Risk factors for *Mycobacterium tuberculosis* infection among children in Greenland

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Objective To examine the risk factors for *Mycobacterium tuberculosis* infection (MTI) among Greenlandic children for the purpose of identifying those at highest risk of infection.

Methods Between 2005 and 2007, 1797 Greenlandic schoolchildren in five different areas were tested for MTI with an interferon gamma release assay (IGRA) and a tuberculin skin test (TST). Parents or guardians were surveyed using a standardized self-administered questionnaire to obtain data on crowding in the household, parents' educational level and the child's health status. Demographic data for each child – i.e. parents' place of birth, number of siblings, distance between siblings (next younger and next older), birth order and mother's age when the child was born – were also extracted from a public registry. Logistic regression was used to check for associations between these variables and MTI, and all results were expressed as odds ratios (ORs) and 95% confidence intervals (CIs). Children were considered to have MTI if they tested positive on both the IGRA assay and the TST.

Findings The overall prevalence of MTI was 8.5% (152/1797). MTI was diagnosed in 26.7% of the children with a known TB contact, as opposed to 6.4% of the children without such contact. Overall, the MTI rate was higher among Inuit children (OR: 4.22; 95% CI: 1.55–11.5) and among children born less than one year after the birth of the next older sibling (OR: 2.48; 95% CI: 1.33–4.63). Self-reported TB contact modified the profile to include household crowding and low mother's education. Children who had an older MTI-positive sibling were much more likely to test positive for MTI themselves (OR: 14.2; 95% CI: 5.75–35.0) than children without an infected older sibling.

Conclusion Ethnicity, sibling relations, number of household residents and maternal level of education are factors associated with the risk of TB infection among children in Greenland. The strong household clustering of MTI suggests that family sources of exposure are important.

Abstracts in عربي, 中文, Français, Русский and Español at the end of each article.

Introduction

Although Greenland has experienced steady improvement in general living standards since World War II, tuberculosis (TB) remains a major health problem throughout the country.[1,2] Overall TB incidence in Greenland doubled in the 1990s[3] and still remained at 130 cases per 100 000 in 2010.[1] The proportion of TB cases comprised of children under the age of 15 years rose from 8% in 1990 to 25% in 1997.[3] Because of this resurgence of TB, in 1999 national health authorities launched a TB control programme consisting of the vaccination of all neonates with bacille Calmette–Guérin (BCG), early case detection and the monitoring of treatment outcomes.[4] In 2007 the programme was revised to include routine screening of children for *Mycobacterium tuberculosis* infection (MTI) at the ages of 6 and 16 years. Despite this effort, TB incidence and the risk of MTI among children remain high.[4,5] Surprisingly, the resurgence of TB in Greenland is not linked to human immunodeficiency virus (HIV) infection or to multidrug resistant TB, both of which are still very uncommon in the country. As of 2010, only 157 HIV-positive cases had been registered despite free HIV testing and only one case of multidrug resistant TB had been documented.[1,6] Instead, it appears to result from microepidemic outbreaks in small towns and remote settlements. TB is 20 times more common among the Inuits of Arctic Canada and Alaska than among non-native white populations.[7–11] This elevated risk suggests that even in resource–rich countries, TB control is difficult in small, hard-to-reach communities with limited health resources.

In 2009, a World Health Organization group proposed a revision of current TB control, targeting strategies to minimize exposure to TB as measured by the presence of MTI.[12] The revision raises the need to better understand the risk factors associated with MTI, especially at the local and regional level, since risk factor profiles vary from place to place and one programme will not necessarily be effective everywhere. The objective of this study was to explore the risk factors for MTI among Greenlandic children to help identify the children at highest risk of infection.

Methods

Study sites and population

An ice cap covers 82% of Greenland's territory, permitting settlements only in coastal areas. The population, which numbers 57 000, is 90% Inuit. Greenland is an integral part

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of the Kingdom of Denmark but is self-governing. Although its population is less affluent than that of Denmark, it is nonetheless wealthy by developing country standards, with a gross national product per capita of 20 000 United States dollars. Health care is provided by the government at Danish standards.[13] The capital, Nuuk, has one national hospital; a local hospital exists in each of the country's five administrative districts, along with additional health centres and nursing stations or clinics. Care is free of charge. However, inequities have not been fully eradicated mainly because small and isolated communities have limited health-care resources and the least experienced health-care workers.[14] Physicians, typically from Denmark, have difficulty communicating with the Inuit population and are usually on short-term assignments, so that gaps between postings sometimes occur. Living in a small community is an independent risk factor for TB disease.[15]

The current study, cross-sectional in design, included all schoolchildren in five different towns and nearby settlements across Greenland: Tasiilaq (November, 2005) in eastern Greenland; Narsaq (May, 2006), Qaqortoq (August, 2006) and Nanortalik (September 2006) in southern Greenland; and Sisimiut (May, 2007), in western Greenland. School attendance is mandatory everywhere in the country for children aged from 6 to 16 years. On 31 December 2006, the study area had 2880 eligible children in that age group (i.e., 25% of the entire Greenlandic population of children 6 to 16 years old), all of whom were invited to participate in the study. We included all schools and identified the children through school protocols.

The surveys were conducted through all local schools in the designated survey areas. Prior to the surveys, the school sent every student home with information about the study and a questionnaire in both Danish and Greenlandic. Enrolment required informed consent signed by a parent or guardian. During the survey a nurse or doctor measured every child's height and weight using a scale and a measuring tape. These measures were used to derive a body mass index (BMI) with a BMI percentile calculator specific for children. The calculation used the basic BMI formula: body weight in kilograms divided by the square of the height in metres. Results compare BMI-for-age percentiles with BMI-for-age growth charts.[16] In Greenland, neonates have been vaccinated with BCG since 1949 except during the period from 1991 to 1996. We ascertained the BCG status of participating children retrospectively by inspecting detailed vaccination records maintained by community nurses at local health-care facilities. We drew a venous blood sample from each child and administered a tuberculin skin test (TST) to each of them.

