CHRONIC SUPPURATIVE OTITIS MEDIA IN CHILDREN IN GREENLAND: FREQUENCY, RISK FACTORS AND DISEASE BURDEN

◊

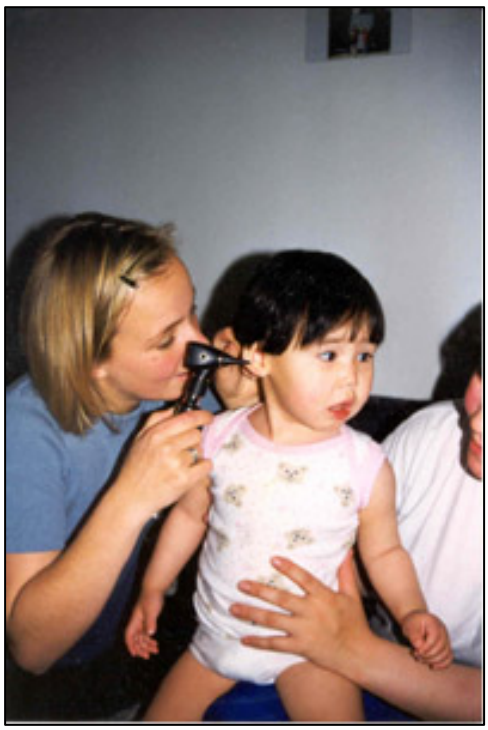
KRONISK MELLEMØREBETÆNDELSE BLANDT BØRN I GRØNLAND: HYPPIGHED, RISIKOFAKTORER OG SYGDOMSBYRDE

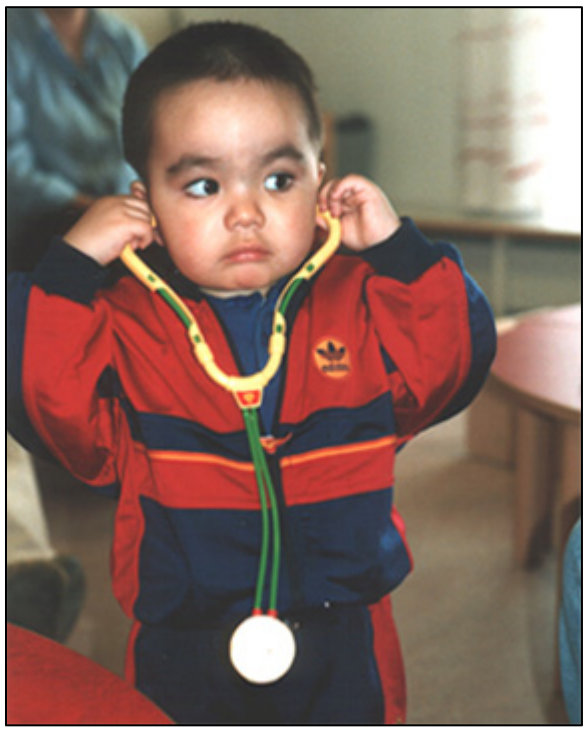
MPH-afhandling

Anders Koch, læge, Ph.D.

Københavns Universitet & Statens Serum Institut

2009





CONTENTS

ACKNOWLEDGEMENTS

First of all I would like to thank the children of Sisimiut, their parents and involved childcare centres and daycare mothers for patiently participating in this long-term project. Second, I would like to thank my Head of Department at Statens Serum Institut, professor Mads Melbye, for many years' collaboration, teaching, support, and encouragement. Third, I would like to thank my MPH superviser Dan Meyrowitsch for fruitful advice, both in the beginning and in the end of the process. Fourth, I would like to thank my coworkers Preben Homøe, MD, PhD, DMSc, statistician Christian Pipper, PhD, Thomas Hjuler, MD, PhD, and statistician Per Sørensen, for taking very active part in the work behind this manuscript. Fifth, I would like to thank the former medical students, but now MDs, (in alphabetic order): Lasse Høgh Andersen, Hanne Elberling, Christoffer and Gitte Holst Hahn, Annemette Hansen, Mette Madsen, Christian Malherbe, Iben Mathiessen, Tine Mortensen, Mette Olesen, and June Pejl, and the Greenlandic interpreters Arnannguaq Amossen, Ivalo Lennert, Anna Lynge, Johanne Noahsen, Pia Pedersen, and Jakobine Sørensen, who diligently carried out much of the field phase of the study in Greenland. Also the seven data typists at Statens Serum Institut, in particular Brian Agerskov and Pernille Homøe, are thanked for their efforts. Last, but not least, the staff at Sisimiut Health Center, Greenland, in particular the chief medical officers Ove Rosing Olsen and the late Peter Dybdahl Andersen and former head nurse Ellis Thierry, are warmly thanked for a fruitful collaboration and for providing optimal working conditions.

This work was carried out during my employment at the Department of Epidemiology Research, Statens Serum Institut, and supported by the Commission for Scientific Research in Greenland (KVUG), the Danish Research Councils, and the Danish National Research Foundation.

Anders Koch, MD, PhD
Department of Epidemiology Research
Statens Serum Institut
Copenhagen, Denmark
August 2009

ABBREVIATIONS

OM	Otitis media
AOM	Acute otitis media
OME	Otitis media with effusion (‘sekretorisk otitis’ in Danish)
CSOM	Chronic suppurative otitis media
COM	Chronic otitis media
URI	Upper respiratory tract infection
LRI	Lower respiratory tract infection
MBL	Mannose binding lectin
RR	Rate ratio/relative risk
CI	Confidence interval

SUMMARY

Background

Inuits of the Arctic experience very high rates of chronic suppurative otitis media (CSOM), a primary cause of permanent hearing loss. The WHO has stated that urgent attention is needed to deal with a massive public health problem in countries with high prevalence of CSOM, including Greenland. Yet not enough is known in Greenland about the epidemiology of and risk factors for CSOM, knowledge of which is essential for possible preventive measures.

Aims

We carried out a population-based prospective cohort study in children living in the west Greenlandic community of Sisimiut with the aims to determine age-specific incidence, median age at debut, and possible risk factors for CSOM, and to estimate the burden of disease associated with CSOM in Greenland in order to identify possible areas for preventive measures.

Material and methods

A cohort of 465 children aged 0-4 years was followed regularly for a 2-year period and cases of CSOM were registered based on medical history and clinical examinations.

Results

The cumulative incidence rate of CSOM at 4 years of age was 14%, and the median age at debut was 336 days. Significant risk factors were being of Greenlandic descent, attending childcare centres, having smokers in the household before the age of 12 months, having a mother who reported having a history of purulent ear discharge, and suffering from a high burden of upper respiratory tract infections. Boys had significantly more often than girls bilateral CSOM. The population-attributable risks associated with each factors (a measure of the relative importance of each risk factor in the given population) were high for attending childcare centres and having smokers in the house. It was not possible to estimate the total burden of disease associated with CSOM in Greenland due to lack of data.

Conclusions

The incidence of CSOM is high among children in Greenland and the median age at debut is low. The identified risk factors and the associated population-attributable risks indicate that preventive measures regarding use of childcare centres and passive smoking may reduce the far too high incidence of CSOM in Greenland with presumed large benefits against this substantial individual and public health problem.

RESUMÉ (IN DANISH)

Baggrund

Hyppigheden af kronisk mellemørebetændelse, en primær årsag til permanent høretab, er meget høj blandt inuitbefolkninger i arktiske egne. WHO har erklæret, at i lande som Grønland med høj forekomst af kronisk mellemørebetændelse er umiddelbar opmærksomhed påkrævet over for det massive folkesundhedsproblem, sygdommen udgør. Der mangler dog viden om epidemiologien og risikofaktorer for kronisk mellemørebetændelse i Grønland; viden, der er nødvendig for mulig forebyggelse.

Formål

Vi gennemførte et populationsbaseret prospektivt kohortestudie blandt børn bosat i den vestgrønlandske kommune Sisimiut med formålene at bestemme den aldersspecifikke incidens af kronisk mellemørebetændelse, medianalder for sygdomsdebut og risikofaktorer, samt at bestemme sygdomsbyrden i Grønland af kronisk mellemørebetændelse med henblik på påvisning af mulige forebyggelsesområder.

Materiale og metoder

En kohorte af 465 børn i alderen 0-4 år blev fulgt regelmæssigt i en 2-års periode og tilfælde af kronisk mellemørebetændelse blev registreret på baggrund af oplysninger om symptomer og kliniske undersøgelser.

Resultater

Den samlede incidens af kronisk mellemørebetændelse i 4-års alderen var 14%, og den mediane debutalder var 336 dage. Signifikante risikofaktorer var det at være af grønlandsk afstamning, at gå i børneinstitution, at have rygere i husstanden i det første leveår, hvis ens mor havde haft flydeøre, og have lidt af mange øvre luftvejsinfektioner. Drenge havde signifikant oftere dobbeltsidig mellemørebetændelse end piger. De relative betydninger af de enkelte risikofaktorer ('the population-attributable risks') var høje i forbindelse med at gå i børneinstitution og have rygere i husstanden. Det var ikke muligt at bestemme sygdomsbyrden af kronisk mellemørebetændelse for det grønlandske samfund på grund af manglende data.

Konklusioner

Incidensen af kronisk mellemørebetændelse er høj blandt børn i Grønland og medianalderen for sygdomsdebut er lav. Risikofaktormønstret indikerer, at forebyggende initiativer i forbindelse med det at gå i børneinstitution og mod passiv rygning kan reducere den alt for høje incidens af kronisk mellemørebetændelse med store fordele over for dette væsentlige individuelle og folkesundhedsproblem.

INTRODUCTION

Background

Otitis media (OM) is one of the most frequent infections in paediatric populations throughout the world [1]. While acute otitis media (AOM) mainly cause fever, pain and general malaise, chronic suppurative otitis media (CSOM) may cause long-term problems in the form of intermittent or permanent purulent ear discharge and hearing loss.

CSOM is particularly frequent in Arctic populations and constitute by WHO standards an important public health problem. Yet, very little is known about the epidemiology of CSOM, not only in Arctic populations, but also on a worldwide basis.

We carried out a prospective population-based longitudinal cohort study among children aged 0-4 years in the community of Sisimiut, West Greenland, of incidence and risk factors for CSOM in order to identify possible areas for prevention.

Otitis media – disease spectrum

Otitis media (OM) denotes infection of the middle ear and covers a variety of manifestations. **Acute otitis media (AOM)** denotes a purulent infection of the middle ear cavity typically resulting in fever, ear pains and general malaise. In industrialised countries most cases of AOM resolve with or without antibiotic treatment, either with or without spontaneous perforation of the tympanic membrane leading to drainage of pus. In some cases **otitis media with effusion (OME)** develops as a consequence of AOM. OME is a pathological state where a mucous secretion develops in the middle ear cavity resulting in reduced compliance of the tympanic membrane and decreased hearing. Many of these cases also resolve spontaneously, while others are treated by insertion of grommets/tympanostomy tubes (‘trommehindedræn’).

After a perforation of the tympanic membrane following AOM the membrane may close after a few days when the pus has been allowed to drain from the middle ear, but in some cases the perforation persists, either with or without chronic purulent secretion from the middle ear cavity [2]. Such a persisting perforation of the tympanic membrane with inflammation of the middle ear and mastoid mucosa (‘slimhinde’) and ear discharge following AOM is termed **chronic suppurative otitis media** (**CSOM**, ‘suppurative’ indicating pus). In contrast, a finding of a permanent perforation of the tympanic membrane without ear discharge should only formally be denoted **chronic otitis media (COM)**, as such a perforation may result from trauma

to the tympanic membrane or to an extruded tympanostomy tube besides from AOM [2]. Both conditions are seen in **Figure 1**.

Figure 1. An otomicroscopic view of the tympanic membrane in case of suppurative otitis media (indicative of chronic suppurative otitis media (CSOM), left) and a dry perforation (indicative of chronic otitis media (COM), right).

CSOM leads to problems both on a short term and on a long term: short-term problems include tympanic membrane perforation impeding bathing, purulent ear discharge and reduced hearing, and long-term problems include damage to the middle ear structures, in particular the ossicles (small middle ear bones), and permanent hearing loss. In rare cases CSOM may lead to cholesteatoma, a non-malignant destructive tumor of the middle ear destroying the surrounding bony structures.

CSOM worldwide

CSOM appears in all populations, but with widely different prevalences. Four groups of populations may be identified, as seen in Figure 2 [2]: The high-prevalence group (group 1) includes Inuits of the Arctic, Australian Aborigines and Native Americans (Apache, Navaho) with prevalences from 4 to 46%, while the low-prevalence group (group 4) include western countries such as the US, UK, Denmark and Finland (prevalence <1%) (revised in [2]). Group 2 includes populations from the South Pacific Islands and Africa (2-6% prevalence) and group 3 Asian countries (Korea, India and Saudi Arabia, 1-2% prevalence).

