practical sense uninhabited. In 1950, 50% of the population lived in settlements and villages, compared to 13% in 2017 [76]. The infrastructure differs greatly from the capital of Nuuk which is inhabited by approximately 15,000 people and, with an airport and elaborate road system, to remote settlements with less than 50 inhabitants, that are only accessible by boat or helicopter. There are no interconnecting roads between the towns.

The country has its own language "Kallaalisut" with distinct dialectic differences between East Greenland and West Greenland [76].

With the arrival of the Norwegian priest Hans Egede in 1721, the time of colonization of Greenland by Denmark began. The colonization ended in 1979 where Greenland gained so-called "home rule", which in practice meant greater responsibilities of matters relating to Greenland. Since 2009 Greenland has had the right to self-govern but is still a part of the Kingdom of Denmark [76].

Ninety percent of the population is considered ethnic Greenlandic Inuit [83]. Genetically, more than 80% of the population is influenced by European, primarily Scandinavian, genes (constituting an average 25% of the genome) [83]. The influence is smaller in historically isolated areas, i.e. the North and East.

Socioeconomic factors

High rates of suicide, binge drinking, smoking as well as incest and domestic violence and increasing levels of obesity are some of the main challenges for overall Greenlandic Inuit health, both mentally and physically [84, 85] Fifty-two percent of the population smoke on an everyday basis and 34% binge drink at least once a month [84].

Life expectancy was 70.3 years in 2011-2015, which is higher than other indigenous populations, but 9.2 years lower than the Danish population [86].

The country's main industry is based on fishing and Greenland receives an annual "block grant" from Denmark equivalent to approximately 1/3 of the country's gross domestic product [76].

Health care in Greenland

Health care in Greenland, including prescription medicine, is free [87].

It is organized in five different health regions, each with one main regional hospital, which also serves as a primary care facility [88]. Larger towns have a separate local health care clinic staffed by doctor(s), nurses and health care workers, and smaller towns have health care clinics with nurses and health care workers. Settlements with more than 50 inhabitants have access to telemedical carts dubbed "Pipaluk" which includes a pulse oximeter, blood pressure monitor, electrocardiogram monitor, otoscope and a camera. Settlements with less than 50 inhabitants have access to a box of medicine.

The country's only specialized hospital is located in Nuuk and is organized into four major areas: psychiatry, internal medicine, emergency medicine and surgery including the ear, nose, and throat (ENT) department [88]. All contacts with the health care system and all prescriptions are linked to a unique identification number and registered in the patient's medical records.

Figure 5 provides an overview of the organizational structure of the health care system in Greenland. A study from 2011 showed that over 1 year, 83% of the population would have been in contact with the health care system, of which more than 75% of the cases were personal contacts [89]. A recent study from 2016 found that Greenlandic children were admitted to hospital more often and for a longer duration than Danish children [90].

Figure 5. The organization of the five Greenlandic health care regions [91].
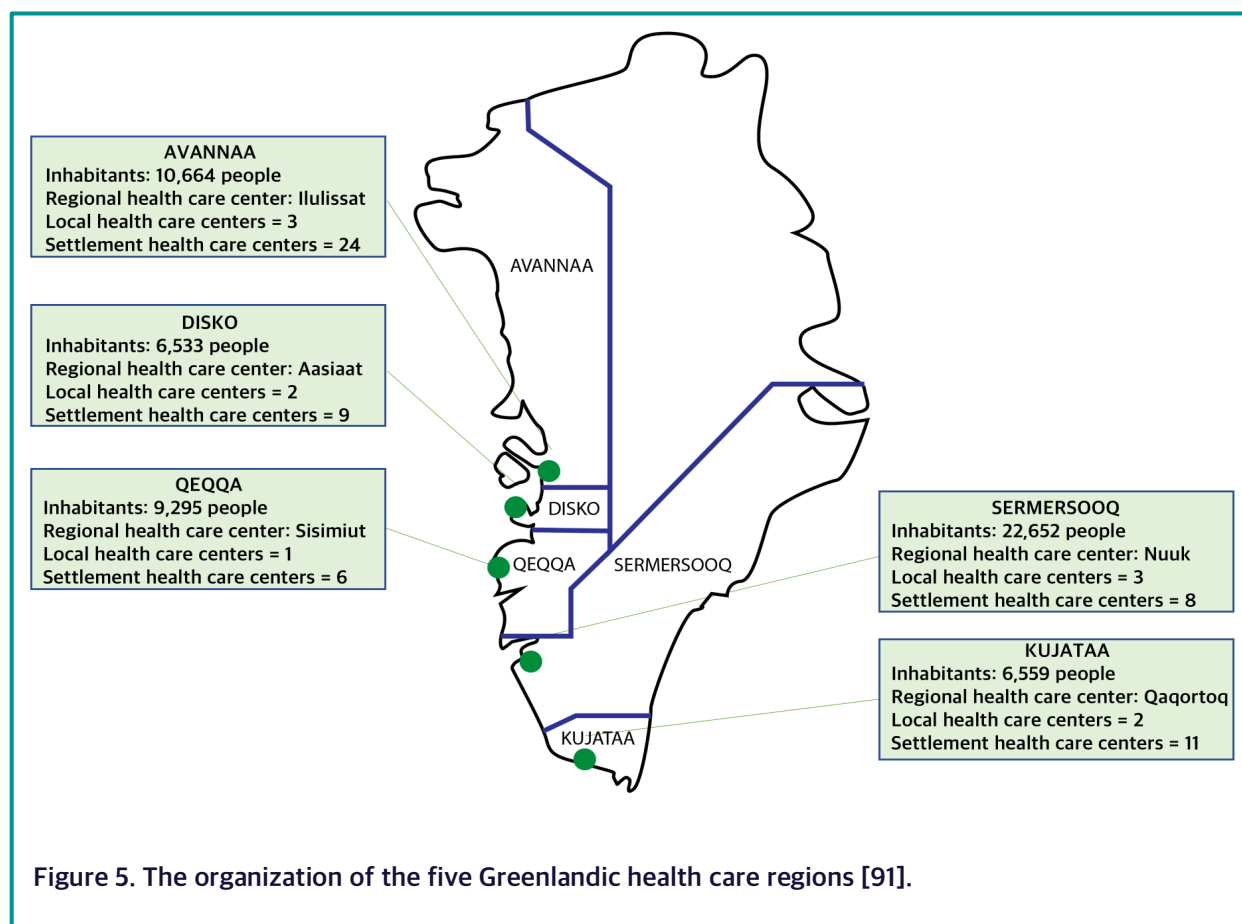
Being a small population with many remote locations, the retention and recruitment of health care personnel is a challenge in Greenland [87]. The University of Greenland, Ilisimatusarfik, provides an internationally renowned Bachelor of Science in nursing, but when pursuing a career as a medical doctor it is still necessary to enroll at universities outside the country. Although many of the local health care workers are part of the community, the system is dependent on recruiting staff from elsewhere, primarily Denmark, resulting in high turnover rates and the possibility of the staff not being familiar with the Greenlandic society [87].

1.9 Telemedicine

Telemedicine may have great potential for improving the level of health care, since access to specialists in Greenland in general is limited. Tele-otoscopy, where images of the tympanic membrane can be stored and subsequently evaluated remotely, may be beneficial in establishing national ear and hearing programs, as well as being cost-effective in remote settings [66]. In a health care system such as the one in Greenland, where a substantial part of the health care work force is based on temporary employment, the need for visual documentation and remote evaluation may be especially beneficial in order to ensure continuous and coherent treatment for the patients. A recent qualitative study of the perceptions of telemedicine among Greenlandic citizens found that implementation of telemedical equipment was considered beneficial and as a productive investment [92].

1.10 Research in small and indigenous populations

The definition of "indigenous populations" is complex. It is even considered unwanted and unnecessary by some, due to the lack of flexibility of a formal, internationally agreed definition [93, 94]. The most used "working definition" is as follows;

> Indigenous communities, peoples and nations are those which, having a historical continuity with pre-invasion and pre-colonial societies that developed on their territories, consider themselves distinct from other sectors of the societies now prevailing on those territories, or parts of them. They form at present non-dominant sectors of society and are determined to preserve, develop and transmit to future generations their ancestral territories, and their ethnic identity, as the basis of their continued existence as peoples, in accordance with their own cultural patterns, social institutions and legal system [93].

Research in indigenous populations presents particular ethical challenges, as the subjects investigated are most often the indigenous populations and the researchers most often non-indigenous. The Danish Greenlandic Society for Circumpolar Health has developed a specific code of conduct that presents guidelines on how to conduct research properly in acceptance with the population, the political system and the health care system [95]. The code of conduct includes paragraphs on involvement and use of the established health care system, separation of research and treatment, as well as dissemination obligations. All studies must obtain ethical approval from the Research Ethics Committee for Scientific Health Research in Greenland. Health research in Greenland typically has a dual purpose: it should serve as information and guidance to the decision-makers on best treatment and areas of focus, while also constituting a unique possibility to investigate health under very special environmental, social and genetic circumstances [96]. The awareness of a balance between these factors is an important ethical issue when planning and conducting research in Greenland.

Overall, the available data from RCTs in indigenous populations is sparse. A search on PubMed for the terms ("Otitis Media"[Mesh]) AND "Randomized Controlled Trial" [Publication Type] revealed 889 papers in total. In comparison, a review of trials conducted among indigenous populations in North America, the Arctic and Australia presented 12 trials in total, including two ongoing where one is the SIUTIT trial included in this thesis, and the other an RCT on watchful waiting versus immediate antibiotic treatment for AOM without perforation among urban Aboriginal and Torres Strait Islander children (the WATCH trial), however these children are considered low-risk, and results will therefore not be applicable for high-risk populations [97].

There is an overrepresentation of trials on Australian Aboriginals. Table 1 provides an overview of RCTs related to OM conducted among indigenous populations in North America, the Arctic and Australia.

Table 1. An overview of published protocols and trials on otitis media in the indigenous populations from the Arctic, North America, and Australia.

Authors	Year	Population	Age	N	Method	Objective
Binks et al. [98]	2015	Australian Aboriginals, pregnant women	17-39 years	227	Open label, allocation concealed, outcome-assessor blinded, community stratified RCT	The effect of 23-valent pneumococcal vaccine in pregnancy on colonization and ear disease among infants
Phillips et al. [99]	2014	Australian Aboriginals	< 13 years	53	Multi-center, parallel group RCT	The effects of multimedia messages on clinic attendance
Stephen et al.[100]	2013	Australian Aboriginals	5-12 years	89	RCT	Impact of 4 weeks of daily swimming on rates of ear discharge
Morris et al.[101]	2010	Australian Aboriginals	6 months to 6 years	320	Double-blinded RCT	Single-dose azithromycin versus seven days of amoxycillin in the treatment of AOM
Leach et al.[40]	2008	Australian Aboriginals	< 12 months	103	Double-blinded RCT	The effects of 24-weeks treatment with amoxicillin versus placebo on OM
Leach et al.[102]	2008	Australian Aboriginals	1 to 16 years	97	RCT	Topical ciprofloxacin versus topical framycetin-gramicidin-dexamethasone for children with CSOM
O'Brien et al. [103]	2008	Navajo and White Mountain Apache children	< 2 years	856	Double-blinded RCT	The efficacy of 7-valent pneumococcal conjugate vaccine against clinical and culture-proven OM
Couzos et al. [104]	2003	Australian Aboriginals	< 15 years	147	Community-controlled, community-based, multicenter, double-blinded RCT	The effectiveness of ototopical ciprofloxacin with framycetin, gramicidin and dexamethasone eardrops together with ear cleaning as treatments for CSOM
Gibson et al. [105]	1996	Australian Aboriginals	3-7 years	26	RCT	The effect of nasal beclomethasone on nasal cytology
Douglas et al. [106]	1986	Australian Aboriginals	6 months - 5 years	60	Double-blinded RCT	The effect of 14-valent pneumococcal vaccine
Ongoing trials						
Demant et al.[53]	2017	Greenlandic Inuit	9-36 months	230	Multi-center, superiority RCT	The effects of VT treatment vs. treatment as usual
Abbott et al.[97]	2016	Australian Aboriginal and Torres Strait Islander children	2-16 years	495	Multi-center open-label, non-inferiority RCT	Watchful waiting compared to antibiotic treatment for AOM without perforation

2. Objectives

The overall aim of this PhD thesis was to improve ear-related health for Greenlandic Inuit children. The thesis includes three studies with the following objectives:

1. To design and conduct a trial using state-of-the-art methodology for testing ventilation tube treatment in Greenlandic Inuit children.

2. To evaluate the usefulness of smartphone otoscopy in diagnosing otitis media in Greenlandic Inuit children, in a realistic setup involving local health care personnel.

3. To explore the perceptions and management strategies among Greenlandic Inuit parents of children suffering from otitis media.

3. Methods

This section provides an overview of the methods used in the three studies.

Detailed descriptions of designs are available in the included papers.

3.1 Settings

All studies were conducted in Greenland, in the towns of Nuuk, Ilulissat, Qaqortoq, Aasiaat, Sisimiut and Tasiilaq. Figure 6 provides an overview of the settings of the three studies.
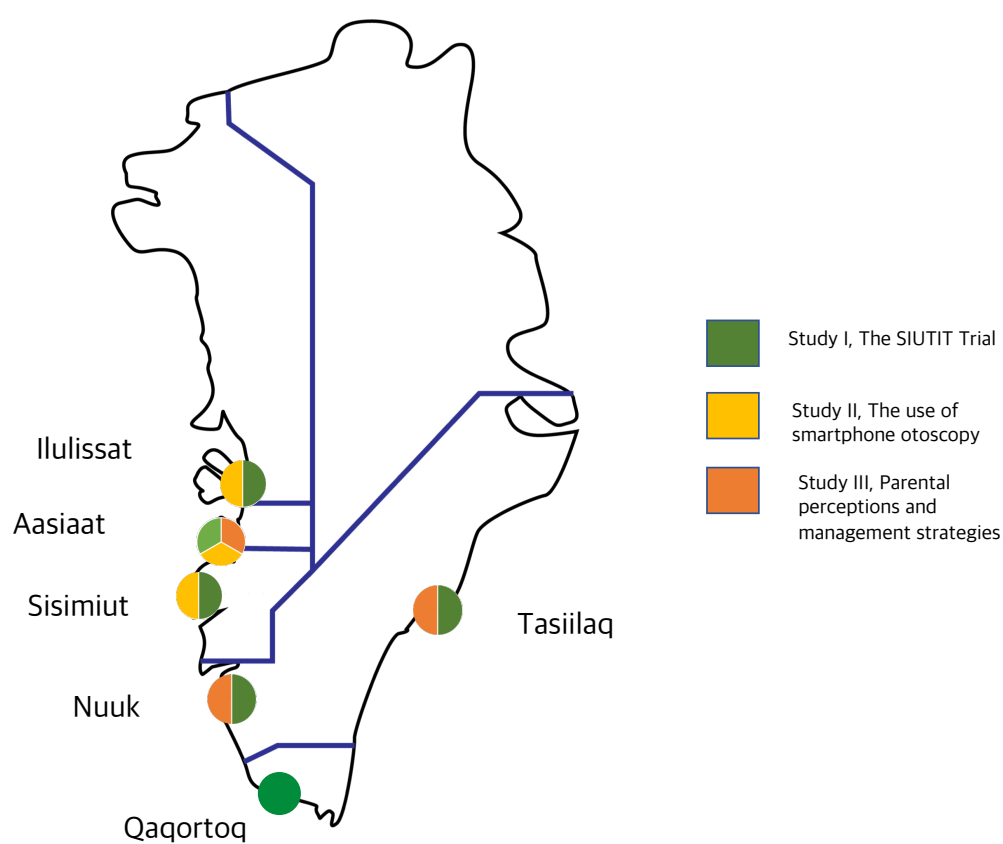

Figure 6. The location of the execution of the three studies. Blue lines indicate the division of the country's administrative health regions.

3.2 Ethnicity

Several proxies for evaluating ethnicity exists, including birthplace and self-identification. In the following studies being Greenlandic Inuit was defined as a person who is born of at least one Greenlandic-born parent who was born of at least one Greenlandic-born parent.

3.3 Study methodologies

Study I, The SIUTIT trial: A randomized controlled trial

The study protocol for the SIUTIT trial represents the first paper in this thesis. The investigator-initiated, multi-center, randomized trial investigates the effects of bilateral VT insertion versus treatment as usual among 9-36-months-old Greenlandic Inuit children with COME and/or rAOM. The trial is a superiority trial, aiming to clarify whether treatment with VT is *superior* to "treatment as usual". Appendix 1 shows the suggested procedure for "treatment as usual" provided to the health care facilities. The SIUTIT trial is based on a centralized web-based randomization, available to the investigators 24 hours a day. The allocation sequence is made as block randomization with different block sizes generated by a computer, unknown to the investigators.

All children in Greenland are offered by law a general health examination at 1 year of age, in which vaccination is included. In the general health examination otoscopy is included as part of the standard examination. In relation to the start of the SIUTIT trial, the health care personnel in the included towns were offered education in tympanometry, written guidelines on the use and interpretation of tympanometry curves were placed in all examination rooms and all personnel were asked to also perform tympanometry in addition to otoscopy. Figure 7 shows a schematic presentation of the inclusion procedure.

Primary outcome is number of visits to health care clinic, which serves as a proxy for disease severity since a blinded outcome involving visualization of the tympanic membrane is not possible. Section 6.4 "Internal validity" further discusses the choice of primary outcome. We considered a difference of two visits to health clinics during the study period as clinically relevant. Based on an estimate of 8 visits in two years in the control group and 6 visits in two years in the experimental group, assuming a standard deviation on five visits for 2 years and based on a statistical power of 0.8 at 5% significance level, the study requires 115 individuals in each intervention group, 230 children in total.

Secondary outcomes include QoL of children and caregivers measured by the validated questionnaires OM-6 and Caregiver Impact Questionnaire (CIQ), number of episodes of AOM and episodes where

systemic antibiotics has been administered and finally proportion of children with uni- or bilateral perforation of the tympanic membrane at the end of the study period. Hence, the effects of VT treatment on the development of CSOM is evaluated as a secondary outcome, as the preliminary power calculation showed that a trial with CSOM as primary outcome would require too many children for the trial to be feasible.
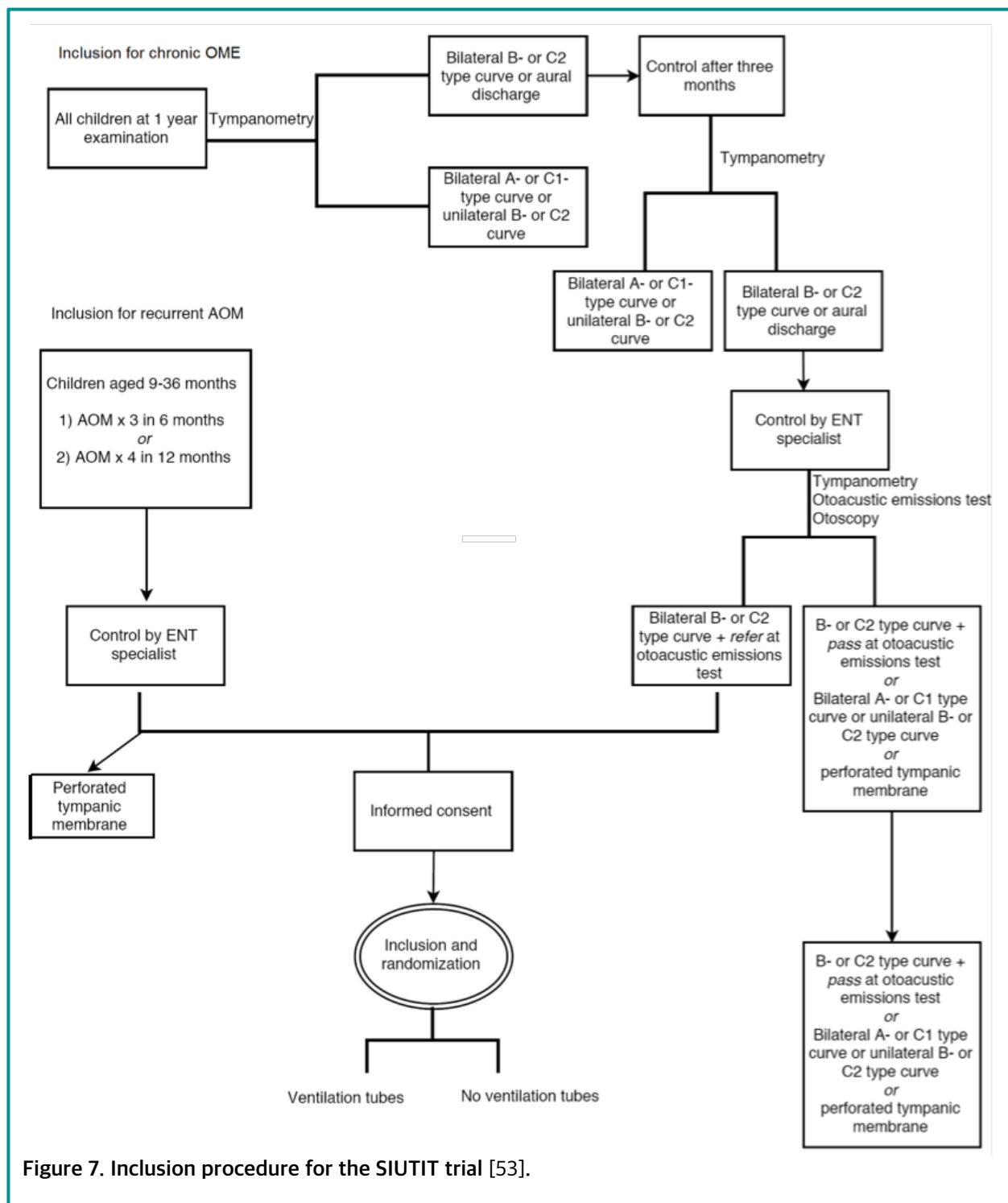
Figure 7. Inclusion procedure for the SIUTIT trial [53].

Study II: A cross-sectional study

In this cross-sectional study we investigated the use of a smartphone otoscopy device, Cupris® when used by local health care workers with different levels of training and education, examining children in rural Greenland (i.e. not the capital).

The otoscopies were performed using Cupris® TYM otoscope device (London, UK), consisting of a hard case with an otoscope applied to it, connected to a smartphone (iPhone 5s, Apple Inc., California, USA). The videos were stored and sent via the Cupris® application for remote assessment by three specialists within otology.

We chose to conduct this study in a pragmatic manner in order to examine the quality of video-otoscopies as if we were to equip the Greenlandic health care system with video-otoscopes, mimicking a real-world setup, where the otoscopes are operated by different and changing health care personnel.

Primary outcome was proportion of otoscopies evaluated as useful for making a diagnosis by the three specialists. Secondary outcomes included the overall distribution of the ratings as well as number of challenges with the video otoscopies.

Sample size was based on convenience sample.

Study III: A qualitative study

In the third study, we used a qualitative approach, interviewing parents of children suffering from OM. The interviews were initially based on an interview guide with questions grounded in the existing literature. However, the questions were open-ended and allowed the interviewer to let the parents talk about the themes they found most important. We aimed to explore the perceptions and management strategies of Greenlandic Inuit parents of children suffering from OM.

In qualitative research sample size cannot be calculated by quantitative means. Often the expression "data saturation" is used, meaning that conducting more interviews will not generate new themes. However, this method is debated, and although other forms of sample size estimation has been suggested, such as the term "Information power", there is no consensus on the matter [107]. In this study the data collection was terminated when the interviews presented themes discussed previously.

3.4 Overall study designs

Table 2. Schematic presentation of overall study designs

	Study I	Study II	Study III
Study design	Interventional study; Study protocol for a randomized controlled trial,	Cross-sectional study	Qualitative study
Intervention	Donaldson ventilation tubes vs. "treatment as usual"	Video-otoscopy	N/A
Setting	Six towns	Three towns on the west coast	Two towns on the west coast and one on the east coast
Inclusion criteria	- Children aged 9-36 months - Children with at least one Greenlandic born parent with at least one Greenlandic born parent - American Society of Anaesthesiologists' physical status classification class 1 and 2 - B- type curve, defined as flat line tympanograms/gradient < 0.04 ml or C2-type curve defined as pressure ≤ -200, measured by tympanometry at two visits 3-4 months apart *or* - three episodes of acute otitis media in 6 months according to medical charts *or* - four episodes of acute otitis media in 12 months according to medical charts - Signed informed consent, signed by the legal guardian	- Children aged 6-72 months - Signed informed consent, signed by the legal guardian	- Parents of children aged 9-72 months - Parents of children with at least one Greenlandic born parent with at least one Greenlandic born parent. - Parents of children fulfilling inclusion criteria for the SIUTIT trial - Signed informed consent
Exclusion criteria	- Children with known generalized immune deficiency - Perforation of the tympanic membrane - American Society of Anaesthesiologists' physical status classification class >2 - Lack of signed informed consent signed by the legal guardian	- Lack of signed informed consent signed by the legal guardian	- Lack of signed informed consent
Number of participants	N = 230	N = 84	N = 27 Three focus group interviews, 13 single/dual interviews

Table 2, continued.

Primary outcome	Number of visits to health clinic during the trial period	Proportion of videos useful for making a diagnosis	Qualitative analysis of perceptions and management strategies for OM
Secondary outcomes	1) Number of episodes of AOM, assessed by medical chart reviews 2) QoL measured by the disease specific questionnaire OM6 and Caregiver Quality of Life 3) Number of episodes where systemic antibiotics have been administered, assessed by medical chart reviews 4) Proportion of children with uni- or bilateral tympanic membrane perforation at final visit.	1) Distribution of ratings on a Likert scale 2) Number of documented challenges with the video-otoscopies	N/A
Blinding	- Assessors of number of visits to health clinics are blinded. - Parents and children are *not* blinded for type of intervention.	Assessors blinded for site, age and operator.	N/A
Time frame for data collection	First patient included February 18, 2016. Ongoing.	July to October 2018	June to July 2018

3.5 Data analyses

Statistical analysis for Study I

All outcomes will be compared in the two intervention groups. Outcomes from all randomized children will undergo analysis according to the assigned intervention group i.e. on an intention-to-treat basis. We will analyze dichotomous outcomes using logistic regression and continuous outcomes using linear regression. Count data will be analyzed using the non-parametric Van Elteren test, as we do not expect our data to be normally distributed. The Van Elteren test is an extension to the Wilcoxon rank-sum test, conceptually equal to combining tests for each stratum, thereby useful in stratified studies [108].

Statistical analysis for Study II

We investigated the agreement among raters using the interrater agreement (IRA) generated by a modified Fleiss' Kappa coefficient. A Kappa coefficient ≤ 0 corresponded to "poor agreement", 0.01-0.2 to "slight agreement", 0.21-0.40 to "fair agreement", 0.41-0.6 to "moderate agreement", 0.61-0.80 to "substantial agreement" and 0.81-1.00 to "almost perfect agreement". We compared continuous variables using the non-parametric one-way ANOVA, the Kruskal-Wallis test, and categorical variables using chi-square test.

Data analyses were performed using SAS Studio (SAS Institute Inc., Cary, NC, USA) and R 3.5.0 (R Core Team, 2018) Significance was set at $p < 0.05$.

Data analysis for Study III

We used a pragmatic qualitative analysis method called systematic text condensation (STC) developed by the Norwegian medical doctor Kirsti Malterud [109]. This method focuses on critical synthesis and interpretation in relation to the practical, clinical world and uses a systematic and stepwise approach to thematic analysis without a specific philosophical methodological framework. The concept of "meaning condensation" is used, where the overall content of the interviews is gradually developed by an iterative, reflexive process.

Data analyses including transcription and coding were performed using NVivo for Mac, version 11.4.2.

3.6 Ethical considerations

All three studies were approved by the Research Ethics Committee for Scientific Health Research in Greenland (Study I: no. 2015-112556, Study II: no. 7960823, Study III: no. 7714708) as well as the Danish Data Protection Agency (Study I: no. 2015-41-4047, Study II: no. REG-041-2018, Study III: no. REG-035-2018).

All participants in the studies were provided with written and oral information, and a signed consent form from the participant or legal guardian was obtained before enrollment/participation.

The SIUTIT trial was registered at ClinicalTrials.gov: NCT02490332.

4. Results

The following provides a short overview of the results generated in the three included studies. Further details can be found in the attached papers.

4.1 Results of Study I

The SIUTIT trial has been initiated in February 2016 and is still ongoing. To date, 31 children have been enrolled in the trial from four different sites. Median age is 20 months, range 9-34 months.

The process of designing and conducting the trial has generated experience with and knowledge about factors needed to be taken into account when conducting trials in remote settings. This is discussed in Section 5. Figure 8 provides an overview of the included patients.