Risk factors

We extracted demographic information on each child from the civil registration system (CRS), which contains information on all Greenlanders.[17] This included parents' place of birth, number of siblings, distance between siblings (next younger and next older), birth order and mother's age when the child was born. Children whose parents were both born in Greenland were considered Inuit, as this method has been shown to accurately identify children of Inuit heritage.[18] By having parents or caretakers complete a standardized self-administered questionnaire, we also obtained information on crowding in the household (total number of dwellers, number of adults and number of children), parents' educational level, health status of the study child and type of heating in the household.

Mycobacterium tuberculosis infection

The venous blood sample was used to test for MTI using the Quantiferon TB-Gold In-Tube (QFN) (Cellestis, Carnegie, Australia) interferon gamma release assay. The QFN was performed according to the manufacturer's instructions. All tests were corrected for background reactivity. Interferon-γ (IFN-γ) results from white blood cell stimulation by the TB antigens were provided by the kit manufacturer (ESAT6, CFP-10 and TB 7.7). A test was considered positive and indicative of MTI if IFN-γ production was ≥ 0.35 international units per millilitre (IU/ml).

The TST was applied to the dorsal aspect of the forearm by the intradermal Mantoux method using 2 tuberculin units (0.1 ml) of RT-23 purified protein derivative (PPD) (Statens Serum Institut, Copenhagen, Denmark), and the result was read 72 hours later by an experienced examiner. According to current Greenlandic TB guidelines, an induration ≥ 12 mm in diameter at the injection site indicates a positive response. Some TST results were missing because testing was refused or the child was lost to follow-up before the reading of the TST.

A child was considered to have MTI only if he/she tested positive both on the QFN and on the TST, regardless of clinical status. Children with negative results on both tests were classified as uninfected.

We treated all children with discordant test results as in need of evaluation for MTI and referred them for the same clinical evaluation and possible TB prophylaxis as children who were dually positive.

Ethical considerations

The study was approved by the Commission for Scientific Research in Greenland (approval No. 505–105). All participants with positive results on either the QFN or the TST were referred to the local medical centre for further evaluation, including a chest X-ray and clinical examination. Children diagnosed with clinically active TB were offered standard TB treatment; those with MTI were treated prophylactically with isoniazid.

Statistical analysis

We used logistic regression with the Proc Genmod procedure (SAS, Cary, USA) to calculate odds ratios (ORs) for the association between MTI and potential risk factors. We accounted for clustering of MTI within families by using generalized estimation equations. Initially, ORs were adjusted for age and sex only. Variables found to be statistically significant were then entered into fully-adjusted models, which included ethnicity, maternal age, age gap between child and next older sibling, and region of residence. All adjustment variables are presented in the tables.

Since contact with a known TB case has been reported to be a main predictor for MTI,[19] we further explored whether such contact modified the risk factor pattern. We determined whether a risk factor was modified by contact with a

Table 1. **Comparison of demographic characteristics of schoolchildren in study population (n=1797) and Greenlandic schoolchildren in general**

Characteristic	Study population[a]	Greenlandic schoolchildren[b]
Total (No.)	1797	10 593
Gender, No. (%)		
Male	892 (49.6)	5382 (50.8)
Female	905 (50.4)	5211 (49.2)
Age (years)		
Mean	11.0	11.2
SD	3.0	3.1
Median	11	12
Range	5–19	6–16
Ethnicity, No. (%)[c]		
Inuit	1734 (96.5)	10 126 (95.6)
Non-Inuit	63 (3.5)	467 (4.4)
Danish	53 (3.0)	417 (3.9)
Other	10 (0.5)	50 (0.5)
Mother's age (years) at child's birth		
Mean	26.7	26.4
SD	5.9	5.9
Median	27	26
Range	15–46	14–52
Mother's total no. of liveborns (including study child)		
Mean	3.1	3.0
SD	1.6	1.5
Median	3	3
Range	1–11	1–11

SD, standard deviation.

[a] Includes participating schoolchildren recruited from five survey districts across Greenland.

[b] Includes all schoolchildren 6–16 years of age living in Greenland as of 31 December 2006 (data from the Danish Civil Registration System [CRS]).

[c] Unlike the rest of the paper, this table presents ethnicity among the study population based on a child's birthplace to facilitate the comparison with the total population of Greenland (data from the CRS).

TB case by assessing for interactions between the risk factor and TB contact after adjustment for each adjustment variable. We estimated age trends using the median age within each age group as a continuous variable. We examined the association between MTI and having an older sibling found to be infected during the survey for all children who had at least one older sibling in the study.

Results

The census recorded 2880 children of eligible age as residents of the study areas. However, migration of households is common in Greenland and the exact number in residence is uncertain. Initially 2218 children (77% of the estimated 2880 children) returned signed consent forms. Of these children, 1886 (85%) were successfully tested with both the QFN and TST. Eighty nine subjects had discordant QFN and TST results: 46 had a positive TST and a negative QFN; 25 had a positive QFN and a negative TST, and 18 had an inconclusive QFN and a negative TST. These subjects were not included in the main analyses. Thus, 1797 (81% of 2880 estimated children) had a definitive MTI assessment. The demographic characteristics of participating children and of children across Greenland in the same age groups are shown in Table 1. Age, gender, mother's age when she gave birth to the child, mother's total number of children and ethnicity were similar in the study population as in the total population of children in Greenland.

In total, 152 (8.5%) of the 1797 children included in the analysis were positive for MTI. This included 48 (26.7%) of the 180 children with a known TB contact (10% of the whole) and 104 (6.4%) of the 1617 children without a known TB contact. Of the 180 children with a reported TB contact, 31% reported a household contact, 22% reported a school contact and 47% did not specify the type of contact. Of 180 children with TB contacts, 122 (68%) reported the time elapsed since the contact. In 52 such cases the contact was reported as having occurred within the past year. Positivity on both tests did not correlate with the time elapsed since the first known TB contact. Of the children who had a known TB contact but whose older siblings were uninfected, 13.9% were MTI positive, as opposed to 35.7% of the children who had at least one infected older sibling (sex- and age-adjusted OR:3.48; 95% CI: 0.80–15.1). An age gap of less than one year between the child and the closest older sibling was a risk factor (OR: 2.48; 95% CI: 1.33–4.63). Among children without a known TB contact, 2.9% were positive for MTI when no older sibling was infected, whereas 27.3% were positive when at least one older sibling was infected (sex- and age-adjusted OR: 14.2; 95% CI: 5.75–35.0). During clinical follow-up of children dually positive, four were diagnosed as having clinically active TB as defined by positive X-ray findings or microbiological evidence of MTI.