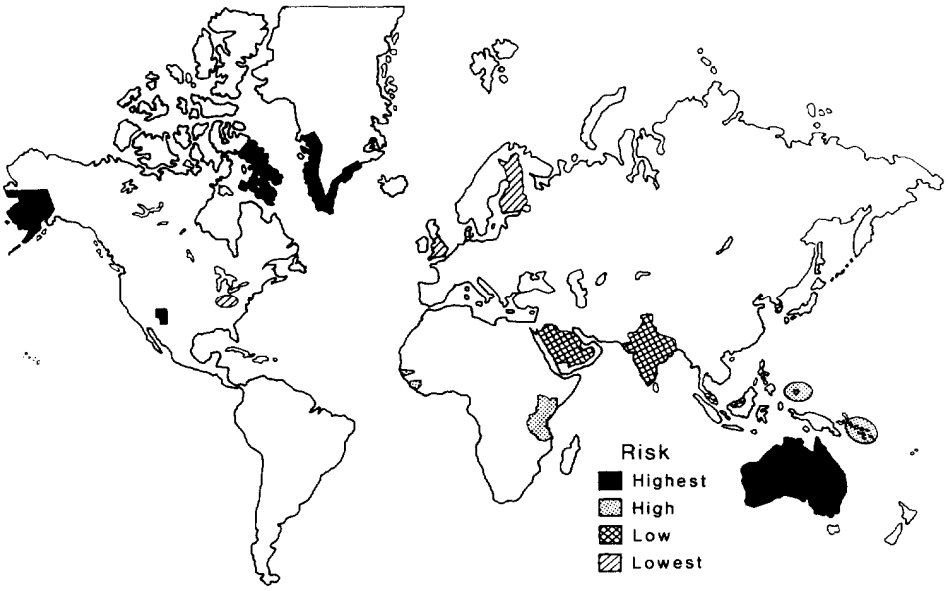


Figure 2. Prevalence of CSOM worldwide (from Bluestone 1998 [2]).

Otitis media in Arctic populations

It has been known for a long time that otitis media is common in Arctic areas. Archaeologically, CT studies of ancient Eskimo crania have estimated the occurrence of OM as judged by the size of the pneumatised cell areas in the temporal bones in 4.7% in crania from before the colonisation in 1721, and in 17.9% in crania from the 18th and the 19th centuries [3]. Using the same method on living Inuits 23.5% showed signs of OM.

In 1940 the Danish doctor Alfred Berthelsen described both acute and chronic OM as being common in Greenland in the 19th and beginning of the 20th century [4], chronic infection in particular in children. In 1956 a survey in Alaska showed that 33% of 899 Eskimos examined had significant hearing loss and 57.9% had lesions of the tympanic membrane [5]. Of all subjects examined, 5.9% were in need of acute mastoidectomi (operation of the bone behind the ear as evidence of severe OM). In Greenland it was not until the 1980s that firm figures were obtained, when the Danish doctors Christian Brahe Pedersen (oto-rhino-laryngologist) and Bengt Zachau-Christiansen (paediatrician) studied OM among children and adults in three towns in west Greenland (Jakobshavn (Ilulissat), Maniitsoq (Sukkertoppen), and Kangaamiut) and found CSOM in 5% and sequelae of OM in 13%, in total 18% [6, 7]. Among the young participants (11-20 years) 8% had CSOM and 14% had sequelae of OM, and among the older participants (41-50 years) 2% had CSOM and 13% had sequelae of OM. It was estimated, using Scandinavian criteria, that 8.6% of the participants would have benefited from an ear operation either to stop otorrhea and/or to improve the hearing.

Ten years later, in 1994, the Danish oto-rhino-laryngologist Preben Homøe carried out studies among children aged 3-8 years in Sisimiut and Nuuk and found signs of CSOM/COM or sequelae in 22.6% of children in Sisimiut and 17.5% of children in Nuuk [8]. These were essentially the same figures as found by Brahe-Pedersen and Zachau Christiansen 10 years earlier. Besides the high frequency it was reported that early age at onset of OM (before one year of age, although this was partly based on parental recording) was frequent in these children [9].

Other studies on OM have been carried out in native Eskimo populations in Alaska and Canada showing essentially the same high prevalence figures. Overall, the prevalence in these populations of CSOM ranges from 4 to 32% and of COM (dry perforations) and COM sequelae from 15 to 17% (reviewed in [10]).

It is essentially unknown why the rate of CSOM is so high in Inuit populations, and both genetic and environmental factors may be involved. A number of studies have addressed risk factors for OM in Inuit, but no consistent findings have been reported. Some studies have found lack of breastfeeding and in-house crowding to be associated with OM [11, 12, 12, 13, 13], while others have not [7, 7, 14, 15, 15]. Only parental reporting of OM and exclusive breastfeeding for more than four months were found to be risk factors for OM [16]. It has been found, however, that upper respiratory tract infections, which may lead to OM, is very frequent among Greenlandic children [17], and that Greenlandic children are early and massively colonised with potential bacterial pathogens in their nasopharynx [18]. Also aberrant anatomy of the Eustachian tube in Inuits has been hypothesised as an explanation [19], although no firm data to support this exist.

Not only among Inuits, but also on a worldwide scale there is surprisingly little knowledge about the epidemiology of CSOM. Thus, while risk factor studies on AOM are abundant, no prospective studies concerning risk factors for CSOM exist [1, 2, 20]. However, factors such as ethnicity, male sex, familial disposition, cessation of breastfeeding, crowding, use of daycare centres, passive smoking, low hygienic standard, and low social class have been suggested [2].

A remarkable feature is, however, that in Canada in the 1980s for unknown reasons a marked reduction in the prevalence of chronic otitis was noted [21]. In contrast, no such reduction has been observed in Greenland [8]. This is remarkable given that social factors have elsewhere been found to be involved in the development of CSOM, and as social conditions in Greenland in recent decades have changed markedly.

As a consequence of the high frequency of CSOM in Greenland, each year a substantial number of Greenlandic patients are referred for surgery for CSOM, either to Rigshospitalet (the University Hospital in Copenhagen) or to Dronning Ingrids Hospital in Nuuk, where an ENT specialist has recently been employed.

CSOM as a public health problem in Greenland

The high frequency of CSOM and the fact that no available evidence indicates a recent decrease in the incidence of CSOM in Greenland shows that CSOM represents a substantial public health problem in Greenland. The WHO has stated that for countries with a prevalence of >4% of CSOM 'urgent attention (is) needed to deal with a massive public health problem', countries in which they include Greenland [22].

Thus, there is a need for preventive measures against CSOM.

There are, however, large gaps in our knowledge of the epidemiology of CSOM in Greenland. The age-specific incidence of CSOM, the median age at debut, duration of episodes and, perhaps most importantly, possible risk factors for CSOM and the associated population-attributable risks are all unknown. Knowledge of these factors, and especially of environmental and possibly modifiable factors, is important in order to device possible public health measures to reduce the far too high prevalence of CSOM in Greenland.

Although genetic factors such as an aberrant Eustachian tube anatomy in Inuit children might partly explain the particularly high incidence of OM in Inuit children, it may be more valuable for intervention to estimate the precise impact of other and modifiable external risk factors such as e.g. use of childcare centres.

Aims

On this background the aims of the present study were prospectively, in children aged 0-4 years and living in Greenland, to estimate the age-specific incidence of CSOM, to estimate the median age at debut, to identify possible risk factors and the associated population-attributable risk, and finally to estimate the COM-related burden of disease in Greenland in order to identify possible areas for preventive measures.

MATERIAL AND METHODS

Study design

The study was designed as a prospective longitudinal cohort study including all children aged 0-4 years and living in Sisimiut, west Greenland. The study period was 1996-1998, divided into 3 parts: *Enrolment phase* (1 April – 11 August 1996), *monitoring phase* (12 August 1996 – 6 August 1998) and *end phase* (7 August – 7 December 1998) (**Figure 3**). Incidence and risk factors for upper and lower respiratory tract infections among children under the age of 2 years at any point of time during the study period have previously been described [23-25].

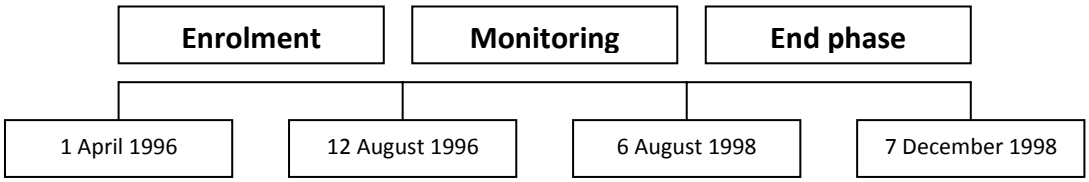


Figure 3. Outline of study period.

Setting

The town of Sisimiut is placed on the West Coast of Greenland at 66.8E N, just north of the Polar circle n (**Figure 4**). It is the second biggest town in Greenland with 5,117 inhabitants (per 1 January 1996), hereof 4,501 (88%) born in Greenland and 616 (12%) born outside of Greenland, mainly in Denmark [26]. This composition is representative of Greenland as a whole (87% vs. 13%, respectively). The town is approximately three kilometres from one end to the other, and all houses are built within town limits. Sisimiut harbours a fishing fleet and some small and medium enterprises and is connected by flights every second day year round to the main airport in Greenland. Also some educational institutions are placed in Sisimiut. Average income is slightly higher for Sisimiut community than for Greenland as a whole (average tax deducible annual income per tax payer DKr 117,243 and 113,257, respectively) [27]. The town is mainly dependent upon fishing and some whaling, but not seal hunting like in other districts. Most people who fish for a living are employed on trawlers.

Two settlements, Sarfannguaq and Itilleq, are placed within the Sisimiut community with 132 and 116 inhabitants, respectively. These settlements are mainly dependent on fishing and hunting.

Housing in Sisimiut consists of traditional Greenlandic wooden single or double family houses, apartments in concrete blocks, and terraced houses constructed by wood and concrete. Most family houses are private, while apartments and terraced houses are mainly owned by a public company ('INI'). The present houses in Sisimiut are from 1 to 60 years old, while apartments and terraced houses are up to 40 years old.

All houses have electricity. All apartments and terraced houses and most family houses have running water all year round, while some private houses have running water in the summer only, and in the winter water is brought to a tank in the house by the public water supply. A few houses collect water at public standpipes. All water from pipelines and standpipes comes from the public water supply. All apartments and terraced houses and many private houses have flush toilets, but some private houses have toilet consisting of a bucket and a plastic bag, which is closed, placed outside the house and removed regularly by garbage men.

One health centre serves Sisimiut with up to five employed doctors at a time and one midwife. All health services in Sisimiut apart from a dental clinic are found at the health centre, which serves as general practice, birth clinic, as well as a regular hospital. All births in the town and the two settlements take place at the local health centre. All health services in Greenland are free, including prescribed medicine.

The project office was located at the Health Centre.

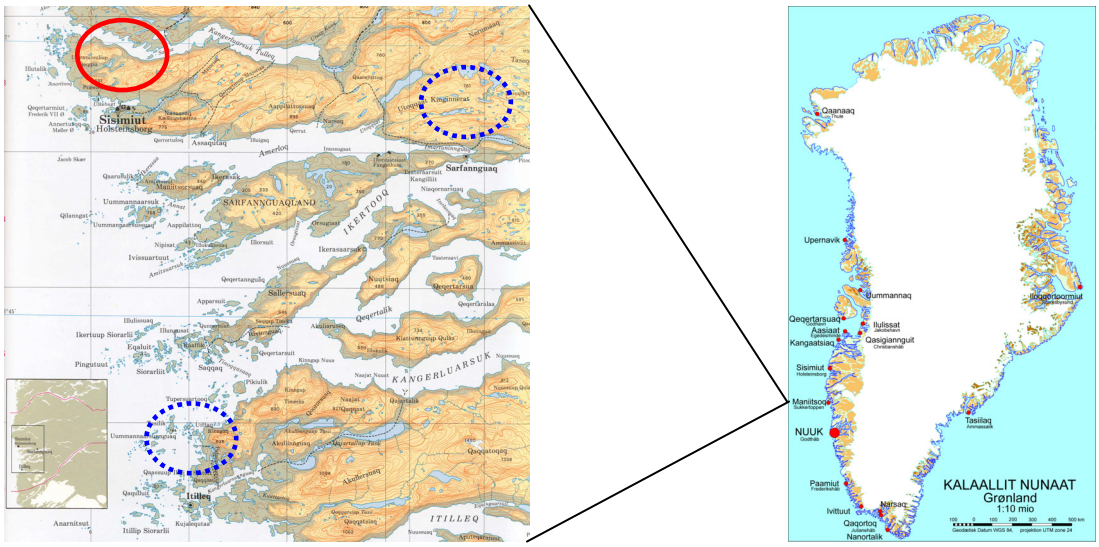


Figure 4. Sisimiut (full circle) and the two settlements Sarfannguaq and Itilleq (dotted circles). Map at right Copyright Kort & Matrikelstyrelsen, Copenhagen, Denmark.