Enrollment

Greenlandic Inuit children aged 9-36 months with
1) Diagnosis of recurrent acute otitis media and/or chronic otitis media with effusion
and
2) Informed consent, signed by legal guardian

Randomized (n=31)

Allocation

VENTILATION TUBES
Allocated to intervention (n=16)
* Received allocated intervention (n=10)
* Did not receive allocated intervention (n=6)
  - Tympanic membrane perforation found at time of operation (n=2)
  - Surgery postponed due to comorbidity (n=1)
  - Surgery postponed due to anesthetic challenges, parents withdrew consent (n=1)
  - Surgery postponed due to anesthetic challenges, the patient no longer fulfilled the inclusion criteria

NO VENTILATION TUBES
Allocated to intervention (n=15)
* Received allocated intervention (n=13)
* Did not receive allocated intervention (n=2)
  - Patient received VT outside the trial (n=1)
  - Withdrawal of consent (n=1)

Lost to follow-up (n=0)

Follow-Up

Lost to follow-up (n=1)
- Patient moved to settlement

Completed to date
n=4
Awaiting final examination n=5

Completed intervention to date

Completed to date
n=3
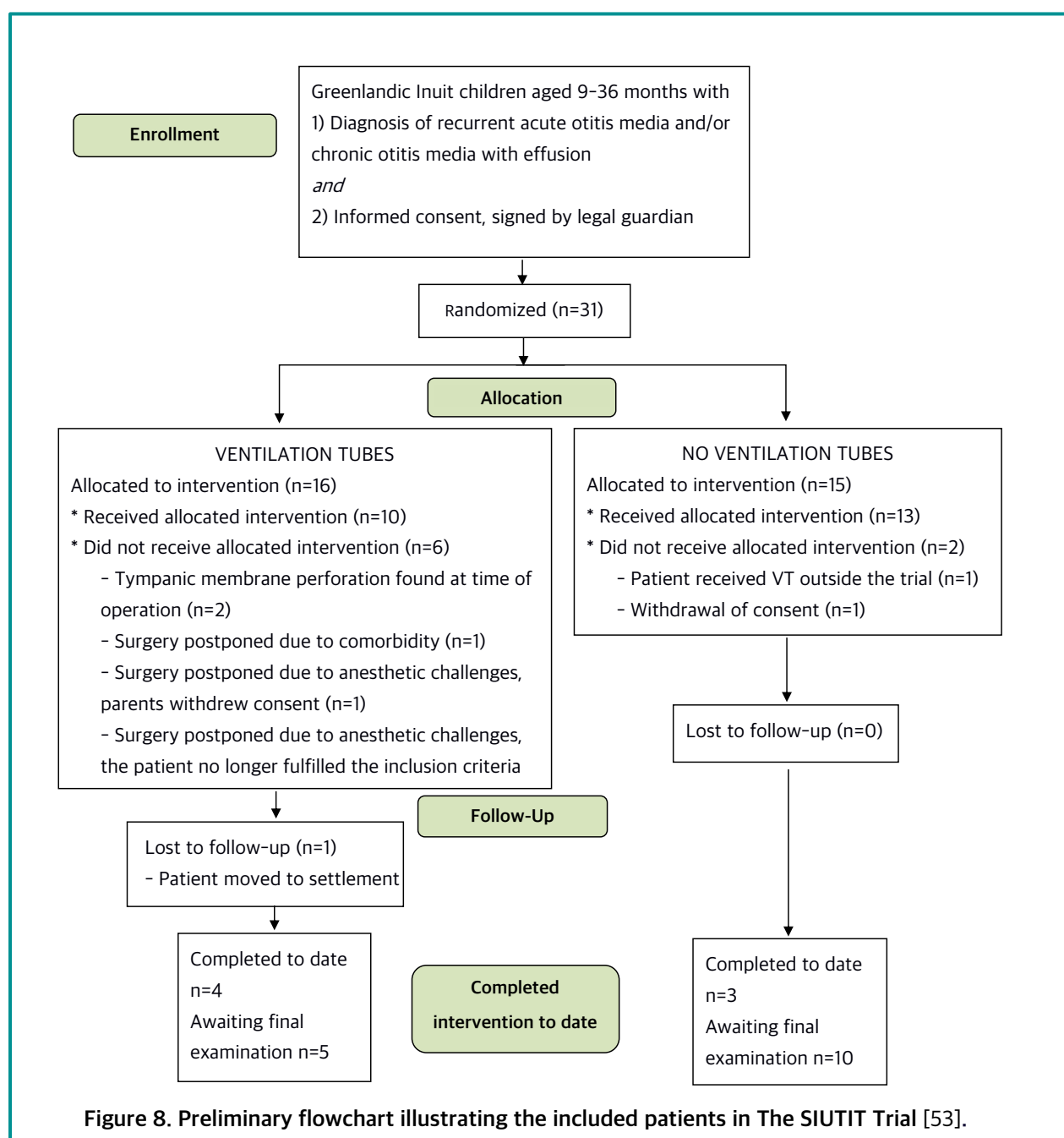Awaiting final examination n=10

Figure 8. Preliminary flowchart illustrating the included patients in The SIUTIT Trial [53].

4.2 Results of Study II

In total, 142 otoscopies were analyzed, obtained from 84 children from three different sites. Table 3 shows baseline characteristics of the participating children. Figure 9 provides a flowchart of the inclusion process and an overview of mean percentage of useful video otoscopies.

Table 3. Baseline characteristics of children included in Study II [110].

		Site 1	Site 2	Site 3	Total
N		36	23	25	84
Sex, % female		30.5	56.5	48	36 (p =0.03)
Age, months (IQR)		27 (13–49.5)	15 (13–69)	48 (13–50)	24.5 (13–52) (p =0.86)
Number of videos		51	43	48	142
Operator	Specialized nurses	10	43	27	80
	Medical student	37	0	4	41
	Medical doctor	2	0	17	19
	Nurse	2	0	0	2

Continuous variables are presented with median and interquartile range. Categorical variables were compared using the chi-square test and continuous variables were compared using the Kruskal–Wallis test.
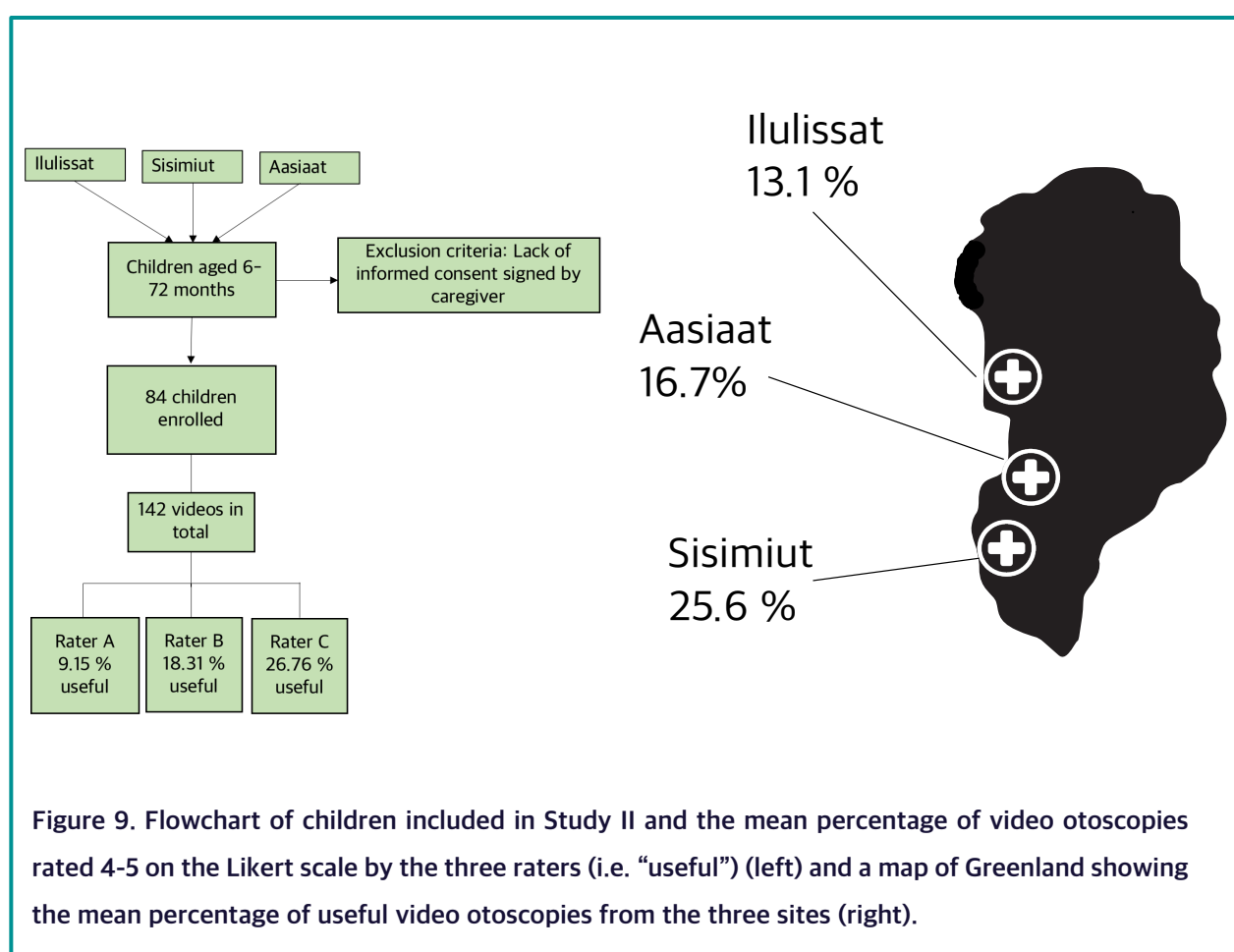

Figure 9. Flowchart of children included in Study II and the mean percentage of video otoscopies rated 4-5 on the Likert scale by the three raters (i.e. "useful") (left) and a map of Greenland showing the mean percentage of useful video otoscopies from the three sites (right).

The mean proportion of video otoscopies rated 4-5 on the Likert scale i.e. defined as "useful" was 18.1%, with a Fleiss' Kappa IRA coefficient of 0.67 95% CI [0.57-0.76] corresponding to substantial agreement among the three raters.

The mean proportion of video otoscopies evaluated as providing challenges for the raters are listed in table 4.

Table 4. Proportion of the 142 video-otoscopies with specific challenges or no challenges and corresponding interrater agreement coefficient [110].

	Wax	**Insertion**	**Focus**	**None**
Mean, %	37.7	68.3	19.0	3.0
IRA	0.55	0.40	0.36	0.92
	95% CI [0.44-0.65]	95% CI [0.30-0.52]	95% CI [0.25-0.46]	95% CI [0.86-0.96]

IRA = Interrater agreement

4.3 Results of Study III

In total, 16 interviews were conducted (6 in Aasiaat, 7 in Tasiilaq and 3 in Nuuk) including 27 parents. Table 5 shows baseline characteristics of parents and their children participating in Study III.

Table 5. Baseline characteristics of parents and children participating in Study III [91].

Site	N		Male parents, n (%)	Median parent age, years [range]	Median children age, months [range]	Mean number of siblings [range]	Diagnosis*		
	Parents	Children					OME	rAOM	CSOM
Capital	12	7	4 (33)	33.5 [25-38]	26 months [19-53]	0.75 [0-2]	3	3	1
West coast	8	6	2 (25)	30 [25-43]	55.5 [39-72]	2 [0-4]	0	4	2
East coast	7	7	1 (14)	29 [23-40]	17 [11-53]	4.3 [0-7]	0	3	4

*Diagnoses are based on medical chart reviews.

Overall, we identified two categories in the analysed data: "perceptions" and "management strategies". The categories could be further divided into predominant themes and subthemes. Figure 10 provides an overview of the identified categories and themes.

Figure 10. A schematic overview of predominant categories, themes and subthemes identified in the data analysis [91].
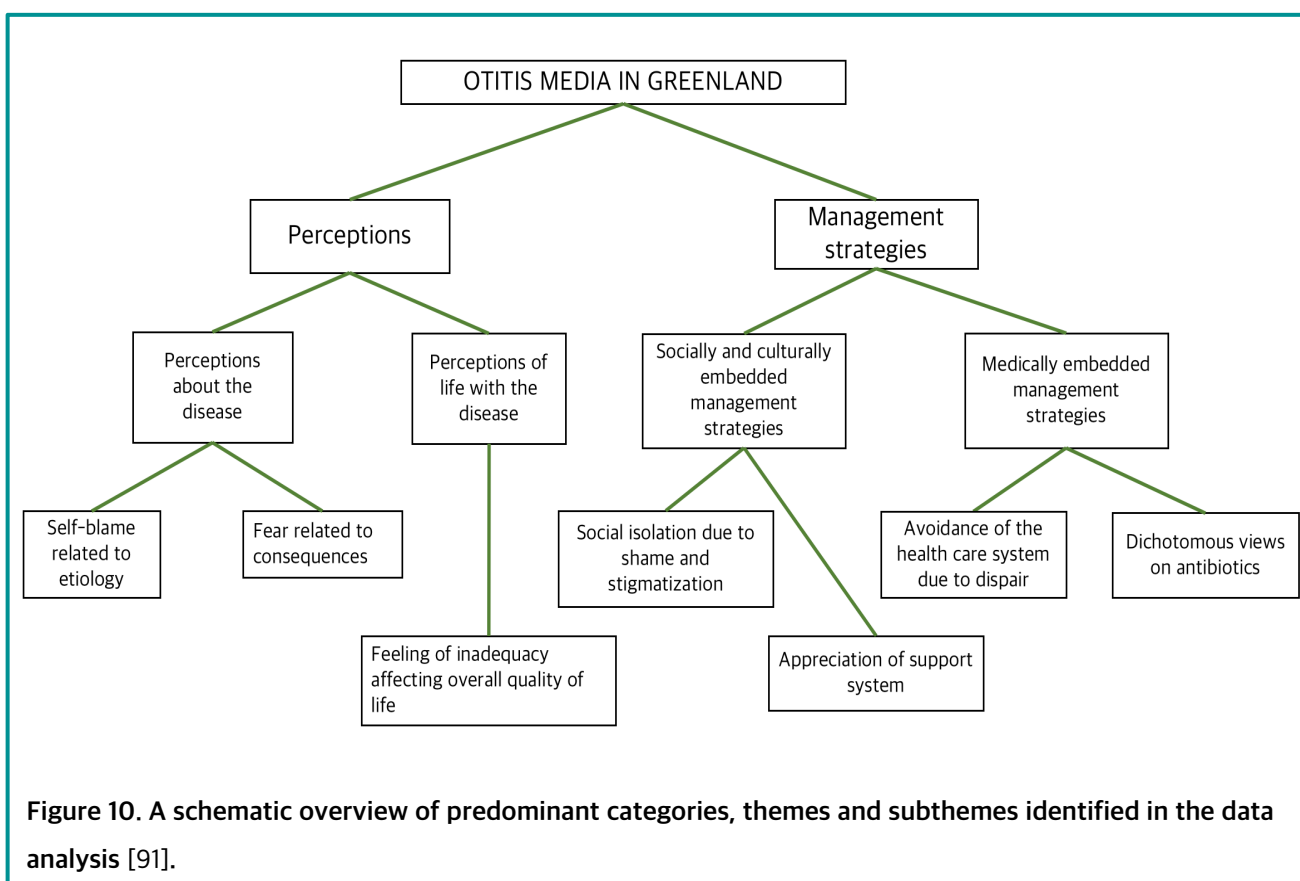
Perceptions about the etiology of the disease seemed to range from a medical explanation model, based on bacteria, virus and fluid in the middle ear, to a more complex understanding of direct causes of actions leading to guilt and self-blame among the parents.

"It has gone backwards, the mucus, the bacteria go into the ears, that is why he got middle ear infection, that it what I have been told."[91]

"I had my son in my arms, and my boyfriend wanted to hit me hard. Could that have done anything? An hour after I had been hit, I took my son's temperature, it had risen to around 38. Then I took care of him and took his temperature after a while, and then it was back to normal. I worry that maybe we have scared him, and that is what is making him sick."[91]

"I have been thinking a lot. I have been smoking during my pregnancy and I have thought if that might be the reason."[91]

The feeling of inadequacy as a parent was widespread further enhanced by social isolation, stigma and shame of having a child with many and/or severe OM, affecting overall quality of life.

"The worst part is that when she cries, even though she is right next to you, there is nothing you can do to help."[91]

"It is very rare that we experience true happiness because it is so hard and we get really tired of having to deal with ear infections all the time. Day and night someone is crying, and that affects the happy feelings. And when they have ear infections all the time the entire family gets affected and we all become sadder."[91]

"One time, our upstairs neighbor came down and asked if we needed help, that was really rough. She asked in a bad way, where she kind of accused us and directly told us that if our daughter cried that much one more time, she would inform the social authorities."[91]

"When the smell begun I stopped hanging with my friends. I do not want other people to comment on the smell. I think that other people find it disgusting. I think it is embarrassing. Then I feel bad taking my kid to the daycare or going to coffee-mik or visit family."[91]

5. Discussion

5.1 General discussion

Study I

As the trial is still ongoing, none of the primary or secondary outcomes have so far been evaluated. We have however gained experience with and knowledge of the challenges associated with research in sparsely populated and hard-to-reach areas, some of which are discussed in the next sections. To our knowledge, this is the second RCT in Greenland ever done*, and thus many of the challenges were unknown to us and not the same as in more well-known settings. The challenges included recruitment and retention of patients, managing the rapid turnover in health care personnel as well as the inherent logistical and economic aspects of conducting research in remote settings. Both parents and personnel may have had preconceived opinions on the better treatment option and practical issues such as Danish anesthesiologists and otologists following Danish guidelines were also contributing factors. Combined, it all presented as challenging in the process of implementing a trial based on state-of-the-art methodology.

Some of the challenges with recruitment and retention of indigenous and minority participants in RCTs have previously been described, as well as the importance of striving for obtain results on this exact subgroup in order to minimize the overall health disparity [111-113]. Factors such as cultural awareness, involvement of local workforce and indigenous knowledge models as well as targeted inclusion strategies are mentioned as key words. A descriptive study from 2014, embedded in an RCT on antibiotic treatment for acute bronchiolitis in indigenous Australian children, reported improvement

_____

* In 1956-62 a cluster randomized, blinded trial was conducted on the West coast of Greenland, led by the Danish medical doctor and tuberculosis-specialist Erik Groth-Petersen [114, 115] The trial investigated the use of the drug isoniazid versus placebo in the treatment of tuberculosis and included approximately 8000 people from 76 settlements, with participation rates ranging 90-100% of the total population in West Greenland. The trial was conducted from a "floating chest-clinic", a ship called Misigssût, carrying x-ray equipment, sputum tests and BCG-vaccinations as well as health care personnel to the settlements. According to reports from Misigssût, it was warmly welcomed by the population; A boat with a family of eight arrived back from reindeer hunt just in time for examination – the family had been rowing for 3 days in a row in order to reach the ship [116]. The report of the trial does not include a section on the information given to the participants nor provides information about signed consent [114]. The Helsinki declaration is from 1964 – 2 years after the ending of the trial [117].

of retention and recruitment of participants by the use of frequent calls and reminders by mobile phone to both parents of the included children as well as the involved clinics [113].

An RCT investigating the impact of the use of text messages on overall ear health, also among indigenous children in Australia, found no direct effect of the intervention, but described the use the text messaging as acceptable to the population [99]. This strategy could be considered for implementation to the SIUTIT trial, as the overall circumstances are comparable. Currently, the parents in the SIUTIT trial are primarily contacted by email, to our knowledge the first study in Greenland to do this, however, this may have been premature as many parents do not check their email on a regular basis.

As previously mentioned, there are relatively few RCTs on OM conducted in high-risk populations and RCTs on the effects of VT treatment has never been conducted among populations with high prevalence of CSOM. It can be speculated that the risk of chronic perforations may be higher among CSOM-prone children, and that VT treatment may in fact complicate the disease further.

As previously mentioned, Leach at al. conducted a trial on the effects of long-term use of antibiotics among the indigenous population in Australia [40]. This trial is an illustrative example of the need to explore differentiated treatment regimens and trials on specific subgroup populations in order to improve ear health among high-risk populations. In Jumla, Nepal, Clarke conducted a cluster-randomized trial with an intervention based on the WHO *Primary Ear and Hearing Care Training Resource* [118, 119]. The primary outcome was difference on *knowledge, attitudes and practices score* measured by questionnaires, in the two groups. The trial found no effect of the educational intervention, however, the overall incidence of CSOM among the children in both intervention groups decreased during the study period.

Study II

Being a small population with many remote locations, staff retention and recruitment is a challenge in Greenland. Telemedicine might provide an opportunity for a higher level of care, especially among Inuit families living in remote towns and settlements, but also in difficult cases in the more specialized settings. However, due to the low proportion of useful otoscopies we found in this study, it seems that focused training and education is essential for improving the overall diagnostic accuracy. The main challenge, improper insertion of the otoscope, may reflect a lack of training and experience among the

health care personnel and also underlines the fact that pediatric otoscopy is difficult, even in experienced hands.

The use of smartphone otoscopy has previously been evaluated in different settings. Mandavia et al. tested the Cupris® device in rural Nepal, where the prevalence of ear disease is high and access to otologists sparse [120]. The authors found that the Cupris® device was a valid tool for diagnostics and decision for referral. However, the examined population was mainly adults and the otoscopies were performed by medical doctors associated with the study, which contrasts our study where the participants were children and the operators mainly non-doctors.

Erkkola-Anttinen et al. tested a smartphone otoscope when operated by parents to children aged 6-35 months suffering from OM [121]. The parents were randomized to either immediate or delayed teaching intervention. The authors found that 62% of the videos in the immediate teaching intervention group were of a sufficient quality, and that main reasons for insufficient image quality were inadequate view of the tympanic membrane, unsatisfactory clarity and interfering cerumen. The teaching intervention improved the quality significantly. This implies that teaching session could also have improved our results and should be considered before implementation.

A recent review on the role of local health care workers in remote locations around the world underlined the value and benefits of employing local work forces in the treatment and screening of OM in remote settings with limited access to specialists [122]. However, the review also states that the level of care is proportional to the training offered, and that intermediate-level training is needed for sufficient quality of otoscopies and automated hearing tests [122].

The use of artificial intelligence in the diagnostic process may improve the possibilities for remote diagnosis [123]. Myburgh et al. tested an algorithm designed for automatic image analysis of the tympanic membrane, showing an accuracy of 78.7% compared to diagnosis made by specialists [124]. However, this still requires high-quality images of the tympanic membrane, obtained by otoscopy, and does therefore not bypass the need for education of local health care personnel.

Study III

The qualitative study revealed that OM in Greenland is a complex disease that affects the lives of the implicated families on several levels and may have dire social and cultural consequences. Considering the potential perceptions and management strategies of parents of Greenlandic Inuit children suffering from OM, may provide a better understanding of and adherence to the suggested treatment regimen.

A recent systematic review of qualitative studies on parents of children suffering from OM identified 17 studies, based on 284 participants [125]. The studies were mainly conducted in high-income countries, but did include two studies on indigenous populations, native Canadians and Australian Aboriginals, respectively [74, 75]. The authors identified seven predominant themes including the themes identified in our study. In the study conducted among Australian Aboriginals, the authors generally found poor understanding of the etiology and development of the disease, which was in contrast to our findings, where the medical explanation models coexisted with a more complex, culturally embedded belief of associations. The authors did not mention guilt, shame and social isolation, which were main concerns among the parents in our study. A study investigating the impact of OM on caregivers in rural Nepal found that the mothers generally blamed themselves for their child's ear disease and were not aware of more medically embedded explanation models [118].

Greenland is considered a land in transition, and the huge differences in sociodemographic factors from the traditional hunting society to modern lifestyle are reflected in our findings. The Greenlandic Inuit parents' views on OM may not be the same as otherwise found in Western countries but are also not equivalent to indigenous populations in Australia and Nepal.

5.2 Choice of age group

All three studies in the present thesis focused on small children, below the age of six, which is the age group with the highest prevalence of OM and the greatest risk of developing CSOM [10, 31, 47, 126]. However, it is also the age group where the diagnosis may be most difficult to make, due to anatomical challenges as well as cooperation problems, which further underlines the need for research in this specific age group. We chose to conduct the studies based on children below the age of six both due to the burden of disease related to this age group as well as the potential to prevent further development of the disease. The age of the child when experiencing first episode of OM is related to the risk of complicated disease, which makes the first years of life crucial for prevention. Research in this specific age group may therefore hold the biggest potential for improvement.

5.3 Validity of the studies

Generally, there are two aspects worth considering when evaluating the overall quality of the studies: internal validity (i.e. are any systematic errors introduced in the studies) and external validity (i.e. can

the study results be applied in other settings and contexts). The validity of the studies included in this thesis is discussed below.

Internal validity

Performance bias

Performance bias occurs in a situation where the investigator may or may not influence the participants due to prior perceptions of advantages and disadvantages of the intervention or knowledge about what treatment group the specific patient is allocated to [127]. Knowledge about allocation provides risk of more or less subconscious behavioral changes such as adherence to protocol, evaluation of symptoms and even selection and omission of results (reporting bias) [128]. In the perfect trial set-up, five different instances would be blinded: patients/parents/guardians, surgeons, data collectors, outcome assessors and data analysists.

Surgical trials pose certain practical challenges and are a vivid example of when the highest scientific standards collide with the highest ethical standards. It is not ethically sound to perform "sham surgeries" where children would undergo anaesthesia without surgery, which would be required in order to blind parents and children [129]. And even if sham surgery was performed, the surgeon would still not be blinded.

Hence, in the SIUTIT trial, patients, parents, surgeons and otological specialists examining the children were not blinded, which poses a risk of performance bias.

Selection bias

Selection bias is a systematic error including patients with specific characteristics not similar to the rest of the population or systematic differences between the two groups that are being compared in an RCT [127]. In the SIUTIT trial the patients were randomly assigned to the two intervention groups, thereby minimizing the risk of selection bias by randomization. The allocation sequence was concealed, thereby making it impossible to predict the allocation of patients.

It is possible that a certain subgroup of all affected children and parents in the population chose to participate in the studies. An intrinsic part of the SIUTIT trial design is that in fact two thirds of the treatment possibilities include "treatment as usual". All children enrolled in the trial are offered a specialist examination once a year, but otherwise treatment in the control group is the same as if the children were not enrolled. If the second arm had offered something "more" some parents might have agreed to participation who would otherwise have declined.

In Study II, we asked all personnel to obtain video-otoscopies on all children, regardless of the reason for contact. If the device was to be implemented in the everyday clinical settings, the use would most likely be limited to cases where the personnel had genuine doubts about a diagnosis. This might lead to a certain subgroup of the personnel actually obtaining the video-otoscopies and would also mean that the involved personnel would have responsibility for suggesting a tentative diagnosis and take the appropriate clinical actions. These factors would perhaps lead to increased quality of the video-otoscopies.

In Study III, the majority of the interviewed parents already had their children enrolled in the SIUTIT trial. This may have supported or facilitated increased awareness of their child's ear disease, thereby making the parents more prone to focus on the negative aspects of OM.

Detection bias

Detection bias refers to the phenomenon where outcome is measured or evaluated differently within the two treatment groups [127]. Blinding of the primary outcome in RCTs is of outmost importance in order to obtain objectively assessed results that are as bias-free as possible.

In the SIUTIT trial, blinding of the primary outcome presented a challenge. Due to the nature of the intervention, it was not possible to blind an outcome based on visualization of the tympanic membrane, since it would be evident to the examiner if the child had received VT or not with either VT in situ or visible sequalae. Therefore, we chose to base our primary outcome on the number of visits to a health clinic during the trial period, assessed by medical chart review. We assume that the number of visits to health clinics will reflect the number of episodes with upper airway/ear-related infections, as this has previously been shown to be the primary reason for visits to health clinics among Greenlandic children [130]. The medical charts will be anonymized prior to assessment of the number of visits to health clinics and any mentions that might reveal the allocation will be deleted, thereby blinding the assessor evaluating the number of visits to health clinic for the intervention.

It is important to note that the primary outcome in the trial is a proxy for the outcome of interest which is OM-related health. We cannot be certain that the visits to health clinic reflects OM-related visits, and there is a risk that a true difference in OM-related visits may be diminished. However, we chose this solution, believing that a blinded primary outcome outweighs the risk of a proxy-based primary outcome. Measurement of QoL by questionnaires is not considered blinded, which poses a high potential risk of bias.

Attrition bias

Attrition bias is defined as systematic differences in withdrawal from the allocated treatment groups. Different adherence to the allocated treatment group may have influenced the retention of patients in The SIUTIT trial. An overall perception that VT is the better treatment offer may have affected the patients' and caregivers' willingness to adhere to the trial. Parents to 3 of the 31 included patients withdrew their consent after randomization and one child received VT in Denmark, although the child was randomized to "no VT". The reasons for the withdrawal may differ, but at least for the child receiving VT treatment in Denmark we must conclude that the parents believed that VT treatment was the better option. The personnel involved in the inclusion process of the children have an important and difficult job in informing the parents about our current knowledge and communicating that we do not know which treatment is better – without expressing own perceptions and beliefs. This may not have been done properly in the mentioned cases.

External validity

The external validity of clinical studies is defined as the degree to which the results can be applied to others - both within the same population and across other similar populations (i.e. the generalizability of the study). In qualitative studies, the concept of generalizability is often replaced with transferability, which can be viewed as synonymous with generalizability although the process of evaluation and the conclusion drawn differs [131].

Greenland holds a unique and small population and is classified as a population with a high risk of OM and sequalae [132]. Due to the overall low number of inhabitants, our results are based on a relatively large percentage of the total population, increasing the generalizability and transferability of the studies. All studies included participants from different towns, taking the differences on socioeconomic factors into consideration. However, none of the studies included participants from the settlements, and it is plausible that results from Study II and III hereby would have changed considerably. The local health care workers in the settlements may generally be less educated than their peers in the larger towns, however, it is possible that they are more experienced with decision-making and diagnoses, as they do not have the same access to medical doctors. It is therefore not obvious that the quality of the smartphone otoscopies would have decreased if tested in the settlements. Inhabitants in the settlements are generally also less educated than in the larger towns, which can be speculated to result in less understanding of the biomedical explanation model of OM in Study III, and more prevalent cultural and emotional perceptions and management strategies.