Table 2 (available at: http://www.who.int/bulletin/volumes/89/10/10-084152) presents age- and sex-adjusted and fully adjusted OR with 95% CIs. After adjustments for age and sex only, the following variables were significant risk factors: increasing age, Inuit ethnicity, young maternal age, narrow age gap (< 1 year) to next older sibling and region of residence (southern, highest; eastern, intermediate; western, lowest). After multivariate adjustment (full adjustment) the following variables were significantly associated with MTI: increasing age, Inuit ethnicity, narrow age gap to next older sibling and region of residence. Variables that were not associated with the risk of infection included: crowding as measured by the total number of dwellers or the number of children in the household, birth order, age difference in years between the child and the next younger sibling, co-morbidity in the child, father's education level and type of heating facilities.

Table 3 (available at: http://www.who.int/bulletin/volumes/89/10/10-084152)

shows the association between having MTI and each of the potential risk factors encountered in children with and without a reported TB contact. We checked whether the effect of each variable was modified by the presence or absence of a known TB contact. The variables whose effect was significantly modified by the presence of a known TB contact were domestic crowding (increased risk: $P = 0.009$) and mother's education (decreased risk: $P = 0.05$). Region of residence was only associated with MTI among children without a known TB contact ($P = 0.03$), with children in southern Greenland having the highest risk.

Discussion

This study is, to our knowledge, the first one to have examined the rates of MTI and its risk factors in children living in the Arctic region. We found that contact with a patient with clinically active TB, increasing age, Inuit ethnicity, and a narrow age difference between the child and the next older sibling were significantly associated with positivity for MTI. However, stratifying for contact with a known TB case modified this picture somewhat. Among the children in the study who had a known TB contact (10%), domestic crowding and low maternal educational level were significant risk factors for MTI, while the only significant risk factor for MTI among children without a known TB contact was the region of residence.

Thus, two different risk factor patterns for MTI exist among children in Greenland, with the presence or absence of a known TB contact being the definitive factor. Among children with a known TB contact, the increased risk of MTI associated with living in crowded conditions may be the result of both easier transmission of *M. tuberculosis* because of closer contact between family members or because more family members are infected with *M. tuberculosis*. Similarly, low maternal education, insofar as it is linked to low socioeconomic status, may favour transmission of MTI within the household because of suboptimal hygienic standards and care for cases with TB. Other studies have also found low socioeconomic status to be associated with poorer general health, which may increase susceptibility to MTI among children living in households with fewer resources.[20]

Even in children without a known TB contact, the source of infection appears to be within the household. A child's risk of MTI was 14 times higher when an older sibling was found to be infected, even when the source of the infection was not known to be within the family. When two children within a family have MTI, both may have been exposed to a third active TB case or one child may have been sequentially exposed to the other. The finding that geographical region of residence was a risk factor for MTI in children without a known TB contact underlines the greater likelihood of community exposure when prevalence is high in the area. While this increased risk would also be true among children with known TB contact, *M. tuberculosis* exposure within the family dominated MTI risk, adjusting away the community-associated risk

In children with and without TB contacts, the increasing risk of MTI with increasing age points to a cumulative risk of acquiring MTI over time, a finding also observed in other studies.[21,22] We have previously reported that the annual risk of MTI in Greenland is 0.8% per year, which translates into a prevalence of MTI of about 13% by the age of 18 years.[5]

Inuit ethnicity was also associated with a higher risk of MTI in children with or without a known TB contact. Both genetic and environmental factors may be at play. Overall, little is known about the genetic susceptibility to tuberculosis, but some have reported that polymorphisms in the genes for mannose binding lectin and for the interferon gamma receptor are associated with susceptibility to *M. tuberculosis*.[23–25] In Greenland, social determinants probably increase the risk of MTI among Inuit children, since Inuit families tend to be larger, to live in more crowded conditions and to be less educated than families in which at least one parent is Danish.[26]

A narrow age gap between a child and a next-older-sibling with MTI was a risk factor for TB both among children with a known TB contact and those without. This finding has been documented in studies of other infectious agents[27,28] but not, to our knowledge, in studies on MTI. Traditionally, children with active TB disease are not considered infectious because they excrete few bacteria. However, in adolescence TB begins to resemble the adult form of the disease and can become sputum positive, as in adults, which poses the risk of transmission.[29–31] It is also possible that a narrow age gap between siblings acts as a proxy for closer interaction with elder siblings or a common social circle, both of which could make for a shared source of infection.

In 2007, the Greenlandic Directorate of Health revised the national TB programme by adding public information campaigns and educational materials for disease prevention programmes.[32] Our findings, based on MTI as the outcome, suggest that future campaigns should primarily target the Inuit population living in high-incidence regions and the inhabitants of small communities and settlements, and that efforts should be made to enhance contact tracing within families of low socioeconomic status. In Greenland, TB screening is routinely performed when children enter school and again when they graduate. This study has shown that if a child screens positive for MTI, intensive investigation of all members of the family should be undertaken promptly.