Study population and cohort formation

The study population was an open population consisting of all children less than three years of age at enrolment living in Sisimiut and the two settlements as of 1 April 1996, and all children born in or moving into Sisimiut (under three years of age) in the subsequent period until 1 June 1998. All children were eligible for enrolment, and no distinction was made on the basis of ethnicity, place of birth, or duration of stay in Sisimiut. Although children were followed to their fourth year birthday, they were only included if younger than three years of age at the time of enrolment in order to obtain monitoring time.

The main data source for identification of children was the Civil Registration System, in which all inhabitants of Greenland and Denmark are registered. In order not to miss children whose parents had not reported to the Civil Registration System in case of moving, also information from the Health Centre and the local authorities in Sisimiut was obtained.

On 1 April 1996 all children aged 0-3 years registered in the Civil Registration System as living in Sisimiut or in one of the two settlements were identified. Also children only registered in health centre files or child-care lists were identified. Simultaneously, and for the subsequent monitoring phase until 1 June 1998, all births at the local health centre were routinely registered. In addition, the Civil Registration System, health centre files and public nursery lists were reviewed at an approximately quarterly basis. In this way children born and moving into Sisimiut in the study period were identified. Although the monitoring period lasted until 6 August 1998, children born later or moving into Sisimiut later than 1 June 1998 were not enrolled in order to obtain monitoring time.

For eligible children living in Sisimiut at the beginning of the study period, an introductory letter was sent to the children's parents, and in the subsequent period until 12 August 1996 ('enrolment phase') a visit was made in the child's home, where detailed information was given and informed consent obtained. Eligible children moving into Sisimiut during the study period were contacted as soon as possible after identification and similarly recruited. For children born in Sisimiut during the study period, the mother was approached as soon as possible after birth (normally within two days hereof) to give information of the study and to obtain informed consent. The first visit at home was not paid until six weeks later, however, since newborns in Sisimiut are seen weekly by visiting nurses for the first five weeks.

Project staff and training

The project staff consisted of Danish medical students and local interpreters. In total 12 medical students were employed during the study with a median time of residency of 7 months (range 2 – 13 months), 2 or 3 at a time. Eight female Greenlandic interpreters were employed more than one month during the study.

At medical school all medical students had had some basic clinical training prior to employment, and were moreover specifically trained prior to departure by two weeks' residency in a paediatric department and one week in an ear-nose-throat department in Denmark. In Greenland the students and interpreters were trained and supervised in the field by the present author and the experienced, preceding medical students for the first weeks after arrival.

Surveillance programme

At enrolment, details of the study were given in words and writing. If parents accepted participation, informed consent was obtained and an interview concerning various background variables was carried out using a standardised questionnaire.

After the enrolment visit and starting from 12 August 1996, children less than two years of age during the monitoring period in Sisimiut town were monitored weekly at a fixed weekday. Children being in homecare or in daycare were visited at home, while those attending childcare centres were visited there. In either case, the mothers or fathers were asked about the child's health in the period since the last visit, usually one week back in time and at the most 14 days (to avoid recall bias). If symptoms of respiratory tract infection within the last seven days before the visit were reported, a brief clinical examination with focus on the respiratory system was carried out. In case severe illness was identified, the parents were urged to attend the health centre, if this had not been done. Otherwise, no action was taken. The medical students did not treat children. If identical symptoms were recorded at two successive visits, the clinical examination would be repeated. However, if at the third and subsequent visits unchanged symptoms were recorded, clinical examination would not be carried out, as little new information would be expected and as not to stress the child unnecessarily. This would typically be the case if cold (runny nose) or ear discharge were recorded as the only symptoms. If, on the other hand, at subsequent visits new symptoms had emerged, for instance if ear discharge was recorded at a visit when cold had previously been recorded this was considered a new situation eliciting a clinical examination.

Every 4^{th} week a clinical examination and growth measurement was carried out irrespective of parental reporting of symptoms. Also information of breastfeeding and other kinds of nutrition was obtained.

Visits were made at a fixed weekday for each child from Monday to Thursday. If parents of those children who were visited in their homes were not at home at the scheduled time, an effort was made to contact them later the same day. If this was unsuccessful, the children were not seen until the next week. Children seen at home were visited by a team of one interpreter and one medical student, or, if the parents spoke sufficient Danish, by two medical students.

In total, six childcare centres for children younger than three years of age exist in Sisimiut. Each of these was visited once a week by one or two study teams consisting of an interpreter and medical student. When the child arrived at the childcare centre in the morning, the mother (or father) was asked about the medical history, and if relevant a clinical examination was carried out in a separate room. As the parents most often were not present at the examinations, members of the staff of the childcare centres assisted at the examinations.

If a child did not turn up at the childcare centre on the day of visit, the parents were contacted. Efforts were made always to pay personal visits, but for practical purposes it was sometimes necessary to contact the parents by phone. Often children were kept at home because of vacation, etc. where the family might not be home. Also in case of illness, the child might be looked after by, for instance, grandparents at their house while the parents were at work. In such cases the parents would be contacted by phone, medical history taken, and clinical examination carried out afterwards in the grandparents' house.

In the end phase of the study, a final visit was made at the children's homes. Besides clinical examination and growth measurement, an interview similar to the enrolment interview was carried out at this visit. Finally, blood samples from the child and its parents were taken.

Figure 5 presents an overview of the monitoring pattern for 25 children chosen at random. All children were enrolled between April and August 1996 and monitored at a weekly basis from 12 August 1996 until turning two years of age, where after they were followed at eight weeks' interval. Most of these children (17/25) were excluded from the study between August and December 1998 as planned, but some left the cohort prior to their two-year birthday (n=5) or before the end phase (n=3). Around Christmas 1996 no visits could be made for three weeks, and around Christmas 1997 similarly for two weeks.

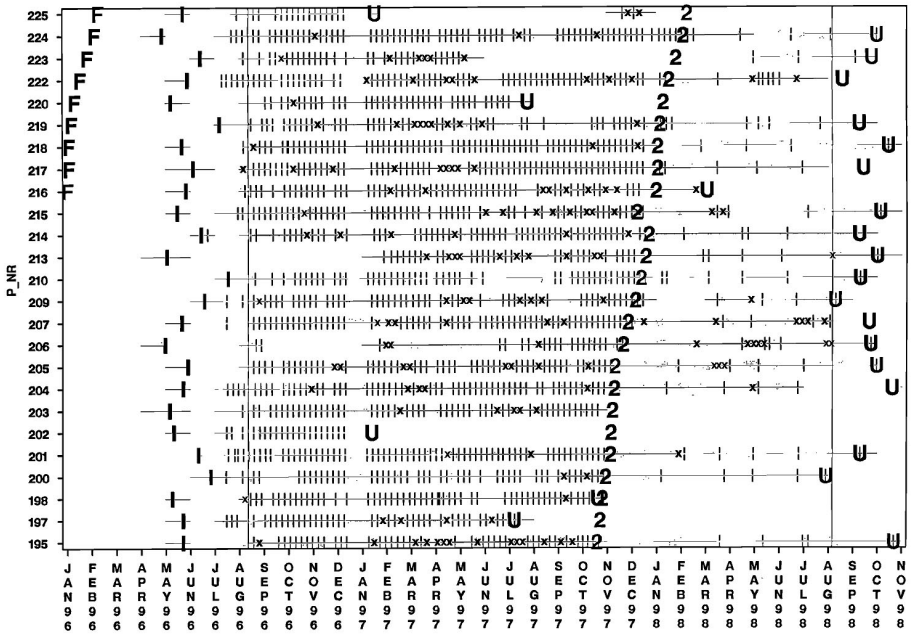


Figure 5: Outlines of monitoring for 25 children chosen at random.
---------- = Time of observation, **F** = Child's birthday, **I** = Day of enrolment, **2** = Two-year birthday, **U** = Exclusion of child, | = Successful visit, **x** = Unsuccessful visit. Limits for monitoring period marked in August 1996 and August 1998.

Registration of symptoms and clinical signs

At the monitoring visits, parents or caretakers were asked about the presence of a number of symptoms in the period since the last visit, but not more than up to 14 days. These questions which would all be answered by a 'yes' or 'no' for each day of the period, were chosen as to screen broadly for respiratory tract infections, as well as for other common illnesses, as to estimate the perceived illness burden, and to delimit time at risk. **Table 1** shows the questions divided into three item groups.

On the questionnaire, questions were written both in Danish and Greenlandic. After translating the questions into Greenlandic, they were retranslated and compared with the original questions in order to assure comparability [28]. The period from 1 April to 12 August 1996 served as a pilot phase for this questionnaire. In this period the questionnaire was refined in total seven times until the final questionnaire was developed.

Table 1. Symptom questions asked at surveillance visits. All questions started with 'Has the child…'.

General condition	Respiratory symptoms	Other symptoms
Been sick (generally affected)	Had a cold (i.e. runny or stuffed nose)	Had fever or felt hot
Been to bed because of illness	Been coughing at daytime	Been vomiting or had nausea
Been at home from childcare centre or daycare because of illness	Been coughing at night-time or in the morning	Had diarrhoea (loose or watery stools more than three times/day)
Attended doctor*	Had earache (pulling at ears)	Had a rash
Taken any medicine**	Had ear discharge	Had other illness***
Had slept restlessly or abruptly	Been hoarse or had a sore throat	
Been drowsy or slept much	Had fast or difficult breathing	
Been eating or drinking less than normal	Had chest indrawing	

* If 'yes', doctor's diagnosis noted
** All types of medicine, both prescribed and not prescribed. If 'yes', name and dose noted
*** If 'yes', name of illness noted

If any respiratory symptom as seen in **Table 1** was reported within the last seven days, a clinical examination with focus on the respiratory system was carried out. Besides common clinical procedures (assessment of general condition and respiration, counting of respiratory rate, inspection of throat, stethoscopy and inspection of skin) this included measurement of axillary temperature, otoscopy, and tympanometry. If signs of illness were found (see below), a throat swab for bacterial and a nasopharyngeal aspirate for viral analyses was taken. Otoscopy was done using non-pneumatic otoscopes (Welch-Allyn). For tympanometry two portable tympanometers were used (Welch-Allyn MicroTymp2, Skaneateles Falls, New York, U.S.A.). Functional checks of tympanometers were done weekly by measuring a cavity with two volumes (0.5 and 2.0 cc). According to factory standards a tolerance of $\forall$0.1 cc was acceptable. None of the two tympanometers ever exceeded this. Different clinical procedures in childcare centres are seen in **Figure 6**.

Great care was taken to assess in particular the child's general condition and respiratory rate when calm, i.e. before the actual examination, as the children often cried during examination, possibly affecting the assessment of these factors. Similarly, care was taken to inspect the tympanic membranes with the child calm.

For each clinical examination, a registration sheet was filled out. Signs were graduated semi-quantitatively by the examiner into grade 1, 2 or 3. One denoted the light or insecure sign, 2 denoted the certain presence of the sign, when the examiner was not in doubt, and 3 denoted the severe sign. The graduation system was semi-quantitative, as the ranges of the different grades were not equidistant. Thus, grade 2 could cover a wider range of severity than group 1 or 3, and a graduation into grade 2 only indicated that the sign was present and pathological, but not in severe form.

In order to obtain a conservative and reliable estimate of the clinical findings in the analyses *only signs of grade 2 or 3 were counted positive*, while signs of grade 1 were considered *negative*.

At enrolment information of prior medical history including episodes of ear discharge was obtained.

At the end of the study period or at exit of the study the children had a venous blood sample drawn in two tubes and the blood divided into serum, plasma, and white blood cell fractions. Biological material was stored at -80° C until further analysis.

Figure 6. Clinical examinations in childcare centres.

Definition of CSOM

CSOM was defined as either 1) parental reporting of at least 14 days purulent ear discharge and objective findings of purulent ear discharge, a tympanic perforation or sequelae (scarring, sclerosis, or fibrosis of the tympanic membrane) or 2) objective findings of at least 14 days purulent ear discharge or tympanic perforation irrespectively of parental reporting, all pertaining to the same ear. The requirement of a period of 14 days as suggested by the WHO [29] was met by identical observations/symptoms at visits of at least 14 days interval without contradictory findings/symptoms in between. The debut time of CSOM was defined as the first time of parental reporting of symptoms in case of definition 1) or the first time of observation in case of definition 2). Thus, definition 2 did not necessarily include otorrhea. If not explicitly stated our definition of CSOM covered both unilateral and bilateral CSOM.