The classification of being a high-risk, indigenous population, as well as the unique challenges with distances, infrastructure and personnel makes the generalization to other populations in the developed world difficult and vice versa, which is why research in this specific population is needed.
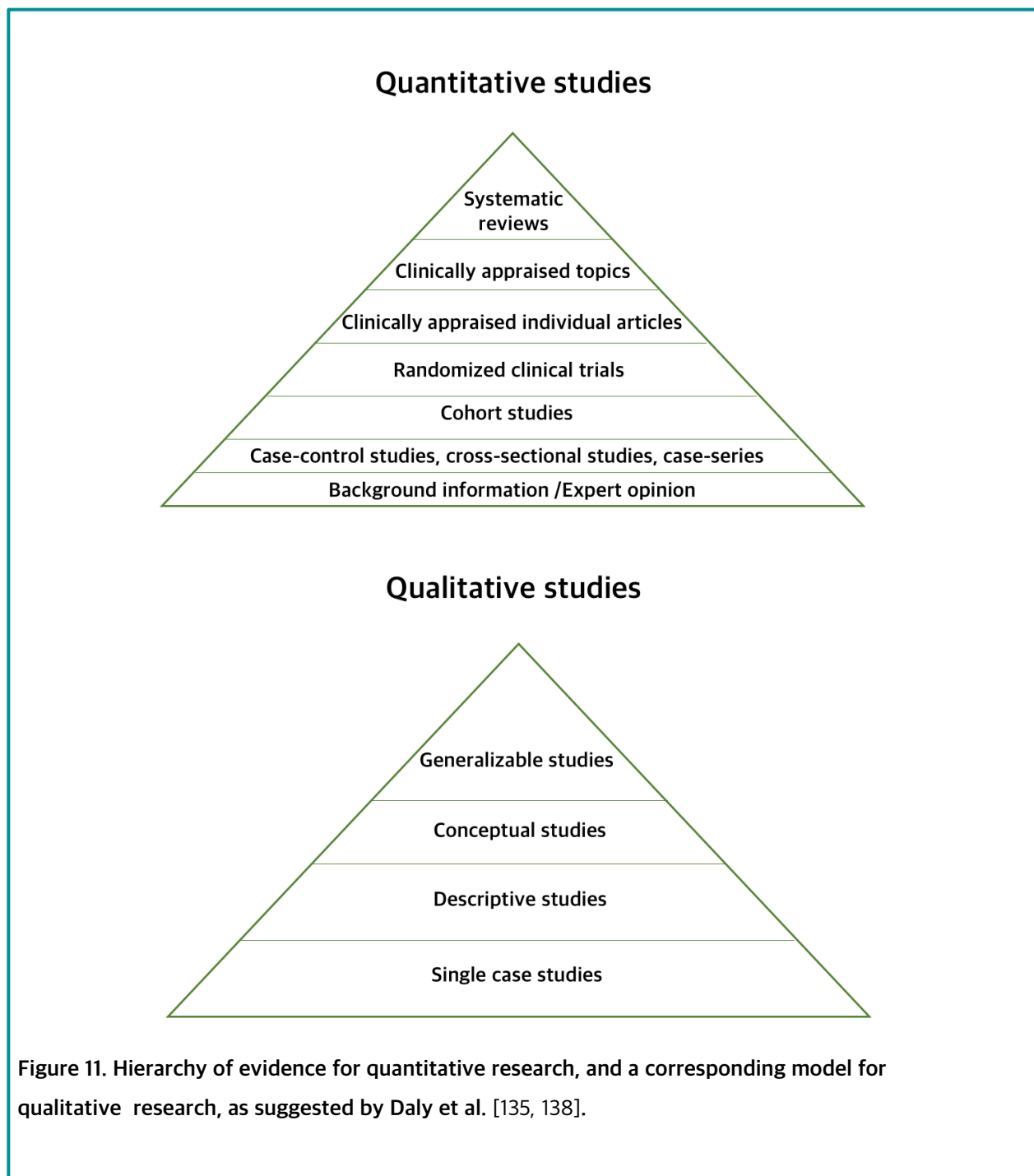
5.4 Rationale for choice of study methodologies

The three studies included in this thesis each represent different methodologies: a protocol for an RCT, a cross-sectional study and a qualitative study. Each methodology holds characteristics and advantages for the type of outcome produced and correlates to the questions being asked.

The hierarchy of evidence places the three studies on different levels of methodological evidence, with the RCT being higher than the cross-sectional study. The hierarchy of evidence was initially developed in 1979 by the Canadian Task Force on periodic health care examinations and how they improved the overall health of the population [133] and is based on the evaluation of clinical interventions and implementation. The placing of qualitative studies in the hierarchy of evidence is debated, and it has been suggested that rather than placing all qualitative research in the bottom of the evidence pyramid, a separate pyramid should exist, thus acknowledging the methodological differences and their mutual combined advantages [134, 135]. However, this implies "generalizability", which for decades has been viewed as conceptually unachievable in qualitative research, but is now considered possible by some researchers, given specific criteria in the theoretical framework of the conducted study [136].

The Cochrane Collaboration has published six systematic reviews on qualitative studies, using the systematic critical-appraisal method GRADE-CERQual, focusing on the *level of confidence* in findings [137]. Overall, quantitative and qualitative research can be viewed as complementary methodologies, finding different angles or answers to different questions, rather than two opposing and contradictory approaches to science [131]. Figure 11 provides illustrations of hierarchy of evidence for quantitative qualitative research.

Quantitative studies

Systematic
reviews

Clinically appraised topics

Clinically appraised individual articles

Randomized clinical trials

Cohort studies

Case-control studies, cross-sectional studies, case-series

Background information /Expert opinion

Qualitative studies

Generalizable studies

Conceptual studies

Descriptive studies

Single case studies

Figure 11. Hierarchy of evidence for quantitative research, and a corresponding model for qualitative research, as suggested by Daly et al. [135, 138].

It can be discussed whether the selected methods in this thesis are the most appropriate. We could have chosen to conduct the SIUTIT trial as a prospective observational study, allowing VT to become a standard treatment in Greenland, and then observe the natural course of OM among children treated with VT and children not treated with VT. However, first of all, in our opinion this would be highly unethical, since VT treatment among high-risk populations has never been investigated. Second of all,

it would not be possible to obtain an unbiased outcome, as the children would not have been randomized, and the risk of confounding of the results would be immense.

Study II was conducted as a cross-sectional study. By conducting it as a cluster-randomized study, allocating the participating towns to either undergoing a teaching intervention versus receiving only written instructions, we could have obtained knowledge about the effectiveness of an increased level of instructions. This was not possible in the cross-sectional study setup. However, the cross-sectional design allowed us to interpret the results from a "real-life" setting, which also holds advantages and valuable information. We could have supplemented and elaborated our results by a qualitative study investigating the underlying reasons for the overall poor quality of the video-otoscopies. Furthermore, a proper teaching intervention could have been applied, se section 6.7.

In Study III, we chose to include parents of children suffering from AOM, OME and CSOM. We could have stratified the interviews on type of disease or even children enrolled in the SIUTIT trial, treated with VT or no VT, thereby examining potential differences. Instead of the qualitative approach we could have used a questionnaire, OM6 or Caregiver Impact Questionnaire as in the SIUTIT trial, however, these are based on predefined questions and would not have permitted the finding of emerging themes. A long-term follow-up observational study, exploring socio-economic differences on OM-free parents/children versus OM-prone parents/children would reveal if the anticipated lower QoL had any measurable consequences on the affected families, although this setup would take years and likely require a high number of participants in order to gain enough power to show statistically significant results.

5.5 Reflections and lessons learned from the SIUTIT trial - challenges and pragmatism versus highest scientific standard

In order to provide knowledge about the best treatment strategy of OM in Greenland, it was necessary to aim for the highest level of evidence, since a similar trial has never been done in a high-risk population such as the Greenlandic. But the inclusion and retention of patients in the SIUTIT trial has proven to be more difficult than anticipated. There may be several reasons for this, and the following section will discuss some of them.

The inclusion of patients was initially based on the referral from general practitioners and other local health care personnel, as this is where the children suffering from OM will first present themselves. The general health examination at the age of 1 seemed to provide an opportunity to identify children

with OME and offer the affected children a follow-up consultation 3 months later, enabling the diagnosis of COME. This would be combined with ongoing continuous inclusion of children suffering from rAOM, who could be referred and included in the trial the day they fulfilled inclusion criteria for rAOM. However, after the first year we had to conclude that the referral of patients from local health personnel was not working properly. First of all, as mentioned in the introduction, the health care system in Greenland is based on few, local long-term employees supplemented by changing personnel on more or less short-term contracts. The long-term professionals carry an enormous responsibility and often have to cover a wide spectrum of health-, social- and human resource management. In order to ensure the retention of information about inclusion criteria and even the existence of the trial, the information would have had to be given a lot more frequently than was the case, even when supplemented with a range of written material.

Secondly, educational sessions on the use of tympanometry, essential for the inclusion of patients suffering from COME, should have been provided more often as well in order to target the personnel sufficiently. Thirdly, fewer of the eligible children underwent the 1-year general health examination than expected, thereby making the process of diagnosing children with COME especially challenging. Given the fact that immunization at 12 months occurs in relation to the 1-year general health examination, we expected that almost all children would attend, but a recent study found immunization rates in the capital of Nuuk to be less than 70% among children aged 12 months [139]. Hence, the inclusion process has had to be revised. During the last year, our approach has been to focus on "raids", where children are invited for a specific ear examination, carried out by personnel related to the SIUTIT trial. Children are still eligible by referral from local capacities, but we are no longer solely dependent on this method of inclusion. Hopefully, this will improve the number of eligible children enrolled in the trial.

Conducting an RCT in a small community also presents further challenges, as parents of children already enrolled may have opinions about the efficiency of the assigned treatment, and thereby facilitating preferences among potential participants. As mentioned in the section about "participation bias" one child allocated to "no VT" received VT outside the trial, reflecting that the parents had decided that the better treatment offer for their child was VT treatment. Proper information about current knowledge and consequences of participation is of crucial importance in the conduction of an RCT, and the fact that most consultations, at least outside the capital, are completed with the use of an interpreter adds the aspect of language barriers to the process. Furthermore, not all inclusion

consultations were performed by the same doctor, increasing the risk of incoherent and inadequate information prior to inclusion.

The Greenlandic Code of Conduct for health researchers in Greenland has a specific paragraph on separating the treatment setting from the inclusion setting [95]. In our setting this was especially difficult because inclusion was often done in relation to the 1-year health examination, creating simultaneous roles as both treating physician and researcher. Assuring the parents that declining participation in the trial would not affect further treatment offers on different health issues was a challenge and requires ethical considerations.

Two of the included patients were found to have perforations of the tympanic membrane at the time of surgery, an exclusion criterion for the SIUTIT trial. The perforation was unacknowledged before inclusion, even though all children also underwent examination with tympanometry, and the removal of excessive wax to obtain a full overview of the tympanic membrane is especially difficult in small children. This reflects the challenging task of diagnosing OM in small children and may be hard to avoid, even in the hands of experienced specialists.

Moreover, two children randomized for surgery had to be postponed because the anesthetic personnel chose to follow the Danish guidelines for anesthesia, which do not recommend general anesthesia for children under the age of two in remote settings.

5.6 In hindsight

Retrospectively, a few overall points can be made.

In a perfect world, The SIUTIT Trial should have been conducted with the use of resident investigators at all six sites simultaneously - someone to be present at the clinic every day, whose sole focus is to include patients for the trial. In this way many of the previously discussed challenges and obstacles could have been avoided. There are many reasons why this is simply not possible, but none the less this would be the optimal way from a purely scientific point of view.

It would have provided valuable insights to include a teaching session when evaluating the smartphone otoscope. Preferably, a proper ear- and hearing related education for all participating operators could have been implemented and the possible improvement documented.

Finally, conducting the qualitative study on subgroups, such as parents to children with AOM/COME vs. CSOM, living in towns vs. living in settlements, could have given a more nuanced view on the perceptions, management strategies and subsequently needs of the affected families.

6. Conclusion

Overall, this thesis has provided insights to some of the main challenges with managing OM in Greenland.

🕮 Paper I: Designing and implementing the second randomized controlled trial in the history of Greenland, we have gained knowledge about the challenges related to conducting trials of high scientific quality in sparsely populated and remote areas. Challenges with recruitment and retention of patients, changing health care personnel, preconceived ideas of the better treatment option and logistical aspects were predominant. These factors need to be taken into account when conducting RCTs in remote and hard-to-reach settings.

🕮 Paper II: The usefulness of smartphone otoscopy proved to be modest in the hands of local health care workers, with one in five video-otoscopies evaluated as useful in the diagnostic process by the three specialist raters. Training is warranted before successful implementation of tele-otoscopy can be expected.

🕮 Paper III: OM in Greenland impacts the affected Greenlandic Inuit families in a complex and severe manner and on several parameters. Guilt, shame, fear and social isolation were predominant factors.

7. Perspectives and clinical implications

The SIUTIT trial is the second RCT in Greenland - only one trial has previously been completed, and this was more than 50 years ago. Improvement of treatment of OM is crucial and trials with a high level of evidence done in high-risk populations are necessary. The Greenlandic Inuit, as well as high-risk populations worldwide need well-conducted trials providing evidence-based guidelines to improve overall healthcare - not only within the field of otology.

The socioeconomic disadvantages of the Greenlandic Inuit are evident and there is no doubt that long-term commitment to the improvement of overall poverty, domestic violence and substance abuse is of utmost importance. However, it should not serve as an excuse for not aiming for the highest level of evidence for medical treatment in a setting where the extrapolation of results from other studies may be problematic or inadequate. This being said, the question of when "the evidence is evident" remains. In a country such as Greenland, where health resources are sparse, it is necessary to at least consider the level of evidence needed before new treatment regimens are implemented. Conducting RCTs in remote areas is time-consuming, expensive and logistically challenging. Researchers should keep the utility of their results in mind when conducting research in Greenland and evaluate the benefits for the Greenlandic Inuit. The thorough and well-conducted epidemiological studies that already exist on Greenlandic Inuit health should be complimented by intervention studies that focus more on decreasing and less on describing.

An ear and hearing program including guidelines for clinicians in Greenland is needed. The program should focus on the epidemiological as well as cultural characteristics of OM among Greenlandic Inuit and should be anchored within the local communities. Education and training of local, permanent personnel should be prioritized, as this may provide the core for long-term improvement of overall ear health. Knowledge about cultural differences between for instance the typical Danish ear patient and the Greenlandic Inuit should be disseminated to doctors and nurses working in Greenland, both short and long term.

8. Conflicts of interests

9. Sources of funding

10. English summary

The prevalence of otitis media (OM) among Greenlandic Inuit is one of the highest in the world. Greenlandic Inuit children have earlier onset of first episode of acute otitis media (AOM) compared to Western countries, and it is estimated that 9-14% of all Greenlandic Inuit children suffer from chronic suppurative otitis media (CSOM).

The etiology of AOM, otitis media with effusion (OME) and CSOM is multi-factorial and the correlation between the disease entities is complex and not fully understood.

OM may lead to hearing loss, impaired educational and cognitive skills and an overall decrease in quality of life as consequence.

There are currently no national treatment guidelines for OM. The organization of the Greenlandic health care system, which faces extreme distances, logistical hardship, and everchanging health-care professionals, provides further challenges to treatment. Furthermore, little is known about the impact of the disease on the family as a whole.

International studies have shown that otitis prone children may benefit from ventilation tube treatment. However, it is unknown whether this can be applied to Greenlandic Inuit children and no trials on the effects of ventilation tubes (VT) in high-risk populations have ever been conducted.

Telemedicine may prove useful in the diagnostic process, enabling specialist evaluation of video otoscopies and thereby enhancing the diagnostic accuracy. And finally, more knowledge about the parental perceptions and management strategies for OM may help the clinician as well as the patient in the treatment process and add guidance to public health approaches.

The objectives of the three papers included in this thesis were to design and conduct a trial on the use of VT treatment among Greenlandic Inuit children, to examine the usefulness of a smartphone otoscope in the hands of local health care personnel, and to investigate the impact of OM on Greenlandic Inuit families.

Paper I was a protocol for a randomized, investigator-initiated, controlled superiority trial on the effects of VT treatment versus treatment as usual on Greenlandic Inuit children, aged 9-36 months. The trial is still ongoing. The trial proved to be more difficult to conduct than expected. Recruitment and retention of patients, changing health care personnel, preconceived ideas on the better treatment

option and logistical aspects all presented as challenging in the process of implementing a trial based on state-of-the-art methodology. The trial has provided valuable insights into factors that needs to be taken into account, when conducting randomized trials in remote and hard-to-reach settings.

Paper II was a cross-sectional study investigating the use of a smartphone otoscope carried out by local health care personnel. We found that less than one in five video otoscopies were useful in the diagnostic process. The primary challenges were improper insertion of the otoscope as well as wax impaction.

Paper III was a qualitative study based on interviews with parents of children suffering from OM. The data analysis was done by systematic text analysis. The analysis showed that OM has other and more serious consequences for Greenlandic Inuit families than otherwise found in the existing literature. Although the majority of the parents acknowledged the biomedical approach as their primary explanation model, this coexisted with self-blame and guilt. The parents were ashamed and felt that others were blaming them, resulting in withdrawal from social gatherings.

In conclusion, this thesis has provided insights into some of the main challenges with managing OM in Greenland. We have designed and implemented only the second randomized controlled trial in the history of Greenland and gained knowledge into the challenges related to conducting trials of high scientific quality in sparsely populated remote areas. There is a need for focusing on local education if tele-otoscopy is to be implemented as a supplementary tool in the diagnostic process of OM in Greenland. And finally, we have documented that OM impacts the affected Greenlandic Inuit families in a severe manner and on several parameters.

11. Dansk resume (Danish summary)

Forekomsten af otitis media (OM) blandt grønlandske Inuit er en af de højeste i verden. Grønlandske Inuitbørn får første episode af akut otitis media (AOM) tidligere end børn i den vestlige del af verden, og det er estimeret at 9-14% af alle grønlandske børn lider af kronisk suppurativ otitis media (CSOM). Ætiologien af AOM, otitis media med effusion (OME) samt CSOM er multi-faktoriel og korrelationen mellem sygdomsenhederne er kompleks og ikke fuldt forstået.

OM kan føre til høretab, nedsat indlæringsevne og kognitiv udvikling samt en overordnet påvirkning af livskvaliteten. Der findes ingen nationale retningslinjer for behandling af OM i Grønland. Organisationen af det grønlandske sundhedssystem, hvor ekstreme afstande, logistiske udfordringer og skiftende sundhedspersonale giver yderligere udfordringer for behandling. Desuden ved vi ikke hvordan sygdommen påvirker familien som helhed.

Internationale studier har vist at drænanlæggelse i trommehinden på børn med kompliceret OM muligvis kan hjælpe. Det er dog uvist om dette kan extrapoleres til grønlandske Inuit børn og forsøg der undersøger effekten af dræn blandt højrisiko-populationer, har aldrig været udført.
Telemedicin kan muligvis være nyttig i den diagnostiske proces, ved at give mulighed for at specialister kan evaluere video-otoskopier og derved øge den diagnostiske sikkerhed.
Og endelig kan mere viden om forældrenes opfattelse af OM måske hjælpe både klinikerne i behandlingsstrategier samt guide beslutningstagere i et bredere folkesundhedsperspektiv.

Formålet med de tre artikler inkluderet i denne tese var at designe og udføre et forsøg der undersøger drænanlæggelse blandt grønlandske Inuit børn, at undersøge brugbarheden af et smartphone-otoskop, i hænderne i lokalt sundhedspersonale, samt at undersøge indvirkningen af OM på grønlandske Inuit familier.

Artikel I var en protokolartikel for et randomiseret, investigator-initieret, kontrolleret forsøg omhandlende effekten af dræn versus vanlig behandling blandt grønlandske Inuit børn i alderen 9-36 måneder. Forsøget kører stadig. Det viste sig at være sværere at gennemføre end forventet. Rekruttering og fastholdelse af patienter, skiftende sundhedspersonale, forudfattede meninger om behandlingseffekt samt logistiske aspekter var alle udfordringer for implementeringen af et forsøg af højeste videnskabelige kvalitet. Processen har givet vigtig viden om faktorer der skal tages højde for ved gennemførsel af et forsøg i svært tilgængelige områder.

Artikel II var en tværsnitsundersøgelse af brugen af smartphone otoskopi udført af lokalt sundhedspersonale. Vi fandt at under en ud af fem otoskopier blev evalueret som brugbar for den diagnostiske proces. De primære udfordringer var ufuldstændig placering af otoskopet samt obstruktion af voks.

Artikel III var et kvalitativt studie baseret på interviews med forældre til børn med OM. Vi analyserede data ved hjælp af metoden Systematisk Tekst Kondensering. Analysen viste at OM har andre og mere alvorlige konsekvenser på grønlandske Inuit familier end tidligere fundet i den eksisterende litteratur. Selvom størstedelen af forældrene anerkendte den biomedicinske tilgang som deres primære forklaringsmodel var der samtidig selvbebrejdelse og skyld. Forældrene skammede sig og følte at andre bebrejdede dem, hvilket resulterede i at mange forældre trak sig fra sociale sammenhænge.

Alt i alt har denne afhandling givet indblik i nogle af de primære udfordringer ved at håndtere OM i Grønland. Vi har designet og implementeret det blot andet randomiserede forsøg i Grønlands historie og fået viden om udfordringerne relateret til at udføre forsøg af høj videnskabelig kvalitet i sparsomt befolkede områder. Der er behov for at fokusere på lokal uddannelse hvis tele-otoskopi skal implementeres som et supplerende værktøj i den diagnostiske proces af OM i Grønland.
Og endelig har vi dokumenteret at OM har alvorlig indvirkning på de ramte grønlandske Inuit familier samt på mange parametre.

12. Eqikkaaneq (Greenlandic summary)

Kalaallit akornanni siutikkut aseruuttoortarneq nunarsuarmi atugaanerpaanut ilaavoq. Kalaallit meerartaat Nunani Killerni meeqqanit siulliullutik tassanngaannaq takkuttumik siutimikkut aseruuttoortarput, Kalaallit meerartaasa anigugassaanngitsumik siutaat maqisartut procentinngorlugit qulaaluat 14-illu akornanniittut missingersorneqarpoq.

Siutikkut aseruuttoorneq marneqanngitsoq tassanngaannaq takkuttoq kiisalu maqisoorneq assigiinngitsunik arlalinnik patsiseqarput, nappaatillu ataqatigiinnerat paasilertoruminaappoq, tamakkiisumillu paasineqarani.

Siutikkut aseruuttoorneq, tusillannermik ilikkagaqarsinnaasutsillu annikillineranik kiisalu ataatsimut isigalugu inuunerup naleqassusaata sunnerneqarneranik kinguneqarsinnaavoq.

Kalaallit Nunaanni nuna tamakkerlugu siutikkut aseruuttoornermi nakorsaanermut maleruagassaqanngilaq. Kalaallit Nunaanni peqqinnissaqarfiup aaqqissuussaanera, isorartussutsit annertoqisut, angallannikkut ataqatigiissaarinermi unammilligassat sulisullu taarseraattut, nakorsaasinnaanermut suli annertunerusunik unammilligassiipput. Tamatuma saniatigut ilaqutariit ataatsimut isigalugit nappaatip qanoq sunniuteqarnera ilisimanngilarput.

Meeqqani ajornartorsiutitalimmik siutimikkut aseruuttoortuni, siutip igalaasaagut paqqersaasiinerup iluaqutaasinnaanera nunarsuaq tamakkerlugu misissuinerit takutippaat. Tamatumali kalaallit meerartaanni atuutsinneqarsinnaanissaa ilisimaneqanngilaq, nunatsinnilu nappaateqalernissamut annertuumik navianartorsiortunut misiliinerit paqqersaatip sunniutaanik ikorfartuisut ingerlanneqarsimanngisaannarlutik.

Nappaammik suussusersiniaanermi immikkut ilisimasallit, siutinut qinngut atorlugu misissuinernik videomut immiussanik naliliisinnaanngorlugit, qarasaasiakkut nakorsiartitsinikkut nappaammik suussusersiniaanerup qularnaannerulernera immaqa iluaqutaasinnaassaaq.

Kiisalu angajoqqaat siutikkut aseruuttoornermut qanoq paasinninnerannik ilisimasaqarneruneq nakorsaasunut nakorsaanermi iliuusissatut siunniussinermut immaqa iluaqutaassaaq aalajangiisussanillu innuttaasut peqqissusaannut atiitunerusumik isiginninnermut aqqutissiuussilluni.

Allaaserisani taakkunani pingasuni tunngavilersorlugu isummiussami matumani ilanngussani, kalaallit meerartaasa akornanni paqqersaasiinermik misissuinermik ilusiliinissaq misiliinissarlu, smartphone atorlugu qinngutip siutinut misissuutip najukkani peqqinnissakkut sullissisunit

atorneqarsinnaaneranik, kiisalu siutikkut aseruuttoornerup nunatsinni ilaqutariinnut sunniutaanik misissuinissaq siunertaapput.

Siulleq, makitsinikkut misissuinermi peqataatitsinikkut, misissuisutut suliniummik aallartitsinikkut, nakorsakkanik assersuussinikkut nakorsaanerup sunniutaanik misissuineq, paqqersaasiinerup pisarnertut nakorsaanermut taarsiullugu nunatsinni meeqqanut qulaaluaniit 36-inut qaammatilinnut sunniutaa pillugu allaaserisaavoq. Misiliineq suli ingerlanneqarpoq. Misiliinerup ingerlannera naatsorsuutigisamiit ajornarnerusoq paasinarsivoq. Napparsimasunik pissarsiniarneq aalaakkaasunillu misissugassaqarniarneq, sulisut taarseraannerat, nakorsaanerup iluaqutaaneranut isummiuteriikkat kiisalu ataqatigiissaarinermut tunngasut tamarmik misiliinermut ilisimatuussutsikkut pitsaassusaa qaffasinnerpaamik piviusunngortitsinissamut unammillernartuupput. Ingerlatsineq, sumiiffinni tikikkuminaatsuni misiliinermik ingerlatsinermi eqqarsaatigisassat pillugit pingaarutilinnik ilisimasaqalersitsivoq.

Allaaserisat aappaat, najukkani peqqinnissakkut sullissisut innuttasunut tamanut sinniisunik smartphone atorlugu siutinik misissuinerannut tunngavoq. Qinngut atorlugu siutinik misissuinerni tallimani ataatsip inortut, nappaammik suussusersiniaanermi atorsinnaasutut naliliivineqarnerat paasivarput. Unammilligassat pingaarnerit tassaapput qinngutip siutinut misissuutip inissilluarsimannginnera kiisalu siutit mineqarpallaarnerat.

Allaaserisat pingajuat meeqqat siutimikkut aseruuttoortut angajoqqaavinik apersuinermik tunngaveqartoq, paasissutissanik naatsorsueqqissaarnermi periutsinik atuinani, misissugassanik pissarsiniarneruvoq. Paasissutissat periuseq aaqqisuussamik eqikkaaneq iluaqutsiullugu misissoqqissaarpagut. Siutikkut aseruuttoornerup, allanik najoqqutassani pioreersuni paasisaniit navianarnerusunik ilaqutariinnut kalaallinut kinguneqarnera, misissueqqissaarnerup takutippaa. Naak angajoqqaat amerlanersaasa nappaatit pinngortarnerannik ilisimatusarnikkut paasisat nassuiaatissamissut pingaarnertut akuerigaluaraat, tamatuma peqatigisaanik imminut avoqqaarlerneq pisuutinnerlu atuupput. Angajoqqaat kanngusupput allaniillu avoqqaarineqartutut misigalutik tamatumalu kinguneriisaanik angajoqqaat amerlasuut inoqatinut akulerunnissamut tunuarterlutik.

Ataatsimut isigalugu ilisimatuutut allaaserisaq una nunatsinni siutikkut aseruuttoortarnerup iliuuseqarfiginissaanut unammilligassat pingaarnerit ilaannut paasissutissiivoq.

Nunatta oqaluttuarisaanerani aatsaat aappassaanik, makitsinikkut misissuinermi peqataatitaqarnikkut misiliinermik piviusunngortitsillutalu ilusiliivugut inukitsunilu ilisimatuussutsikkut qaffasissumik pitsaassusilimmik misiliinermut atatillugu unammilligassat ilisimasaqarfigilerlugit.

Qarasaasiakkut nakorsiartitsissut atorlugu siutit qinngullugit misissuineq, nunatsinni siutikkut aseruuttoornerup suussusersinissaanut sakkussat ilaattut atuutilersinneqassappat, najukkani ilinniartitsinissamik ukkassinissaq pisariaqarpoq.

Kiisalu siutikkut aseruuttoornerup kalaallini ilaqutariinni eqqorneqartuni uuttuutinilu amerlasuuni navianaatilimmik sunniuteqarnera uppernarsivarput.

13. References

1. Lieberthal AS, Carroll AE, Chonmaitree T, et al. (2013) The Diagnosis and Management of Acute Otitis Media. Pediatrics 131:964-999.