Our study has several strengths. The study population comprised approximately 17% of the total population of Greenland in the relevant age groups. The sample population was almost identical in its demographic characteristics to the population of Greenland as a whole. Because enrolment in the study was based on school attendance, which is mandatory in Greenland, our study sample is not likely to be biased by differences in access to health care. We know from previous experience that school lists, which form the basis for registering children in the communities, often include children temporarily or permanently absent from the area. We therefore consider a participation rate of 62% to be acceptable and the sampled population to be representative of the entire population of Greenland. Furthermore, we diagnosed MTI conservatively (i.e. requiring positivity on both QFN and TST), which minimizes the chances of misclassification. However,

it is possible that earlier TB treatment mitigated the response to QFN and TST in some children[33] Finally, the use of information from national registers minimized recall bias, but bias resulting from the non-participation of sick children cannot be ruled out. Furthermore, the responses to the questionnaire may be subject to recall bias. However, since the study participants did not know their MTI status, any misclassification was non-differential and would, if anything, underestimate the true effect of our association with MTI.

In conclusion, the present study revealed that family crowding as well as increasing age, Inuit ethnicity, region of residence and age difference between siblings are factors associated with MTI among children in Greenland. However, having had known contact with a person with active TB markedly modified the risk factor profile. Domestic crowding and low maternal educational level emerged as risk factors among children with a known TB contact but not among those who had no known contact with a TB patient. These findings can be used to target future public health interventions specifically at Greenlandic children with the highest risk of MTI. ■

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Competing interests: None declared.

مخلص

عوامل اختطار العدوى بالمتفطرة السلية بين الأطفال في غرينلاند

الغرض فحص عوامل اختطار العدوى بالمتفطرة السلية بين أطفال غرينلاند لغرض تحديد أشد عوامل الاختطار للعدوى.

الطريقة بين عامي 2005 و 2007، أجرى اختبار للكشف عن العدوى بالمتفطرة السلية على 1797 طفلاً في المدارس في غرينلاند في خمس مناطق مختلفة، عن طريق قياس إنطلاق غاما-إنترفيرون، واختبار التوبركولين الجلدي. وقد جرى مسح للآباء أو من يرعون هؤلاء الأطفال باستخدام استبيان معياري ذاتي التعبئة، لجمع المعطيات حول الازدحام في المنزل، ومستوى تعليم الأبوين، والحالة الصحية للطفل. وجرى أيضاً استخلاص المعطيات الديموغرافية من السجلات العامة لكل طفل- مثل مكان ولادة الأبوين، وعدد الإخوة، والمباعدة بين ولادات الإخوة (الفترة بين التالي في الصغر والفترة بين التالي في الكبر)، وترتيب الولادة، وعمر الأم عند ولادة الطفل. واستخدم التحوّف اللوجستي لمراجعة الارتباطات بين هذه المتغيرات والعدوى بالمتفطرة السلية، وقد جرى التعبير عن جميع النتائج عن طريق نسب الأرجحية وفاصلات الثقة 95%. وجرى اعتبار الأطفال مصابين بالمتفطرة السلية إذا كانت فحوصهم إيجابية في اختبار قياس إنطلاق غاما-إنترفيرون، واختبار التوبركولين الجلدي.

النتائج بلغ المعدل الإجمالي لانتشار العدوى بالمتفطرة السلية 8.5% (1797/152). وتم تشخيص الإصابة بالمتفطرة السلية في 26.7% من الأطفال المعلوم وجود مخالطين لهم مصابين بالسل، مقارنة بـ 6.4% في ثلاثة أطفال ليس لديهم مخالطون مصابون بالسل. وكان إجمالي معدل الإصابة بالمتفطرة السلية أعلى بين أطفال الإسكيمو (نسبة الأرجحية: 4.22؛ فاصلة الثقة 95%: 1.55-11.5)، وبين الأطفال المولودين في غضون عام من ولادة الأخ الذي يكبرهم مباشرة (نسبة الأرجحية: 2.48؛ فاصلة الثقة 95%: 1.33-4.63). وقد عدّل التبليغ الذاتي عن وجود مخالطين مصابين بالسل المرتسم ليشمل الازدحام في المنزل وانخفاض مستوى تعليم الأم. وكان من الأرجح للأطفال الذين سبق لهم التعرض لمخالطين أكبر سناً ومصابين بالمتفطرة السلية أن تكون فحوصهم إيجابية للإصابة بالمتفطرة السلية (نسبة الأرجحية: 14.2؛ فاصلة الثقة 95%: 5.75-35.0) مقارنة بالأطفال الذين لم يتعرضوا لإخوة مصابين.

الاستنتاج يعد الأصل العرقي، والعلاقة بالإخوة، وعدد المقيمين في المنزل، ومستوى تعليم الأمهات من العوامل التي ترتبط باختطار الإصابة بالسل بين الأطفال في غرينلاند. ويدل ظهور مجموعات منزلية مصابة بالمتفطرة السلية على أهمية مصادر التعرض للعدوى داخل الأسرة.

摘要

格陵兰儿童结核杆菌感染的危险因素

目的 旨在调查格陵兰儿童结核杆菌感染（MTI）的危险因素，从而确定哪些儿童的感染风险最高。

方法 2005到2007年间，对5个不同区域的1797名格陵兰学龄儿童进行干扰素释放试验（IGRA）和结核菌素试验（TST），确定其是否存在结核杆菌感染。同时运用标准化自报问卷对学童父母或监护人进行调查，获取有关家庭拥挤程度、家长教育水平和儿童健康状况的资料。每位儿童的人口统计资料可以从公共登记处提取，如父母籍贯、兄弟姐妹个数、兄弟姐妹年龄距离（上一个或下一个兄弟姐妹），出生顺序和孩子出生时母亲年龄，。运用逻辑回归检查这些变量与结核杆菌感染之间的关联，并且所有结果均以比值比（ORs）和95%可信区间（CIs）表示。如果儿童干扰素释放试验和结核菌素试验结果均呈阳性，则认为存在结核杆菌感染。