Risk factors

Risk factor information covered 1) background information obtained primarily by an interview at the enrolment visit using a standardised questionnaire, 2) analyses of mutations in the gene for Mannose binding lectin (MBL), and 3) registrations of symptoms of upper and lower respiratory tract infections (URI and LRI, respectively).

The standardised questionnaire was designed as to collect detailed information on a number of potential risk factors and background variables in the following item categories ethnicity, socio-economic factors, birth history, crowding, housing, smoking, childcare, breastfeeding, and parental history of respiratory and ear disease.

For comparability with other studies the questionnaire was designed as to use questions and formulations from the 'Greenlandic Health Interview Survey' [30] whenever relevant and applicable. Questions from this survey have later been developed into a standard questionnaire for Greenland [28], but this was not available at the time of designing the present questionnaire. Experience with the questionnaire was obtained during a pilot phase and the questionnaire was subsequently revised and implemented in the study period.

The information given at the end of the study period was used to validate the information derived from the enrolment interview. In case of discrepancies, reasons for this were explored and in case of misunderstandings or wrong information at time of enrolment, this was corrected.

Some of the background information obtained through questionnaires could be validated in official files and registers. Thus, a register of *housing* comprising year of construction, size and number of rooms for most houses and apartments in Greenland is kept by 'Grønlands Statistik', the official statistical office of Greenland. Information of *building material* of houses and *water supply* is available through Sisimiut local administration. All *births* in Greenland are reported to the Chief Medical Officer in Greenland. From 1991 a register of information from birth notifications has been kept regarding birth variables such as for instance gestational age, weight and length at birth. Information on attendance of *public childcare* (childcare centres and daycare) is kept on file at the Sisimiut local administration. Information of *date and place of birth* for children, parents and other family members living in the same household is registered in the Civil Registration System, which also contains information on *children's change of address.* Information obtained at the enrolment interviews was checked in these registers, and as regards birth variables, only those recorded in the register were used.

Ethnicity

Ethnicity was determined by biological parents' place of birth. This information was checked in the Civil Registration System. If both parents were born in Greenland, the child was defined as Greenlander. If both were born outside Greenland, the child was defined as Caucasian (Danish or other) and with parents of mixed place of birth as of mixed ethnicity.

Birth variables

Gestational age, weight and length at birth were recorded from the *Birth register* for Greenland. Mother's age at the child's birth was calculated from her date of birth as checked in the Civil Registration System.

Socio-economic and parental factors

Socio-economic and parental factors included family type, (biological) parents' previous history of OM, ear discharge (ever/never and episodes more than 14 days), parents school and vocational education, parents' employment status, and income and social class of household. All social factors regarding parents were defined as for social parents, i.e. parents living in the household of the child, whether biological or step-/adoptive. *Family type* was divided into nuclear families (families with a mother and a father), single-parent families (only one parent and one or more children) and extended families (families with three generations or two adult relatives living together) [31]. *Parents vocational education* was divided into not having any education at all, having finished short courses of a total duration of less than one year (e.g. truck drivers) *or* having dropped out of education prematurely, having a short or medium long practical education of one to four years' duration with a substantial practical element (e.g. skilled workers or assistant nurses), having a medium-long theoretical education (e.g. nurses or school teachers) or having a long theoretical education (academic). *Employment status* was defined as being employed, unemployed or studying. If the parent was on maternity leave or other kind of leave from regular work, the parent was defined as employed. For those employed, information on type of job was obtained. If the parent was independent, the number of subordinates was obtained. If the parent was unemployed, information on cause of unemployment was obtained. According to the Danish Social Classification System those employed were divided into employees, independent, skilled and unskilled workers [32]. As this system does not include the category hunter/fisher, which is a common employment in Greenland, these persons were classified as unskilled workers, if they did not have any education, and as skilled, if they had a short or medium-long practical education. On the basis of vocational training and employment status, parents were classified into *social classes* according to the Danish Social Classification system [32]. This system operates with five groups: 1) persons with academic education or top executives, 2) persons with a longer, but not academic, education or independent with 6-20 subordinates, 3) other employees or independent with 0-5 subordinates, 4)

skilled workers and 5) unskilled workers. *Social class of the family* was defined as the social class of the parent of the highest social class [32]. As it is not clear to what extent the Danish social classification applies to the Greenlandic society [33, 34, 34] and in particular to different types of families, it was decided only to analyse the effect of social class in families with both a father and a mother.

Housing

Housing variables included mainly type and size of house and total number of rooms. *Type of house* included traditional Greenlandic single or double family house, terrace houses or blocks of apartments. *Total number of rooms* excluded kitchen, toilet, etc.

Crowding

For each person in the household age, gender and relation to index child was registered. Age was controlled in the Civil Registration System. A person was defined as living in the household if stated so by the parents. As measures of *overall crowding* we used the *total number of persons* living in the household, number of *children aged 0-5 years*, number of *children aged 5-15 years* and the *number of adults* (older than 15 years) living in the household. As measures of night-time crowding we used the number of children aged 0-5 years, number of children aged 5-15 years and the number of adults *sleeping in the same room as the child* and the corresponding figures for persons of the same age groups *sleeping in the same bed as the child*.

Smoking

For each person living in the household it was noted *whether he or she smoked* and if so, the *total average number of cigarettes smoked per day*.

Childcare

Childcare was divided into being in *homecare* (being looked after at home), attending *daycare ('dagpleje')* or *childcare centres ('institution')*. *Daycare* was defined as being looked after outside the home on a daily basis, but not in a childcare centre, whether for instance with grandparents or in a public daycare with other children. In Sisimiut daycare exists both as private and public daycare. In average four children attend the same place of daycare. In Sisimiut six public childcare centres for children 0-3 years of age exist, one of them built in the monitoring period. One is a nursery for children below three years of age only, while the others are combined nurseries and kindergartens. Nursery children are, however, always taken care of in separate rooms. On average, 10-15 nursery children are being looked after in each room. Information on childcare was collected at enrolment, updated monthly during the monitoring period and again at the final

interview. At the end of the study period, all information regarding childcare was furthermore checked with the files at Sisimiut Community. Thus, the exact time of start for each place of childcare for each child was registered.

Breastfeeding status

Breastfeeding and the use of other milk products, supplementary and adult food were registered. In Sisimiut, formula, dry milk as well as whole milk in the form of long time durable milk ('UHT') is available all year round. At enrolment the mother was asked whether the child had ever been breastfed and if so, if it was still breastfed (exclusively or partly). If the child had stopped completely, the age in months of which was noted. During the monitoring period the mother was asked monthly about the child's breastfeeding (exclusively, partly or none), and use of other milk products (formula, dry or fresh milk), supplementary and adult food. A child was considered *exclusively* breastfed if reported so by the mother without supplementation of any other kinds of food or milk products, *partly* if breastfeeding was reported along with the use of other milk or food products and *weaned* if complete termination of breastfeeding was reported.

The *date of change of breastfeeding status*, i.e. the date at which the child shifted from for instance being exclusively to partly breastfed, was defined as the *day of the visit at which the new status was first reported*. *Age at weaning* was defined as the age at termination of breastfeeding as defined above at which no subsequent use of breastfeeding was reported. For those weaned prior to the monitoring period the age at weaning was defined as the age reported by the mother, while for those weaned in the monitoring period the day of the visit at which termination was first reported defined the age.

Mannose binding lectin insufficiency

Mannose binding lectin (MBL) is a protein involved in the innate immunity. A variety of mutations in the gene coding for the protein have been described, some of which may lead to an insufficient serum level of MBL. [35-37]. Among children of this cohort aged 0-2 years at any point of time during the observational period we have previously shown that MBL-insufficient children are at greater risk of acute respiratory tract infections, especially in the vulnerable window of infancy from 6-17 months of age, when the children are maximally susceptible to infections [25]. For this study the same children, which constitute a part of the total cohort (n=252), had the association between MBL insufficiency and CSOM analysed. MBL genotypes were determined from stored blood samples at the Department of Clinical Immunology at Rigshospitalet. A detailed definition of MBL sufficiency and insufficiency and description of methods are given in [25].

Upper and lower respiratory tract infections (URI and LRI)

Information of respiratory symptoms for each day of observation was obtained at the weekly/monthly visits. The symptoms nasal discharge, cough and/or hoarseness without symptoms of LRI defined a day with URI. Likewise the symptoms fast or difficult breathing and/or chest indrawing with or without symptoms of URI defined a day of LRI. Historic prevalence of URI and LRI, respectively, was used as measure of disease burden. For each child number of past days with symptoms of URI and LRI, respectively, served as nominators and total number of past days with information of symptoms as denominator.

Statistical analyses

The cumulative risk of CSOM since birth and length of episodes of CSOM were estimated by one minus Kaplan-Meier curves.

Effects of risk factors on the age-specific hazard rate were evaluated by rate ratios/relative risk (RR) in a Cox regression. All analyses were carried out in SAS for UNIX v. 8.2.

Three steps were carried out:

First, the risk factors were analysed one at a time adjusted for the basic variables: sex, and season (December-February, March-May, June-August, and September-November).

Second, we performed a multivariate analysis in which all risk factors from the previous analyses with p-values less than 10% except for URI and LRI were included and adjusted for the basic variables. To obtain a final model, we successively removed variables with the highest p-values until all p-values were below 5%. Effects of significant factors were further evaluated by their population-attributable risks (PARs), i.e. the drop in incidence due to elimination of the factor

$$PAR=(RR-1)*F/((RR-1)*F+1)$$

where F denotes the frequency of exposed children. To test the role of respiratory symptoms we subsequently performed the same stepwise analysis with URI and LRI included in the starting model.

Third, we investigated the effect of breastfeeding on the risk of CSOM. The cumulative risk when being breastfed and the cumulative risk when not being breastfed was compared non-parametrically by a simulation based supremum test [38].

Each risk factor item group was described by a number of different risk factors which obviously correlated largely. For most risk factors information was available for all children. However, for some risk factors, which demanded a larger degree of data cleaning, information was only readily available for a subset of children, namely the 294 children in the cohort who had at any time during the study period been younger than 2 years of age and who have been described previously [23-25]. In order not to do unnecessary data cleaning it was decided to explore all risk factors individually in the univariate model (step 1) and only keep the risk factors based on a subset of the individuals in the final analyses if they contributed with any particular and additional information not covered by the remaining risk factors in that item group.

Burden of disease

Besides population-attributable risk associated with significant risk factors for CSOM in this cohort as a measure of burden of disease, the total burden of disease associated with CSOM in Greenland was sought estimated by counting the number of operations for CSOM made locally at different district hospitals in Greenland (made regularly by specialised surgical teams of ENT specialists since 2006), at Dronning Ingrids Hospital in Nuuk, or at Rigshospitalet in Copenhagen, Denmark, to which Greenlandic citizens for years have been referred. However, as explained under 'Results' this proved not to be possible at all.

Ethical considerations

The study rested on informed consent orally and in writing from the parents or legal caretakers and fulfilled the Helsinki Declaration II and was approved by the Commission for Scientific Research in Greenland (J. No. 505-03) that acts as scientific ethical board for research in Greenland, and by the Data Protection Board in Denmark (J. No. 1996-1200-039).

RESULTS

In total 465 children (228 boys) participated with a median time of follow up of 2 years 7 months. The participation rate was 86%; 51 children (9%) or parents of whom did not agree in participation, and 26 children (5%) could not be located prior to the end of study.

The children included 358 Inuit children (77%, both parents born in Greenland), 14 Danish (3%, both parents born in Denmark), 37 mixed (8%), and 56 (12%) of unknown descent (only birthplace of one parent known).

During the study period 55 children developed CSOM with a median age of debut of 336 days (range 1 day – 3 years and 4 months). Thirty children (55%) developed unilateral and 25 children (45%) developed bilateral CSOM. The total risk of developing CSOM before 4 years of age was 14% (**Figure 8**). The hazard rate was highest from birth to seven months of age (**Figure 9**).

As each child could have more than one episode of CSOM the length of the longest episode was estimated. The median length was 199 days (25% - 75% quartiles 56 – 483 days). Episodes for 30% of children were censored.

Tables 2-4 show the results of the univariate risk factor analyses for unilateral and bilateral CSOM. Greenlandic children had a significantly higher risk of CSOM compared with children of Danish/mixed descent (Danish and mixed children combined because of few Danish children). Children with high prevalence of URI had a significantly higher risk of CSOM than children with low prevalence, while LRI did not increase the risk. Having a mother with a long school education was protective against CSOM (no effect for father's school education). There was no effect of parents' formal education (data not shown) or social class. There was a significantly higher relative risk of CSOM for children with siblings compared with those without, although there was no dose response effect by number of siblings. There was no association with other crowding parameters, including night-time crowding (number of persons in same sleeping room as the child, data not shown). There was an increased relative risk of CSOM for children attending childcare as opposed to those who did not, but there was no interaction with age for children younger or older than 1 year. Having smokers in the household did not imply any overall increased relative risk of CSOM, but when stratified on age there was a markedly increased relative risk of CSOM among children aged 0-11 months with smokers in the household, while there was no such increased risk among older children. Finally, mother's reporting of having had ear discharge implied a higher relative risk of CSOM compared with not

reporting having had ear discharge, while other markers of ear pathology among parents or siblings (ear discharge, having a diagnosis of OM, or impaired hearing) were not associated with CSOM (data not shown).