2. Heidemann CH, Lous J, Berg J, et al. (2016) Danish guidelines on management of otitis media in preschool children. Int J Pediatr Otorhinolaryngol 87:154-163. doi: 10.1016/j.ijporl.2016.06.003

3. Schilder AGM, Chonmaitree T, Cripps AW, et al. (2016) Otitis media. Nat Rev Dis Prim 2:16063. doi: 10.1038/nrdp.2016.63

4. Rosenfeld RM, Shin JJ, Schwartz SR, et al. (2016) Clinical Practice Guideline: Otitis Media with Effusion Executive Summary (Update). Otolaryngol Head Neck Surg 154:201-14. doi: 10.1177/0194599815624407

5. Rovers MM, Schilder AGM, Zielhuis GA, Rosenfeld RM (2004) Otitis media. Lancet (London, England) 363:465-73. doi: 10.1016/S0140-6736(04)15495-0

6. World Health Organization, Health A (2004) Chronic suppurative otitis media Burden of Illness and Management Options.

7. Bluestone CD (1998) Epidemiology and pathogenesis of chronic suppurative otitis media: Implications for prevention and treatment. Int J Pediatr Otorhinolaryngol 42:207-223. doi: 10.1016/S0165-5876(97)00147-X

8. Bhutta MF, Thornton RB, Kirkham L-AS, et al. (2017) Understanding the aetiology and resolution of chronic otitis media from animal and human studies. Dis Model Mech 10:1289-1300. doi: 10.1242/dmm.029983

9. Morris P (2012) Chronic suppurative otitis media. BMJ Clin. Evid. 2012:

10. Homøe P, Kværner K, Casey JR, et al. (2017) Panel 1: Epidemiology and Diagnosis. Otolaryngol - Head Neck Surg (United States). doi: 10.1177/0194599816643510

11. Lous J, Ryborg CT, Damsgaard JJ, Munck AP (2012) Tympanometry in general practice: use, problems and solutions. Fam Pract 29:726-732. doi: 10.1093/fampra/cms045

12. Froom J, Culpepper L, Grob P, et al. (1990) Diagnosis and antibiotic treatment of acute otitis media: report from International Primary Care Network. BMJ 300:582-586. doi: 10.1136/bmj.300.6724.582

13. Ovnat Tamir S, Shemesh S, Oron Y, Marom T (2017) Acute otitis media guidelines in selected developed and developing countries: uniformity and diversity. Arch Dis Child 102:450-457. doi: 10.1136/archdischild-2016-310729

14. Helenius KK, Laine MK, Tähtinen PA, et al. (2012) Tympanometry for Discrimination of Otoscopic Diagnoses in Young Ambulatory Children. Pediatr Infect Dis J 1. doi: 10.1097/INF.0b013e31825cac94

15. Smith CG, Paradise JL, Sabo DL, et al. Tympanometric Findings and the Probability of Middle-Ear Effusion in 3686 Infants and Young Children. doi: 10.1542/peds.2005-1879

16. Verhoeff M, Van Der Veen EL, Rovers MM, et al. (2006) Chronic suppurative otitis media: A review. Int J Pediatr Otorhinolaryngol 70:1-12. doi: 10.1016/j.ijporl.2005.08.021

17. Stol K, Verhaegh SJC, Graamans K, et al. (2013) Microbial profiling does not differentiate between childhood recurrent acute otitis media and chronic otitis media with effusion. Int J Pediatr Otorhinolaryngol 77:488-93. doi: 10.1016/j.ijporl.2012.12.016

18. Jensen RG, Johansen HK, Bjarnsholt T, et al. (2017) Recurrent otorrhea in chronic suppurative otitis media: is biofilm the missing link? Eur Arch Oto-Rhino-Laryngology 274:2741-2747. doi: 10.1007/s00405-017-4586-8

19. Sidell D, Shapiro NL, Bhattacharyya N (2012) Demographic influences on antibiotic prescribing for pediatric acute otitis media. Otolaryngol Head Neck Surg 146:653-8. doi: 10.1177/0194599811431228

20. Monasta L, Ronfani L, Marchetti F, et al. (2012) Burden of disease caused by otitis media: Systematic review and global estimates. PLoS One 7:e36226. doi: 10.1371/journal.pone.0036226

21. Bhutta MF, Bhutta MF (2015) Evolution and Otitis Media: A Review, and a Model to Explain High Prevalence in Indigenous Populations. Hum Biol 87:92-108. doi: 10.13110/humanbiology.87.2.0092

22. Homøe P, Christensen RB, Bretlau P (1996) Prevalence of otitis media in a survey of 591 unselected Greenlandic children. Int J Pediatr Otorhinolaryngol 36:215-230. doi: 10.1016/0165-5876(96)01351-1

23. Morris PS, Leach AJ, Silberberg P, et al. (2005) Otitis media in young Aboriginal children from remote communities in Northern and Central Australia: a cross-sectional survey. BMC Pediatr 5:27. doi: 10.1186/1471-2431-5-27

24. Bruneau S, Ayukawa H, Proulx JF, et al. (2001) Longitudinal observations (1987-1997) on the prevalence of middle ear disease and associated risk factors among Inuit children of Inukjuak, Nunavik, Quebec, Canada. Int J Circumpolar Health 60:632-9.

25. Curns AT, Holman RC, Shay DK, et al. (2002) Outpatient and hospital visits associated with otitis media among American Indian and Alaska native children younger than 5 years. Pediatrics 109:E41-1. doi: 10.1542/PEDS.109.3.E41

26. Koch A, Homøe P, Pipper C, et al. (2011) Chronic suppurative otitis media in a birth cohort of children in Greenland: population-based study of incidence and risk factors. Pediatr Infect Dis J 30:25-9. doi: 10.1097/INF.0b013e3181efaa11

27. Avnstorp MB, Homøe P, Bjerregaard P, Jensen RG (2016) Chronic suppurative otitis media, middle ear pathology and corresponding hearing loss in a cohort of Greenlandic children. Int J Pediatr Otorhinolaryngol 83:148-53. doi: 10.1016/j.ijporl.2016.01.017

28. Rovers MM, De Kok IMCM, Schilder AGM (2006) Risk factors for otitis media: An international perspective. Int J Pediatr Otorhinolaryngol 70:1251-1256. doi: 10.1016/j.ijporl.2006.01.003

29. Homøe P, Christensen RB, Bretlau P (1999) Acute otitis media and sociomedical risk factors among unselected children in Greenland. Int J Pediatr Otorhinolaryngol 49:37-52. doi: 10.1016/S0165-5876(99)00044-0

30. Lasisi AO, Olaniyan FA, Muibi SA, et al. (2007) Clinical and demographic risk factors associated with chronic suppurative otitis media. Int J Pediatr Otorhinolaryngol 71:1549-1554. doi: 10.1016/j.ijporl.2007.06.005

31. Koch A, Homøe P, Pipper C, et al. (2011) Chronic Suppurative Otitis Media in a Birth Cohort of Children in Greenland. Pediatr Infect Dis J 30:25-29. doi: 10.1097/INF.0b013e3181efaa11

32. Coleman A, Wood A, Bialasiewicz S, et al. (2018) The unsolved problem of otitis media in indigenous populations: a systematic review of upper respiratory and middle ear microbiology in indigenous children with otitis media. Microbiome 6:199. doi: 10.1186/s40168-018-0577-2

33. Leach A, Morris P (2001) Perspectives on infective ear disease in indigenous Australian children. J Paediatr Child Health 37:529-530. doi: 10.1046/j.1440-1754.2001.00729.x

34. Leach AJ, Boswell JB, Asche V, et al. (1994) Bacterial colonization of the nasopharynx predicts very early onset and persistence of otitis media in Australian aboriginal infants. Pediatr Infect Dis J 13:983-9.

35. Jervis-Bardy J, Sanchez L, Carney AS (2014) Otitis media in Indigenous Australian children: review of epidemiology and risk factors. J Laryngol Otol 128:S16-S27. doi: 10.1017/S0022215113003083

36. Homøe P, Prag J, Farholt S, et al. (1996) High rate of nasopharyngeal carriage of potential pathogens among children in Greenland: results of a clinical survey of middle-ear disease. Clin Infect Dis 23:1081-90.

37. Schilder AGM, Marom T, Bhutta MF, et al. (2017) Panel 7: Otitis Media: Treatment and Complications. Otolaryngol Neck Surg 156:S88-S105. doi: 10.1177/0194599816633697

38. Venekamp RP, Sanders SL, Glasziou PP, et al. (2015) Antibiotics for acute otitis media in children. Cochrane Database Syst Rev 2015:CD000219. doi: 10.1002/14651858.CD000219.pub4

39. Leach AJ, Morris PS (2006) Antibiotics for the prevention of acute and chronic suppurative otitis media in children. Cochrane Database Syst Rev. doi: 10.1002/14651858.CD004401.pub2

40. Leach AJ, Morris PS, Mathews JD (2008) Compared to placebo, long-term antibiotics resolve otitis media with effusion (OME) and prevent acute otitis media with perforation (AOMwiP) in a high-risk population: A randomized controlled trial. BMC Pediatr 8:23. doi: 10.1186/1471-2431-8-23

41. Simon F, Haggard M, Rosenfeld RM, et al. (2018) International consensus (ICON) on management of otitis media with effusion in children. Eur Ann Otorhinolaryngol Head Neck Dis 135:33-39. doi: 10.1016/j.anorl.2017.11.009

42. Venekamp RP, Burton MJ, van Dongen TM, et al. (2016) Antibiotics for otitis media with effusion in children. Cochrane Database Syst Rev CD009163. doi: 10.1002/14651858.CD009163.pub3

43. Gunasekera H, Morris PS, McIntyre P, Craig JC (2009) Management of children with otitis media: A summary of evidence from recent systematic reviews. J Paediatr Child Health 45:554-563. doi: 10.1111/j.1440-1754.2009.01564.x

44. Rosenfeld RM, Schwartz SR, Pynnonen MA, et al. (2013) Clinical practice guideline: Tympanostomy tubes in children. Otolaryngol Head Neck Surg 149:S1-35. doi: 10.1177/0194599813487302

45. National Institute for Health and Care Excellence. In: www.nice.org.uk/guidance/CG60.

46. Schilder AGM, Lok W, Rovers MM (2004) International perspectives on management of acute otitis media: A qualitative review. Int J Pediatr Otorhinolaryngol 68:29-36. doi: 10.1016/j.ijporl.2003.09.002

47. Todberg T, Koch A, Andersson M, et al. (2014) Incidence of otitis media in a contemporary Danish National Birth Cohort. PLoS One 9:e111732. doi: 10.1371/journal.pone.0111732

48. Browning GG, Rovers MM, Williamson I, et al. (2010) Grommets (ventilation tubes) for hearing loss associated with otitis media with effusion in children. Cochrane database Syst Rev CD001801. doi: 10.1002/14651858.CD001801.pub3

49. Hellström S, Groth A, Jörgensen F, et al. (2011) Ventilation tube treatment: a systematic review of the literature. Otolaryngol Head Neck Surg 145:383-95. doi: 10.1177/0194599811409862

50. Venekamp RP, Mick P, Schilder AG, Nunez DA (2018) Grommets (ventilation tubes) for recurrent acute otitis media in children. Cochrane Database Syst Rev. doi: 10.1002/14651858.CD012017.pub2

51. Steele DW, Adam GP, Di M, et al. (2017) Effectiveness of Tympanostomy Tubes for Otitis Media: A Meta-analysis. Pediatrics 139:e20170125. doi: 10.1542/peds.2017-0125

52. Lous J, Ryborg CT, Thomsen JL (2011) A systematic review of the effect of tympanostomy tubes in children with recurrent acute otitis media – ClinicalKey. Int J Pediatr Otorhinolaryngol 75:1058-1061. doi: 10.1016/j.ijporl.2011.05.009

53. Demant MN, Jensen RG, Jakobsen JC, et al. (2017) The effects of ventilation tubes versus no ventilation tubes for recurrent acute otitis media or chronic otitis media with effusion in 9 to 36 month old Greenlandic children, the SIUTIT trial: study protocol for a randomized controlled trial. Trials 18:30. doi: 10.1186/s13063-016-1770-x

54. Guyatt GH, Oxman AD, Vist GE, et al. (2008) GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 336:924-6. doi: 10.1136/bmj.39489.470347.AD

55. Boonacker CW, Rovers MM, Browning GG, et al. (2014) Adenoidectomy with or without grommets for children with otitis media: an individual patient data meta-analysis. Health Technol Assess (Rockv) 18:1-118. doi: 10.3310/hta18050

56. van den Aardweg MT, Schilder AG, Herkert E, et al. (2010) Adenoidectomy for otitis media in children. Cochrane Database Syst Rev. doi: 10.1002/14651858.CD007810.pub2

57. Osma U, Cureoglu S, Hosoglu S (2019) The complications of chronic otitis media: report of 93 cases. J Laryngol Otol 114:97-100. doi: 10.1258/0022215001905012

58. Homøe P, Jensen RG, Brofeldt S Acute mastoiditis in Greenland between 1994-2007. Rural Remote Health 10:1335.

59. Graydon K, Waterworth C, Miller H, Gunasekera H (2019) Global burden of hearing impairment and ear disease. J Laryngol Otol 133:18-25. doi: 10.1017/S0022215118001275

60. Bennett K, Haggard M, Silva PA, Stewart IA (2001) Behaviour and cognitive outcomes from middle ear disease. Arch Dis Child 80:28-35. doi: 10.1136/adc.85.2.91

61. Teasdale TW, Sorensen MH (2007) Hearing loss in relation to educational attainment and cognitive abilities: A population study. Int J Audiol 46:172-175. doi: 10.1080/14992020601089484

62. Kral A, O'Donoghue GM (2010) Profound Deafness in Childhood. N Engl J Med 363:1438-1450. doi: 10.1056/NEJMra0911225

63. Da Costa C, Eikelboom RH, Jacques A, et al. (2018) Does otitis media in early childhood affect later behavioural development? Results from the Western Australian Pregnancy Cohort (Raine) Study. Clin Otolaryngol. doi: 10.1111/coa.13094

64. Homøe P, Christensen RB, Breatlau P (1995) Hearing in elementary school children in Nuuk and Sisimiut, Greenland. Arctic Med Res 54:145-50.

65. Jensen RG, Koch A, Homøe P (2013) The risk of hearing loss in a population with a high prevalence of chronic suppurative otitis media. Int J Pediatr Otorhinolaryngol 77:1530-5. doi: 10.1016/j.ijporl.2013.06.025

66. Bhutta MF (2019) Models of service delivery for ear and hearing care in remote or resource-constrained environments. J Laryngol Otol 133:39-48. doi: 10.1017/S0022215118002116

67. World Health Organization (2013) Multi-country assessment of the national capacity to provide hearing care.

68. Brouwer CNM, Rovers MM, Maillé AR, et al. (2005) The impact of recurrent acute otitis media on the quality of life of children and their caregivers. Clin Otolaryngol 30:258-265. doi: 10.1111/j.1365-2273.2005.00995.x

69. Greenberg D, Bilenko N, Liss Z, et al. (2003) The burden of acute otitis media on the patient and the family. Eur J Pediatr 162:576-81. doi: 10.1007/s00431-003-1260-5

70. Lee J, Witsell DL, Dolor RJ, et al. (2006) Quality of Life of Patients With Otitis Media and Caregivers: A Multicenter Study. Laryngoscope 116:1798-1804. doi: 10.1097/01.mlg.0000231305.43180.f6

71. Holl K, Rosenlund M, Giaquinto C, et al. (2015) The Impact of Childhood Acute Otitis Media on Parental Quality of Life in a Prospective Observational Cohort Study. Clin Drug Investig 35:613-24. doi: 10.1007/s40261-015-0319-1

72. Rosenfeld RM, Goldsmith AJ, Tetlus L, Balzano A (1997) Quality of life for children with otitis media. Arch Otolaryngol Head Neck Surg 123:1049-54.

73. Boruk M, Lee P, Faynzilbert Y, Rosenfeld RM (2007) Caregiver well-being and child quality of life. Otolaryngol - Head Neck Surg 136:159-168. doi: 10.1016/J.OTOHNS.2006.09.005

74. Wuest J (1991) Harmonizing: A North American Indian Approach to Management of Middle Ear Disease with Transcultural Nursing Implications. J Transcult Nurs 3:5-14. doi: 10.1177/104365969100300103

75. Jeffries-Stokes C, Lehmann D, Johnston J, et al. (2004) Aboriginal perspective on middle ear disease in the

arid zone of Western Australia. J Paediatr Child Health 40:258-264. doi: 10.1111/j.1440-1754.2004.00360.x

76. Statistics Greenland (2018) Greenland in Figures 2018.

77. Chatwood S, Bjerregaard P, Young TK (2012) Global health–a circumpolar perspective. Am J Public Health 102:1246-9. doi: 10.2105/AJPH.2011.300584

78. Bjerregaard P, Kue Young T, Dewailly E, Ebbesson SO (2004) Review Article: Indigenous health in the Arctic: An overview of the circumpolar Inuit population. Scand J Public Health 32:390-395. doi: 10.1080/14034940410028398

79. Bjerregaard P, Dahl-Petersen IK, Larsen CVL (2018) Measuring social inequality in health amongst indigenous peoples in the Arctic. A comparison of different indicators of social disparity among the Inuit in Greenland. SSM – Popul Heal 6:149-157. doi: 10.1016/j.ssmph.2018.08.010

80. Bruce M (2011) The International Union for Circumpolar Health–an important actor in circumpolar health. Int J Circumpolar Health 70:3-5. doi: 10.3402/ijch.v70i1.17792

81. The Arctic Council. https://arctic-council.org/index.php/en/. Accessed 22 May 2019

82. Níels Einarsson. (2004) Arctic human development report. Stefansson Arctic Institute

83. Moltke I, Fumagalli M, Korneliussen TS, et al. (2015) Uncovering the Genetic History of the Present-Day Greenlandic Population. doi: 10.1016/j.ajhg.2014.11.012

84. Larsen CVL, Hansen C, Ingemann C, et al. (2019) Public Health in Greenland 2018, National Institute of Public Health.

85. Curtis T, Larsen FB, Helweg-Larsen K, Bjerregaard P (2002) Violence, sexual abuse and health in Greenland. Int J Circumpolar Health 61:110-122. doi: 10.3402/ijch.v61i2.17443

86. Anderson I, Robson B, Connolly M, et al. (2016) Indigenous and tribal peoples' health (The Lancet-Lowitja Institute Global Collaboration): a population study. Lancet 388:131-157. doi: 10.1016/S0140-6736(16)00345-7

87. Niclasen B, Mulvad G (2010) Health care and health care delivery in Greenland. Int J Circumpolar Health 69:437-487. doi: 10.3402/ijch.v69i5.17691

88. Government of Greenland (2010) Redegørelse om Sundhedsreformen.

89. Lynge Pedersen M, Rolskov A, Lindskov Jacobsen J, et al. (2012) Frequent use of primary health care service in Greenland: an opportunity for undiagnosed disease case-finding. Int J Circumpolar Health 71:18431. doi: 10.3402/ijch.v71i0.18431

90. Kløvgaard M, Nielsen NO, Sørensen TL, et al. (2016) Children in Greenland: disease patterns and contacts to the health care system. Int J Circumpolar Health 75:32903. doi: 10.3402/IJCH.V75.32903

91. Demant MNM, Larsen CVL, Homøe P (2019) Parental Perceptions and Management Strategies for Otitis Media in Greenland. Int J Pediatr Otorhinolaryngol 125:15-22. doi: 10.1016/J.IJPORL.2019.06.013

92. Nielsen LO, Krebs HJ, Albert NM, et al. (2017) Telemedicine in Greenland: Citizens' Perspectives. Telemed e-Health 23:441-447. doi: 10.1089/tmj.2016.0134

93. Asia Pacific Forum, United Nations Office of the High Commissioner for Human Rights (2013) The United Nations Declaration on the Rights of Indigenous Peoples: A Manual for National Human Rights Institutions. 152. doi: 10.2174/1874285800903010069

94. Gracey M, King M (2009) Indigenous health part 1: determinants and disease patterns. Lancet 374:65-75. doi: 10.1016/S0140-6736(09)60914-4

95. Danish Greenlandic Society for Circumpolar Health (2015) Code of Conduct.

96. Bjerregaard P, Mulvad G, Olsen J (2003) Studying health in Greenland: obligations and challenges. Int J

Circumpolar Health 62:5-16.

97. Abbott P, Gunasekera H, Leach AJ, et al. (2016) A multi-centre open-label randomised non-inferiority trial comparing watchful waiting to antibiotic treatment for acute otitis media without perforation in low-risk urban Aboriginal and Torres Strait Islander children (the WATCH trial): study protocol for a randomised controlled trial. Trials 17:119. doi: 10.1186/s13063-016-1247-y

98. Binks MJ, Moberley SA, Balloch A, et al. (2015) PneuMum: Impact from a randomised controlled trial of maternal 23-valent pneumococcal polysaccharide vaccination on middle ear disease amongst Indigenous infants, Northern Territory, Australia. Vaccine 33:6579-6587. doi: 10.1016/j.vaccine.2015.10.101

99. Phillips JH, Wigger C, Beissbarth J, et al. (2014) Can mobile phone multimedia messages and text messages improve clinic attendance for Aboriginal children with chronic otitis media? A randomised controlled trial. J Paediatr Child Health 50:362-7. doi: 10.1111/jpc.12496

100. Stephen ATN, Leach AJ, Morris PS (2013) Impact of swimming on chronic suppurative otitis media in Aboriginal children: a randomised controlled trial. Med J Aust 199:51-5.

101. Morris PS, Gadil G, McCallum GB, et al. (2010) Single-dose azithromycin versus seven days of amoxycillin in the treatment of acute otitis media in Aboriginal children (AATAAC): a double blind, randomised controlled trial. Med J Aust 192:24-29. doi: 10.5694/J.1326-5377.2010.TB03396.X

102. Leach A, Wood Y, Gadil E, et al. (2008) Topical Ciprofloxin Versus Topical Framycetin-Gramicidin-Dexamethasone in Australian Aboriginal Children With Recently Treated Chronic Suppurative Otitis Media. Pediatr Infect Dis J 27:692-698. doi: 10.1097/INF.0b013e31816fca9d

103. O'Brien KL, David AB, Chandran A, et al. (2008) Randomized, controlled trial efficacy of pneumococcal conjugate vaccine against otitis media among Navajo and White Mountain Apache infants. Pediatr Infect Dis J 27:71-73. doi: 10.1097/INF.0b013e318159228f

104. Couzos S, Lea T, Culbong M, et al. (2003) Effectiveness of ototopical antibiotics for chronic suppurative otitis media in Aboriginal children: a community-based, multicentre, double-blind randomised controlled trial. Med J Aust 179:185-190. doi: 10.5694/J.1326-5377.2003.TB05496.X

105. Gibson PG, Stuart JE, Wlodarczyk J, et al. (1996) Nasal inflammation and chronic ear disease in Australian Aboriginal children. J Paediatr Child Health 32:143-7.

106. Douglas RM, Hansman D, McDonald B, et al. (1986) Pneumococcal vaccine in aboriginal children - a randomized controlled trial involving 60 children. Community Health Stud 10:189-196. doi: 10.1111/j.1753-6405.1986.tb00099.x

107. Malterud K, Siersma VD, Guassora AD (2016) Sample Size in Qualitative Interview Studies. Qual Health Res 26:1753-1760. doi: 10.1177/1049732315617444

108. Tamborrino M JJ, M T, P W, et al. (2015) Count Data Analysis in Randomised Clinical Trials. J Biom Biostat. doi: 10.4172/2155-6180.1000227

109. Malterud K (2012) Systematic text condensation: A strategy for qualitative analysis. Scand J Public Health 40:795-805. doi: 10.1177/1403494812465030

110. Demant M, Jensen R, Bhutta M, et al. Smartphone otoscopy by non-specialist health workers in rural Greenland: a cross-sectional study. Unpublished

111. Glover M, Kira A, Johnston V, et al. (2015) A systematic review of barriers and facilitators to participation in randomized controlled trials by Indigenous people from New Zealand, Australia, Canada and the United States. Glob Health Promot 22:21-31. doi: 10.1177/1757975914528961

112. Yancey AK, Ortega AN, Kumanyika SK (2005) Effective recruitment and retention of minority research participants. Annu Rev Public Health 27:1-28. doi: 10.1146/annurev.publhealth.27.021405.102113

113. McCallum GB, Versteegh LA, Morris PS, et al. (2014) Mobile phones support adherence and retention of indigenous participants in a randomised controlled trial: strategies and lessons learnt. BMC Public Health 14:622. doi: 10.1186/1471-2458-14-622

114. Groth-Petersen E, Gad U, Wilbek E (1964) The results of the chemoprophylactic trial in Greenland during the first four years. Bull Int Union Tuberc 35:116-8.

115. Horwitz O, Payne PG, Wilbek E (1966) Epidemiological basis of tuberculosis eradication. 4. The isoniazid trial in Greenland. Bull World Health Organ 35:509-526.

116. Stein K (1957) Røntgenskibet "Misigissût.

117. World Health Organization (1964) World Medical Association Declaration of Helsinki.

118. Clarke S (2017) A mixed methods study of chronic otitis media in Jumla Nepal.

119. (2017) WHO | Primary ear and hearing care. WHO

120. Mandavia R, Lapa T, Smith M, Bhutta MF (2018) A cross-sectional evaluation of the validity of a smartphone otoscopy device in screening for ear disease in Nepal. Clin Otolaryngol 43:31-38. doi: 10.1111/coa.12898

121. Erkkola-Anttinen N, Irjala H, Laine MK, et al. (2018) Smartphone Otoscopy Performed by Parents. Telemed e-Health tmj.2018.0062. doi: 10.1089/tmj.2018.0062

122. O'Donovan J, Verkerk M, Winters N, et al. (2019) The role of community health workers in addressing the global burden of ear disease and hearing loss: a systematic scoping review of the literature. BMJ Glob Heal 4:e001141. doi: 10.1136/bmjgh-2018-001141

123. Marom T, Kraus O, Habashi N, Tamir SO (2005) State of the Art Review Emerging Technologies for the Diagnosis of Otitis Media. doi: 10.1177/0194599818809337

124. Myburgh HC, van Zijl WH, Swanepoel D, et al. (2016) Otitis Media Diagnosis for Developing Countries Using Tympanic Membrane Image-Analysis. EBioMedicine 5:156-160. doi: 10.1016/j.ebiom.2016.02.017

125. Chando S, Young C, Craig JC, et al. (2016) Parental views on otitis media: systematic review of qualitative studies. Eur J Pediatr 175:1295-1305. doi: 10.1007/s00431-016-2779-6

126. Homøe P, Christensen RB, Bretlau P, Preben Homøe, Rene B. Christensen, (1999) Acute Otitis Media and Age at Onset among Children in Greenland. Acta Otolaryngol 119:65-71. doi: 10.1080/00016489950181963

127. Higgins J, Green S (editors) Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011].

128. Karanicolas PJ, Farrokhyar F, Bhandari M (2010) Practical tips for surgical research: blinding: who, what, when, why, how? Can J Surg 53:345-8.

129. Macklin R (1999) The Ethical Problems with Sham Surgery in Clinical Research. N Engl J Med 341:992-996. doi: 10.1056/NEJM199909233411312

130. Koch A, Sørensen P, Homøe P, et al. (2002) Population-based study of acute respiratory infections in children, Greenland. Emerg Infect Dis 8:586-93. doi: 10.3201/eid0806.010321

131. Malterud K (2001) Qualitative research: Standards, challenges, and guidelines. Lancet 358:483-488. doi: 10.1016/S0140-6736(01)05627-6

132. Homoe P (2001) Otitis Media in Greenland. Int J Circumpolar Health 60:1-54.

133. (1979) The periodic health examination. Canadian Task Force on the Periodic Health Examination. Can Med Assoc J 121:1193-254.

134. Giacomini MK (2001) The rocky road: qualitative research as evidence. Evid Based Med 6:4-6. doi: 10.1136/ebm.6.1.4

135. Daly J, Willis K, Small R, et al. (2007) A hierarchy of evidence for assessing qualitative health research. J Clin Epidemiol 60:43-9. doi: 10.1016/j.jclinepi.2006.03.014

136. Carminati L (2018) Generalizability in Qualitative Research: A Tale of Two Traditions. Qual Health Res 28:2094-2101. doi: 10.1177/1049732318788379

137. Lewin S, Glenton C, Munthe-Kaas H, et al. (2015) Using Qualitative Evidence in Decision Making for Health and Social Interventions: An Approach to Assess Confidence in Findings from Qualitative Evidence Syntheses (GRADE-CERQual). PLOS Med 12:e1001895. doi: 10.1371/journal.pmed.1001895

138. Copenhagen Trial Unit. http://www.ctu.dk/. Accessed 1 Apr 2019

139. Albertsen N, Fencker IM, Noasen HE, Pedersen ML (2018) Immunisation rates among children in Nuuk. Int J Circumpolar Health 77:1426948. doi: 10.1080/22423982.2018.1426948

14. Appendix

Flowchart for current treatment for otitis media in Greenland.

Translated and adapted from "Har patienten mellemørebetændelse? Diagnostik og behandling" by

Ramon Gordon Jensen, Susanne Brofeldt and Preben Homøe, Nuuk Health Center, 2011.

Fluid in the middle ear?