结果 结核杆菌感染的总发病率为8.5%(152/1797)。与肺结核患者有接触的儿童中，26.7%被诊断存在结核杆菌感染，而与肺结核患者没有接触的儿童中，此比例为6.4%。总体而言，因纽特儿童（比值比：4.22；95%可信区间：1.55-11.5）和那些与上一个哥或姐的年龄距离不足一年的儿童(比值比：2.48；95%可信区间：1.33-4.63) 相比结核杆菌的感染率较高。自我报告的肺结核接触史修正了原有人口统计资料情况，从而将家庭拥挤程度和母亲教育水平较低也包括在内。与那些没有受感染的哥哥或姐姐的儿童相比，有结核杆菌感染阳性的哥哥或姐姐的儿童在结核杆菌感染测试中更容易呈阳性（比值比：14.2，95%可信区间：5.75-35.0）。

结论 种族、兄弟姐妹关系、家庭居民数量和母亲的教育水平是格陵兰儿童肺结核感染相关的危险因素。结核杆菌感染的强家庭聚集性表明家庭暴露源很重要。

Résumé

Facteurs de risque d'une infection à *Mycobacterium tuberculosis* chez les enfants au Groenland

Objectif Examiner les facteurs de risque d'une infection à Mycobacterium tuberculosis (MTI) parmi les enfants groenlandais afin d'identifier ceux qui présentent le risque d'infection le plus élevé.

Méthodes Entre 2005 et 2007, 1797 écoliers groenlandais de cinq régions différentes ont été testés pour le dépistage de l'infection à MTI au moyen d'un test de détection de l'interféron gamma (IGRA) et d'un test cutané à la tuberculine (TST). Une enquête a été proposée aux parents ou aux tuteurs à l'aide d'un auto-questionnaire standardisé en vue d'obtenir des données sur la composition des ménages, le niveau d'éducation des parents et l'état de santé de l'enfant. Des données démographiques relatives à chaque enfant – à savoir le lieu de naissance des parents, le nombre de frères et sœurs, la différence d'âge entre les frères et sœurs (suivant et précédent), l'ordre de naissance et l'âge de la mère à la naissance de l'enfant – ont également été extraites d'un registre public. Le principe de régression logistique a été appliqué pour vérifier les éventuelles associations entre ces variables et l'infection à MTI. Tous les résultats étaient exprimés en odds-ratios (OR) et en intervalle de confiance à 95% (IC). Les enfants étaient considérés comme atteints de MTI si le test IGRA et le TST étaient tous les deux positifs.

Résultats La prévalence globale de l'infection à MTI était de 8,5% (152/1797). On a diagnostiqué une infection à MTI chez 26,7% des enfants ayant été en contact de façon avérée avec une personne atteinte de tuberculose, pour 6,4% d'enfants n'ayant pas eu un tel contact. Globalement, le taux d'infection à MTI était plus élevé chez les enfants inuits (OR: 4,22; IC à 95%: de 1,55 à 11,5) et chez les enfants nés moins d'un an après la naissance de l'enfant précédent (OR: 2,48; IC à 95%: de 1,33 à 4,63). Un contact déclaré avec une personne tuberculeuse modifiait le profil, ainsi qu'un nombre élevé de personnes au foyer et une éducation peu élevée de la mère. Les enfants ayant un frère ou une sœur plus âgé atteint d'une infection à MTI risquaient davantage d'avoir eux-mêmes un résultat positif au dépistage de MTI (OR: 14,2; IC à 95%: de 5,75 à 35.0) que les enfants n'ayant ni frère ni sœur infecté.

Conclusion L'ethnicité, les relations avec les frères et sœurs, le nombre de personnes vivant au foyer et le niveau d'éducation maternelle sont des facteurs associés au risque d'infection par la tuberculose parmi les enfants du Groenland. La forte concentration de l'infection à MTI dans les foyers indique que les sources familiales d'exposition sont importantes.

Резюме

Факторы риска заражения микобактериями туберкулеза у детей в Гренландии

Цель Исследовать факторы риска заражения микобактериями туберкулеза (МБТ) среди гренландских детей с целью выявления пациентов с наивысшим риском заражения.

Методы В период с 2005 по 2007 год 1797 школьников из пяти районов Гренландии прошли обследование на заражение МТБ путем проведения анализа секреции гамма-интерферона (IGRA) и туберкулиновой пробы кожи (ТПК). Для получения данных о скученности проживания в домохозяйстве, уровне образования родителей и состоянии здоровья ребенка был проведен опрос родителей или опекунов с использованием стандартной анкеты для самостоятельного заполнения. Кроме того, из государственного реестра были извлечены демографические данные о каждом ребенке: место рождения родителей, число братьев/сестер, период времени между рождениями братьев/сестер (ближайшего младшего и ближайшего старшего ребенка в семье), очередность рождения и возраст матери при рождении ребенка. Для проверки корреляции между этими переменными и заражением МБТ использовалась логистическая регрессия, а все результаты были выражены в виде отношения шансов (ОШ) и 95%-ного доверительного интервала (ДИ). Считалось, что дети заражены МБТ, если при обследовании у них был получен положительный результат в обоих анализах (IGRA и ТПК).

Результаты В целом распространенность инфекции, вызванной заражением МБТ, составляла 8,5% (152/1797). Заражение МБТ было диагностировано у 26,7% детей, о которых было известно, что они контактировали с больным ТБ, и у 6,4% детей, не имевших этого контакта. В целом показатель заболеваемости МБТ был более высоким у инуитских (эскимосских) детей (ОШ: 4,22; 95% ДИ: 1,55–11,5) и у детей, которые родились менее чем через год после рождения ближайшего старшего ребенка в семье (ОШ: 2,48; 95% ДИ: 1,33–4,63). Данные самооценки о контакте с больным ТБ приводили к изменению набора характеристик и включению в него скученности проживания в домохозяйстве и низкого уровня образования матери. У детей, имевших старшего брата/сестру с положительным результатом обследования на заражение МБТ, вероятность положительной реакции в обследованиях на заражение МБТ была значительно выше (ОШ: 14,2; 95% ДИ: 5,75–35,0), чем у детей, не имевших старшего брата/сестру, зараженных МБТ.

Вывод Факторами, коррелирующимися с риском заражения ТБ у детей на Гренландии, являются этническая принадлежность, наличие братьев/сестер и уровень образования матери. Интенсивная кластеризация случаев заражения МБТ по домохозяйствам говорит о важности семейных источников экспозиции.