The common multivariate model consisted of the following variables: ethnicity, having siblings, childcare, mother's school education and reporting of ear discharge ever, the interaction between smokers in household and age, besides the three basic variables sex, age, and season. The variables were removed stepwise from the model in the following order at the following p-values: smokers in household for children older than 12 months (0.56), having siblings (0.15), and mother's school education (0.13). **Table 5** shows the final multivariate model with population-attributable risk for each level of the variables.

Table 6 shows the final model when URI and LRI was added to the common multivariate model. Only childcare and URI remained significant in the final model.

Similar risk factor analyses for bilateral CSOM alone showed that being of male sex, having smokers in the household (for children 0-11 months of age), having one's mother having had ear discharge herself, and having siblings were significant risk factors (**Table 7**). Only Greenlandic children had bilateral CSOM.

Figure 10 shows the age-dependent risk of CSOM in children breastfed (exclusively or partly) compared with children not breastfed. There was no risk difference of CSOM between the two groups (supremum test p=0.99 among children aged 0-2 years). In contrast there was a clear difference from one year of age among children exclusively breastfed vs. non-exclusively or having stopped breastfeeding, as none of the children exclusively breastfed developed CSOM (**Figure 11**). However, this was based on only 68 children with information of the transition from exclusively to non-exclusively breastfeeding, besides a major risk of confounding, as none of the children exclusively breastfed attended daycare or childcare centres.

As mentioned under 'Material and Methods it was not possible to estimate the total burden of disease associated with CSOM in Greenland. By contact to the Department of Health, the Greenlandic Home Rule, it was informed that these operations (and other similar) are not registered centrally, but only locally under each patient's medical file. Thus, there is no central registration of patients operated locally at the district hospitals, no central registration at the Department of ENT (part of Surgical Department at Dronning Ingrids Hospital in Nuuk), and no central registration in Greenland of patients being referred to the Department of Head and Neck Surgery at Rigshospitalet. Neither do economic analyses help: at Dronning Ingrids Hospital a day of hospitalisation is registered at the same cost irrespectively of treatments carried out (DKr

4,684/day), and DRG (Diagnose Related Group) rates are not used in Greenland Although monthly bills are sent from Rigshospitalet to Greenland for the number of patients treated and operated by department, it is not possible from the bills to differentiate between patients being operated for CSOM and patients being treated for other diseases. As going through individual medical files in Greenland would represent an enormous task this was not possible in connection with this study.

DISCUSSION

Study design – strengths and limitations

This study is, to our knowledge, the first population-based prospective longitudinal cohort study of incidence and risk factors for CSOM in childhood. While risk factor studies for AOM are abundant, only three other studies in widely different settings (Israel, Holland and Nigeria) have addressed risk factors for CSOM in childhood, which may be more relevant to this potentially severe manifestation of OM, and all were case-control studies with information of risk factors collected at the time of disease [39-42].

Power

Although power calculations were not carried out prior to the study, the fact that Sisimiut is the second-biggest town of Greenland, that we achieved a very high participation rate, and that we achieved a statistically significant risk factor pattern indicates that our sample size was not too small.

Bias

We achieved a very high participation rate (86%), which minimizes selection bias. However, there was a tendency that more Danish children than Greenlandic children refused participation. However, this was of minor importance, as the main purpose of the study was to look at CSOM in Greenlandic children and less in pure Danish children who were temporary settlers in Greenland

We followed children from birth and recorded CSOM using objective measures, which minimizes recall bias as opposed to studies which rely on parental reports of CSOM which invariably leads to recall bias. In most cases the exact time of CSOM development was determined based on own observations made at visits with short intervals, but as some children were not followed from birth (and all children only from their 6^{th} week of living) some children might have developed CSOM before start of the observation period and the exact time of CSOM might have to be based on parental reports according to definition. This leads to recall bias, the existence of which in this material is evident as age of CSOM development for one child was stated to be one day after birth. However, it is not evident whether this recall bias leads to systematically under- or overestimation of the exact time of debut. Most likely the median age at debut may be less precisely determined in contrast to being systematically under- or overestimated.

As not all children were followed from birth, and as some were not followed for different intervals e.g. in case of travel, episodes of CSOM might have eluded notification. Thus, this may lead to slightly more conservative estimates of CSOM incidence. However, a firm diagnosis of CSOM was important while the oppo-

site situation might have resulted in non-differential misclassification leading among others to statistically less secure risk factor estimates.

Confounding

Confounding between the individual risk factors will be discussed below.

Definition of CSOM

In accordance with WHO standards we chose a period of 14 days' purulent ear discharge or perforation to define an episode of CSOM [29]. While others have used periods from 14 days to 3 months [2] we believe that in our study a period of 14 days did not bias registration of CSOM episodes, as the median length of the longest CSOM episode for each child was 119 days (25%-75% percentiles 56-483 days).

Although a dry perforation was included in the definition of CSOM the facts that ear discharge was observed in or reported by 95% of the children with CSOM and that none of the children reported noise trauma or grommet insertion, which are other causes of dry tympanic perforations [20], we believe that in this population dry perforations reflect previous cases of CSOM.

Incidence of CSOM

We found a cumulative risk of CSOM of 14% at age 4 years. Earlier cross-sectional studies from west coast towns in Greenland including Sisimiut found prevalence rates of CSOM (defined as CSOM or sequelae of OM) of 19% (1984) and 20% (1993-94) among children aged 3-8 years [7, 8]. Rates of CSOM in both studies were equal throughout the age interval (3-8 years) indicating that the CSOM had been established by age 3 years. Theoretically our cumulative risk should equal prevalence rate at 4 years of age given that all CSOM cases persisted up to 4 years of age. Although our figure of 14% cumulative risk of CSOM appears lower than earlier prevalence figures, which may most likely be explained by different CSOM definitions and study methods, this figure is still alarmingly high and demonstrates the substantial risk for children in Arctic areas [2].

CSOM appeared very early in these children. The highest hazard rate was observed in the period from birth to 7 months of age. In another high-risk population of Australian Aboriginals 33% of tympanic membrane perforations was established at age 6 months (our figure 22%), 72% at age 1 year (our figure 57%), and 93% at age 18 months [43] (our figure 78%). The period 6-18 months is commonly termed the vulnerable period of infancy, when the child is maximally susceptible to infectious diseases. In this cohort we have previously shown that the incidence of upper (URI) and lower respiratory tract (LRI) infections was highest in children

aged 6-17 months, almost twice as high than in children aged 0-5 months [23]. As AOM is often preceded by URI it is surprising that the risk of CSOM in this population is highest before 7 months of age. This may indicate a particular proneness to OM in Greenlandic children, more than that explained by URI in general, or that anatomical factors such as small size of middle ear spaces are involved.

Risk factor analyses

The risk factor pattern reflected both genetic and environmental factors. The role of genetic factors was suggested by the higher risk of CSOM in children of Greenlandic descent and of mothers who reported having had ear discharge herself, although some degree of recall bias regarding the latter cannot be excluded. Given the well-known high risk of CSOM in Inuit populations it was not surprising that Greenlandic children had higher risk of CSOM than mixed/Danish [7, 8]. Also, Greenlandic and Danish descent not only reflects genetic differences, but also differences in distribution of sociodemographic factors characterising Greenlanders and Danes. Although we included and adjusted for a large number of such risk factors (socioeconomic status, family structure, crowding, etc.) in our analyses, we cannot exclude residual confounding. Studies concerning AOM including studies of twins have shown that heredity is a significant for developing AOM [44-46].

A particular genetic risk factor could be the lack of Mannose Binding Lectin (MBL). In this cohort we have previously shown that lack of MBL is associated with risk of acute respiratory tract infections, in particular in children aged 6-17 months of age [25]. In accordance with other OM studies we found no association between lack of MBL and risk of CSOM [47].

Attending daycare or childcare centres significantly increased the risk of CSOM independently of age. Likewise measures for domestic crowding (number of persons and siblings in household) appeared to increase the risk of CSOM, although insignificant. Similar associations between domestic crowding, childcare attendance and risk of OM have been found previously, both for AOM and for CSOM [16, 39, 48-50].

Short duration of breastfeeding has been shown associated with AOM [48, 51, 52] and CSOM [42], although in two studies the associations disappeared when adjusted for other factors [42, 48]. In Greenland exclusive breastfeeding for more than 4 months was shown associated with AOM [16]. We found that breastfeeding as such did not protect against CSOM, but exclusively breastfeeding did, irrespectively of the length of the period. However, none of the children exclusively breastfed attended childcare centre, so it was not possible to adjust for childcare attendance as a confounder. That breastfeeding as such had no effect indicates a

minor role, if any, of breastfeeding against CSOM in this population. In contrast there was no indication of long breastfeeding having a deleterious effect.

Respiratory tract infections (RTI) have been found associated with an increased risk of CSOM [40, 42], but not consistently [39]. We found that URI, but not LRI, was a risk factor for CSOM, and that the effects of other risk factors observed in Table 5, except for attending childcare centres, disappeared after adjustment for URI. While the biological mechanism behind may be that URI impair ventilation, protection and bacterial clearance of the Eustachian tube [1], the risk factor pattern associated with URI is unclear. Two models, both consistent with our findings, may explain the role of URI: URI may be an independent risk factor for CSOM, but URI may also be an intermediate step between other risk factors (e.g. attending childcare centres, passive smoking) and development of CSOM. This is illustrated in **Figure 7**. Although the exact role of URI cannot be determined the findings indicate that special attention should be given towards children with a high prevalence of URI to reduce the risk of CSOM.

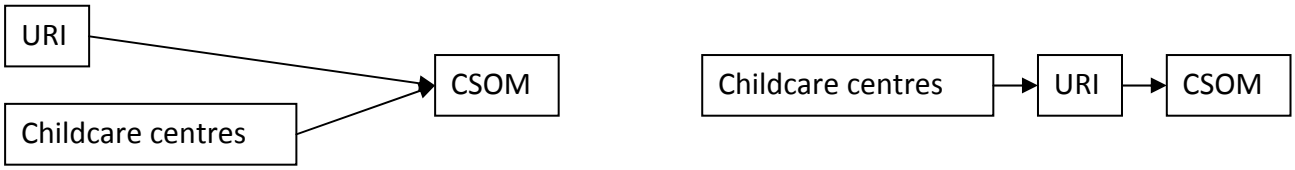


Figure 7. Possible models for the role of URI in the development of CSOM: as an independent risk factor for CSOM in line with others (e.g. childcare centres, left), or as an intermediate factor in he pathogenesis of CSOM (right).

External validity

It may be argued that Sisimiut is not a typical Greenlandic town and that the results cannot be inferred to other parts of Greenland. However, Sisimiut was explicitly chosen for the study to optimize generalisability/external validity of the study. Sisimiut is the second largest town of Greenland and the population comprises approximately 10% of the population of Greenland. Thus, although power calculations were not done beforehand, the size of the town and the significant risk factor pattern obtained indicate the suitability of Sisimiut as study area. Nuuk, the largest town of Greenland, has a large Danish-speaking population and may be less representative of the general ethnic mixture of Greenland. The study was population-based without exclusion criteria. However, generalisability/external validity may still be hampered by a number of factors: first, not all children were included in the study. In particular, less Danish children par-

ticipated than Greenlandic. Second, children were followed for various lengths of time, as some dropped out preliminarily. Third, the population of Sisimiut may not be representative of Greenland as a whole: there is easy access to the outside world both by plane and ship resulting in easy access to imported food items. Also the average income in Sisimiut is slightly higher than in the rest of Greenland and the way of living relatively more western than in some other locations.

It may also be argued that these results may have changed, as data collection took place more than 10 years ago and that the distribution of risk factors may have changed in the meantime. However, while the population-attributable risks associated with the individual risk factors may change given change in the frequency of these factors in the individual population, the individual effect of each risk factor as such is less likely to be dependent upon the actual risk factor frequencies. Furthermore, recent (2009) and unpublished own data from a field study among children in the town of Maniitsoq and Kangaamiut indicate that the frequency of CSOM has only changed little since 1984. As changes in living conditions in these two west Greenlandic towns appear quite parallel to those occurring in Sisimiut (they are now within the same community, the community of Qeqqata), it appears little likely that the frequency of CSOM in Sisimiut should have changed dramatically since 1996-98. Finally, although the incidence of CSOM in children should decrease in the years to come, given the chronic nature of CSOM and sequelae the fraction of persons in Sisimiut/Greenland with CSOM or sequelae will still remain high for many years and thus constitute a public health problem.