- **Tympanometry: A curve** → **Not otitis media** No fluid/perforation
- **Tympanometry: B curve - large volume** → **Perforation** No fluid
  - Referral for surgery from the age of 9. Children with bilateral perforations can be referred from the age of 7.
  - Valsalva maneuvre, Otovent. → Referral for the SIUTIT trial if type B or C2 curve verified by tympanometry for > 3 months.
- **Tympanometry: B curve - normal volume or C2 curve** → **Otitis media with effusion** Fluid and no acute symptoms
- **Otoscopy: Red/unclear, bulging tympanic membrane** → **Acute otitis media** Fluid + 1 acute symptom
  - Pain
  - Fever
  - Irritability (infants)
  - Abdominal pain (infants)

If the child is in pain: paracetamol

a) Oral antibiotics should be administered if one of the following criteria is fulfilled
- Age under 2
- Affected general condition
- Symptoms for acute otitis media have lasted for more than 3 days
- Difficult to follow-up

b) Children who do not comply with criteria mentioned above can be observed for 2 days. If no progress, give antibiotics.

→ Referral for the SIUTIT trial if three episodes in 6 months or four episodes in 12 months.

→ If treatment fails: clinical reevaluation. Second line antibiotic treatment.

NO

Ear discharge?

YES

How long has is lasted? → **Otoscopy and medical history**

- **Acute otitis media** with discharge lasting < 2 weeks

Aural toileting and topical antiseptics and

a) Oral antibiotics should be administered if one of the following criteria is fulfilled
- One other symptom of acute otitis media
- Affected general condition

b) Children who do not fulfill the criteria above can continue aural toileting and topical antiseptics for one week.

Control after one week.

→ If treatment fails after oral antibiotics - swab if possible. Clinical reevaluation. Second line antibiotic treatment. If only discharge, treat as chronic suppurative otitis media.

- **Chronic suppurative otitis media** with discharge lasting > 2 weeks

Aural toileting and topical antiseptics + antibiotics (ear drops)

Control after one week.

→ If no effect, make sure that aural toileting, topical antiseptics and topical antibiotics have been administered correct. Swab if possible. Continue treatment for one more week. Change to second line antibiotics, preferably after swab test results.

If more than 3 episodes of discharge in 6 months or if discharge continues despite changing antibiotcs, referral to specialist.

Patients with ear discharge should attend follow-up consultation after 1 week, in order to evaluate the efficacy of the treatment.

The patient must receive both verbal and written instructions for aural toileting as well as the application of antiseptics and antibiotics.

PAPER I

Trials

CrossMark

The effects of ventilation tubes versus no ventilation tubes for recurrent acute otitis media or chronic otitis media with effusion in 9 to 36 month old Greenlandic children, the SIUTIT trial: study protocol for a randomized controlled trial

Malene Nøhr Demant[1*], Ramon Gordon Jensen[1], Janus Christian Jakobsen[2,3], Christian Gluud[2] and Preben Homøe[1,4*]

Abstract

Background: The prevalence of otitis media in Greenlandic children is one of the highest in the world. International studies have shown that otitis-prone children may benefit from tubulation of the tympanic membrane. However, it is unknown whether these results can be applied to Greenlandic children and trials on the effects of ventilation tubes in high-risk populations have, to our knowledge, never been conducted.

Methods: The trial is an investigator-initiated, multicentre, randomized, blinded superiority trial of bilateral ventilation tube insertion versus treatment as usual (no tube) in Greenlandic children aged 9–36 months with chronic otitis media with effusion or recurrent acute otitis media. With randomization stratified by otitis media subtype and trial site, a type 1 error of 5% and a power of 80%, a total of 230 participants are needed to detect a decrease of two visits to a health clinic during 2 years, which is considered the minimal clinical relevant difference. The primary outcome measure will be assessed blindly by investigating medical records. Secondary outcome measures are number of episodes of acute otitis media, quality of life, number of episodes of antibiotics administration and proportion of children with tympanic membrane perforations.

Discussion: This trial will provide evidence-based knowledge of the effects of ventilation tubes in children with middle ear infections from the high-risk Greenlandic population. Furthermore, this trial will improve the understanding of conducting randomized clinical trials in remote areas, where management of logistical aspects is particularly challenging.

Trial registration: ClinicalTrials.gov, NCT02490332. Registered on 14 February 2016.

Keywords: Otitis media, Randomized clinical trials, Ventilation tubes, Grommets

* Correspondence: malenedemant@gmail.com; prho@regionsjaelland.dk
[1]Department of Otorhinolaryngology and Maxillofacial Surgery, Zealand University Hospital, Køge, Denmark
Full list of author information is available at the end of the article

Background

Otitis media is one of the most common reasons for children to contact health clinics and insertion of ventilation tubes in the tympanic membrane remains the most frequent type of paediatric surgery in the USA as well as the main reason for prescription of out-of-hospital antibiotics to paediatric patients [1–3]. The worldwide socioeconomic consequences of the disease are substantial, owing to treatment and management of the disease and parental absence from work [4].

The prevalence of otitis media and other acute respiratory tract infections in Greenlandic children is one of the highest in the world; 20% of schoolchildren have impaired hearing in the frequencies of normal speech [5–10]. This pattern is also seen in, for example, the indigenous population in Australia [11]. Many theories have been suggested to explain the high prevalence in certain indigenous populations, such as anatomical features, poverty or limited access to health-care, as well as a high bacterial load in the nasopharynx [12–15]. Studies have shown that the prevalence of chronic suppurative otitis media in the two largest towns in Greenland, Nuuk and Sisimiut, is 9% to 14%, which is a public health problem requiring urgent attention, according to the World Health Organization [6, 7, 12]. A total of 91% of children with chronic suppurative otitis media develop permanent hearing loss, which underlines the importance of treatment and management of the disease [9].

Previous studies have shown that risk factors for the development of chronic suppurative otitis media are associated with the number of upper respiratory tract infections, as well as attendance of day care, mothers' educational status, passive smoking and socioeconomic factors, similar to known risk factors for acute otitis media found in other studies worldwide [7, 8, 10, 16]. It has been suggested that children with chronic otitis media with effusion, as well as recurrent acute otitis media, are more prone to develop chronic suppurative otitis media, and treatment of these conditions might therefore decrease the number of children with chronic suppurative otitis media [6, 17]. The cumulative incidence of chronic suppurative otitis media in Greenland is 14% at the age of 4, with the highest hazard rate between 6 and 12 months [7]. This indicates that the disease develops early in childhood, and calls for intervention as early as possible in otitis-prone children, to limit progression to chronic perforations.

Ventilation tubes are inserted in the tympanic membrane to equalize pressure and allow drainage of middle ear fluid.

According to guidelines from the UK, the USA and Denmark [1, 3, 18–21], there are two indications for the insertion of ventilation tubes in children:

- Chronic otitis media with effusion and hearing loss

- Recurrent acute otitis media

Chronic otitis media with effusion is defined as fluid in the middle ear cavity lasting ≥3 months. Recurrent acute otitis media is defined as ≥3 episodes of acute otitis media within 6 months or ≥4 episodes of acute otitis media within 12 months [21].

Guidelines on the treatment of otitis media with effusion are fairly similar and have been recently updated in both the USA and the UK [3, 20]. However, guidelines on treatment of recurrent acute otitis media vary and different guidelines currently exist in the USA, while there are no national guidelines in the UK [1, 19, 21]. This might explain part of the observed international differences in the number of ventilation tube insertions for recurrent acute otitis media [22].

The mentioned international guidelines on treatment with ventilation tubes are generally based on evidence of low methodological quality concerning such outcomes as number of otitis media episodes after treatment, quality of life after treatment, reduction in chronic tympanic membrane perforations after treatment and number of episodes of aural discharge after treatment, according to the GRADE evaluation of quality of evidence [18, 21, 23, 24]. Furthermore, it is primarily children from Western trial populations, and not children from high-risk otitis-prone populations, such as the Inuit in Greenland, who have been randomized in the previous trials. Currently, there are no national guidelines or programmes to ensure prevention and treatment of otitis media and impaired hearing in Greenland. The Greenlandic Ministry of Health has considered introducing ventilation tube insertion as a more consistent treatment modality in order to decrease the burden of otitis media in the country. However, trials on the effects of ventilation tubes among children in high-risk populations have, to our knowledge, never been conducted. We therefore argue that it is both medically and ethically necessary to conduct a randomized clinical trial before ventilation tubes are made part of the routine treatment of children with chronic otitis media with effusion and recurrent acute otitis media in Greenland. Moreover, ventilation tube treatment is currently not a part of standard care in Greenland and this provides a unique opportunity to investigate the unbiased effect of the treatment, which would not be possible in populations where ventilation tube treatment is already standard treatment.

Methods/Design
Objective and hypothesis

The primary objective of the trial will be to assess the effects of bilateral insertion of ventilation tubes versus 'treatment as usual' with no ventilation tubes in children 9–36 months old with chronic otitis media with effusion or recurrent acute otitis media in Greenland, measured by

number of visits to health clinic for 2 years after randomization, assessed by investigating medical records.

The null hypothesis is:

- There is no difference in the number of visits to health clinics for children with chronic otitis media with effusion or recurrent otitis media treated with bilateral ventilation tubes, compared with children not treated with ventilation tubes.

Design

We have designed an investigator-initiated, parallel-group, multicentre, randomized clinical superiority trial of bilateral ventilation tube insertion versus treatment as usual (no ventilation tube) in Greenlandic children with chronic otitis media with effusion or with recurrent acute otitis media.

The Consolidated Standards of Reporting Trials (CONSORT) flow chart for the trial is shown in Fig. 1 [25]. The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) participant timeline is

given in Table 1 and the SPIRIT checklist is given in Additional file 1 [26].

We will consider all patients followed at a participating trial site for participation and include patients if they comply with the inclusion and exclusion criteria listed in Table 2.

The inclusion procedure is shown in Fig. 2.

We will include children aged 9–36 months. Infants younger than this age group require special anaesthesiological care, which cannot be offered in Greenland for ventilation tube insertion. The upper age limit has been set as low as possible in order to intervene before progression of the disease, while ensuring adequate sample size in this small population. We have attempted to reduce the number of exclusion criteria to as few as possible. However, children with orofacial cleft, Down's syndrome and immune deficiency are, for other reasons, known to be at very high risk of chronic otitis media with effusion and recurrent acute otitis media and are therefore not comparable with other children. Children already treated with ventilation tubes can also not be included.

Fig. 1 Consolidated Standards of Reporting Trials (CONSORT) trial flow chart
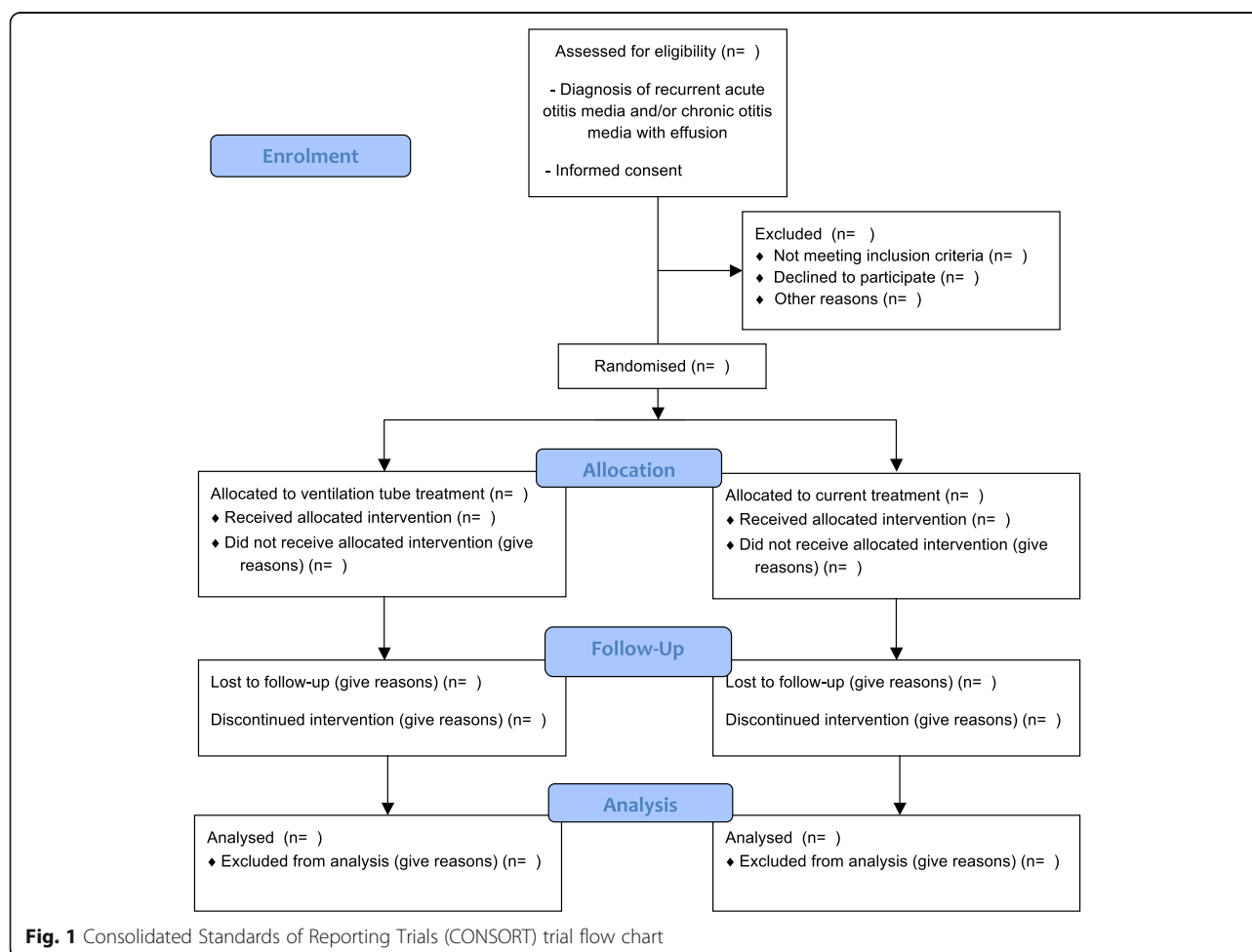
Table 1 Participant timeline, Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) diagram

Time point	Study period					
	Enrolment	Allocation				Close-out
Enrolment:	$-t_1$	0	t_1	$t_1 + 3$ months	$t_1 + 1$ year	$t_1 + 2$ years
Eligibility screen	X					
Informed consent	X					
Allocation	X					
Interventions:		X				
Ventilation tube insertion			X		X	
No ventilation tube insertion			X		X	
Assessments:						
Sex, age, ethnicity, socioeconomic factors	X					
Number of visits to health clinic						X
Questionnaires: Otitis Media-6 and Caregiver impact	X		X	X	X	X
Safety variables						X

Trial site and personnel

The trial sites are hospitals and health clinics in six Greenlandic towns: Nuuk, Sisimiut, Ilulissat, Aasiaat, Qaqortoq and Tasiilaq. The Greenlandic health-care system is divided into primary and secondary sectors. The only large and secondary referral hospital is in the capital, Nuuk [27].

The personnel performing the initial selection and screening of participants will be the regular staff at the Greenlandic health clinics and hospitals, for instance nurses, assistants and doctors of different specialities and ranks.

Randomization

The enrolment of patients will be conducted by an ear, nose and throat (ENT) specialist and the coordinating investigator. We will use centralized stratified web-based randomization. Prior to randomization, a computer will generate randomization sequences with varying block sizes that are unknown to the investigators. An internet-based randomization system will be set up conducting

randomization stratified according to centre (trial site) and type of otitis media, i.e., recurrent acute otitis media or chronic otitis media with effusion at baseline (yes or no). The randomizing investigator will access the internet site through a personal information number. Patients who meet both criteria for chronic otitis media with effusion and recurrent acute otitis media will be considered in the recurrent acute otitis media group. The patients will be randomly allocated 1:1 into the two intervention groups.

Interventions

The experimental intervention consists of bilateral insertion of ventilation tubes (Donaldson) in the tympanic membranes, administered under general anaesthesia.

Short-term ventilation tubes will be used, consistent with the tube type applied in the majority of other studies, and in accordance with the type that is expected to be introduced in Greenland [18, 23]. If the tympanic

Table 2 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Children aged 9–36 months	Children with orofacial cleft
Children with at least one Greenlandic born parent and at least one Greenlandic born grandparent	Children with Down's syndrome
American Society of Anaesthesiologists' physical status classification class 1 and 2	Children with known generalized immune deficiency
B-type curve, defined as flat line tympanograms or gradient <0.04 ml, or C2-type curve, defined as pressure ≤ −200 dPa, measured by tympanometry at two visits three-four months apart or	Children formerly treated with ventilation tubes
three episodes of acute otitis media in 6 months according to medical charts or	Lack of signed informed consent, signed by the legal guardian
tour episodes of acute otitis media in 12 months according to medical charts	
Signed informed consent, signed by the legal guardian	

Fig. 2 Inclusion procedure flowchart. AOM, acute otitis media; ENT, ear, nose and throat; OME, otitis media with effusion

membrane is infected at the time of ventilation tube insertion, topical antibiotics will be given (Cilodex® [dexamethasone + ciprofloxacin] eardrop suspension, 3 mg + 1 mg, dexamethasone + ciprofloxacin) at a dose of four drops twice daily for 5 days.

If children in the intervention group seek medical assistance for ear problems after the insertion of ventilation tubes, these ear problems will be treated according to current practice in Greenland, which includes systemic antibiotic treatment (amoxicillin 40–90 mg/(kg day)), as

well as aural toilette and topical antibiotics (ciprofloxacin 1 ml/3 mg, three drops, twice daily, or Cilodex® [dexamethasone + ciprofloxacin] eardrop suspension, 3 mg + 1 mg, four drops twice daily for 5–7 days).

The control intervention will be based on the current practice in Greenland, which includes systemic antibiotic treatment (amoxicillin, 40–90 mg(kg day)), as well as aural toilette and topical antibiotics (ciprofloxacin 1 ml/ 3 mg, three drops, twice daily). Children in the control group will not be offered ventilation tubes for any circumstance until at least 2 years after the first ENT visit and randomization.

Children in both the intervention group and control group will have an ENT examination, including otoscopy by an ENT specialist at least once a year and at the end of the study period, 2 years after randomization.

Outcomes

To assess the primary outcome in as unbiased a manner as possible, it is necessary to choose an outcome that does not require visualization of the tympanic membrane, as this might reveal the trial intervention allocation of the patient (the ventilation tube or sequelae to such a tube would be visible). Therefore, the primary outcome will be the number of visits to health clinics during 2 years after randomization, determined according to the medical records, assessed blinded to intervention. In otherwise healthy children, the number of visits to health clinics can be assumed to reflect the number of episodes related to the ear or upper respiratory tract, as this is thought to be the primary reason for contact to health clinics for children aged 9–36 months [28].

It is currently not possible to assess hearing level as an outcome measure because there are no facilities available in Greenland able to meet the high standard of hearing evaluation, which would be necessary to detect differences in hearing levels of 4 dB [23]. We therefore postulate that an effect of ventilation tubes on otitis media with effusion might be reflected in a change in the number of visits to health clinics. The number of episodes of acute otitis media, based on medical records, will be included as a secondary outcome measure but will not be used as a primary outcome measure because the treatment providers and the outcome assessors will often not be sufficiently blinded to the trial intervention allocation.

Primary outcome measure

This is the number of visits to health clinic during 2 years after the randomization, based on medical records, evaluated by designated assessors blinded to the intervention.

Secondary outcome measures

1. Number of episodes of acute otitis media during the 2 years after the randomization, based on medical records, evaluated by designated assessors blinded to the intervention
2. Quality of life, measured on a 0–100 scale by the validated Otitis Media-6 questionnaire [29, 30] and the Caregiver Impact Questionnaire [31, 32], assessed at randomization, 3 months after randomization, 1 year after randomization and at the end of the trial, 2 years after randomization
3. Number of episodes during the 2 years after randomization where oral or intravenous antibiotics have been administered, based on medical records, evaluated by designated assessors blinded to the intervention
4. Proportion of children with unilateral or bilateral tympanic membrane perforations in the intervention and control group at the end of the trial 2 years after randomization, based on otoscopical photos, which will be anonymized and evaluated by an ENT specialist without knowledge of the intervention
5. Serious adverse events during the 2 years after the randomization: any adverse event that results in death, is life threatening, requires hospitalization or prolongation of existing hospitalization or results in persistent or significant disability or incapacity [33]

Exploratory outcomes

1. Number of episodes of aural discharge during the 2 years after randomization, based on medical records, evaluated by designated assessors blinded to the intervention

The primary outcome measure as well as secondary outcome measures 1 and 3 and the exploratory outcome measure will be based on medical records, while secondary outcome measure 4 will be based on clinical examination. Secondary outcome measure 2 will be based on questionnaires; the first questionnaires will be completed at the clinical examination related to randomization, the remaining questionnaires will be sent to the participants' legal guardians by email and completed online.

Blinding

Owing to the type of the intervention, blinding of patients, parents and caregivers is not possible. However, the outcome assessors will be blinded to intervention and we also consider the number of visits to health clinics according to medical records (the primary outcome measure) as blinded. Outcome assessors will be ENT specialists.

Blinding of the number of visits at the health-care centre is ensured by initial blinding of medical records by an investigator, and hereafter evaluation by two outcome assessors calculating the number of visits from the medical records. A third assessor may provide further evaluation in the event of any disagreement. Blinding of otoscopical results is ensured by the use of otoscopical photos, which will be anonymized and evaluated by an ENT specialist without knowledge of the intervention.

Blinding of quality-of-life measures cannot be obtained as the child and the parents are not blinded for the intervention. Therefore, this outcome measure must be considered at high risk of bias.

Assessment of adverse events

Adverse events and adverse reactions will be assessed at every ENT visit.

Participant discontinuation and withdrawal

Parents of participating children can withdraw their consent to participate at any time. To be able to analyze data at an intention-to-treat basis the investigator must ask for permission to use already collected data for data analysis.

The investigator or treating physician may discontinue the patient from further participation in the trial if the patient is diagnosed with any of the exclusion criteria. The investigator and treating physician will encourage the patient to continue the follow-up assessment and previously collected data should be used in further analysis.

We will monitor adherence to the control regimen. Parents of participating children will be reminded, at the time point for intervention and assessments, by email. Those who do not adhere to the control regimen specified will be further contacted by phone call and email.

Data management

Data will be entered in the data management system Easy Trial. Easy Trial hold standards according to the Danish Data Protection Agency, i.e., data are stored on private servers. Case report forms in electronic format will be used, as well as case report forms on paper. The paper case report forms will be entered in the data management system twice by two personnel independently to promote data quality. The personnel will otherwise not be related to the trial. Patients will be identified by patient identification number, which is also used at randomization. The trial is conducted according to regulations by the Danish Data Protection Agency and only people related to the trial and the central randomization centre will have access to data.

Missing data will be minimized by checking the completed questionnaires when returned to the investigators. If there are any missing answers, the parents of the included children will emailed a request to supply the missing answers.

Statistical plan and data analysis

Based on power $(1 - \beta) = 0.80$, $\alpha = 0.05$ (two-sided) and standard deviation of five visits to health clinics and

- An estimated eight visits to health clinics during 2 years in the control group and
- An estimated six visits to health clinics during 2 years in the experimental group

we need a sample size of 99 individuals in each intervention group.

As we do not expect that data are normally distributed, the non-parametric van Elteren test will be used; thus, we obtain 99/0.86 = 115 participants per intervention group or 230 participants in total [34].

The two interventions will be compared regarding all outcomes. The analysis of the outcomes will be based on the intention-to-treat principle, i.e., all randomized participants will be included in the analysis, regardless of how much treatment they have received. Per-protocol analysis may be considered if important deviations from the protocol compromise the validity of the intention-to-treat analysis.

Dichotomous outcomes will be analyzed using logistic regression, continuous outcomes will be analyzed using linear regression and count data will be analyzed using the van Elteren test [34]. Our primary analysis will be adjusted for the stratification variables used in the randomization (trial site and type of otitis media). In secondary analysis, we will adjust all analyses (except when non-parametric tests are used) for additional significant design variables (age, sex, attending daycare, smokers in the household, diet, family history of otitis media). The statistical analysis will be described in detail in a separate paper published before the analysis of the trial results begins.

If only data are missing on the dependent outcome, we will use per-protocol data but we will interpret out results with caution if these missing data potentially bias our results. Otherwise, if more than 5% of the outcome data are missing, multiple imputation will be used (STATA 14). However, the 5% cut-off is not definitive. The imputation result will be considered the primary overall result. This analysis will be supplemented by the following sensitivity analyses:

1. 'Best-worst-case' scenario: It will be assumed that all participants lost to follow-up in the experimental group have a mean score +2 standard deviations and have no event; and all those with missing outcomes in the control group have a mean score of −2 standard deviations and have an event.
2. 'Worst-best-case' scenario: It will be assumed that all participants lost to follow-up in the experimental

group have a mean score of –2 standard deviations and have an event; and all those lost to follow-up in the control group have a mean score +2 standard deviations and have no event [35].

Results from both scenarios will be presented in our trial publication.

If the null hypotheses on the primary outcome measures are not rejected, our main conclusion will be that we found no significant difference between the two interventions. The analysis of the remaining outcome measures will be presented for hypothesis-generating purposes.

Discussion

This trial will provide evidence-based knowledge of the effects of ventilation tubes in children with middle ear infections. Furthermore, the effects of ventilation tube administration in a high-risk population, such as the Greenlandic, have never, to our knowledge, been investigated and this trial will improve the understanding of conducting randomized clinical trials in remote areas, where management of logistical aspects is particularly challenging.

The strengths of this trial are the inclusion of children at high risk of developing otitis media and sequelae thereof; the central randomization regarding both generation of allocation sequence and allocation concealment; the primary outcome measure that monitors use of the health-care system; and our attempts to blind as many outcome measures as possible. Our trial also has limitations. First, no updated systematic review of the effects of ventilation tubes is currently available. We refer to previous Cochrane reviews published in 2008 and 2010, respectively [18, 23] but the methodology of these reviews is not optimal and the literature search has not been sufficiently updated. We are writing a protocol for a systematic review assessing the effects of ventilation tubes; this protocol will be registered on PROSPERO. As soon the protocol is registered, we will perform a literature search and begin writing the review. Nevertheless, it is a major methodological limitation that we cannot sufficiently take into account a complete and valid overview of previous studies on the effects of ventilation tubes. Further methodological limitations are a lack of blinding to the intervention regarding a number of the outcome measures and potential problems with drop-out during follow-up, owing to lack of interest, migration or logistics.

Dissemination policy

The Greenlandic population will be informed of the trial as well as its final results through national media. All participating health clinics and hospitals will be visited by the coordinating investigator and instructed in objectives and screening or inclusion procedures. The final and interim results will be presented at NUNA MED, an international conference on Greenlandic medicine and health held every third year.

Trial results will be published in English, Danish and Greenlandic.

The Government of Greenland will be informed of the final results before a press release is issued but will have no influence on the reporting of the results.

Trial status

We launched the randomization on 18 February 2016. At the end of June, six children had been enrolled and randomly allocated to a group.

Additional file

Additional file 1: SPIRIT 2013 Checklist. (DOCX 61 kb)

The personnel at the hospitals and health clinics will give written information about the trial to the child's legal guardian when the patient is first considered for screening or inclusion. Further oral and written information will be given at the first visit by the ENT specialist, where the written informed consent will be obtained.

It will be stressed that this is a research project, a randomized clinical trial, and that participation can be withdrawn at any time, without consequences for future treatment at the health clinic. The cultural aspects of respect of authorities as well as different ways of expressing decline will be considered. Furthermore, the trial is registered at ClinicalTrials.gov (NCT02490332) and approved by the Danish Data Protection Agency (no. 2015-41-4047).

This trial is conducted according to regulations by the Danish Data Protection Agency. Only people related to the trial and the central randomization centre will have access to data.

Author details

[1]Department of Otorhinolaryngology and Maxillofacial Surgery, Zealand University Hospital, Køge, Denmark. [2]Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark. [3]Department of Cardiology, Holbæk Hospital, Holbæk, Denmark. [4]Institute of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark.