Resumen

Factores de riesgo de la infección por *Mycobacterium tuberculosis* en niños de Groenlandia

Objetivo Examinar los factores de riesgo de la infección por *Mycobacterium tuberculosis* (IMT) en niños groenlandeses con el fin de identificar a aquellos están expuestos a un mayor riesgo.

Métodos Entre 2005 y 2007, se analizó a 1797 niños en edad escolar de Groenlandia en cinco zonas diferentes para detectar la presencia de la IMT mediante un análisis de liberación de interferón gamma (IGRA, por sus siglas en inglés) y una prueba cutánea de tuberculina (PCT). Los padres o tutores respondieron a un cuestionario autoadministrado y normalizado para obtener datos sobre el número de habitantes del hogar, el nivel educativo de los padres y el estado de salud del niño. También se extrajeron datos demográficos de cada niño de un registro público (es decir, el lugar de nacimiento de los padres, el número de hermanos, la diferencia entre hermanos (entre el que le sigue y el que le precede), el orden de nacimiento y la edad de la madre cuando nació el niño). Se utilizó una regresión logística para comprobar las asociaciones entre estas variables y la IMT. Asimismo, todos los resultados se expresaron como cocientes de probabilidades (CP) e intervalos de confianza (IC) del 95%. Se estableció que los niños tenían la IMT en caso de resultado positivo tanto del análisis IGRA como de la PCT.

Resultados La prevalencia global de la IMT fue del 8,5% (152/1797). Se diagnosticó la IMT en el 26,7% de los niños de los que se tenía constancia de un contacto con la tuberculosis, en contraposición con el 6,4% de estos niños que no habían tenido dicho contacto. En general, la tasa de la IMT resultó ser más elevada en niños *inuit* (CP: 4,22; IC del 95%: 1,55-11,5) y entre niños nacidos menos de un año después del nacimiento del hermano que les precede (CP: 2,48; IC del 95%: 1,33-4,63). La notificación de un contacto con la tuberculosis modificaba el perfil para incluir el número de habitantes del hogar y el bajo nivel educativo de la madre. Los niños que tenían un hermano mayor cuya prueba de IMT fue positiva tenían muchas más probabilidades de que su prueba también ofreciese un resultado positivo (CP: 14,2; IC del 95%: 5,75-35,0) en comparación con los niños que no tenían un hermano mayor infectado.

Conclusión La etnia, las relaciones fraternales, el número de habitantes del hogar y el nivel de educación materno son factores asociados al riesgo de sufrir una infección de tuberculosis en niños de Groenlandia. La gran concentración en el hogar de la IMT sugiere que las fuentes familiares de exposición son importantes.

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Table 2. **Potential risk factors for *Mycobacterium tuberculosis* infection (MTI) among 1797 Greenlandic schoolchildren, 2005–2007**

Risk factor	Children		Age- and sex-adjusted		*P*	Fully adjusted[a]		*P*
	Without MTI	With MTI	OR	95% CI		OR	95% CI	
Sex	**1797**	**152**			**0.83**			**0.93**
Female	903	77	0.96	0.69–1.35	–	1.02	0.72–1.42	–
Male[b]	894	75	1	–	–	1	–	–
Age (years)	1797	152	–	–	0.002	–	–	0.01
5–7[b]	282	19	1	–	–	1	Reference	–
8–10	500	30	1.01	0.57–1.78	–	1.03	0.59–1.77	–
11–13	596	49	1.42	0.81–2.48	–	1.36	0.80–2.32	–
14–15	296	36	2.19	1.24–3.87	–	2.19	1.26–3.82	–
≥16	123	18	2.52	1.23–5.16	–	1.89	0.94–3.80	–
OR per additional year of age	–	–	1.12	1.05–1.19	0.0003	1.10	1.04–1.17	0.002
Ethnicity	1797	152	–	–	0.007	–	–	0.005
Inuit	1593	148	3.88	1.44–10.5	–	4.22	1.55–11.5	–
Non-Inuit[b]	204	4	1	–	–	1	–	–
Mother's age (years) at birth of study child	1797	152	–	–	0.009	–	–	0.14
15–19	228	29	1.73	1.14–2.61	–	1.44	0.88–2.34	–
≥ 20[b]	1569	123	1	–	–	1	–	–
Type of residence	1662	136	–	–	0.17	–	–	0.37
Family[b]	1513	111	1	–	–	1	–	–
Orphanage, dorm	102	18	1.63	0.87–3.03	–	1.40	0.75–2.63	–
Foster family	47	7	1.76	0.77–4.00	–	1.58	0.68–3.70	–
No. of adults in household (CF 1)	1608	128	–	–	0.28	–	–	0.43
1–2[b]	1273	104	1	–	–	1	–	–
3+	335	24	0.72	0.45–1.26	–	0.82	0.50–1.34	–
Average no. of people per room (CF 2)	1408	100	–	–	0.08	–	–	0.10
< 1	268	14	0.71	0.36–1.41	–	0.84	0.42–1.69	–
1–1.49[b]	610	39	1	–	–	1	–	
≥ 1.50	530	47	1.44	0.91–2.27	–	1.57	0.95–2.58	–
Study child in own room (CF 3)	1653	137	–	–	0.23	–	–	0.15
Yes[b]	894	72	1	–	–	1	–	–
No	759	65	1.28	0.72–1.48		1.33	0.90–1.97	
Sum of CFs[c]	1797	152	–	–	0.74	–	–	0.76
0 CF[b]	734	61	1	–	–	1	–	–
1 CF	587	54	1.23	0.83–1.83	–	1.21	0.81–1.81	–
2 CFs	391	29	1.04	0.62–1.74	–	1.11	0.67–1.86	–
3 CFs	85	8	1.25	0.53–2.93	–	1.33	0.61–2.90	–
OR per additional CF	–	–	1.05	0.86–1.28	0.63	1.08	0.89–1.31	0.44

