Tuberculosis in Greenland – current situation and future challenges

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ABSTRACT

Objective. To describe the tuberculosis (TB) epidemiology in Greenland in 1998-2002 and to identify possible obstacles for reducing the TB incidence. Study design/methods. TB notification data were collected from the annual reports of the Chief Medical Officer, and culture verification data were collected from the International Reference Laboratory of Mycobacteriology at Statens Serum Institut, Denmark. Results. The TB incidence in Greenland reached a peak of 185/100,000 in 2001. In 1999-2001, the majority of cases were related to an outbreak in the Southern districts. In 1998-2002, 0.5% drug-resistance was found among patients living in Greenland in contrast to 13.1% drug-resistance found previously among Inuit patients in Denmark. In 1998-2001, microscopy positive cases made up 65% of all culture confirmed cases and DNA subtyping demonstrated the emergence of Mycobacterium tuberculosis strains that were previously infrequently found. Conclusion. It is important to eliminate factors that fuel the epidemic and to improve general living conditions in Greenland. Treatment seems effective as limited drug-resistance is detected. TB reduction will therefore depend on early detection of active disease and thorough contact tracing. Greenland will face a pool of persons latently infected some of whom will progress to active disease. Sufficient resources need to be allocated for TB control in the years to come.

Key Words: Outbreak, high-incidence, drug, RFLP, transmission, delay

INTRODUCTION

During the last century, the incidence of tuberculosis (TB) in Greenland has decreased substantially. In 1985, it reached the lowest registered level of 25/100,000 (1). Since then, the incidence has increased to 85/100,000 in 1990 and 172/100,000 in 1997 (2). In 1990-1997, Søborg C and co-workers found the increasing incidence of tuberculosis related to micro-epidemics in small isolated settlements. They also found that the increasing incidence affected primarily children and young adults. E.g. TB among children aged 0-14 yrs increased from 4 cases in 1990 to 26 cases in 1997. The reasons were found to be multi-factorial, including patients’ and doctors’ delay, lack of medical personnel and poor housing conditions.

During the last years, there have been several initiatives to strengthen TB control in Greenland. In 1996, BCG vaccination of newborns was re-implemented, and in 1999, a TB group consisting of lung physicians and the chief medical officer was established. They identified a TB incidence of 10/100,000 in 2010 as a key target. In addition, this group prepared written guidelines for TB in Greenland covering diagnostics, treatment, control, notification, contract tracing, vaccination, preventive treatment and screening (3). Also, this group coordinates TB activities, and the group has now expanded with two nurses, one of whom helps in the districts and settlements.

The aim of the present study was to evaluate the latest development in the TB situation in Greenland from 1998 to 2002 and to identify future challenges that might interfere with TB reduction.
MATERIAL AND METHODS

Patients
Data on TB notifications covering 1998-2002 were collected from the annual reports from the Office of the Chief Medical Officer in Greenland (4-8), and data on culture confirmation were collected from the International Reference Laboratory of Mycobacteriology (IRLM) at Statens Serum Institut (SSI). Specimens and processing techniques.
After transfer from Greenland to IRLM (SSI), non-sterile specimens were decontaminated with NaOH/N-acetyl-L-Cysteine and the sediment was used to prepare smears and to inoculate Löwenstein-Jensen slants and liquid culture media (Bactec until May 2000, MGIT/MycO-F-Lytic vials thereafter). Smears were stained with auramine-rhodamine and examined at 200x magnification. Smears with 10 or more acid-fast bacteria were considered positive. Inoculated culture vials were examined for mycobacterial growth and Mycobacterium tuberculosis was identified by AccuProbe (GenProbe, San Diego, Calif.) or InnoLipa (InnoGenetics, Ghent, Belgium).

Drug susceptibility testing was performed on the first isolate from each patient with the proportion method (Bactec) for rifampin, isoniazid, ethambutol, pyrazinamid and streptomycin. If 1% of the bacterial population was resistant to rifampin, isoniazid, ethambutol or streptomycin, the whole population was considered resistant. 10% were used for pyrazinamide according to the manufacturers recommendations (9).

DNA subtyping was performed on the first isolate of M. tuberculosis from each patient. When sufficient growth of M. tuberculosis was obtained, the isolates were subcultured in Dubos medium containing Tween 80 (SSI Diagnostics, Hilleroed, Denmark). After 3-4 weeks’ incubation, the bacteria were harvested by centrifugation and heat killed (90°C for 30 min.), and RFLP was performed using the standardized method (10): DNA was extracted and digested with PvuII. After separation on agarose gel, the digested DNA was transferred to nylon membranes (Hybond N+; Amersham; UK) and probed with a chemiluminescence-labelled 245-bp sequence of IS6110. The fingerprints obtained were scanned and analysed by computer using the Bionumerics software version 2.5 (Applied Maths, Kortrijk, Belgium) with a band position tolerance of 2% and the Dice coefficient for calculating similarities. A “cluster” was defined as two or more strains exhibiting 100% identical IS6110 RFLP patterns, whereas “unique strains” differed by at least one band from any other strains analysed (11).