References

1. Rosenfeld RM, Schwartz SR, Pynnonen MA, Tunkel DE, Hussey HM, Fichera JS, Grimes AM, Hackell JM, Harrison MF, Haskell H, Haynes DS, Kim TW, Lafreniere DC, LeBlanc K, Mackey WL, et al. Clinical practice guideline: tympanostomy tubes in children. Otolaryngol Head Neck Surg. 2013;149(1 Suppl):S1–35.
2. Sidell D, Shapiro NL, Bhattacharyya N. Demographic influences on antibiotic prescribing for pediatric acute otitis media. Otolaryngol Head Neck Surg. 2012;146(4):653–8.
3. Rosenfeld RM, Shin JJ, Schwartz SR, Coggins R, Gagnon L, Hackell JM, Hoelting D, Hunter LL, Kummer AW, Payne SC, Poe DS, Veling M, Vila PM, Walsh SA, Corrigan MD. Clinical practice guideline: otitis media with effusion executive summary (update). Otolaryngol Head Neck Surg. 2016; 154(2):201–14.
4. Ahmed S, Shapiro NL, Bhattacharyya N. Incremental health care utilization and costs for acute otitis media in children. Laryngoscope. 2014;124(1):301–5.
5. Homøe P, Jensen RG. Mellemørebetændelse i Grønland (Middle ear infections in Greenland). Månedsskrift for Almen Praksis (Journal of The Danish College of General Practitioners). 2013;91:228–37.
6. Homøe P, Christensen RB, Bretlau P. Prevalence of otitis media in a survey of 591 unselected Greenlandic children. Int J Pediatr Otorhinolaryngol. 1996;36(3):215–30.
7. Koch A, Homøe 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;30(1):25–9.
8. Jensen RG, Homøe P, Andersson M, Koch A. Long-term follow-up of chronic suppurative otitis media in a high-risk children cohort. Int J Pediatr Otorhinolaryngol. 2011;75(7):948–54.
9. Jensen RG, Koch A, Homøe P. The risk of hearing loss in a population with a high prevalence of chronic suppurative otitis media. Int J Pediatr Otorhinolaryngol. 2013;77(9):1530–5.
10. Homøe P, Christensen RB, Bretlau P. Acute otitis media and sociomedical risk factors among unselected children in Greenland. Int J Pediatr Otorhinolaryngol. 1999;49(1):37–52.
11. Morris PS, Leach AJ, Silberberg P, Mellon G, Wilson C, Hamilton E, Beissbarth J. Otitis media in young Aboriginal children from remote communities in Northern and Central Australia: a cross-sectional survey. BMC Pediatr. 2005;5:27.
12. WHO. Report of a WHO/CIBA foundation workshop 1996, prevention of hearing impairment from chronic otitis media, London, UK, 19–21 November 1996. Geneva: WHO; 1996.
13. Homøe P, Prag J, Farholt S, Henrichsen J, Hornsleth A, Kilian M, Jensen JS. High rate of nasopharyngeal carriage of potential pathogens among children in Greenland: results of a clinical survey of middle-ear disease. Clin Infect Dis. 1996;23(5):1081–90.
14. Jacoby P, Carville KS, Hall G, Riley TV, Bowman J, Leach AJ, Lehmann D. Crowding and other strong predictors of upper respiratory tract carriage of otitis media-related bacteria in Australian Aboriginal and non-Aboriginal children. Pediatr Infect Dis J. 2011;30(6):480–5.
15. Smith-Vaughan H, Byun R, Nadkarni M, Jacques NA, Hunter N, Halpin S, Morris PS, Leach AJ. Measuring nasal bacterial load and its association with otitis media. BMC Ear Nose Throat Disord. 2006;6:10.
16. Hoffman HJ, Daly KA, Bainbridge KE, Casselbrant ML, Homøe P, Kvestad E, Kvaerner KJ, Vernacchio L. Panel 1: Epidemiology, natural history, and risk factors. Otolaryngol Head Neck Surg. 2013;148(4 Suppl):E1–E25.
17. Tos M. Upon the relationship between secretory otitis in childhood and chronic otitis and its sequelae in adults. J Laryngol Otol. 2007;95(10):1011–22.
18. McDonald S, Langton Hewer CD, Nunez DA. Grommets (ventilation tubes) for recurrent acute otitis media in children. Cochrane Database Syst Rev. 2008;4:CD004741.
19. Lieberthal AS, Carroll AE, Chonmaitree T, Ganiats TG, Hoberman A, Jackson MA, Joffe MD, Miller DT, Rosenfeld RM, Sevilla XD, Schwartz RH, Thomas PA, Tunkel DE. The diagnosis and management of acute otitis media. Pediatrics. 2013;131(3):e964–99.
20. National Institute for Health and Care Excellence. www.nice.org.uk/guidance/CG60 [Accessed 2 January 2016]
21. Heidemann CH, Lous J, Berg J, Christensen JJ, Håkonsen SJ, Jakobsen M, Johansen CJ, Nielsen LH, Hansen MP, Poulsen A, Schousboe LP, Skrubeltang C, Vind AB, Homøe P. Danish guidelines on management of otitis media in preschool children. Int J Pediatr Otorhinolaryngol. 2016;87:154–63.
22. Schilder AGM, Lok W, Rovers MM. International perspectives on management of acute otitis media: a qualitative review. Int J Pediatr Otorhinolaryngol. 2004;68(1):29–36.
23. Browning GG, Rovers MM, Williamson I, Lous J, Burton MJ. Grommets (ventilation tubes) for hearing loss associated with otitis media with effusion in children. Cochrane Database Syst Rev. 2010;10:CD001801.
24. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schünemann HJ. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336(7650):924–6.
25. Moher D, Schulz K, Altman D. The CONSORT statement: revised recommendations for improving the quality of reports of parallel group randomized trials. BMC Med Res Methodol. 2001;1:2.
26. Chan A-W, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Ann Intern Med. 2013;158:200–7.
27. Niclasen B, Mulvad G. Health care and health care delivery in Greenland. Int J Circumpolar Health. 2010;69(5):437.
28. Koch A, Sørensen P, Homøe P, Mølbak K, Pedersen FK, Mortensen T, Elberling H, Eriksen AM, Olsen OR, Melbye M. Population-based study of acute respiratory infections in children, Greenland. Emerg Infect Dis. 2002;8(6):586–93.
29. Rosenfeld RM, Goldsmith AJ, Tetlus L. Quality of life for children with otitis media. Arch Otolaryngol Head Neck Surg. 1997;123(10):1049–54.
30. Heidemann CH, Godballe C, Kjeldsen AD, Johansen EC, Faber CE, Lauridsen HH. The Otitis Media-6 questionnaire: psychometric properties with emphasis on factor structure and interpretability. Health Qual Life Outcomes. 2013;11:201.
31. Boruk M, Lee P, Faynzilbert Y, Rosenfeld RM. Caregiver well-being and child quality of life. Otolaryngol Head Neck Surg. 2007;136:159–68.
32. Heidemann CH, Godballe C, Kjeldsen AD, Johansen EC, Faber CE, Lauridsen HH. Otitis media and caregiver quality of life: psychometric properties of the modified Danish Version of the Caregiver Impact Questionnaire. Otolaryngol Head Neck Surg. 2014;151(1):142–9.
33. European Parliament and the Council of the European Union. Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. 2001. https://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_20/dir_2001_20_en.pdf
34. Jakobsen JC, Tamborrino M, Winkel P, Haase N, Perner A, Wetterslev J, et al. Count data analysis in randomised clinical trials. J Biometrics Biostatistics. 2015;6:227.
35. Jakobsen JC, Wetterslev J, Winkel P, Lange T, Gluud C. Thresholds for statistical and clinical significance in systematic reviews with meta-analytic methods. BMC Med Res Methodol. 2014;14:120.

36. International Committee of Medical Journal Editors, Recommendations, Defining the Role of Authors and Contributors, http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html [Accessed 01 Jan 2016].
37. ICH harmonised tripartite guideline: guideline for good clinical practice. Essential documents for the conduct of a clinical trial. J Postgraduate Med. 2001;47(4):264–7.
38. Greenlandic Medical Society, Code of conduct. http://gmsnet.dk/test/wp-content/uploads/2015/10/CodeOfConduct_final.pdf [Accessed 2 Jan 2016]

PAPER II

Smartphone otoscopy by non-specialist health workers in rural Greenland:

a cross-sectional study

Authors:

Malene Nøhr Demant, MD[1,2] (Corresponding author), malenedemant@gmail.com

Ramon Gordon Jensen, MD, PhD[3]

Mahmood F. Bhutta, FRCS DPhil[4]

Gunnar Hellmund Laier, M.Sc., PhD[5]

Jørgen Lous, MD, DMSc.[6]

Preben Homøe, MD, DMSc.[1,2,4], prho@regionsjaelland.dk

[1] Department of Otorhinolaryngology and Maxillofacial Surgery, Zealand University Hospital, Lykkebækvej 1, 4600 Køge, Denmark

[2] University of Greenland, Ilisimatusarfik, Manutooq 1, 3905, Nuussuaq, Greenland

[3] Department of Otolaryngology, Head and Neck Surgery & Audiology, Rigshospitalet, Blegdamsvej 9, 2100, Copenhagen Ø, Denmark

[4] Ear, Nose and Throat Department, Brighton and Sussex University Hospitals, Eastern Road, Brighton, East Sussex, BN2 5BE, United Kingdom

[5] Production Research and Innovation, Region Zealand, Alleen 15, 4180 Sorø, Denmark

[6] Institute of Public Health, Research Unit for General Practice, University of Southern Denmark, Campusvej 55, 5230 Odense, Denmark

[7] Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Blegdamsvej 3B, 2200 Copenhagen N, Denmark

Declarations of interests: none.

Abstract

Introduction

Greenland has one of the highest prevalences of otitis media in the world. However, access to ear specialists throughout Greenland is limited and currently there are no national guidelines for treatment or prevention. Tele-otoscopy may be beneficial in optimizing diagnosis and treatment. The smartphone otoscopy device, Cupris®, has previously been validated when used by medical doctors on a population primarily consisting of adults. In this study we evaluated the usability of the Cupris® otoscope when used by local health care workers with different levels of training and education, examining children aged 1-6 years.

Methods

We conducted a cross-sectional study in three Greenlandic towns. Health care personnel were asked to perform video-otoscopy on children contacting the health clinic for any reason. The videos were sent for remote evaluation by three ear specialists who rated the videos on a 5-point Likert scale and provided information on challenges with the videos. The dichotomous outcome "not useful/useful" was defined as 1-3 and 4-5 on the Likert scale, respectively.

Results

In total, 142 videos were recorded on 84 patients. Mean proportion of useful videos was 18.1%, with a modified Fleiss' Kappa interrater agreement coefficient of 0.67 95% CI [0.57-0.76] corresponding to substantial agreement among three raters.

Conclusions

In this study the usefulness of the Cupris® TYM otoscope did not prove to be sufficient with the presented instruction in the hands of local health care workers when examining Greenlandic children. Focus on training and education of local health personnel is crucial and warranted before advantageous implementation for non-specialist health care workers can be expected.

Keywords: Otitis media, telehealth, smartphone otoscopy, remote communities, Greenland

1. Introduction

Worldwide, otitis media (OM) is one of the most prevalent pediatric diseases and a common reason for prescription of antibiotics [1,2]. The burden on society as well as on individual families is large, and the socioeconomic consequences due to parental absence from work substantial [3,4]. Correct diagnosis and management of OM is of importance, especially in high risk populations ([5,6]. Greenland has one of the highest prevalences of OM in the world, where chronic suppurative otitis media affects 9-14%, constituting an urgent health problem that needs immediate action according to World Health Organization (WHO) criteria [7-10]. However, access to ear specialists throughout Greenland is limited and currently there are no national guidelines for treatment or prevention. The remote location and difficult access to the majority of Greenland's towns and settlements present logistical challenges in diagnosis and management of disease [11]. Hence, the need for telemedicine is evident.

In rural Australia, where logistical and epidemiological challenges are similar to the Greenlandic, images of pediatric otoscopy performed by experienced ear specialists have been shown to be valid for remote diagnosis among children of aboriginal origin, and tele-pediatric otolaryngology consultations have demonstrated economic benefits [12,13].

Greenland has devices for telemedicine available in all towns and settlements with more than 50 inhabitants. These telemedicine carts include amongst other things a video-otoscope which allows health workers to send images for evaluation by an ear specialist. However, these devices are not used regularly, supposedly due to their rather tedious start-up, difficulties with managing the otoscope, and storage in other examination rooms due to their size.

Cupris® TYM otoscope (London, UK, figure 1) is a device that is connected to a smartphone using the built-in camera and light [14]. It can provide still images as well as video-otoscopy, with images stored on a secure server which can be sent to a specialist for further evaluation.
In a previous study in Nepal the Cupris® device was found to provide otoscopic images that were valid for diagnosis and deciding if a patient should be referred for further evaluation [15]. However, in that study the device was used by experts and mostly in adults. It is not known if the Cupris® device can also reliably be used by non-specialist health care workers, or in young children.

A recent review by O'Donovan et al. including 38 studies from around the globe focused on the role of community health workers in managing ear disease [16]. The review concluded that community health

workers may play an important part in improving ear related health, but the amount of training needed as well as possibilities for support by specialists is diverse and depends on the specific context.

In this study we investigated the use of the Cupris® otoscope in an everyday clinical situation where untrained local health care workers examined children aged 1-6 years.

2. Materials and Methods

2.1 Study design

We followed the STROBE guidelines for reporting observational studies from the EQUATOR Network [17]. The study was a cross-sectional study conducted from July to October 2018 in three different Greenlandic towns, based on a convenience sample.

2.2 Setting and personnel

The vast geographical distribution of Greenland makes logistical aspects of health services especially challenging. The country inhabits approximately 55,000 people, but the population is scattered into several towns and settlements with populations ranging from approximately 15,000 inhabitants in the capital, Nuuk, 2000-5000 inhabitants in smaller towns and 50 inhabitants or less in some settlements. The health care system is organized in five regions, each including one regional hospital. The country's only larger secondary health care facility is in the capital, which is also the base for the only permanent Ear- Nose and Throat (ENT) specialist in the country. Smaller towns are visited by ENT specialists once or twice a year and people in the settlements travel to the nearest town for consultations, in what may be termed a satellite model of care [18].

To create a realistic study setup, we chose to call upon health care personnel in three smaller towns, all with approximately 4-5000 inhabitants, thereby omitting the capital where access to ENT specialists is relatively facile.

In the included towns, otoscopies are performed by a variety of personnel: general nurses, specialized nurses (nurses specialized in the health of children and youths), medical students, doctors in training, general practitioners and medical doctors with non-ENT specialization.

We chose to let the sites decide who should perform the otoscopies and how to incorporate it into their everyday clinical work. However, all participants had some experience with otoscopy and basic knowledge in ear anatomy.

2.3 Study population

All children aged 6 to 72 months, attending the health care clinics for any reason, were eligible. Exclusion criteria were lack of informed consent signed by parent/guardian.

2.4 Intervention

Images were obtained using the Cupris® TYM otoscope on an iPhone 5s (Apple Inc., California, USA). We chose to obtain video instead of still images because several other studies have found videos to have better validity for diagnosis [15,19]. The three sites were provided with written practical step-by-step instructions for the setup of the iPhone and the application (see Appendix). All health personnel had the possibility to contact the first author for further instructions through telephone or email, which several, but not all, chose to use.

Data were captured on the Cupris® application which allows secure exchange between an examiner and specialist. Video-otoscopies were recorded by the local health care personnel and immediately sent to the first author through the Cupris® application. These videos were anonymized and incorporated into a web-based questionnaire, with no additional clinical information provided.

Three ENT specialists (authors RGJ, MFB, PH) were asked to evaluate the videos on the quality of image capture. There was no discussion between the specialists. For each video the specialists rated whether the video was helpful in visualizing the tympanic membrane on a five-point Likert scale from "strongly agree" to "strongly disagree" A second question asked specialists to comment on any challenges to visualization, with options for wax impaction, improper insertion of the otoscope, or unfocused image. There was also an option for free field text to add additional comments.

2.5 Data analysis and outcomes

The primary outcome was proportion of videos considered useful for making a diagnosis as assessed by the three raters. The rating on the Likert scale was used to classify the videos as useful (rated as "agree" or "strongly agree") or not useful (rated as neither agree nor disagree, disagree, or strongly disagree) Secondary outcomes were the distribution of the Likert scale and documented challenges with video-otoscopy.

Inter-rater agreement (IRA) was measured using a modified Fleiss' Kappa coefficient in R 3.5.0 (R Core Team, 2018) [20], which is not affected by Kappa paradoxes for ordinal data and the percentile bootstrap confidence interval [20-22]. A Kappa coefficient ≤ 0 was considered as "poor agreement", 0.01-0.2 as "slight agreement", 0.21-0.40 as "fair agreement", 0.41-0.6 as "moderate agreement", 0.61-0.80 as "substantial agreement" and 0.81-1.00 as "almost perfect agreement". IRA was calculated per ear.

Categorical variables were compared using chi-square test and continuous variables using Kruskal–Wallis test. Data analysis of frequencies and cross-tabulations were undertaken using SAS Studio (SAS Institute Inc., Cary, NC, USA). Significance was set at $p < 0.05$.

2.6 Ethical considerations

The study was approved by The Research Ethics Committee for Scientific Health Research in Greenland, no. 7960823 and The Danish Data Protection Agency, no. REG-041-2018, and conducted in accordance with the Greenlandic Code of Conduct for health researchers [23]. All guardians to the participants provided informed consent.

3. Results

In total, 84 children were included in the study, 48 males and 36 females, with a median age of 24.5 months. Not all children were examined in both ears, hence providing a total of 142 otoscopies. Table 1 provides baseline characteristics, stratified by site.

The mean proportion of "useful" videos was 18.1%, with substantial agreement among the raters.

The distribution of answers on the Likert scale is shown in figure 2.

Table 2 summarizes the usefulness of the videos, in total, and stratified by site and rater.

The mean percentages of useful videos were 13.1% in Site 1, 25.6% in Site 2 and 16.7% in Site 3.

Table 3 summarizes the challenges the raters experienced when evaluating the video-otoscopies. The most prevalent challenge was "insertion", IRA corresponding to "fair agreement".

Table 4 shows the usefulness of the videos stratified on three age groups.

The IRA showed "substantial agreement" for the youngest children but only "fair" and "moderate agreement" among the older children.

4. Discussion

4.1 Findings and clinical implications

Overall, less than 1 in 5 of the recorded video-otoscopies were considered useful in the diagnostic process by the three raters. The agreement among the raters was substantial, although there was less concordance in the reported types of challenges. Suboptimal insertion of the otoscope was the most prevalent reason for poor quality of the video. We believe that this reflects lack of routine with pediatric otoscopy and that pediatric otoscopy is difficult, especially in inexperienced hands [24]. This is worth bearing in mind when evaluating the limitations to tele-otoscopy - even a well-functioning device needs operators who can perform the task of pediatric otoscopy.

When stratifying otoscopies in three different age groups, the mean percentage of useful videos increased with age, supporting that the younger the child, the more difficult the otoscopy.

Wax impaction was mentioned in more than a third of all otoscopies, however the definition of "Wax impaction" may have differed among the three raters, as one of the raters noted that wax was often the reason for poor focus although the tympanic membrane was not actually fully impacted. In the newest clinical guideline update from American Academy of Pediatrics, wax impaction is defined as accumulation of cerumen that causes symptoms or prevents a needed assessment [25]. In this study we chose not to provide wax removal for the children as this can be an unpleasant procedure, both physically and psychologically, and our cohort had no ear symptoms. Previous validations of smartphone otoscopy have excluded patients with excessive wax or provided wax removal prior to examination, however we wished to reflect the real-life clinical setting in Greenland [15,26]. Accordingly, another study not providing prior wax removal found that 58 out of 80 ears had too much wax for diagnosis [27].

The interpretation of the word "useful" can also differ between raters. It depends on whether it is compared to expected findings from otoscopy - or no imaging at all, which is the case in remote areas. For instance, seeing otorrhea in the ear canal or a dry canal could provide useful information, in a setting with a high prevalence of chronic suppurative otitis media, even though the tympanic membrane was not fully visualized. The three raters had almost perfect agreement on which videos were not affected by any challenges, although only 3% of the videos qualified for this.

From a clinical perspective, it is debatable what percentage of "useful" videos would be necessary to justify implementation, but less than 1 in 5 seems insufficient. More detailed training and instruction, accompanied by wax removal prior to otoscopy, would likely improve the usefulness of the otoscopies. The Cupris® device has been validated when used by medical doctors on a population primarily consisting of adults, in contrast to our study where the device was tested on small children in the hands of changing health care personnel with different backgrounds and levels of education [15,28]. Shah et al. tested a similar device (CellScope, Inc., San Francisco) operated by parents to children aged 17 or younger [27]. They compared remote diagnoses based on parent videos and remote diagnoses based on physician videos to diagnoses made in a regular otolaryngology examination (including pneumatic otoscopy). The authors found that there was a low IRA (kappa = 0.42) on diagnoses based on parent videos as compared to diagnoses made an otolaryngology examination. The IRA on diagnoses based on specialist videos compared to otolaryngology examination was high (kappa = 0.74). Erkkola-Anttinen et al. tested the CellScope device on parents to children aged 6-35 months [29]. Here they randomized parents to either

receive immediate hands-on training or delayed training. The teaching intervention consisted of lessons on basic anatomy, diagnostic criteria and practical instructions for use. The intervention improved the technical quality of the parent videos significantly, as 62 % of the videos were found of a sufficient technical quality in the immediate teaching group versus 22 % of the videos in the delayed teaching group. After applying the teaching intervention to the delayed teaching group, the percentage of useful videos increased to 64 % [29].

In Western Nepal, where a community-based ear health program that has been functional for more than 10 years, the local health care workers were found to have otoscopy qualifications similar to otolaryngology trainees, supporting long-term focus on teaching local assets [30]. In our study, the operators did not receive any hands-on personal instructions before use but were only provided with written step-by-step instructions focused on the technical aspects of the device, without systematic feedback on the quality of the otoscopies. A more thorough educational session on how to visualize the tympanic membrane and proper insertion of the device might have improved the quality of the videos. Even though all involved in this study were health care personnel with some prior knowledge in ear anatomy and training in otoscopy, it seems that proper hands-on training is necessary prior to implementation.

Correct diagnosis of OM is crucial for sufficient and appropriate treatment, but the diagnosis process can be difficult [24,31]. For decades otoscopy has been the primary tool for diagnosing OM and The American Academy of Pediatrics still bases the clinical guidelines on otoscopy, supplemented by tympanometry and pneumatic otoscopy [32]. However, otoscopy on small children, who are the typical patients at target, is difficult, and any initiative to improve or supersede the pediatric otoscopy will be valuable. Laine et al. examined the clinical use of tympanometry on symptomatic children, performed by trained nurses [33]. In 66 % of all visits, the nurses managed to obtain bilateral tympanometry. However, test results able to exclude AOM (i.e. A or C1 curves) were only found in 20 % of the visits, due to inexperienced nurses, uncooperative children and rarity of exclusive test results, which questions the clinical usefulness. Similarly, the authors investigated if nurses performing tympanometry on asymptomatic children could exclude middle ear effusion (MEE), and stated that the found tympanograms were reliable, but the exclusion of MEE could only be obtained in 41 % of all visits [34].

Spectral gradient acoustic reflectometry (SG-AR) holds the advantage that an airtight seal is not needed, as it is in tympanometry measurements, and therefore might be easier to perform on uncooperating young children. Teppo et al. investigated the use of SG-AR by nurses who had received a short tutorial,

on both symptomatic and asymptomatic patients with a mean age of 23 months [35]. SG-AR was performed successfully in 79 % of the examined ears, and showed acceptable negative and positive predictive values of, albeit a lower diagnostic accuracy than when performed by physicians.

In a recent pilot study conducted in the Philippines, the authors describe a methodology based on local nurses performing diagnostic tests on Filipino teenagers, where all diagnoses are made in the US, except decisions for referral to local otolaryngologists [36]. All nurses underwent a one-day hand-on training by US otolaryngologists/audiologists. The diagnostic tests included video-otoscopy, tympanometry, distortion product otoacoustic emissions and audiometry. The authors concluded that the skills of the nurses combined with the robust technology is sufficient for large-scale otological screening, without the requirement of local otolaryngologists [36].

New techniques for the diagnosis of OM are currently being developed, such as algorithm-based diagnostic tools or optical coherence tomography, but these are all still expensive and/or not readily available in primary health care settings [37].

4.2 Strengths and limitations

We included children below the age of 7, thereby representing the age group most susceptible to middle ear infections. We conducted the study with a pragmatic approach trying to evaluate the use of the device in a realistic everyday clinical setup. We chose not to have a "gold standard" for comparison but focused on the feasibility of the device in a Greenlandic setting, with challenges similar to other remote communities, especially in the circumpolar regions. However, the training in the use of the smartphone otoscopy was only written instructions and the children did not have ear wax removal before otoscopy.

5. Conclusions

In this study the usability of the Cupris® TYM otoscope did not prove sufficient in the hands of local health care workers when examining Greenlandic children, when provided with only written instructions. The main reason seemed to be a lack of expertise among the health care workers, and the presence of ear wax. Smartphone otoscopy holds potential to become a valuable contribution to telemedicine and thereby improving ear-related heath in remote areas, but, in person or otherwise detailed training of local health personnel may be necessary before advantageous implementation can be expected.

6. Acknowledgements

6. Funding

References

[1]   A.G.M. Schilder, T. Chonmaitree, A.W. Cripps, R.M. Rosenfeld, M.L. Casselbrant, M.P. Haggard, R.P. Venekamp, Otitis media, Nat. Rev. Dis. Prim. 2 (2016) 16063. doi:10.1038/nrdp.2016.63.

[2]   D. Sidell, N.L. Shapiro, N. Bhattacharyya, Demographic influences on antibiotic prescribing for pediatric acute otitis media., Otolaryngol. Head. Neck Surg. 146 (2012) 653-8. doi:10.1177/0194599811431228.

[3]   S. Ahmed, N.L. Shapiro, N. Bhattacharyya, Incremental health care utilization and costs for acute otitis media in children., Laryngoscope. 124 (2014) 301-5. doi:10.1002/lary.24190.

[4]   S. Chando, C. Young, J.C. Craig, H. Gunasekera, A. Tong, Parental views on otitis media: systematic review of qualitative studies, Eur. J. Pediatr. 175 (2016) 1295-1305. doi:10.1007/s00431-016-2779-6.

[5]   A. Koch, P. Sørensen, P. Homøe, K. Mølbak, F.K. Pedersen, T. Mortensen, H. Elberling, A.M. Eriksen, O.R. Olsen, M. Melbye, Population-based study of acute respiratory infections in children, Greenland., Emerg. Infect. Dis. 8 (2002) 586-93. doi:10.3201/eid0806.010321.

[6]   R.G. Jensen, P. Homøe, M. Andersson, A. Koch, Long-term follow-up of chronic suppurative otitis media in a high-risk children cohort., Int. J. Pediatr. Otorhinolaryngol. 75 (2011) 948-54. doi:10.1016/j.ijporl.2011.04.017.

[7]   A. Koch, P. Homøe, C. Pipper, T. Hjuler, M. Melbye, Chronic suppurative otitis media in a birth cohort of children in Greenland: population-based study of incidence and risk factors., Pediatr. Infect. Dis. J. 30 (2011) 25-9. doi:10.1097/INF.0b013e3181efaa11.

[8]   R.G. Jensen, A. Koch, P. Homøe, Long-term Tympanic Membrane Pathology Dynamics and Spontaneous Healing in Chronic Suppurative Otitis Media, Pediatr. Infect. Dis. J. 31 (2012) 139-144. doi:10.1097/INF.0b013e318238c0a4.

[9]   World Health Organization, Chronic suppurative otitis media. Burden of Illness and Management Options, Geneva, Schwitzerl. (2004). http://www.who.int/pbd/publications/Chronicsuppurativeotitis_media.pdf (accessed December 22, 2018).

[10]   P. Homøe, R.B. Christensen, P. Bretlau, Acute Otitis Media and Age at Onset among Children in Greenland, Acta Otolaryngol. 119 (1999) 65-71. doi:10.1080/00016489950181963.

[11]   B. Niclasen, G. Mulvad, Health care and health care delivery in Greenland, Int. J. Circumpolar Health. 69 (2010) 437-487. doi:10.3402/ijch.v69i5.17691.

[12]   C.Q. Xu, A.C. Smith, P.A. Scuffham, R. Wootton, A cost minimisation analysis of a telepaediatric otolaryngology service, BMC Health Serv. Res. (2008). doi:10.1186/1472-6963-8-30.

[13]   R.H. Eikelboom, M.N. Mbao, H.L. Coates, M.D. Atlas, M.A. Gallop, Validation of tele-otology to diagnose ear disease in children, Int. J. Pediatr. Otorhinolaryngol. 69 (2005) 739-744. doi:10.1016/J.IJPORL.2004.12.008.

[14]   Cupris, http://www.cupris.com/tym-otoscope Title, (accessed December 22, 2018).

[15]   R. Mandavia, T. Lapa, M. Smith, M.F. Bhutta, A cross-sectional evaluation of the validity of a smartphone otoscopy device in screening for ear disease in Nepal, Clin. Otolaryngol. 43 (2018) 31-38.

doi:10.1111/coa.12898.

[16] J. O'Donovan, M. Verkerk, N. Winters, S. Chadha, M.F. Bhutta, The role of community health workers in addressing the global burden of ear disease and hearing loss: a systematic scoping review of the literature, BMJ Glob. Heal. 4 (2019) e001141. doi:10.1136/bmjgh-2018-001141.

[17] E. von Elm, D.G. Altman, M. Egger, S.J. Pocock, P.C. Gøtzsche, J.P. Vandenbroucke, The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: Guidelines for Reporting Observational Studies, Ann. Intern. Med. 147 (2007) 573. doi:10.7326/0003-4819-147-8-200710160-00010.

[18] M.F. Bhutta, Models of service delivery for ear and hearing care in remote or resource-constrained environments, J. Laryngol. Otol. 133 (2019) 39-48. doi:10.1017/S0022215118002116.

[19] M.F. Bhutta, E.A. Hedge, A. Parker, M.T. Cheeseman, S.D.M. Brown, Oto-endoscopy: A reliable and validated technique for phenotyping otitis media in the mouse, Hear. Res. 272 (2011) 5-12. doi:10.1016/J.HEARES.2010.09.002.

[20] P. Quatto, E. Ripamonti, Package "raters" A Modification of Fleiss' Kappa in Case of Nominal and Ordinal Variables, 2015. https://cran.r-project.org/web/packages/raters/raters.pdf (accessed February 15, 2019).