Perspectives - implications for prevention and additional research

These results show that interventional measures may be used to reduce the high frequency of CSOM in Greenland. While the risk factor pattern indicates genetic factors to be involved in the development of CSOM in Greenlanders (in spite of possible recall bias and residual confounding) a number of environmental and possibly modifiable risk factors were also identified. During the last century Greenland has rapidly moved towards a western life style. This includes working outside of the home for many parents with a large number of children attending daycare or childcare centres. At the time of this study maternity leave after giving birth was 4 months, after which the child had to be cared for outside of the home. Similarly, in this cohort there were smokers in 80% of the children's homes. Although the prevalence of smoking is decreasing in Greenland in recent years, the decrease is slow compared with other countries. The population-attributable risks associated with attending childcare centres and passive smoking indicate that efforts against these factors may have substantial effects against CSOM. For childcare centres concrete actions could include delay in the age of entering childcare centres (reduction of children in the most susceptible age), having sick children staying at home and having fewer children in each centre/room (reduction in

exposure), and having better hygienic standards and in particular hand hygienic standards (reduction in transmission). Hand washing has been shown to be effective in reduction of transmission of respiratory pathogens, e.g. influenza virus that is transmitted via droplets [53]. For passive smoking a reduction in parental smoking (at least indoor smoking) is crucial. These measures may not only reduce the risk of CSOM but also of other respiratory tract infections that contribute substantially to the total burden of disease in Greenlandic children [23, 24] and may be an intermediate step in the pathogenesis of AOM and CSOM. Finally, reducing the far too high rate of smoking in Greenland may have many positive effects not only to persons being exposed to passive smoking but in particular to the active smokers themselves.

The findings in this and previous studies also suggest that attention from the medical system should be given towards children with AOM, in particular early and/or recurrent AOM, and frequent respiratory tract infections. In a number of countries guidelines for treatment of AOM in children include a period of 'watchful waiting' followed only by antibiotics if the child fails to improve in the next 48-72 hours (e.g. [54]). A recent meta-analysis has shown that antibiotic treatment is associated with a more favourable clinical course in children with AOM, compared both with placebo with 'watchful waiting', although the treatment effect is rather limited. It might therefore be considered to apply a more aggressive antibiotic strategy in case of AOM in Greenland using antibiotics earlier than what is normally recommended in Denmark and similar countries. However, the present study cannot supply data to support this recommendation and more firm knowledge of the effects of antibiotic treatment of AOM in Greenland is warranted.

This study has raised a number of further questions. First, firm figures for the disease burden associated with CSOM in Greenland are warranted, not least for political reasons to support decision making regarding prevention and treatment of this important public health problem. One possibility would be analyses of the Greenlandic Inpatient Register that has existed since 1987 and theoretically contains information of all hospitalisations/operations for CSOM in Greenland since 1987. However, the register has not been used for scientific nor administrative purposes, and analyses await validation of the register, which are currently being undertaken by the Department of Epidemiology Research at Statens Serum Institut. It may also be argued if firm figures have not already been achieved, given the statement by the WHO of the need of urgent attention towards a massive public health problem in countries with a prevalence of >4% of CSOM, a figure met by far in Greenland [22].

Second, there is a need for further studies of risk factors including immunological factors and involved microorganisms. The incidence of invasive pneumococcal disease in Arctic areas is high (REF) and *S. pneumoniae* is on a worldwide scale a major pathogen involved in the pathogenesis of AOM. Introduction of a 7-

valent pneumococcal vaccine in the childhood vaccination programme in Alaska has markedly reduced the incidence of invasive disease related to vaccine-type pneumococci. There are considerations in Greenland to introduce a pneumococcal vaccine into the childhood vaccination programme, and with a possible side effect of this to reduce the incidence of AOM in Greenland, more knowledge about the role of in particular *S. pneumoniae* in the pathogenesis of AOM in Greenlandic children is warranted.

Third, there is a need for knowledge about the association between AOM and development of CSOM in Greenlanders, i.e. the degree and rate at which AOM leads to CSOM, and the effects of antibiotic treatment in order to devise locally optimal treatment of AOM. Unanalysed data collected in this study might partly be able to illuminate these questions. Another possible study would be a controlled study of children with AOM seen at the district hospitals randomised to a 'watchful waiting' group and an intervention group.

Fourth, there is a need to monitor the long-term effects of CSOM in Greenlandic children, in particular regarding impact on hearing and learning abilities. The children have now reached an age at which such follow-up studies are feasible, and these studies are currently ongoing.

Conclusions

We confirmed that chronic suppurative otitis media (CSOM) is highly prevalent in Greenlandic Inuit children (a cumulative incidence of 14% at age 4 years) and appears very early in life, on average before one year of age. The risk factor pattern indicated both genetic and environmental factors to be of importance, as being of Greenlandic descent as opposed to being of Danish or of mixed descent, having a mother with a history of ear discharge, attending childcare centres, and being exposed to passive smoking in the home before the age of 12 months all increased the risk of CSOM. Also boys were significantly more often at risk of bilateral CSOM than girls. Upper respiratory tract infections (URI) strongly increased the risk of CSOM, but whether URI is an independent risk factor or an intermediate step in the pathogenesis of CSOM is unknown. It was not possible to estimate the total burden of disease associated with CSOM in Greenland due to lack of data. The risk factor pattern indicates that public health measures regarding in particular use of childcare centres and passive smoking may be taken with presumed large benefits against this substantial individual and public health problem with hazards of life-long hearing impairment.

REFERENCES

1. Verhoeff M, van d, V, Rovers MM, Sanders EA, Schilder AG. Chronic suppurative otitis media: a review. Int J Pediatr Otorhinolaryngol **2006**; 70:1-12

2. Bluestone CD. Epidemiology and pathogenesis of chronic suppurative otitis media: implications for prevention and treatment. Int J Pediatr Otorhinolaryngol **1998**; 42:207-23

3. Homøe P, Lynnerup N, Skovgaard LT, Rasmussen N. Estimation of otitis media in ancient populations. A study of past and present Greenlandic Inuit. J Laryngol Otol **1996**; 110:1114-9

4. Berthelsen A. Grønlandsk medicinsk statistik og nosografi. Undersøgelser og erfaringer fra 30 aars grønlandsk lægevirksomhed. 117 ed. **1940**; p. 1-234.

5. Hayman CR, Kester FE. Eye, ear, nose and throat infections in natives of Alaska. Northwest Medicine **1957**; 56:423-30

6. Pedersen CB, Zachau-Christiansen B. Chronic otitis media and sequelae in the population of Greenland. Scand J Soc Med **1988**; 16:15-9

7. Pedersen CB, Zachau-Christiansen B. Otitis media in Greenland children: acute, chronic and secretory otitis media in three- to eight-year-olds. J Otolaryngol **1986**; 15:332-5

8. Homøe P, Christensen RB, Bretlau P. Prevalence of otitis media in a survey of 591 unselected Greenlandic children. Int J Pediatr Otorhinolaryngol **1996**; 36:215-30

9. Homøe P, Christensen RB, Bretlau P. Acute otitis media and age at onset among children in Greenland. Acta Otolaryngol **1999**; 119:65-71

10. Homøe P. Otitis media in Greenland. Studies on historical, epidemiological, microbiological, and immunological aspects. Int J Circumpolar Health **2001**; 60 Suppl 2:1-54

11. Schaefer O. Otitis media and bottle-feeding. An epidemiological study of infant feeding habits and incidence of recurrent and chronic middle ear disease in Canadian Eskimos. Can J Public Health **1971**; 62:478-89

12. Timmermans FJ, Gerson S. Chronic granulomatous otitis media in bottle-fed Inuit children. Can Med Assoc J **1980**; 122:545-7

13. Berg O, Adler Nissen J. Housing and sickness in South Greenland: a sociomedical investigation. In: Shephard RJ, Itoh S, eds. Circumpolar Health.Toronto: University of Toronto Press, **1976**. p. 627-35.

14. Reed D, Dunn W. Epidemiologic studies of otitis media among Eskimo children. Public Health Rep **1970**; 85:699-706

15. Bjerregaard P. Housing standards, social group, and respiratory infections in children of Upernavik, Greenland. Scand J Soc Med **1983**; 11:107-11

16. Homøe P, Christensen RB, Bretlau P. Acute otitis media and sociomedical risk factors among unselected children in Greenland. Int J Pediatr Otorhinolaryngol **1999**; 49:37-52

17. Koch A, Sorensen P, Homoe P, et al. Population-based study of acute respiratory infections in children, Greenland. Emerg Infect Dis **2002**; 8:586-93

18. Homøe P, Prag J, Farholt S, et al. 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**; 23:1081-90

19. Ratnesar P. Chronic ear disease along the coasts of Labrador and Northern Newfoundland. J Otolaryngol **1976**; 5:122-30

20. Bluestone CD, Klein JO. Otitis media, atelectasis and eustachian tube dysfunction. In: WB Saunders, ed. Pediatric otolaryngology.Philadelphia: **1996**. p. 388-90.

21. Baxter JD, Stubbing P, Goodbody L, Terraza O. The light at the end of the tunnel associated with the high prevalence of chronic otitis media among Inuit elementary school children in the Eastern Canadian Arctic is now visible. Arctic Med Res **1992**; 51:29-31

22. WHO. Chronic suppurative otitis media. Burden of Illness and Management Options. Geneva: WHO; **2004**.

23. Koch A, Sørensen P, Homøe P, et al. Population-based study of acute respiratory infections in children, Greenland. Emerg Infect Dis **2002**; 8:586-93

24. Koch A, Mølbak K, Homøe P, et al. Risk factors for acute respiratory tract infections in young Greenlandic children. Am J Epidemiol **2003**; 158:374-84

25. Koch A, Melbye M, Sørensen P, et al. Acute respiratory tract infections and mannose-binding lectin insufficiency during early childhood. JAMA **2001**; 285:1316-21

26. Grønlands Statistik. Grønlands Befolkning 1996 (in Danish). 1996:1 ed. Nuuk, Grønland: Grønlands Statistik, **1996**; p. 1-95.

27. Grønlands Statistik. Grønland 1996. Statistisk Årbog [in Danish; Statistical yearbook].Nuuk, Greenland: Grønlands Statistik, Grønlands Hjemmestyre, **1996**; p. 1-618.

28. Bjerregaard P. Metoder i undersøgelser med spørgeskemaer. 1997; Nuuk, Greenland: Nuuk Offset; **1997** p. 249-53.

29. WHO. Report by the Director General. Prevention of Deafness and Hearing Impairment. Geneva; **1986**. Report No.: Document A39/14.

30. Bjerregaard P, Curtis T, Senderovitz F, Christensen U, Pars T. Levevilkår, livsstil og helbred i Grønland [in Danish; Health, life style, and living conditions in Greenland]. Copenhagen: DIKE; **1995**. Report No.: 4.

31. Curtis T, Iburg KM, Bjerregaard P. Familie, børn og sundhed i Grønland [in Danish; Family, children, and health in Greenland]. 9 ed. Copenhagen: DIKE, **1997**; p. 1-63.

32. Enevoldsen B, Michelsen N, Friis-Hasche E, Kamper-Jørgensen F. Sociale klassifikationer. II. Svalastoga's inddeling efter social status, rangorden og Socialforskningsinstituttets socialgruppeinddeling [in Danish; Social classification II. Stalastoga's subdivision according to social status, rank, and the social grouping employed by the Institute for Social Research]. Ugeskr Laeger **1980**; 142:544-50

33. Bjerregaard P, Curtis T. Social and cultural factors as determinants of self-rated health in Greenland. Int J Circumpolar Health **1998**; 57 Suppl 1:622-5

34. Thomsen K, Curtis T, Bjerregaard P. The role of hunting in a socioeconomic classification for Greenland. Int J Circumpolar Health **1998**; 57 Suppl 1:626-9

35. Garred P, Madsen HO, Svejgaard A. Genetics of human mannan-binding protein. In: Ezekowitz RAB, Sastry K, Reid KBM, eds. Collectins and innate immunity.Austin, Texas: R.G. Landes, **1996**. p. 139-64.

36. Madsen HO, Garred P, Thiel S, et al. Interplay between promotor and structural gene variants control basal serum level of mannan-binding protein. J Immunol **1995**; 155:3013-20

37. Madsen HO, Satz ML, Høgh B, Svejgaard A, Garred P. Different molecular events result in low protein levels of mannan- binding lectin in populations from southeast Africa and South America. J Immunol **1998**; 161:3169-75

38. Martinussen T, Scheike TH. Additive hazards model. Dynamic Regression Models for Survival Data. Springer, **2006**. p. 103-65.