RESULTS

In 1998-2002, the number of patients with culture-confirmed TB was rather constant, but significant variations were observed in the number of notified cases (Figure 1). The incidence varied between 107/100,000 in 1998 and 185/100,000 in 2001. When comparing culture confirmation in 1998-2000 with 2001-2002, a significant difference was found (z=13.7 => p<0.001), based on 112 confirmed cases out of 167 notified cases in 1998-2000 and 91 confirmed cases out of 191 notified cases in 2001-2002. In 1998-2001, microscopy positive cases made up 115 (65%) of all 175 culture-confirmed cases. Among a subset of specimens received from 11th April to 10th May 2003, the mean transfer time was 9 days (range 1-35 days) (Table I).
Among patients with culture-verified TB, drug susceptibility testing is carried out on the first *M. tuberculosis* complex isolate. Only one (0.5%) drug resistant isolate (streptomycin resistant) was found among the isolates from 218 patients in 1998-2002. In contrast, drug resistance was demonstrated in isolates from 14 (13.1%) out of 107 Inuit TB patients living in Denmark in 1991-1998. Among these, ten patients had poly-resistance against isoniazide and streptomycin and additionally 4 patients had mono-drug resistant *M. tuberculosis* (isoniazide n=1, pyrazinamide n=2, and streptomycin n=1). No patients of Inuit origin living in Denmark had multi-drug resistant TB.

During 1998-2002, RFLP patterns from 198 individual patient isolates were analysed: 86% of the patients had an isolate that clustered with other patient isolates. Greenland Cluster (GC)-1 accounted for 14 cases (7%) in Upernavik, GC-2 accounted for 46 cases (23%), 34 of which were found in Qaqortoq, Narssaq or Nanortalik, and 10 cases were found in Ilulissat, Nuuk or Aasiaat. Seven (3.5%) patients had Danish Cluster 1 strains. Other clusters emerged: GC-18 with 18 cases (9%) in Nanortalik, GC-28 with 12 cases (6%) in Qaqortoq or Narssaq, and GC-9 with 19 cases (10%) in Tasiilaq or Ittoqqortoormiit.

**DISCUSSION**

In general, a number of stages are found on the road to TB elimination (12). After implementation of efficient detection and effective treatment in the whole country, a reduction in TB deaths and TB prevalence is seen. This stage is followed by a much slower reduction in TB incidence. The next stage is a reduced prevalence of infection.

The TB incidence in Greenland has increased dramatically, from 25/100,000 in 1985 to 185/100,000 in 2001. Although improved living conditions in coming years may influence the TB incidence in Greenland in a favourable way, it is of utmost importance to identify and eliminate factors that fuel the TB epidemic.

In 1999-2001, the majority of cases were found in the three southernmost districts of Greenland – Nanortalik, Narssaq, and Qaqortoq. Altogether 107 cases were notified from 1st January 2001 to 13th February 2002. This led to a thorough outbreak investigation in February 2002. Mantoux testing was carried out on 2,030 (80.1%) persons of a total population of 2,516. As part of the outbreak investigation, the lung physician from Dronning Ingrids Hospital in Nuuk evaluated diagnoses of previously diagnosed patients. This evaluation led to changes for 58 patients: 26 had their TB treatment terminated and 32 had therapy changed to preventive therapy only (13).

In association with this outbreak, a high proportion of patients had therapy initiated on a combination of clinical findings, Mantoux, and X-ray. A clinical TB diagnosis provides a more uncertain diagnosis as compared to culturing of *M. tuberculosis* complex, but can be justified in order to initiate treatment at an early stage of disease. A lower proportion of culture confirmation is understandable when facing an outbreak, as long as specimens are still being submitted for culture before initiation of treatment in order to continue surveillance of drug resistance and TB transmission as these analyses require the isolation of *M. tuberculosis*.