[21] R. Falotico, P. Quatto, On avoiding paradoxes in assessing inter rater agreement, 22 (2010) 151-160. https://boa.unimib.it/handle/10281/53341 (accessed March 7, 2019).

[22] D. Marasini, P. Quatto, E. Ripamonti, Assessing the inter-rater agreement for ordinal data through weighted indexes, Stat. Methods Med. Res. 25 (2016) 2611-2633. doi:10.1177/0962280214529560.

[23] Greenlandic Medical Society, Code of Conduct, (n.d.). http://gmsnet.dk/test/wp-content/uploads/2015/10/CodeOfConduct_final.pdf (accessed May 1, 2018).

[24] P.M. Jensen, J. Lous, Criteria, performance and diagnostic problems in diagnosing acute otitis media, Fam. Pract. 16 (1999) 262-268. doi:10.1093/fampra/16.3.262.

[25] S.R. Schwartz, A.E. Magit, R.M. Rosenfeld, B.B. Ballachanda, J.M. Hackell, H.J. Krouse, C.M. Lawlor, K. Lin, K. Parham, D.R. Stutz, S. Walsh, E.A. Woodson, K. Yanagisawa, E.R. Cunningham, Clinical Practice Guideline (Update): Earwax (Cerumen Impaction) Executive Summary, Otolaryngol. Neck Surg. 156 (2017) 14-29. doi:10.1177/0194599816678832.

[26] K.M. Rappaport, C.C. McCracken, J. Beniflah, W.K. Little, D.A. Fletcher, W.A. Lam, A.L. Shane, Assessment of a Smartphone Otoscope Device for the Diagnosis and Management of Otitis Media, Clin. Pediatr. (Phila). 55 (2016) 800-810. doi:10.1177/0009922815593909.

[27] M.U. Shah, M. Sohal, T.A. Valdez, C.R. Grindle, iPhone otoscopes: Currently available, but reliable for tele-otoscopy in the hands of parents?, Int. J. Pediatr. Otorhinolaryngol. 106 (2018) 59-63. doi:10.1016/J.IJPORL.2018.01.003.

[28] J.R. Richards, K.A. Gaylor, A.J. Pilgrim, Comparison of traditional otoscope to iPhone otoscope in the pediatric ED ☆, (2015). doi:10.1016/j.ajem.2015.04.063.

[29] N. Erkkola-Anttinen, H. Irjala, M.K. Laine, P.A. Tähtinen, E. Löyttyniemi, A. Ruohola, Smartphone Otoscopy Performed by Parents, Telemed. e-Health. (2018) tmj.2018.0062. doi:10.1089/tmj.2018.0062.

[30] R. Youngs, N. Weir, P. Tharu, R.B. Bohara, D. Bahadur, Diagnostic otoscopy skills of community ear assistants in Western Nepal, J. Laryngol. Otol. 125 (2011) 27-29. doi:10.1017/S0022215110001891.

[31] A.G.M. Schilder, T. Marom, M.F. Bhutta, M.L. Casselbrant, H. Coates, M. Gisselsson-Solén, A.J. Hall, P. Marchisio, A. Ruohola, R.P. Venekamp, E.M. Mandel, Panel 7: Otitis Media: Treatment and Complications, Otolaryngol. - Head Neck Surg. (United States). 156 (2017). doi:10.1177/0194599816633697.

[32] A.S. Lieberthal, A.E. Carroll, T. Chonmaitree, T.G. Ganiats, A. Hoberman, M.A. Jackson, M.D. Joffe, D.T. Miller, R.M. Rosenfeld, X.D. Sevilla, R.H. Schwartz, P.A. Thomas, D.E. Tunkel, The diagnosis and management of acute otitis media., Pediatrics. 131 (2013) e964-99. doi:10.1542/peds.2012-3488.

[33] M.K. Laine, P.A. Tähtinen, O. Ruuskanen, E. Löyttyniemi, A. Ruohola, Can trained nurses exclude acute otitis media with tympanometry or acoustic reflectometry in symptomatic children?, Scand. J. Prim. Health Care. 33 (2015) 298-304. doi:10.3109/02813432.2015.1118835.

[34] M.K. Laine, P.A. Tähtinen, O. Ruuskanen, E. Löyttyniemi, A. Ruohola, Can nurses exclude middle-ear effusion without otoscopy in young asymptomatic children in primary care?, Scand. J. Prim. Health Care. 33 (2015) 115-120. doi:10.3109/02813432.2015.1030174.

[35] H. Teppo, M. Revonta, H. Lindén, A. Palmu, Detection of middle-ear fluid in children with spectral gradient acoustic reflectometry: A screening tool for nurses?, Scand. J. Prim. Health Care. 24 (2006) 88-92. doi:10.1080/02813430600699997.

[36] K.H. Chan, S. Dreith, K.M. Uhler, V. Tallo, M. Lucero, J. De Jesus, E.A. Simões, Large-scale otoscopic and audiometric population assessment: A pilot study., Int. J. Pediatr. Otorhinolaryngol. 117 (2019) 148-152. doi:10.1016/j.ijporl.2018.11.033.

[37] T. Marom, O. Kraus, N. Habashi, S.O. Tamir, State of the Art Review Emerging Technologies for the Diagnosis of Otitis Media, (2005). doi:10.1177/0194599818809337.

Tables and figures

Table 1, Showing baseline characteristics on 84 Greenlandic Inuit children visiting Greenlandic health care clinics, examined with the Cupris© TYM smartphone otoscope.

		Site 1	Site 2	Site 3	Total
N		36	23	25	84
Sex, % female		30.5	56.5	48	36 $p = 0.03$
Age, months		27 (13-49.5)	15 (13-69)	48 (13-50)	24.5 (13-52) $p = 0.8$
Number of videos		51	43	48	142
Operator	**Specialized nurses**	10	43	27	80
	Medical student	37	0	4	41
	Medical doctor	2	0	17	19
	Nurse	2	0	0	2

Continuous variables are presented with median and interquartile range. Categorical variables were compared using the chi-square test and continuous variables were compared using the Kruskal-Wallis test.

Table 2, Showing the usefulness of 142 Cupris® TYM smartphone otoscope videos from 84 Greenlandic Inuit children, recorded by health care personnel in three different Greenlandic health care clinics. The dichotomous outcome not useful/useful was defined as 1-3 and 4-5 on the Likert scale, respectively.

	N (%) Useful, site			Interrater agreement (useful/not useful)	N (%) Useful, rater	P-value
	Site 1	Site 2	Site 3			
	p = 0.47*	p = 0.01*	p = 0.04*			
Rater A	5 (9.8)	5 (11.6)	3 (6.3)		13 (9.2)	**P = 0.0006**
Rater B	6 (11.8)	11 (25.6)	9 (18.75)	0.67 95 % CI [0.57-0.76]	26 (18.3)	
Rater C	9 (17.7)	17 (39.5)	12 (25)		38 (26.8)	

Categorical variables were compared using the chi-square test. Interrater agreement was investigated using a modified Fleiss' Kappa coefficient, including 95% confidence interval (CI).

Table 3, Showing proportion of the 142 video-otoscopies from Greenlandic Inuit children recorded with the Cupris® TYM smartphone otoscope with challenges with wax, insertion, focus or no challenges.

	Wax		Insertion		Focus		None	
	N (%)	Mean (%)	N (%)	Mean (%)	N (%)	Mean (%)	N (%)	Mean (%)
Rater A	38 (26.8)		105 (73.9)		21 (14.8)		1 (0.7)	
Rater B	52 (36.6)		91 (64.1)		59 (41.6)		3 (2.1)	
Rater C	23 (16.2)	37.7	95 (66.9)	68.3	1 (0.7)	19.0	9 (6.3)	3.0
Interrater agreement	0.55 95 % CI [0.44-0.65]		0.40 95 % CI [0.30-0.52]		0.36 95 % CI [0.25-0.46]		0.92 95 % CI [0.86-0.96]	

Interrater agreement was investigated using a modified Fleiss' Kappa coefficient, including 95% confidence interval (CI).

Table 4, Showing the usefulness of 142 Cupris® TYM smartphone otoscope videos from 84 Greenlandic Inuit children, recorded by health care personnel in three different Greenlandic health care clinics, stratified on three age groups. The dichotomous outcome not useful/useful was defined as 1-3 and 4-5 on the Likert scale, respectively.

	N (%)	N (%) useful, rater A	N (%) useful, rater B	N (%) useful, rater C	Mean (%) of the three rater evaluations	Interrater agreement
< 24 months	66 (46.5)	1 (1.5)	5 (7.6)	7 (10.6)	6.6	0.73 [0.67-0.80]
24-48 months	25 (17.6)	3 (12)	5 (20)	9 (36)	22.7	0.48 [0.20-0.72]
> 48 months	51 (35.9)	9 (17.7)	16 (31.4)	22 (43.1)	30.7	0.60 [0.50-0.67]

Interrater agreement was investigated using a modified Fleiss' Kappa coefficient, including 95% confidence interval (CI).
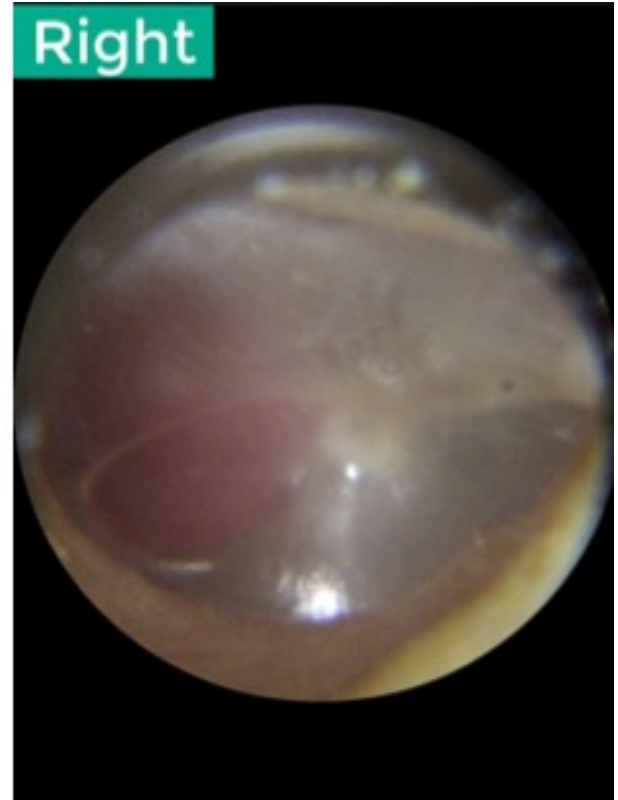
Figure 1,

Left: The Cupris® TYM smartphone otoscope (London, UK) on an iPhone 5s (Apple Inc., California, USA)

Right: Example of otoscope image obtained with Cupris® TYM smartphone otoscope. The image shows a right tympanic membrane with visible air bubble and cone of light.
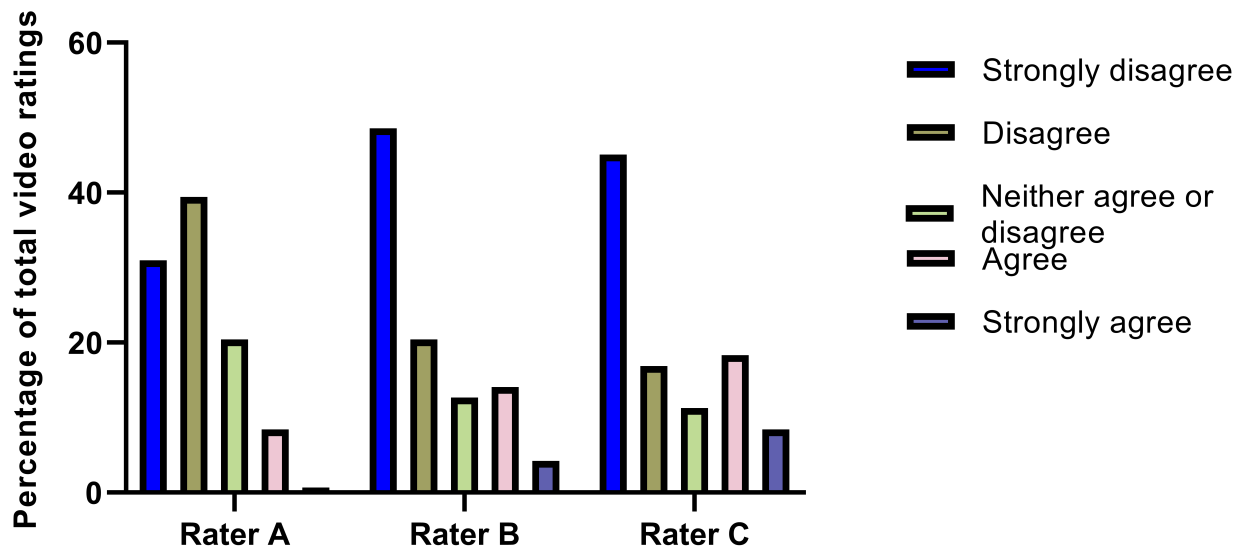
Figure 2,

Bar chart showing results from the specialist evaluation of the quality of 142 video-otoscopies performed on 84 Greenlandic Inuit children in health care clinics in Greenland. The raters were presented with the following statement: "The video-otoscopy was helpful in visualizing the tympanic membrane" and asked to rate the degree to which they agreed on a 5-point Likert scale.

Appendix

Step-by-step instructions for smartphone otoscopy and the Cupris® -application

Start by giving the parents a short introduction to the project and ask if they would like to participate. Please underline the fact that participation is completely voluntary and that declining will have no consequences for further treatment or examination of their child.

- Give the parent(s) the informed consent form. Let them read it and, if there are no further questions, ask them to sign it. Please save the consent form.
- Enter the pin code: xxxxxx
- Tap "OK" to "No SIM card installed".
- Make sure that the phone has access to the internet (Settings, wifi)
- Open the Cupris® app
- Enter pass code: xxxx
- Tap the Otoscope icon in the lower left corner.
- Place the speculum on the otoscope.
- Choose "Video".
- Choose "*Left*" or "*Right*"
- Record the video, max 30 seconds.
- Tap the small image of the video in the lower left corner (if the image has disappeared, enter "Gallery" from the main page, find the video in "Videos" and tap the small circle on the image)
- Tap the "Share" icon in the lower left corner
- Tap "Add to Chat"
- Choose "Cupris Greenland 2018".
- Add the patients date of birth by adding it in the "New message" field, below the video.

PAPER III
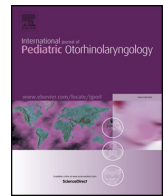
Parental perceptions and management strategies for otitis media in Greenland

Malene Nøhr Demant[a,b,*], Christina Viskum Lytken Larsen[c], Preben Homøe[a,b,d]

[a] Department of Otorhinolaryngology and Maxillofacial Surgery, Zealand University Hospital, Lykkebækvej 1, 4600, Køge, Denmark
[b] University of Greenland, Ilisimatusarfik, Manutooq 1, 3905, Nuussuaq, Greenland
[c] National Institute of Public Health, University of Southern Denmark, Studiestræde 8, 1455, Copenhagen K, Copenhagen, Denmark
[d] Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Blegdamsvej 3B, 2200, Copenhagen N, Denmark

A B S T R A C T

Introduction: Otitis media (OM) in Greenland is a substantial problem and the country prevalence is among the highest in the world. However, little is known about how Greenlandic Inuit parents perceive and manage everyday life with children suffering from OM. We hypothesize that having a child with OM has consequences for the families that go beyond the advice and treatment offered in primary health care.
Methods: We conducted a qualitative study based on semi-structured interviews and focus groups with parents to children suffering from OM. The interviews took place in three different Greenlandic regions; the capital Nuuk and two smaller towns in West and East Greenland. Access to specialized health care differs among the regions, creating an underlying difference on the limitations of referral and thereby level of care. We conducted the data analysis using Systematic Text Condensation.
Results: In total, 27 parents participated in the study. Although most parents perceived OM as a result of genetic or environmental dispositions, individual perceptions and cultural beliefs of causal associations between behavior and OM co-existed with the general understanding of medical explanation models. This created a sense of guilt among the parents. Some parents felt in control of managing the disease of the child and used medically well-established strategies. Others felt frustrated and considered contact to the health clinics as futile, thereby managing the disease by 'waiting it out'. Emerging themes were shame and stigma related to the symptoms of OM, which led to social isolation as a consequence for several of the families.
Conclusion: Our results indicate that Greenlandic Inuit families are impacted by OM in a complex and severe manner. Guilt, shame and social isolation were predominant themes influencing the everyday life of the affected families. Perceptions and management strategies go beyond the scope of the medical explanation models which poses a potential challenge for the parents' experiences with the present treatment offer. The results underline the need to develop a broader approach to prevention and treatment for OM - both at the clinical level as well as part of public health promotion at the community level.

1. Background

Otitis media (OM) in the Arctic is a substantial problem and the prevalence in Greenland is among the highest in the world [1–4]. Greenlandic Inuit children have an earlier onset of first episode of acute otitis media (AOM) compared to children in Western countries [5] and 9–14% of all children suffer from chronic suppurative otitis media (CSOM), a pattern also seen among other Inuit populations in the Arctic [2,4,6] Thus, the burden of middle ear pathology in Greenland is well-established, and the majority of Greenlandic Inuit families have encountered its effects and sequelae first-hand. However, currently there

are no national treatment guidelines, it is not known what the best treatment option is for OM in a high-risk population as the Greenlandic Inuit and little is known about how Greenlandic Inuit parents to children suffering from OM perceive and manage the disease [7].

In the widely used quantitative disease-specific questionnaire OM-6, the quality of life (QoL) of children suffering from OM is being measured, based on parent/caregiver's evaluation [8]. Several studies using the questionnaire have found the most impacted areas to be "physical suffering" and "caregiver concerns" [8–10]. Accordingly, questionnaires aimed at caregivers have found decreased QoL of caregivers to children suffering from OM compared to the general population [11]. However,

in these questionnaires, elaborating *how* it affects everyday life and the underlying causes of the concerns is not possible, hence the importance of qualitative studies. Findings from qualitative studies conducted among Western populations support that overall QoL of families living with OM is negatively impacted and provide more detailed information about the reasons why [12–14]. Qualitative studies conducted among Native Canadians and Aboriginals in Australia suggest that transcultural differences in the views of OM do exist and that the treatment strategies and focus areas should be modified accordingly [15,16].

It has been widely established that including parents in the decision-making process will lead to better compliance and higher satisfaction with treatment, even if the treatment differs from the initial expectations of the parents [17]. Being able to share appropriate and relevant information about treatment options depends on prior understanding of the parents' concerns and beliefs [18]. Furthermore, public health initiatives may be more efficient when the cultural context and perspectives are taken into consideration.

We hypothesize that having a child with OM has consequences for the families that go beyond the advice and treatment offered in primary health care due to the nature and potential sequelae of the disease in young children.

The aim of this study is to explore the perceptions and management strategies among Greenlandic Inuit parents to children suffering from OM.

2. Materials and methods

We followed the COREQ guidelines from The EQUATOR Network [19].

2.1. Design and participants

We conducted a qualitative study based on semi-structured interviews and focus groups with parents to children suffering from OM, defined as recurrent acute otitis media (rAOM), chronic otitis media with effusion (COME) or CSOM. Recruitment was based on the inclusion criteria for the ongoing randomized controlled trial, The SIUTIT Trial, however it was adapted to include children already enrolled in the trial [7]. The SIUTIT Trial investigates the effects of ventilation tube insertion, aiming to contribute to the development of evidence-based treatment regimens. The primary outcome of the trial is the number of visits to health clinics, and in order to get a better understanding of this quantitative outcome we decided to interview parents to children either eligible for the trial or already enrolled. Table 1 shows inclusion and exclusion criteria for this study, similar to criteria for the SIUTIT Trial, but modified to accommodate children already enrolled in the trial. Being "Greenlandic Inuit" was defined as being the child of at least one parent born in Greenland, who was the child of at least one parent born in Greenland, as done previously [7].

Information about the children's diagnoses was obtained from medical charts. Where a specialist confirmed diagnosis was not available, the first author (MND) made an assessment based on the chart review.

We conducted both single- dual- and focus group interviews. Focus group interviews were conducted in the capital where the interviewer did not require an interpreter. Therefore, it was possible for the interviewer to follow the conversation and intervene if necessary. The design of the focus groups allowed for a collective expression of opinions thus facilitating a permissive environment allowing complex emotional views [20].

Dual- and single interviews were conducted in the two towns, where an interpreter was needed in the majority of the interviews. The single interviews allowed an in-depth understanding of the views of the parent, while the dual interviews added the combined views of both parents.

Interviews were based on a predefined interview guide anchored in the theoretical framework of the study and based on preexisting literature [20] (Appendix). The initial structure of the interview guide was gradually adapted throughout the data collection. The interview guide was based on open-ended questions, allowing the parents to elaborate at will. The semi-structured interview allowed for detailed information about specific topics with the possibility to explore the deeper meaning of the statements [21]. The author's preunderstanding of the subject was written down and taken into account as well as field notes about the participants [22].

All quotes have been changed into first-person narrative although it was translated as third-person narrative. We chose to do this in order to diminish the effect of the translation.

2.2. Setting

The vast geographical area of Greenland includes 56,000 inhabitants scattered in 5 regions, 16 towns and approximately 60 villages, with population ranging from 17,000 in the capital Nuuk to less than 50 people in the smallest settlements [23,24]. Ninety percent of the inhabitants are ethnic Greenlandic Inuit [25].

The socioeconomic and infrastructural differences are great, comparing the modern city of Nuuk to the poorer and less developed areas on the East Coast and the utmost North [23,24]. There are no roads connecting the communities in Greenland, and all health care related transportation between the towns is by sea or air [26].

Healthcare in Greenland, including prescription medicine, is free.

In order to give a representative outline of Greenland we conducted the interviews in three different Greenlandic regions; the capital, a town on the West Coast of Greenland and a smaller town on the East Coast of Greenland. Access to specialized health care, including Ear, Nose, and Throat (ENT) specialists, differs among the regions, creating an underlying difference on the limitations of referral and thereby level of care. The country's only secondary health care facility is located in the capital, whereas the rest of the country is visited by specialists on an

Table 1
Inclusion and exclusion criteria.

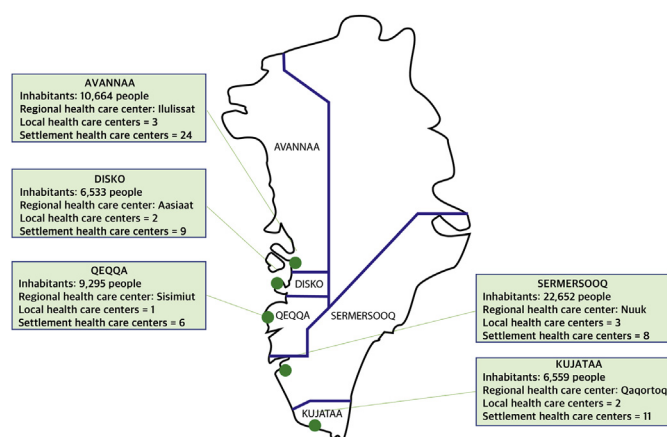| Inclusion criteria	Exclusion criteria
Parents to	Parents to
Children aged 9–72 months	Children with orofacial cleft
Children with at least one Greenlandic born parent and at least one Greenlandic born grandparent	Children with Down's syndrome
American Society of Anaesthesiologists' physical status classification class 1 and 2	Children with known generalized immune
B-type curve, defined as flat line tympanograms or gradient < 0.04 ml, or C2-type curve, defined as pressure ≤ − 200 dPa, measured by tympanometry at two visits three-four months apart	deficiency
or	Lack of signed informed consent
three episodes of acute otitis media in 6 months according to medical charts	
or	
four episodes of acute otitis media in 12 months according to medical charts	
Signed informed consent	

Fig. 1. Map showing the organizational structure of the Greenlandic health care centers. There are currently five regions with one regional health care center each. In the smaller towns there are 11 health clinics in total, staffed with medical doctors. In settlements with more than 50 inhabitants there are health care centers staffed with nurses and/or health care workers. In settlements with less than 50 inhabitants there are no health care workers, but the inhabitants have access to a "medicine box".

The Queen Ingrid Hospital in Nuuk is the country's only secondary health care sector.

annual basis. ENT specialists usually visit the towns once a year.

Fig. 1 shows the organization of the Greenlandic health care centers

In the capital parents were invited for three focus group sessions, including up to six parents. In the smaller town on the West Coast, a town with approximately 3,000 inhabitants, interviews were performed as single or dual (both parents present) interviews, all conducted with the use of an interpreter trained within the health care system. On the East Coast, in a town with approximately 2,000 inhabitants, the single or dual interviews were also performed with the use of an interpreter, trained within the health care system. It was not possible to use the same interpreter in all interviews due to the differences in dialect of Kalaallisut (the Greenlandic language) on the East- and West Coast.

Interviews were conducted either at the health care facilities or in the parent's home, depending on the preferences of the parents. All interviews were conducted in quiet, private surroundings and the only participants were the parent/parents, the first author and an interpreter, if needed.

Interviews were audio-recorded and subsequently transcribed. Where interviews were conducted in Kalaallisut only the translated part of was transcribed.

2.3. Recruitment

Parents in the capital area and in the smaller town on the West Coast were invited to participate in relation to their children's participation in The SIUTIT Trial. In the town on the East Coast, parents to children who fulfilled the inclusion criteria were invited, although the children had

not (yet) been enrolled in the trial.

Recruitment of children and parents continued until data saturation was reached.

2.4. Ethical considerations

The study was approved by The Research Ethics Committee for Scientific Health Research in Greenland, no. 7714708 as well as the Danish Data Protection Agency, no. REG-035-2018.

We obtained signed informed consent from all participants, and underlined the fact that participation was voluntary and rejecting would have no consequences for future treatment of them or their children. The study was conducted in accordance with the Greenlandic Code of Conduct for health researchers [27].

2.5. Data analyses

We conducted the data analysis using Systematic Text Condensation (STC), a cross-case method developed by Malterud [28]. STC is based on phenomenological principles and shares the offset of the subjective experience of an individual's life world [29,30]. However, STC uses a more pragmatic approach allowing thematic analysis across cases with the purpose of synthesizing descriptions of overall meaningful units in a systematical manner [23,29,31]. The approach favors intersubjectivity and transparency in the analysis process and consists of four steps: i) Overall impression by reading the transcripts and finding preliminary themes ii) Definition of meaningful units in the material, creating code groups iii) Condensing meaning of the defined units and create sub-groups, and iv) Synthesizing the content of the meaning condensates and thereby describe the data focusing on the initial research question [28]. The analysis is described as iterative and inductive, meaning that it is an ongoing process in which the coding groups are initially based on the structure of the interview guide, but is gradually revised as the reading of the interview reveals additional themes.

The data analysis including transcription and coding was conducted in the qualitative analysis program NVivo for Mac, version 11.4.2 by the first author.

3. Results

In total, 27 parents participated in the study. Mean number of siblings and number of children with CSOM was highest on the East Coast. Parental age and number of male participants was highest in the capital. Table 2 shows baseline characteristics of the participants stratified on the three sites.

The mean duration of interviews were 55 min (range 45–67 min) for focus group interviews, and 29 min (range 18–35) in the town on the West Coast and 31 min (range 18–46 min) in the town on the East Coast for single and dual interviews.

Based on the data analysis we identified two overall categories, 'Parental perceptions' and 'Management strategies', which could be further divided into themes and subthemes. Fig. 2 provides an overview of the categories, themes and subthemes identified in the data. Table 3

Table 2
Baseline characteristics of participants.

Site	N		Male parents n (%)	Median parent age, years [range]	Median children age, months [range]	Mean number of siblings [range]	Diagnosis[a]		
	Parents	Children					COME	rAOM	CSOM
Capital	12	7	4 (33)	33.5 [25–38]	26 months [19–53]	0.75 [0–2]	3	3	1
West coast	8	6	2 (25)	30 [25–43]	55.5 [39–72]	2 [0–4]	0	4	2
East coast	7	7	1 (14)	29 [23–40]	17 [11–53]	4.3 [0–7]	0	3	4

COME = chronic otitis media with effusion, rAOM = recurrent acute otitis media, CSOM = chronic suppurative otitis media.

[a] Diagnoses are based on medical charts. Where a specialist confirmed diagnosis was not available, the first author (MND) made an assessment based on chart reviews.
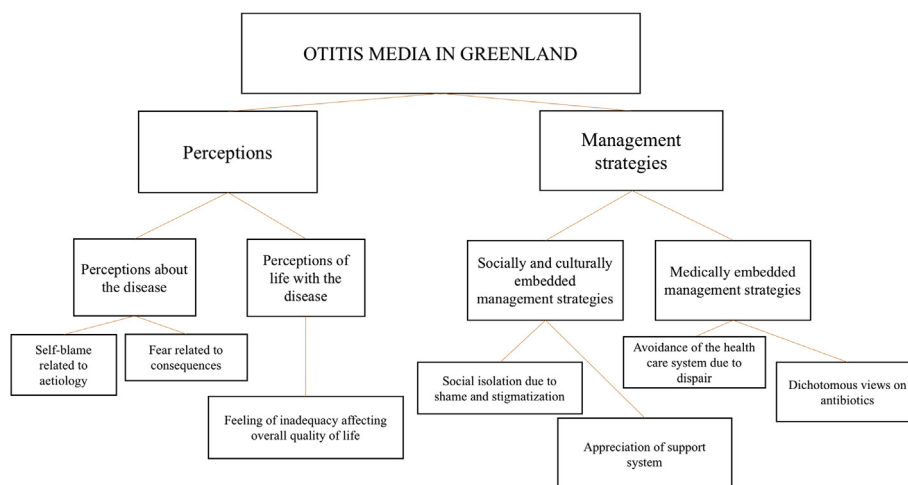
Fig. 2. Overview of categories, themes and subthemes.

shows quotations supporting the underlying themes and subthemes.