39. Fliss DM, Shoham I, Leiberman A, Dagan R. Chronic suppurative otitis media without cholesteatoma in children in southern Israel: incidence and risk factors. Pediatr Infect Dis J **1991**; 10:895-9

40. Lasisi AO, Olaniyan FA, Muibi SA, et al. Clinical and demographic risk factors associated with chronic suppurative otitis media. Int J Pediatr Otorhinolaryngol **2007**; 71:1549-54

41. Lasisi AO, Olayemi O, Irabor AE. Early onset otitis media: risk factors and effects on the outcome of chronic suppurative otitis media. Eur Arch Otorhinolaryngol **2008**; 265:765-8

42. Van der Veen EL, Schilder AG, van HN, Verhoeff M, Zielhuis GA, Rovers MM. Predictors of chronic suppurative otitis media in children. Arch Otolaryngol Head Neck Surg **2006**; 132:1115-8

43. Morris PS, Leach AJ, Silberberg P, et al. Otitis media in young Aboriginal children from remote communities in Northern and Central Australia: a cross-sectional survey. BMC Pediatr **2005**; 5:27

44. Kvaerner KJ, Tambs K, Harris JR, Magnus P. Distribution and heritability of recurrent ear infections. Ann Otol Rhinol Laryngol **1997**; 106:624-32

45. Casselbrant ML, Mandel EM, Fall PA, et al. The heritability of otitis media: a twin and triplet study. JAMA **1999**; 282:2125-30

46. Kvestad E, Kvaerner KJ, Roysamb E, Tambs K, Harris JR, Magnus P. Otitis media: genetic factors and sex differences. Twin Res **2004**; 7:239-44

47. Ruskamp JM, Hoekstra MO, Rovers MM, Schilder AG, Sanders EA. Mannose-binding lectin and upper respiratory tract infections in children and adolescents: a review. Arch Otolaryngol Head Neck Surg **2006**; 132:482-6

48. Daly KA, Brown JE, Lindgren BR, Meland MH, Le CT, Giebink GS. Epidemiology of otitis media onset by six months of age. Pediatrics **1999**; 103:1158-66

49. Kero P, Piekkala P. Factors affecting the occurrence of acute otitis media during the first year of life. Acta Paediatr Scand **1987**; 76:618-23

50. Alho OP, Koivu M, Sorri M, Rantakallio P. Risk factors for recurrent acute otitis media and respiratory infection in infancy. Int J Pediatr Otorhinolaryngol **1990**; 19:151-61

51. Aniansson G, Alm B, Andersson B, et al. A prospective cohort study on breast-feeding and otitis media in Swedish infants. Pediatr Infect Dis J **1994**; 13:183-8

52. Duncan B, Ey J, Holberg CJ, Wright AL, Martinez FD, Taussig LM. Exclusive breast-feeding for at least 4 months protects against otitis media. Pediatrics **1993**; 91:867-72

53. Grayson ML, Melvani S, Druce J, et al. Efficacy of soap and water and alcohol-based hand-rub preparations against live H1N1 influenza virus on the hands of human volunteers. Clin Infect Dis **2009**; 48:285-91

54. American Academy of Pediatrics.Subcommittee on Management of Acute Otitis Media. Diagnosis and management of acute otitis media. Pediatrics **2004**; 113:1451-65

Table 2. Univariate risk factor analyses for chronic suppurative otitis media (CSOM) in 465 children aged 0-4 years in Sisimiut, Greenland, with adjustment for season and sex. Child-related, birth, health, and social factors. All p-values test for homogeneity unless otherwise stated.

Risk factor	N	RR	95% CI	*P*
Seasonality				0.33
December-February	-		1 (ref.)	
March-May	-	0.60	0.27, 1.34	
June-August	-	1.13	0.57, 2.24	
August-November	-	0.73	0.33, 1.59	
Birth variation				0.27
December-February	102		1 (ref.)	
March-May	125	0.71	0.35, 1.43	
June-August	117	0.51	0.24, 1.08	
September-November	121	0.54	0.26, 1.15	
Sex				0.76
Girls	237		1 (ref.)	
Boys	228	1.08	0.64, 1.84	
Ethnicity*				0.03
Greenlandic	358		1 (ref.)	
Other (mixed/Danish)	51	0.28	0.07, 1.15	
Mother's age at child's birth				0.26, 0.45**
15-19	145		1 (ref.)	
20-24	61	1.79	0.73, 4.39	
25-29	119	1.51	0.71, 3.23	
30-34	89	1.76	0.79, 3.92	
35+	40	2.80	1.14, 6.86	
Gestational length				0.22
<37 weeks	11	2.25	0.70, 7.22	
37+ weeks	451		1 (ref.)	
Birth weight				0.93
<2500 g	9	0.79	0.11, 5.77	
2500-2999 g	43	1.14	0.48, 2.69	
3000-3999 g	324		1 (ref.)	
4000+ g	87	0.83	0.40, 1.72	
Upper respiratory tract infections (URI)***				0.004
			1 (ref.)	
(1)		6.31	1.82, 21.91	
Lower respiratory tract infections (LRI)***				0.9
			1 (ref.)	
(1)		0.57	0, 4434	
Mannose-binding lectin (MBL) insufficiency******				0.75
Sufficient	239		1 (ref.)	
Insufficient	13	0.74	0.10, 5.39	

(**Table 2 continued),** Univariate risk factor analyses for chronic suppurative otitis media (CSOM) in 465 children aged 0-4 years in Sisimiut, Greenland, with adjustment for season and sex. Child-related, birth, health, and social factors. All p-values test for homogeneity unless otherwise stated.

Ear discharge ever, biological mother				0.002
No	380		1 (ref.)	
Yes	50	2.96	1.60, 5.47	
Otitis media ever, biological mother				0.10
No	268		1 (ref.)	
Yes	157	1.57	0.92, 2.69	
Impaired hearing, biological mother				0.57
No	384		1 (ref.)	
Yes	55	1.25	0.59, 2.66	
School education, mother				0.02, 0.92**
8^{th} class	36		1 (ref.)	
9^{th} to 10^{th} class	137	0.66	0.23, 1.89	
11^{th} to 12^{th} class	238	1.30	0.51, 3.30	
Baccalaureate	45	0.17	0.02, 1.50	
School education, father				0.82, 0.45**
8^{th} class	81		1 (ref.)	
9^{th} to 10^{th} class	112	0.95	0.46, 1.97	
11^{th} to 12^{th} class	136	0.88	0.43, 1.80	
Baccalaureate	27	0.52	0.12, 2.31	
Social class **§**				0.26
1-2	23		1 (ref.)	
3	50	0.52	0.10, 2.57	
4	88	1.58	0.46, 5.44	
5	80	1.19	0.34, 4.22	

RR = Relative risk, CI = Confidence interval

* Defined as Greenlandic, Danish or mixed according to biological parents' place of birth. Due to the low number of pure Danish children, children of Danish and mixed descent had to be combined

** Test for trend

*** One unit's increase, i.e. RR corresponds to comparison between population with prevalence 0% and prevalence 100%

**** Only validated for a subpopulation of 288 children

§ Classified according to the Danish social classification system [32] on the basis of vocational training and employment status with hunters/fishers classified as unskilled workers. Social class: 1: Persons with academic education or top executives, 2: persons with a longer, but not academic education or independent with 6-20 subordinates, 3: other employees or independent with 0-5 subordinates, 4: skilled workers, 5: unskilled workers or hunters/fishers.
Social class was defined as the highest social class of parents. Estimates were similar if Father's social class was used instead of that of the parents combined.

Table 3. Univariate risk factor analyses for chronic suppurative otitis media (CSOM) in 465 children aged 0-4 years in Sisimiut, Greenland, with adjustment for season and sex. Housing, crowding, sibling, and childcare parameters. All p-values test for homogeneity unless otherwise stated.

Risk factor		N	RR	95% CI	*P*
Type of house *					0.78
Single or double family house		68		1 (ref.)	
Terrace		81	1.32	0.51, 3.37	
Apartment		138	1.34	0.56, 3.17	
No. of rooms in household					0.57
1		15	2.63	0.91, 7.56	
2		76	0.88	0.40, 1.96	
3		215		1 (ref.)	
4		111	1.02	0.52, 2.00	
5+		32	1.22	0.42, 3.50	
Number of persons in household**					0.25
2-3		100		1 (ref.)	
4		138	2.06	0.92, 4.63	
5		120	1.23	0.50, 3.02	
6+		107	1.68	0.70, 4.06	
Number of persons per room					0.64, 0.34***
1		211		1 (ref.)	
2		194	1.20	0.68, 2.14	
3+		44	1.47	0.63, 3.43	
Siblings in household					0.03
No		125		1 (ref.)	
Yes		340	2.12	1.00, 4.49	
Number of siblings in household					0.18
0		125		1 (ref.)	
1		165	2.30	1.04, 5.10	
2		105	2.02	0.84, 4.82	
3+		70	1.83	0.69, 4.88	
Childcare					0.01
Home		§		1 (ref.)	
Daycare		§	1.96	0.79, 4.87	
Childcare centre		§	2.88	1.46, 5.70	
Childcare by age					0.04, 0.90#
0-11 months	Home	§		1 (ref.)	
	Daycare	§	2.14	0.74, 6.14	
	Childcare centre	§	2.70	1.18, 6.18	
+12 months	Home	§		1 (ref.)	
	Daycare	§	1.66	0.28, 9.92	
	Childcare centre	§	3.16	0.90, 11.09	

RR = Relative risk, CI = Confidence interval

* Only validated for a subpopulation of 288 children

** If dichotomised in number of persons 2-3 and 3+ in household RR for 3+ 1.67, p-value 0.16

*** Test for trend

§ Time dependent variable, number irrelevant

Test for interaction

Table 4. Univariate risk factor analyses for chronic suppurative otitis media (CSOM) in 465 children aged 0-4 years in Sisimiut, Greenland, with adjustment for season and sex. Smoking parameters. All p-values test for homogeneity unless otherwise stated.

Risk factor		N	RR	95% CI	*P*
Smokers in household					0.46
No		93		1 (ref.)	
Yes		372	1.30	0.64, 2.66	
Smokers in household by age					0.09, 0.04*
0-11 months	No			1 (ref.)	
	Yes		2.75	0.84, 8.97	
+12 months	No			1 (ref.)	
	Yes		0.58	0.22, 1.5	
Number of smokers in household by age					0.16
0-11 months	0	93		1 (ref.)	
	1	110	2.03	0.52, 7.86	
	2	212	3.43	1.03, 11.44	
	3+	50	1.32	0.22, 7.89	
+12 months	0	93		1 (ref.)	
	1	110	0.42	0.10, 1.68	
	2	212	0.72	0.26, 1.99	
	3+	50	0.33	0.04, 2.76	
Mother smoking **					0.22
No		98		1 (ref.)	
Yes		186	1.54	0.75, 3.16	
No. of cigarettes mother **					0.25
0		98		1 (ref.)	
1-4		48	1.87	0.76, 4.62	
5-9		69	1.94	0.85, 4.42	
10+		67	0.98	0.37, 2.59	
Father smoking **					0.03
No		82		1 (ref.)	
Yes		175	2.41	1.00, 5.77	
No. of cigarettes father **					0.09
0		82		1 (ref.)	
1-4		21	3.76	1.21, 11.7	
5-9		30	2.90	0.97, 8.66	
10+		87	2.14	0.83, 5.52	
Total no. of cigarettes smoked in household **					0.01
0		54		1 (ref.)	
1-9		72	4.84	1.07, 21.87	
10-19		67	6.85	1.57, 29.84	
20+		78	3.27	0.72, 4.94	

RR = Relative risk, CI = Confidence interval

* Test for interaction

** Only validated for a subpopulation of 288 children

Table 5. Final multivariate model for chronic suppurative otitis media (CSOM) in children aged 0-4 years in Sisimiut, Greenland, with adjustment for basic variables (sex and seasonality). In total 384 children with full records of the variables included in the analysis.

Risk factor		RR	95% CI	*P*	Population-attributable risk	95% CI
Seasonality				0.52		
December-February		1 (ref.)				
March-May		0.60	0.26, 1.40			
June-August		1.00	0.49, 2.06			
September-November		0.71	0.31, 1.60			
Sex				0.79		
Girls		1 (ref.)				
Boys		1.08	0.61, 1.89			
Ethnicity				0.02		
Greenlandic		1 (ref.)				
Other (Danish/Mixed)		0.18	0.02, 1.3		0.80	-0.25, 0.97
Childcare*				<0.01		
Home		1 (ref.)				
Daycare		2.50	0.97, 6.43		0.06	-0.02, 0.14
Childcare centre		3.18	1.53, 6.61		0.51	0.26, 0.76
Smokers in household				0.01		
0-11 months	No	1 (ref.)				
	Yes	4.56	1.07, 19.4		0.74	0.05, 0.94
Ear discharge, biological mother				<0.01		
No		1 (ref.)				
Yes		3.27	1.74, 6.13		0.21	0.08, 0.37

RR = Relative risk, CI = Confidence interval

* The frequencies of children in daycare and childcare centres were computed as the average of age-specific frequencies.