Risk factor	Children		Age- and sex-adjusted		*P*	Fully adjusted[a]		*P*
	Without MTI	With MTI	OR	95% CI		OR	95% CI	
Age difference (years) with next older sibling[d]	1235	95	–	–	0.03	–	–	0.03
< 1 (including twin)	61	12	2.04	1.00–4.16	–	2.08	1.07–4.04	–
1[b]	287	25	1	–	–	1	–	–
2	218	10	0.50	0.25–1.01	–	0.50	0.24–1.04	–
≥ 3	669	48	0.83	0.52–1.30	–	0.88	0.56–1.40	–
Mother's education	1104	75	–	–	0.33	–	–	0.31
8th grade and no further schooling	117	12	1.26	0.53–3.00	–	1.61	0.69–3.78	–
8th grade and skilled labour	243	18	1.09	0.56–2.10	–	1.04	0.53–2.02	–
10th grade and skilled labour[b]	492	35	1	–	–	1	–	–
10th grade, 3 years vocational training & courses and bachelor's degree[e]	6	1	2.80	0.40–19.5	–	1.84	0.18–18.7	–
High school and skilled labour	154	5	0.43	0.17–1.08	–	0.41	0.15–1.11	–
High school and bachelor's/master's degree	92	4	0.65	0.22–1.90	–	0.71	0.24–2.09	–
OR per additional level of maternal education	–	–	0.83	0.6–1.03	0.09	0.80	0.64–1.01	0.06
Region	1797	152	–	–	< 0.0001	–	–	< 0.0001
East[b]	367	28	1	–	–	1	–	–
South	1100	118	1.44	0.90–2.32	–	1.51	0.94–2.42	–
West	420	6	0.18	0.07–0.44	–	0.20	0.08–0.48	–
BMI (kg/cm²)[f]	1777	148	–	–	0.63			0.49
Underweight	16	1	1.13	0.24–5.33	–	1.83	0.31–10.7	–
Normal[b]	1398	111	1	–	–	1	–	–
Overweight	295	25	0.97	0.61–1.53	–	0.95	0.60–1.50	–
Obese	68	11	1.58	0.77–3.22	–	1.69	0.78–3.65	–
Obese (measured by BMI)[g]	1777	148	–	–	0.20	–	–	0.16
No[b]	1709	137	1	–	–	1	–	–
Yes	68	11	1.59	0.79–3.21	–	1.71	0.80–3.66	–

BMI, body mass index; CF, crowding factor; CI, confidence interval; OR, odds ratio.

[a] Adjusted for sex, age, ethnicity, mother's age, region and difference in age between study child and next older sibling.

[b] Reference category.

[c] The sum of the CFs was obtained by adding the three CFs given in the table, as follows: CF 1 was added when 3 or more adults lived in the household; CF 2, when the average number of people per room was at least 1.5; and CF 3, when the study child did not have their own room.

[d] Subanalysis for < 1 year difference versus ≥ 1 year difference between the age of the study child and that of the next older sibling: OR = 2.48 (95% CI: 1.33–4.63).

[e] Instead of qualifying for entrance to a bachelor's programme through three years of upper secondary school, children in Denmark and Greenland can qualify for entrance by completing three years of certified vocationally oriented training and courses.

[f] BMI categories were defined according to age- and sex-specific percentiles evaluated by Centers for Disease Control and Prevention BMI-for-age growth charts for girls and boys. Definitions were as follows: underweight, < 5th percentile; normal weight, 5th percentile to < 85th percentile; overweight, 85th percentile to < 95th percentile; obese, ≥ 95th percentile.

[g] Obesity was defined as in previous footnote; underweight, normal weight and overweight were combined into a single category.

Table 3. **Odds ratios (ORs) for *Mycobacterium tuberculosis* infection (MTI), by potential risk factors, among 1797 Greenlandic schoolchildren stratified by TB contact**

Potential risk factor	Without known TB contact					With known TB contact					Test for effect modification of TB contact
	Children		OR	95% CI	*P*	Children		OR	95% CI	*P*	*P*
	No.	With MTI				No.	With MTI				
Sex	1617	104	–	–	0.76	180	48	–	–	0.55	0.50
Female	812	50	0.94	0.62–1.41	–	91	27	1.24	0.61–2.52	–	–
Male[a]	805	54	1	–	–	89	21	1	–	–	–
Age (years)	1617	104	–	–	0.002	180	48	–	–	0.29	–
5–7[a]	249	9	1	–	–	33	10	1	–	–	–
8–10	449	21	1.43	0.71–2.89	–	51	9	0.86	0.26–2.80	–	–
11–13	534	29	1.55	0.76–3.14	–	62	20	1.85	0.56–6.07	–	–
14–15	272	28	3.14	1.55–6.36	–	24	8	2.10	0.55–7.95	–	–
≥16	113	17	3.30	1.43–7.61	–	10	1	0.33	0.03–3.94	–	–
OR per each additional year of age	–	–	1.14	1.06–1.23	0.0003	–	–	1.05	0.92–1.20	0.45	0.29[c]
Ethnicity	1617	104	–	–	0.03	180	48	–	–	0.03	0.44
Inuit	1439	101	3.55	1.15–11.0	–	154	47	8.53	1.19–61.4	–	–
Non-Inuit[a]	178	3	1	–	–	26	1	1	–	–	–
Mother's age (years) at birth of study child	1617	104	–	–	0.24	180	48	–	–	0.12	0.32
15–19	205	20	1.39	0.80–2.40	–	23	9	2.70	0.78–9.28	–	–
≥20[a]	1412	84	1	–	–	157	39	1	–	–	–
Type of residence	1488	88	–	–	0.44	174	48	–	–	0.68	0.89
Family dwelling[a]	1355	69	1	–	–	158	42	1	–	–	–
Orphanage, dorm	93	14	1.28	0.60–2.75	–	9	4	2.00	0.34–11.6	–	–
Foster family	40	5	1.84	0.69–4.90	–	7	2	1.60	0.17–15.0	–	–
No. of adults in household (CF 1)	1437	81	–	–	0.06	171	47	–	–	0.15	0.02
1–2[a]	1133	71	1	–	–	140	33	1	–	–	–
2+	304	10	0.50	0.24–1.02		31	14	2.18	0.76–6.25	–	–
Average no. of people per room (CF 2)	1266	60	–	–	0.77	142	40	–	–	0.57	–
<1	244	10	0.85	0.39–1.83	–	24	4	0.98	0.21–4.57	–	–
1–1.49[a]	556	27	1	–	–	54	12	1	–	–	–
≥1.50	466	23	1.15	0.59–2.26	–	64	24	1.62	0.62–4.18	–	–
OR per each additional category	–	–	1.17	0.7–1.77	0.47	–	–	1.37	0.68–2.79	0.38	0.71[c]
Study child in own room (CF 3)	1482	89	–	–	0.64	171	48	–	–	0.26	0.48
Yes[a]	807	53	1	–	–	87	19	1	–	–	–
No	675	36	1.13	0.69–1.84	–	84	29	1.57	0.71–3.45	–	–