3.1. Parental perceptions

The parents' views on the disease were related to perceptions about the disease itself and perceptions about life with the disease.

3.1.1. Perceptions about the disease
3.1.1.1. Self-blame related to aetiology. When asked about the aetiology of the disease, the majority of the parents stated the belief that OM is a result of genetic or environmental dispositions. They recognized the correlation of upper airway infections and OM and generally supported the biomedical approach as the primary explanation model. However, when discussing the concept of OM-prone behavior, the biomedical approach seemed to be discarded and somewhat forgotten. Individual perceptions and cultural beliefs of causal associations between parental behavior and the occurrence of OM co-existed with the general understanding of medical explanation models. Many correlated OM with behavioral issues such as smoking during pregnancy, general stress and worries or even domestic violence. These conceptions revealed an evident feeling of guilt and speculations of what they as parents could have done differently. A clear tendency in many interviews was that as the interviews proceeded, the discussion about the development of OM got gradually more entangled in self-blame and remorse and less conceptually centered about bacteria, virus and anatomy. Conversations started off focused on biomedical issues but often ended up with the parent(s) questioning their abilities and competencies as caregivers.

The concept of fluid in the middle ear was widely established and understood throughout both the capital and in the smaller towns, although there was some divergence of opinion with regard to origin; some parents believed the fluid to be a consequence of external stimulus, such as bottle feeding and bathing where others considered the fluid to be proportional with the mucus production in relation to rhinitis.

Few parents had never thought about the origin and development of the disease. They underlined the randomness and described an acceptance of the disease as a condition of life itself and a natural phase of childhood – a Greenlandic childhood disease, inevitably connected to being Greenlandic Inuit.

Traditional views, such as not wearing knitted clothing, general living conditions and nutrition were generally mentioned as direct causes of development of OM, although often mentioned in relation to confusion and uncertainness. Smoking exposure and heredity were mentioned by several parents as associated to OM.

The main sources of information were family and friends, health care personnel and the internet, in the smaller towns especially from Facebook groups where information is written in Greenlandic as opposed to more broad internet searches which generally require language skills in Danish or English.

3.1.1.2. Fear related to consequences. The spectrum of the parents' thoughts on consequences of OM was wide. Some viewed the disease as a part of normal development and did not consider OM to pose a substantial risk to their child's overall health. However, others were processing fear of meningitis, convulsion and sudden death, often due to past experiences, rumors and stories about other children. Hearing loss and impact on cognitive development and education was a predominant concern for many, some noticing their own or other family member's struggle with hearing impairment, reflecting the inheritable element of the disease.

Almost all the parents mentioned seeing their child in pain and the fear and frustration of not being able to relieve it, as one of the greatest consequences of the disease.

3.1.2. Perceptions of life with the disease
3.1.2.1. Feeling of inadequacy affecting overall quality of life. When directly asked if the many episodes of OM had had any impact on what they would describe as overall "QoL in the family" almost all parents answered yes, without any doubt. The primary reason for this was that they felt they could not help their child and that it made them feel inadequate as a parent.

Especially in the capital, both parents were working and had to do so at different times in order to minimize the amount of absence from work. Hence, they had had long periods of time where they did not spent time together as a couple. Many said that they had been fighting a lot and that the lack of sleep as well as the crying and screaming of the child had taken its toll on the overall well-being, also affecting their mental surplus for taking care of siblings.

3.2. Management strategies

The overall handling of and coping with the disease was done on primarily two levels; culturally and emotionally embedded management strategies and medically embedded management strategies.

3.2.1. Culturally and socially embedded management strategies
3.2.1.1. Social isolation due to shame and stigmatization. The interviews revealed a profound stigmatization of parents to children suffering from OM, leading to different degrees of social isolation. The shame of

Table 3
Illustrative quotations.

a. Parental perceptions

Themes	Subthemes	Quotes
Perceptions about the disease	Self-blame related to aetiology	"I blame myself a lot. Could the reason be that maybe I haven't kept the house clean enough, or have I given them the bottle while they were lying down, is that the reason? Is it because I bathe them, and they are lying in the water for too long that they get constant infections in the ear?"
		"I had my son in my arms, and my boyfriend wanted to hit me hard. Could that have done anything? An hour after I had been hit, I took my son's temperature, it had risen to around 38. Then I took care of him and took his temperature after a while, and then it was back to normal. I worry that maybe we have scared him, and that is what is making him sick."
		"You start to feel that you are a bad mother, a bad parent. Did I do it right, why does she keep getting sick? Is it our fault, even though it might not be, I don't know?"
	Fear related to consequences	"We have heard that ear infections can enter the brain, right? It can cause meningitis."
		"I worry because I can tell that their hearing is becoming impaired. It is scary when you think about the future, what it may lead to."
Perceptions of life with the disease	Feeling of inadequacy affecting overall quality of life	"The worst part is that when she cries, even though she is right next to you, there is nothing you can do to help."
		"When you child is in pain, you desperately want to relieve it. But you can't."
		"'I have to work at night. If I take care of him during the day I have to go to work at night and finish my tasks. We take turns. We didn't see each other last year."
		"It is very rare that we experience true happiness because it is so hard and we get really tired of having to deal with ear infections all the time. Day and night someone is crying, and that affects the happy feelings. And when they have ear infections all the time the entire family gets affected and we all become sadder."

b. Management strategies

Themes	Subthemes	Quotes
Culturally and socially embedded management strategies	Social isolation due to shame and stigmatization	"We used to join social gatherings in the sport centre. We have actually stopped doing that, and we also stopped joining birthdays and coffee-mik when we are invited. We mostly stay at home. I know that if we go out other people comment on the smell from my children's ears. Is it because you never bathe them? That is why we have stopped seeing other people."
		"When the smell began I stopped hanging with my friends. I do not want other people to comment on the smell. I think that other people find it disgusting. I think it is embarrassing. Then I feel bad taking my kid to the daycare or going to coffee-mik or visit family."
		"One time, our upstairs neighbor came down and asked if we needed help, that was really rough. She asked in a bad way, where she kind of accused us and directly told us that if our daughter cried that much one more time, she would inform the social authorities."
		"There are times where I feel that it is embarrassing, especially when the daycare says that her ears are smelling, then I start to feel that I am not a good mother. I feel that they look down on me, and she feels that too. She holds her head down and looks like she feels it is embarrassing when the other children also say that it smells."
	Appreciation of support system	"If I had not had my parents, I would not have finished my education. You need help from others. My mother used to take care of her when she had middle ear infection, so I could go to school."
Medically embedded management strategies	Avoidance of the health care system due to despair	"I think it was the same every time it happened, so in the end it was useless to call every time she had an ear infection. I think that at a certain time we just stopped calling and let it pass by itself."
		"We used to go to the doctor, but now if he has ear pain, we clean it ourselves. We don't go anymore. We used to go to the doctor, and we have been there so many times. But when we go there, they just give us ear drops. It is normal for us. Mop and clean and mop again."
	Dichotomous views on antibiotics	" I think that if a child has an ear infection it needs penicillin. It is important to me. If I find out that my child has an ear infection, I want her to be treated with penicillin. In my opinion it can be very dangerous if it is not treated."
		"To keep his immune defense, I have given him pain killers when he has been feeling worst instead of trying to give him penicillin or trying to get some. I want him to get over it by himself."
		"We have said no to antibiotics several times, because we think he gets it too many times and too often."

having a child with OM directedly affected the families' everyday habits and combined with ear pain and episodes of fever it caused them to stay indoors and missing out on communal activities. The parents described feeling uncomfortable when asked about their child's many ear infections and that family and colleagues were blaming them and their way of raising children. One parent mentioned that a neighbor had threatened to call the social services because he was certain that the parents were abusing their child, since the child was screaming so often, and they were now living in constant fear of being reported. As a consequence, they no longer participated in social gatherings.

Especially parents to children with CSOM seemed affected on social interactions, due to both the visual component of the ear discharge, as well as the smell. Several parents described how reactions from surroundings would also make the child become aware of their condition, and make the child feel embarrassed when going to the daycare. Consequently, the parents preferred to keep their child out of daycare as much as possible.

3.2.1.2. Appreciation of support system. Some parents stated that if they had not had help from their families, they would have either had to get a new job or quit their education due to absence, lack of sleep and overall energy deficiency. Almost all parents mentioned the importance

of having a support system in relation to either valuing an existing one or expressing the wish of having it. Losing one's job was a concern for many. Several had mainly met understanding from their workplace but had spent all their vacation time staying home taking care of their children. A parent described being suspected of pretending to have a sick child and had to show her child's medication in order to overcome the accusations.

3.2.2. Medically embedded management strategies
3.2.2.1. Avoidance of the health care system due to despair. All families had been in contact with the health care system several times due to OM. Many had eventually stopped going, because they felt it was useless. Some had learned to cope with discharge and ear pain themselves and felt in control of the disease without the help from health care professionals and others struggled with finding an overall timeline and progression in the treatment provided, and thus perceived it as futile. Some parents stated that they felt unwanted and unwelcome at the health care centers, and that the advice and treatment given was always the same. In the smaller towns the majority of the parents have to use an interpreter when speaking to doctors. Here, several mentioned that they were suspicious of whether the interpreters communicated what the doctor said, or if they were providing their own opinion, further supporting the prevalent skepticism and wariness of the suggested treatment.

The level of feeling in control of the disease correlated with the level of frustration among the parents, i.e. the parents who were most frustrated were the ones who did not have many management strategies.

3.2.2.2. Dichotomous views on antibiotics. Treatment of OM with antibiotics was well-known among all parents and generally gave rise to two distinct beliefs; that antibiotics had a deleterious effect on their child's overall health or that antibiotic treatment was of utmost importance. Hence, some parents were very restrictive on the amount of antibiotics given to their child, sometimes not complying with prescriptions given by the doctor. Their main concern was the possibility of antibiotic resistance and damage to their child's immune system. Many had the experience that antibiotics do not work anyway, and they might as well wait it out. Others believed that treatment with antibiotics should happen as fast as possible and would contact the health care facility as soon as they suspected another episode of OM and insist on treatment. Their experience was that the faster the treatment, the less serious the infection and the smaller the risk of complications. Disbelief in antibiotics did not seem to correlate with initial perception of the aetiology of the disease but was primarily based on advice and stories from relatives and friends.

4. Discussion

Although medically well-established explanation models seemed to be predominant, it coexisted with emotionally and culturally embedded beliefs of causal associations between parental behavior and the occurrence of OM, affecting the parents' perceptions of the disease. These apparently conflicting perceptions created a profound sense of guilt and inadequacy among the parents, consequently leading to socially retarding and limiting behavior, affecting overall QoL. This was further facilitated by the feeling of being stigmatized and blamed by society for their child's disease. The management strategies included social isolation and avoidance of contact with the health care system, which might reflect different levels of family resources and underlines the need for differentiated treatment strategies.

4.1. Comparison with existing literature

Impact of OM on caregiver QoL has been investigated in several studies in quantitative, psychometric measures, primarily on European and American populations, and has proven significantly decreased QoL

when compared to parents of healthy children [9,11,31]. Parents to children diagnosed with rAOM evaluate their child's QoL lower than parents to children suffering from mild-to-moderate chronic illnesses, such as chronic bronchitis, allergies and intestinal problems [11]. However, few studies exist among indigenous populations and so called high-risk populations, where the prevalence of AOM, OME and especially CSOM is generally higher than in the Western world [32–34] In Australia, the indigenous population has a higher prevalence of OM as well as more severe and persistent episodes than the non-indigenous population [35]. In a qualitative study of parental views on OM in the Wongutha Tribe in Western Australia, the authors found that the parents in general primarily worried about loss of hearing as a consequence of the disease [16]. The aetiology of the disease was poorly understood and ear discharge was the main reason for contact with health clinics. The authors mentioned deleterious effects on the child's self-esteem, but did not mention guilt, shame or social isolation among parents, in contrast to what we found to be predominant in our study. Currently, Australia has implemented ear and hearing-programs directed specifically at the indigenous population, initiatives that has been welcomed by the parents [36].

In Nepal, where the population is also considered at high risk for developing OM, a recent qualitative study investigated mothers' understanding of their children's ear infections and its implications for daily life [37]. The study found that the mothers generally were unaware of symptoms other than ear discharge, and that the predominant explanatory model for the aetiology of OM was that the mother had been breastfeeding her child in a wrong way, causing breast milk to enter the ear cavity thus causing infection. Hence, here the issue of blame and guilt was more prevalent, similar to our findings, since many of the mothers described blaming themselves for their children's ear infections. The poor understanding found in both Nepal and Australia was, however, not reflected in our findings, where the parents were generally well aware of medical explanation models shared with Western medicine.

A mixed method study conducted by Augustussen et al. investigated the level of satisfaction of relatives to patients treated for advanced cancer in Greenland [38]. The study found that 71% of the questioned relatives were "dissatisfied" or "very dissatisfied" with level of inclusion in the decision-making process related to treatment and care, which contrasts findings from Denmark and Norway where the corresponding numbers were 14% and 38% were, respectively. The authors discuss that the high level of dissatisfaction in Greenland could be due to more severe social consequences that affects the entire family, which corresponds with our findings [38].

Previous studies have found the prevalence of hearing loss among Greenlandic adolescents to be three times higher than in the US, primarily due to CSOM [39,40]. CSOM may also lead to impaired educational skills, thereby having potential deleterious impact on societal development and progression [41]. In this study we included parents to children with rAOM, COME and CSOM. This resulted in a broad spectrum of the disease. However, it seemed that the level of anxiety, guilt and worry was distributed evenly among the subtypes of the disease. This might support the fact that most Greenlandic Inuit families have encountered OM-related consequences first-hand through family and friends and indicates that the awareness of having the disease has consequences other than purely practical implications.

Greenland is a country in transition, and contrasts in modern, western lifestyle versus the traditional hunter society are outspoken. It may be difficult to find a "one model fits all" when considering the different aspects of life in the small settlements and towns compared to the capital. The views of the Greenlandic Inuit parents may not be equal to the indigenous population in Australia or Nepal, however, our study implies that a purely Western model also does not comply with the Greenland Inuit perception of OM.

4.2. Strengths and limitations

We have not found similar qualitative studies in the literature investigating the perception and management of OM in an Arctic setting, where the populations are among those most affected by OM in the world [4]. The qualitative approach facilitates an elaborate and broad investigation, not restricted to predefined themes in existing questionnaires.

Most of the interviews in the smaller towns were conducted with an interpreter, as the first author do not speak East or West Greenlandic. This might have omitted details and nuances of the parents' answers and added a barrier in the communication, especially among the questions of a more sensitive and culturally delicate character. The questions were constructed in a different language, which also may have influenced the meaning and underlying preunderstanding.

Our study did not include parents and children from the settlements, where it is possible that the perceptions would differ substantially.

On a linguistic note, it is important to mention that in the Greenlandic language (both East and West) the word for "ear infection" "siuserineq" (West) and "tusaattunneq" (East) is the same as the word for "ear pain", which might have confused the terminology – and may do so on an everyday basis when Danish doctors diagnose Greenlandic speaking patients. "Siutikkut maqisoorpoq" means "something coming out of the ear" and "siulluppoq" means "having a bad ear" – terms also intermittently used to describe middle ear infections. However, we did have access to the children's medical charts and concordance with the initial inclusion criteria was ensured.

All children and their parents had previously been in contact with the health care system, which must be considered as a bias of this study, since we did not manage to get the perspective from families who do not use the health care system at all. It is possible that these families would have provided different angles. Participation in the SIUTIT Trial, where the issue of OM is discussed at several consultations, might also have influenced the parents' perception of the disease.

4.3. Implications

This study may serve as a help to clinicians and public health authorities to increase awareness about the understandings, worries and misconceptions of OM of Greenlandic Inuit parents, as well as considering and accepting the sometimes serious consequences and impact of a disease often considered trivial and diminished. It underlines the need to explore the parents' understanding of the disease and the underlying concerns, as these may differ from relatively mild to fearing for their child's life. A physician not considering the parent's perceptions and management strategies might make wrongful assumptions about the needs of the child as well as the parent, ultimately leading to insufficient or irrelevant treatment.

5. Conclusion

Our results show that OM generally has consequences for the family as a whole as well as the individual. It indicates that Greenlandic Inuit families are impacted by OM in a complex and severe manner and that the disease coexists in an entanglement where guilt, shame and social isolation are predominant themes influencing the everyday life of the affected families. The parental perceptions of the disease and the management strategies go beyond the scope of the medical explanation and treatment models which poses a potential challenge for the parents' experiences with the present treatment offer and indicate that the consequences of the disease reach far beyond ear pain and fever. Due to the high prevalence of OM in Greenland the results of our study underline the need to develop a broader approach to prevention and treatment for OM - both at the clinical level as well as a part of public health promotion at the community level.

Declarations of interests

None.

Appendix. Interview guide

Topics (elaborated in parenthesis)	Suggested questions
Awareness of disease (Facts and knowledge about the disease, aetiology of disease, source of information, myths and legends)	- What is middle ear infection? - Why do you get it? - Where do you obtain the information from? - Is middle ear infection dangerous? - Why is there sometimes fluid coming out of your child's ear? - Where does it come from?
Motivation to seek help/Reasons for contact to health clinic (Fear of complications, guilt, definition of symptoms)	- How did your child feel? - How were you convinced that your child was sick? - What made you decide that it was time to go see a doctor? - How do you feel when going to the health clinic with your sick child?
Impact on the family (Social isolation, disturbance of sleep, absence from work, stigmata and judgement)	- How does middle ear infection affect your everyday life? - How do you feel about telling friends and family about your child having middle ear disease?
Adherence/Management of disease (Disempowerment, dismissal, trust in the health care workers)	- How is middle ear infection best treated? - How do you know? - What do the doctors/nurses say?
Seeking support from others than health personnel	- Do you discuss your child's ear infections with friends/family/facebook-group/others? - Could your experience be relevant to other families and if so, how would you share your knowledge?
Barriers to get help (Lack of continuity, ever-changing health personnel, language-barriers)	- How well-informed do you feel after consulting a nurse/doctor? - Have you experienced any uncertainties or been in doubt of what to do?

References

[1] P. Homøe, R.B. Christensen, P. Bretlau, Acute otitis media and sociomedical risk factors among unselected children in Greenland, Int. J. Pediatr. Otorhinolaryngol. 49 (1999) 37–52, https://doi.org/10.1016/S0165-5876(99)00044-0.

[2] P. Homøe, R.B. Christensen, P. Bretlau, Prevalence of otitis media in a survey of 591 unselected Greenlandic children, Int. J. Pediatr. Otorhinolaryngol. 36 (1996) 215–230, https://doi.org/10.1016/0165-5876(96)01351-1.

[3] A. Koch, P. Sørensen, P. Homøe, K. Mølbak, F.K. Pedersen, T. Mortensen, H. Elberling, A.M. Eriksen, O.R. Olsen, M. Melbye, Population-based study of acute respiratory infections in children, Greenland, Emerg. Infect. Dis. 8 (2002) 586–593, https://doi.org/10.3201/eid0806.010321.

[4] Chronic Suppurative Otitis Media Burden of Illness and Management Options, (2004) http://www.who.int/pbd/publications/Chronicsuppurativeotitis_media.pdf , Accessed date: 14 February 2018.

[5] P. Homøe, R.B. Christensen, P. Bretlau, Acute otitis media and age at onset among children in Greenland, Acta Otolaryngol. 119 (1999) 65–71, https://doi.org/10.1080/00016489950181963.

[6] A. Koch, P. Homøe, C. Pipper, T. Hjuler, M. Melbye, Chronic suppurative otitis media in a birth cohort of children in Greenland: population-based study of incidence and risk factors, Pediatr. Infect. Dis. J. 30 (2011) 25–29, https://doi.org/10.1097/INF.0b013e3181efaa11.

[7] M.N. Demant, R.G. Jensen, J.C. Jakobsen, C. Gluud, P. Homøe, The effects of ventilation tubes versus no ventilation tubes for recurrent acute otitis media or chronic otitis media with effusion in 9 to 36 month old Greenlandic children, the SIUTIT trial: study protocol for a randomized controlled trial, Trials 18 (2017) 30, https://doi.org/10.1186/s13063-016-1770-x.

[8] R.M. Rosenfeld, A.J. Goldsmith, L. Tetlus, Quality of life for children with otitis media, Arch. Otolaryngol. Head Neck Surg. 123 (1997) 1049–1054, https://doi.org/10.1001/archotol.1997.01900100019002.

[9] J. Lee, D.L. Witsell, R.J. Dolor, S. Stinnett, M. Hannley, Quality of life of patients with otitis media and caregivers: a multicenter study, Laryngoscope 116 (2006) 1798–1804, https://doi.org/10.1097/01.mlg.0000231305.43180.f6.

[10] M. Richards, C. Giannoni, Quality-of-Life outcomes after surgical intervention for otitis media, Arch. Otolaryngol. Neck Surg. 128 (2002) 776, https://doi.org/10.1001/archotol.128.7.776.

[11] C.N.M. Brouwer, M.M. Rovers, A.R. Maille, R.H. Veenhoven, D.E. Grobbee, E.A.M. Sanders, A.G.M. Schilder, The impact of recurrent acute otitis media on the quality of life of children and their caregivers, Clin. Otolaryngol. 30 (2005) 258–265, https://doi.org/10.1111/j.1365-2273.2005.00995.x.

[12] S. Chando, C. Young, J.C. Craig, H. Gunasekera, A. Tong, Parental views on otitis media: systematic review of qualitative studies, Eur. J. Pediatr. 175 (2016) 1295–1305, https://doi.org/10.1007/s00431-016-2779-6.

[13] S. Meherali, A. Campbell, L. Hartling, S. Scott, Understanding parents' experiences and information needs on pediatric acute otitis media, J. Patient Exp. (2018), https://doi.org/10.1177/2374373518771362 237437351877136.

[14] M.P. Hansen, J. Howlett, C. Del Mar, T.C. Hoffmann, Parents' beliefs and knowledge about the management of acute otitis media: a qualitative study, BMC Fam. Pract. 16 (2015) 82, https://doi.org/10.1186/s12875-015-0297-7.

[15] J. Wuest, Harmonizing: a North American Indian approach to management of middle ear disease with transcultural nursing implications, J. Transcult. Nurs. 3 (1991) 5–14, https://doi.org/10.1177/104365969100300103.

[16] C. Jeffries-Stokes, D. Lehmann, J. Johnston, A. Mason, J. Evans, D. Elsbury, K. Wood, Aboriginal perspective on middle ear disease in the arid zone of Western Australia, J. Paediatr. Child Health 40 (2004) 258–264, https://doi.org/10.1111/j.1440-1754.2004.00360.x.

[17] P.J. Lucas, C. Cabral, A.D. Hay, J. Horwood, A systematic review of parent and clinician views and perceptions that influence prescribing decisions in relation to acute childhood infections in primary care, Scand. J. Prim. Health Care 33 (2015) 11–20, https://doi.org/10.3109/02813432.2015.1001942.

[18] J. Kai, Parents' difficulties and information needs in coping with acute illness in preschool children: a qualitative study, BMJ 313 (1996) 987–990, https://doi.org/10.1136/BMJ.313.7063.987.

[19] A. Tong, P. Sainsbury, J. Craig, Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups, Int. J. Qual. Heal. Care. 19 (2007) 349–357, https://doi.org/10.1093/intqhc/mzm042.

[20] S. Kvale, S. Brinkmann, InterViews : Learning the Craft of Qualitative Research Interviewing, n.d https://www.saxo.com/dk/interviews_svend-brinkmann_paperback_9781452275727?gclid=EAIaIQobChMI6cfi0tm_

[21] S. Kvale, The qualitative research interview, J. Phenomenol. Psychol. 14 (1983) 171–196, https://doi.org/10.1163/156916283X00090.

[22] K. Malterud, Qualitative research: standards, challenges, and guidelines, Lancet 358 (2001) 483–488, https://doi.org/10.1016/S0140-6736(01)05627-6.

[23] P. Bjerregaard, C.V.L. Larsen, Three lifestyle-related issues of major significance for public health among the Inuit in contemporary Greenland: a review of adverse childhood conditions, obesity, and smoking in a period of social transition, Publ. Health Rev. 39 (2018) 5, https://doi.org/10.1186/s40985-018-0085-8.

[24] P. Bjerregaard, I.K. Dahl-Petersen, C.V.L. Larsen, Measuring social inequality in health amongst indigenous peoples in the Arctic. A comparison of different indicators of social disparity among the Inuit in Greenland, SSM - Popul. Heal. 6 (2018) 149–157, https://doi.org/10.1016/j.ssmph.2018.08.010.

[25] Statistics Greenland, www.stat.gl, (2019) , Accessed date: 22 March 2019.

[26] B. Niclasen, G. Mulvad, Health care and health care delivery in Greenland, Int. J. Circumpolar Health 69 (2010) 437–487, https://doi.org/10.3402/ijch.v69i5.17691.

[27] Greenlandic Medical Society, Code of Conduct, (2015) http://gmsnet.dk/test/wp-content/uploads/2015/10/CodeOfConduct_final.pdf , Accessed date: 1 May 2018.

[28] K. Malterud, Systematic text condensation: a strategy for qualitative analysis, Scand. J. Publ. Health 40 (2012) 795–805, https://doi.org/10.1177/1403494812465030.

[29] A. Giorgi, The theory, practice, and evaluation of the phenomenological method as a qualitative research procedure, J. Phenomenol. Psychol. 28 (1997) 235–260, https://doi.org/10.1163/156916297X00103.

[30] K. Malterud, Theory and interpretation in qualitative studies from general practice: why and how? Scand. J. Publ. Health 44 (2016) 120–129, https://doi.org/10.1177/1403494815621181.

[31] M. Boruk, P. Lee, Y. Faynzilbert, R.M. Rosenfeld, Caregiver well-being and child quality of life, Otolaryngol. Head Neck Surg. 136 (2007) 159–168, https://doi.org/10.1016/j.otohns.2006.09.005.

[32] P. Homøe, K. Kvaerner, J.R. Casey, R.A.M.J. Damoiseaux, T.M.A. Van Dongen, H. Gunasekera, R.G. Jensen, E. Kvestad, P.S. Morris, H.M. Weinreich, State of the art review panel 1, Epidemiol. Diagn. 156 (2017) 1–21, https://doi.org/10.1177/0194599816643510.

[33] M.F. Bhutta, Evolution and otitis media: a review, and a model to explain high prevalence in indigenous populations, Hum. Biol. 87 (2015) 92, https://doi.org/10.13110/humanbiology.87.2.0092.

[34] R. DeAntonio, J.-P. Yarzabal, J.P. Cruz, J.E. Schmidt, J. Kleijnen, Epidemiology of otitis media in children from developing countries: a systematic review, Int. J. Pediatr. Otorhinolaryngol. 85 (2016) 65–74, https://doi.org/10.1016/j.ijporl.2016.03.032.

[35] P.S. Morris, A.J. Leach, P. Silberberg, G. Mellon, C. Wilson, E. Hamilton, J. Beissbarth, Otitis media in young Aboriginal children from remote communities in Northern and Central Australia: a cross-sectional survey, BMC Pediatr. 5 (2005) 27, https://doi.org/10.1186/1471-2431-5-27.

[36] C. Jones, M. Sharma, S. Harkus, C. McMahon, K. Taumoepeau, K. Demuth, K. Mattock, L. Rosas, R. Wing, S. Pawar, A. Hampshire, A program to respond to otitis media in remote Australian Aboriginal communities: a qualitative investigation of parent perspectives, BMC Pediatr. 18 (2018) 99, https://doi.org/10.1186/s12887-018-1081-3.

[37] S. Clarke, A Mixed Methods Study of Chronic Otitis Media in Jumla Nepal, (2017) http://handle.unsw.edu.au/1959.4/60232 , Accessed date: 24 January 2019.

[38] M. Augustussen, L. Hounsgaard, M.L. Pedersen, P. Sjøgren, H. Timm, Relatives' level of satisfaction with advanced cancer care in Greenland – a mixed methods study, Int. J. Circumpolar Health 76 (2017) 1335148, https://doi.org/10.1080/22423982.2017.1335148.

[39] R.G. Jensen, A. Koch, P. Homøe, The risk of hearing loss in a population with a high prevalence of chronic suppurative otitis media, Int. J. Pediatr. Otorhinolaryngol. 77 (2013) 1530–1535, https://doi.org/10.1016/j.ijporl.2013.06.025.

[40] M.B. Avnstorp, P. Homøe, P. Bjerregaard, R.G. Jensen, Chronic suppurative otitis media, middle ear pathology and corresponding hearing loss in a cohort of Greenlandic children, Int. J. Pediatr. Otorhinolaryngol. 83 (2016) 148–153, https://doi.org/10.1016/j.ijporl.2016.01.017.

[41] World Health Organization, Chronic Suppurative Otitis Media, Burden of Illness and Management Options, Geneva, Schwitzerl, 2004http://www.who.int/pbd/publications/Chronicsuppurativeotitis_media.pdf , Accessed date: 22 December 2015.