Table 6. Final multivariate model for chronic suppurative otitis media (CSOM) in children aged 0-4 years in Sisimiut, Greenland, with upper respiratory tract infections included in the starting model with adjustment for basic variables (sex and seasonality). In total 370 children with full records of the variables included in the analysis.

Risk factor	RR	95% CI	*P*	Population-attributable risk	95% CI
Seasonality			0.13		
December-February	1 (ref.)				
March-May	1,34	0.5, 3.6			
June-August	0.57	0.17, 1.97			
September-November	1.97	0.8, 4.9			
Sex			0.40		
Girls	1 (ref.)				
Boys	1.34	0.68, 2.63			
Childcare*			<0.01		
Home	1 (ref.)				
Daycare	5.4	1.45, 20.3		8%	1%, 15%
Childcare centre	7.7	2.61, 23.0		72%	47%, 98%
Upper respiratory tract infections**			0.02		
No	1 (ref.)				
Yes	5.7	1.38, 23.5		46%	6%, 80%

RR = Relative risk, CI = Confidence interval

* The frequencies of children in daycare,and childcare centres were computed as the average of age-specific frequencies

** The frequency of upper respiratory tract infections was computed as the overall prevalence of upper respiratory tract infections in the population

Table 7. Final multivariate model for bilateral chronic suppurative otitis media (CSOM) in children aged 0-4 years in Sisimiut, Greenland, with adjustment for basic variables (sex, age, and seasonality). Only children of Greenlandic descent (children with two parents born in Greenland) developed bilateral CSOM. In total 418 children with full records of the variables included in the analysis.

Risk factor		RR	95% CI	*P*
Seasonality				0.76
December-February		1 (ref.)		
March-May		1.42	0.4, 5.05	
June-August		1.91	0.57, 6.36	
September-November		1.48	0.41, 5.27	
Sex				0.03
Girls		1 (ref.)		
Boys		2.54	1.05, 6.15	
Smokers in household				0.047
0-11 months	No	1 (ref.)		
	Yes	5.07	0.67, 38.5	
Ear discharge, biological mother				0.01
No		1 (ref.)		
Yes		3.81	1.57, 9.22	
Siblings in household				0.01
No		1 (ref.)		
Yes		4.45	1.05, 18.9	

Figure 8. Cumulative risk of developing chronic suppurative otitis media (unilateral and bilateral) in 465 children aged 0-4 years in Sisimiut, Greenland (dotted lines 95% confidence interval).

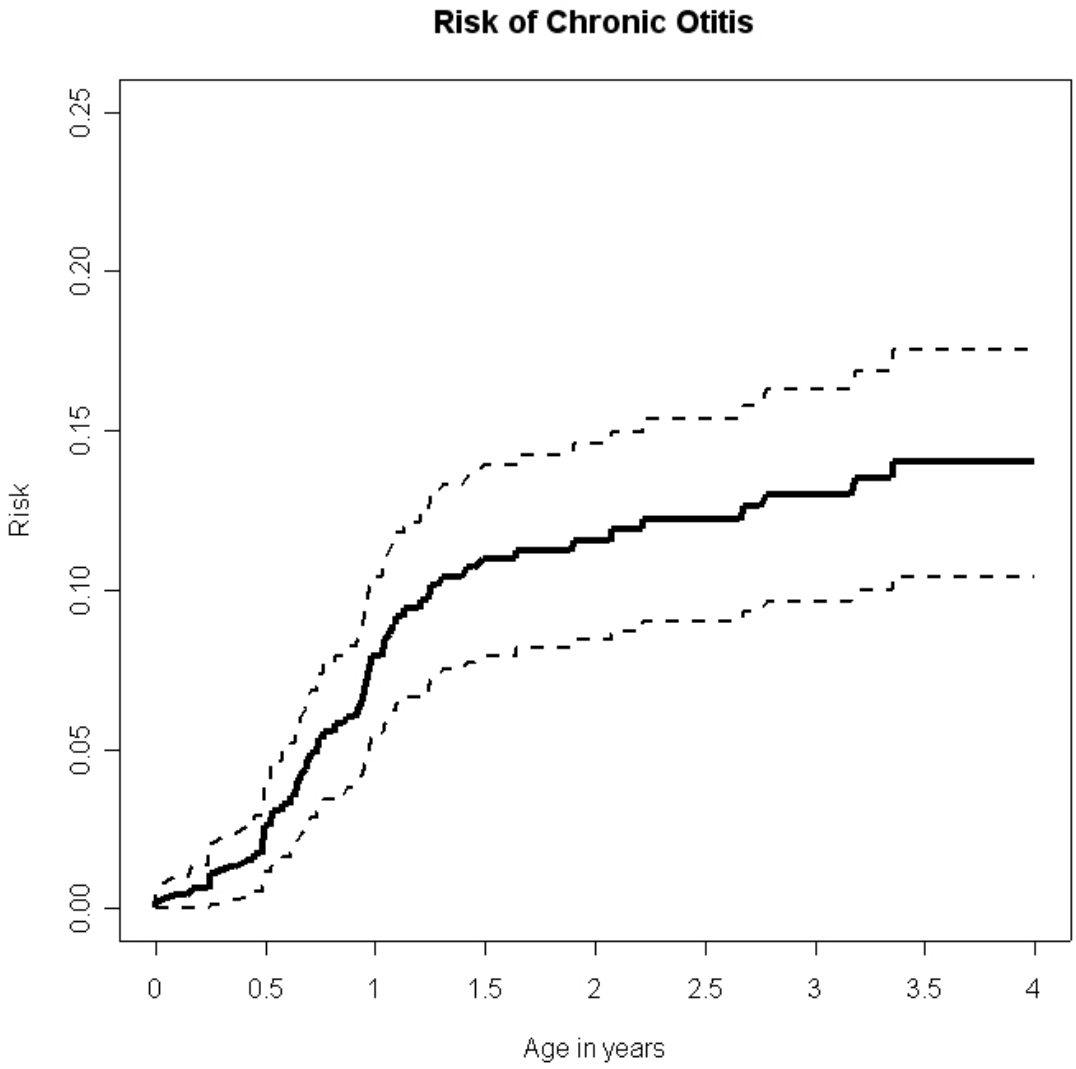


Figure 9. Age dependent hazard rate of developing chronic otitis media (unilateral and bilateral) in 465 children aged 0-4 years in Sisimiut, Greenland.

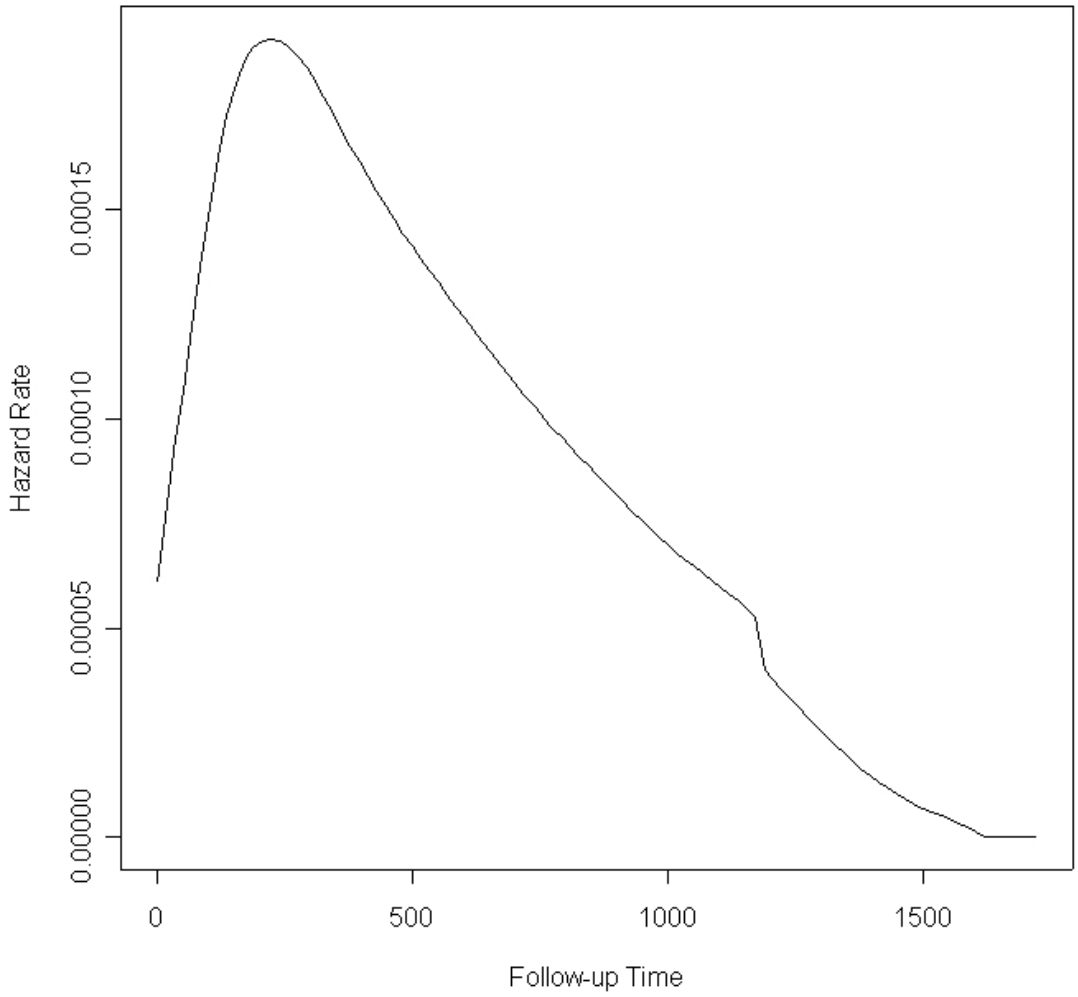


Figure 10. Cumulative risk of remaining free of chronic suppurative otitis media (unilateral and bilateral) for children breastfed (entirely or non-entirely) compared with children having stopped breastfeeding in 465 children aged 0-4 years in Sisimiut, Greenland (dotted lines 95% confidence intervals).

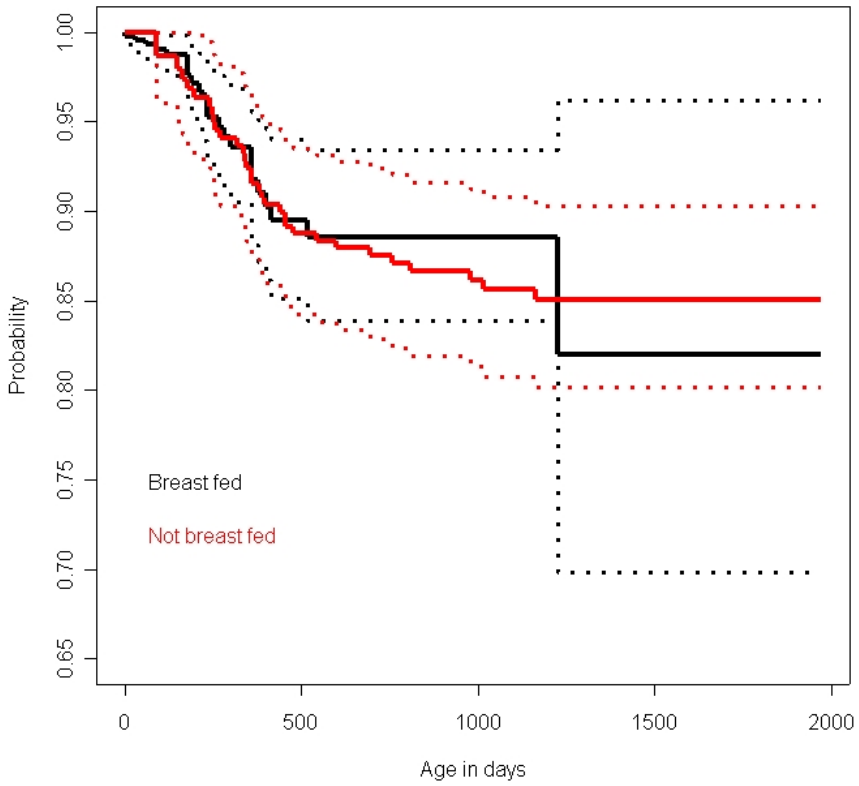


Figure 11. Cumulative risk of remaining free of chronic suppurative otitis media (CSOM, unilateral and bi-lateral) for children entirely breastfed compared with children not entirely breastfed/having stopped breastfeeding in 68 children aged 0-4 years in Sisimiut, Greenland.