Potential risk factor	Without known TB contact					With known TB contact					Test for effect modification of TB contact
	Children		OR	95% CI	*P*	Children		OR	95% CI	*P*	*P*
	No.	With MTI				No.	With MTI				
Sum of CFs[b]	1617	104	–	–	0.45	180	48	–	–	0.11	–
0 CFs[a]	666	52	1	–	–	68	9	1	–	–	–
1 CF	529	36	0.95	0.60–1.51	–	58	18	2.82	1.04–7.60	–	–
2 CFs	350	15	0.72	0.38–1.37	–	41	14	2.52	0.89–7.16	–	–
3 CFs	72	1	0.28	0.04–1.81	–	13	7	4.24	1.04–17.3	–	–
OR per each additional CF	–	–	0.82	0.64–1.06	0.13	–	–	1.54	1.00–2.30	0.03	0.009[c]
Age difference (years) with next older sibling	1113	62	–	–	0.19	122	33	–	–	0.17	0.90
<1 (including twin)	52	7	1.80	0.74–4.42	–	9	5	3.47	0.90–13.3	–	–
1[a]	256	17	1	–	–	31	8	1	–	–	–
2	197	6	0.47	0.19–1.16	–	21	4	0.56	0.11–2.84	–	–
≥3	608	32	0.90	0.52–1.58	–	61	16	1.04	0.35–3.04	–	–
Mother's education	977	45	–	–	0.57	127	30	–	–	0.01	–
1: 8th grade and no further schooling	100	4	0.84	0.20–3.51	–	17	8	3.92	1.21–12.7	–	–
2: 8th grade and skilled labour	215	11	0.96	0.39–2.32	–	28	7	0.87	0.21–3.59	–	–
3: 10th grade and skilled labour[a]	427	22	1	–	–	65	13	1	–	–	–
4: 10th grade, 3 years vocational training & courses, and bachelor's degree [d]	5	1	3.25	0.39–27.4	–	1	0	–	–	–	–
5: High school and skilled labour	142	3	0.37	0.11–1.27	–	12	2	0.41	0.09–1.96	–	–
6: High school and bachelor's/master's degree	88	4	1.03	0.34–3.10	–	4	0	–	–	–	–
OR per each additional education level	–	–	0.93	0.71–1.20	0.56	–	–	0.55	0.34–0.88	0.01	0.05[c]
Region	1617	104	–	–	0.0002	180	48	–	–	0.97	0.03
East[a]	331	19	1	–	–	36	9	1	–	–	–
South	880	83	1.58	0.91–2.75	–	130	35	1.15	0.42–3.16	–	–
West	406	2	0.09	0.02–0.40	–	14	4	1.10	0.21–5.71	–	–
BMI[e]	1599	101	–	–	0.03	178	47	–	–	0.62	–
Underweight	14	1	3.11	0.43–22.7	–	2	0	–	–	–	–
Normal[a]	1260	76	1	–	–	138	35	1	–	–	–
Overweight	262	14	0.74	0.42–1.31	–	14	4	0.61	0.08–4.45	–	–
Obese	63	10	2.52	1.07–5.91	–	5	1	1.10	0.38–3.17	–	–

Potential risk factor	Without known TB contact					With known TB contact					Test for effect modification of TB contact
	Children		OR	95% CI	*P*	Children		OR	95% CI	*P*	*P*
	No.	With MTI				No.	With MTI				
OR per increase in BMI class	–	–	1.15	0.76–1.75	0.51	–	–	1.14	0.50–2.38	0.72	0.99[c]
Obese (measured by BMI)[f]	1599	101	–	–	0.02	178	47	–	–	0.62	0.19
No[a]	1536	91	1	–	–	173	46	1	–	–	–
Yes	63	10	2.51	1.09–5.78	–	5	1	0.63	0.10–4.01	–	–

BMI, body mass index; CF, crowding factor; CI, confidence interval.

The estimates were fully adjusted for the following variables: sex, age, ethnicity, mother's age at birth of study child, region and age difference between study child and next older sibling.

[a] Reference category.

[b] The sum of the CFs was obtained by adding the three CFs given in the table, as follows: CF 1 was added when 3 or more adults lived in the household; CF 2, when the average number of people per room was at least 1.5; and CF 3, when the study child did not have their own room.

[c] Interaction test performed as test for homogeneity of trends.

[d] Instead of qualifying for entrance to a bachelor's programme through three years of upper secondary school, a person in Denmark and Greenland can qualify for entrance by completing three years of certified vocationally oriented training and courses.

[e] BMI categories were defined according to age- and sex-specific percentiles evaluated by Centers for Disease Control and Prevention BMI-for-age growth charts for girls and boys. Definitions were as follows: underweight, <5th percentile; normal weight, 5th percentile to <85th percentile; overweight, 85th percentile to <95th percentile; obese, ≥95th percentile.

[f] Obesity was defined as in previous footnote; underweight, normal weight and overweight were combined into a single category.