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Tuberculosis Transmission in Danish Children: A Nationwide Register-Based Study

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Abbreviated title & running head: Tuberculosis Transmission in Danish Children

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**BACKGROUND:** Tuberculosis (TB) remains a major public health issue among children worldwide. Data on TB transmission in children living in low-incidence countries is limited.

**METHODS:** We studied TB transmission in ethnic Danish children younger than 15 years of age between 2000-2013. Identification of children with TB disease and information on demographics and TB contacts were retrieved from the national TB surveillance register and the International Reference Laboratory of Mycobacteriology.

**RESULTS:** In total, 88 children with TB disease were identified in the study period, corresponding to a mean annual incidence of 6.9 per 1 000 000 children younger than 15 years of age. The male to female ratio was 1.3. Median age was 5 years (IQR 3-8.5). Seventy-three (83%) children had a known TB contact of which 60% was among household contacts with recent TB, predominantly parents. Sixty-six (75%) children were classified as part of epidemiological clusters. Thirty-five (40%) children had culture verified TB of which information on genotypes was available for 34 (97%). Of these, 35% belonged to cluster C2/1112-15, the most prevalent cluster among adult Danes.

**CONCLUSIONS:** We found on-going TB transmission in Danish children within the households of a low TB incidence population. These findings emphasize the need for early diagnosis of TB in children, thorough contact tracing and increased focus on risk groups.

**Keywords:** Pediatric, child, source, infection, epidemiology
Introduction

Pediatric tuberculosis (TB) is a very serious and potentially life-threatening condition and children are more prone to progress to disseminated severe disease than adults (1). Young children are primarily infected due to recent exposure to an adult with TB disease (2). Of those who develop disease, most children do so in the first year following infection (3). Pediatric TB indicates on-going TB transmission in the society and children infected with *Mycobacterium tuberculosis* (MtB) represent a reservoir for disease later in life (4). For these reasons continuous surveillance and case detection are crucial.

The TB burden among children has been relatively neglected historically, as global public health focus has aimed to reduce TB transmission to which children’s contribution has been believed to be small (5). Only recently has pediatric TB been recognized as an important part of the global End TB Strategy (6) and there is now increased awareness of the importance of contact tracing as a tool to reduce the TB burden among children (7). However, despite emerging awareness, pediatric TB remains an important public health issue globally and data on TB transmission to children in low-incidence countries, such as Denmark, is limited.

With a TB incidence of 6.3 per 100 000 population per year (8) Denmark is a low-incidence country where the highest TB incidence occurs in foreign-born populations and in certain risk groups (9). Foreign-born children represent almost 80% of all children with TB diseases in Denmark and it has been suggested that these children were most likely infected before entering Denmark (10). Transmission between Danes and migrants is limited and the risk of infection highest for migrants (11). BCG vaccination is not part of the current national Danish childhood vaccination program, as it was faced out during the early 1980s due to low TB incidence (12). Denmark has
a long history of TB prevention and control programs and has some of the world’s oldest and most comprehensive TB registers (9). Although public health efforts have been carried out for decades, it seems that TB continuously spreads in Denmark, especially among socially marginalized subpopulations with the genotype C2/1112-15 in a large dominant cluster (13). To monitor national TB prevention and control, the European Centre for Disease Prevention and Control defined four epidemiological indicators of disease burden and transmission (14). One was the 10-year trend in the ratio of case notification rate in children to that in adults. This trend reflects the change in the level of recent transmission and treatment efficiency in the country. A declining ratio indicates lower transmission over time (12). The overall ratio has been declining in Denmark in the past decades, which according to the ECDC target should indicate early case finding and effective treatment. Interestingly, the ratio when calculated for ethnic Danes, was in fact slightly increasing in the period 2000-2009 (10), which potentially reflects suboptimal TB prevention and control among Danes in Denmark, though case numbers were small (13).

The aim of this study was to investigate TB transmission among Danish children using data on epidemiology and Mtb genotypes.

**Materials and Methods**

**Study population**

The current data is based on the previous national pediatric TB database (10) and inclusion of new ethnic Danish TB cases from 2010-2013. In the present study, we retrospectively investigated the ethnic Danish children subpopulation only, in order to focus on Danish transmission patterns and to avoid including many children where disease transmission most likely took place outside Denmark. We included all Danish
children below 15 years of age diagnosed with TB in the period 2000-2013. Danish ethnicity was defined as children born in Denmark with Danish-born parents.