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**Table I.** Specimens’ transfer time from Greenland to IRLM at Statens Serum Institut, Copenhagen, Denmark.

| Transfer time | 1997, 2<sup>nd</sup> quarter | 2003, 11<sup>th</sup> April - 10<sup>th</sup> May |
|---------------|-------------------------------|-----------------------------------------------|
|               | mean range                    | mean range                                   |
| Nuuk          | 10 1-55 6 3-37                |                                              |
| Tassilaq      | 6 3-11 8 3-10                 |                                              |
| Qasigiannguit | 16 5-56 -                   |                                              |
| Asiaat        | 10 4-18 10 6-17              |                                              |
| Paamiut       | 9 8-10 -                    |                                              |
| Qeqertarsuaq  | 8 7-9 -                     |                                              |
| Sisimut       | 8 4-16 8 5-11               |                                              |
| Ilulisat      | 5 3-7 6 4-9                 |                                              |
| Qaqortoq      | 6 3-13 8 3-13               |                                              |
| Nanortalik    | 18 5-70 7 5-9               |                                              |
| Narssaq       | 9 2-23 10 3-19              |                                              |
| Ittoqortoormit| 8 4-15 -                    |                                              |
| Maniitsoq     | 8 1-21 -                    |                                              |
| Uummannaq     | 3 2-4 9 1-12                |                                              |
| Upernavik     | 12 1-21 17 6-35             |                                              |
| Greenland     | 9 1-70 9 1-35               |                                              |
Successful culture depends primarily on the quality of the specimen, transfer time and the decontamination procedure. The mean transfer time of nine days was unchanged from the 2nd quarter of 1997. Transfer times of up to 10 weeks were found in 1997. Although not fully comparable in numbers, such time-consuming transfer times were not observed in 2003. The transfer time is not optimal, as a higher proportion of specimens may be contaminated due to growth of other micro-organisms and because a substantial loss of culture positivity is normally seen after 7 days of transport (14). Specimens should therefore be protected from light and kept cool during transportation if possible.

Only one case of anti-TB drug resistance was found in 1998-2002 compared to three cases found in 1990-1997 (2). The low rates indicate that the treatment of TB in earlier years was good and that very few resistant strains are circulating at present. It may be argued that resistant bacteria in a specimen containing a mixture of sensitive and resistant bacteria (heteroresistance) may die during transportation. Rinder and colleagues have demonstrated the presence of heteroresistance for isoniazid, streptomycin and ethambutol in clinical specimens (15). If the low level of drug resistance observed in Greenland were due to methodological problems, one would expect some patients to develop resistant \textit{M. tuberculosis} cultures – either during treatment or later in association with a relapse. Although very low levels of drug resistance were found, clinicians in Greenland must have a high suspicion of resistance in foreigners and Greenlanders who have been living abroad. Among Greenlanders living in Denmark the rate of drug resistance was 13.1\% in 1991-1998. The introduction of TB drug resistance in Greenland in combination with the difficulties due to infrastructure and climate could make the management of patients with drug resistance TB a real challenge.

DNA subtyping of isolates demonstrated no difference in the rate of clustering as 85\% and 86\% of the patients had isolates that clustered with other patient isolates in 1992-1997 and 1998-2002, respectively. In 1992-1997, 3 main clusters were found: GC-1 in Upernavik, GC-2 in Qaqortoq, Narssaq and Nanortalik, and Danish C1 in Southwest and on the East coast. Compared to 1992-1997, the proportion of GC-1 and Danish Cluster 1 decreased in 1998-2002 whereas the proportion of GC-2 increased. GC-2 was found not only in the South but also in Ilulissat, Nuuk and Aasiaat. Apart from these well-known clusters, other clusters did emerge: 18 cases of GC-18 were found in Nanortalik, 12 cases of GC-28 were found in Qaqortoq and Narsaq, and 19 cases in Tasiilaq and Ittoqqortoormiit belonged to GC-9.

In conclusion, it is of outmost importance to eliminate the factors that continue to fuel the TB situation in Greenland. Housing, alcohol consumption and nutrition are important factors that need improvement in order to reduce TB in Greenland. Other cornerstones on the road to elimination are the early detection of patients with active disease, effective treatment and thorough contact tracing. Although formalities for effective TB control are already in place in Greenland, a reduction of TB incidence to 10/100,000 in 2010...
may turn out to be difficult to achieve. Almost two thirds of the patients with culture confirmed TB are infectious to others, and DNA fingerprinting and the outbreak in the South indicate that significant active transmission occurs. Regular screening visits to the settlements may improve the detection rate, allow for earlier diagnoses and thereby lower the proportion of infectious patients. Education and close collaboration between the districts and the TB group may improve the quality of the diagnoses made. The treatment seems to be effective as very little resistance is detected. The main problems are therefore to establish correct diagnoses and to reduce transmission. Also, in the years to come Greenland will have to face a pool of persons latently infected, some of whom will progress to active disease. Therefore resources should be allocated not only for diagnostics and treatment of disease and contact tracing, but the possibility of preventive therapy should be considered. Sufficient financial and personnel resources in the health system will be required for TB control for many years to come. Possible reporting to the global TB programme may also draw further attention to the TB situation in Greenland.

Acknowledgements.
The authors wish to express their gratitude towards the organizers of the 12th International Congress on Circumpolar Health; Health professionals dealing with TB in Greenland and finally the TB group for excellent collaboration during the years. Håkan Miörner kindly provided data regarding transfer times in 1997.

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