Data sources

We retrieved data on all notified TB cases among Danish children below the age of 15 years between January 2000 and December 2013 from The Danish national TB surveillance system, which is hosted by The Department of Infectious Disease Epidemiology and Prevention at Statens Serum Institut (SSI), Denmark. The notification system is paper based and a standardized form is used for most of the notifiable diseases. The notification form includes data on demographics, concomitant clinical manifestations, disease verification, and suspected source information. The form is filled-in by the hospital physician in charge of treatment and sent to SSI with a copy to the Danish Patient Safety Authority, which has regional public health officers formally in charge of local TB prevention and control. Information retrieved from the notification form, including information about epidemiologically-linked patients to a reported case, is entered in the surveillance database. An epidemiological link is defined as cases where patients are related e.g. household, close friend/relative, day-care-centre or school or other shared geographical setting. Epidemiologically-linked cases are assigned to a unique outbreak number and referred to as epidemiological clusters. In cases of family clusters, where relations were notified but the identity of the possible source case was unclear in the notification form (i.e. “mother” or “grandfather”), we searched for linkage through the Danish Civil Registry, which contains information on family members of children identified with personal identification numbers.

Microbiological data, including genotypes of Mtb isolates, on children with TB diseases and known sources were retrieved from The Mycobacteria Database at the
International Reference Laboratory of Mycobacteriology at SSI and matched with the epidemiological data. Genotyping was performed on all isolates by Restriction Fragment Length Polymorphism (RFLP) (15) from the beginning of the study period until 2006. Genotyping with 24-locus-based Mycobacterial Interspersed Repetitive Units – Variable Numbers of Tandem Repeats (MIRU-VNTR) (16) was initiated in 2007, and retrospectively all isolates since 2004 have been analysed with this method. The large RFLP clusters generally correspond to specific MIRU-VNTR genotypes. For example, the large RFLP cluster 2 (C2) corresponds to the MIRU-VNTR genotype 1112-15. Before 2004, for the smaller or unique RFLP clusters the corresponding MIRU-VNTR genotype is unknown and vice versa. To increase the chance to detect unexpected transmissions, RFLP genotypes with less than 10 persons in the whole Mycobacteria Database occurring among children and their contacts, were also analysed with MIRU-VNTR. The results from genotyping were stored in the laboratory register together with laboratory findings and some case-related information. Based on the postal codes of the children and genotypes of their isolates, we investigated potential source cases living in the same municipalities. Information on vital status, sex, time of diagnosis and home address of child cases and biological parents was retrieved from the Danish Civil Registration System. By combining epidemiological and microbiological data, we identified additional TB case-source relations within the households and families. A known TB contact was defined as a source case when they appeared in the notification system or identified by genotype. Source cases were generally classified as either known, unknown or potential, and additionally stratified as either household or non-household exposure. If the source cases had TB within 3 years, this was classified as recent TB.
Data analyses and statistics

Demographic characteristics, disease manifestations, microbiological test results and sources of infection are presented as numbers and percentages. The Chi-squared test was used to compare culture-positive with culture-negative children. Annual incidence rates were calculated as the number of incident cases per 1 000 000 children below 15 years of age identified from the Danish governmental statistical database; “Statistics Denmark” (http://www.dst.dk/en/Statistik). All statistical analyses were conducted using Microsoft Excel 2011 and STATA 14 (Stata-Corp LP, College Station, Texas).

Approvals
The study was approved by the Danish Data Protection Agency (14/32021, J.no.: 2012-54-0100).

Results

Demographics
Characteristics of the study population are summarized in Table 1. In total, 88 cases of TB were reported among Danish children younger than 15 years of age between 2000-2013 in Denmark, corresponding to a mean annual incidence of 6.9 per 1 000 000 Danish children per year. The male-to-female ratio was 1.3. Median age was five years (IQR 3.0- 8.5 years). Eighteen (20%) children were below two years of age. In total, 70 (80%) children had pulmonary TB. Tuberculous meningitis was the most common extrapulmonary manifestation of TB with a total of seven cases, of which five were below five years of age.

Thirty-five (40%) of the children had culture-confirmed TB of which 49% were under the age of five. We found slightly more extrapulmonary TB cases among culture-positive children (29% versus 15%). The diagnosis was supported by chest X-ray in
one third and by Tuberculin Skin Test (TST) in 20% of the cases. Overall, there were no statistically significant differences between culture-positive and culture-negative children regarding demographics or disease characteristics (Table 1).

**Source case and contact investigation:**

All but two children were reported to have acquired TB in Denmark. Seventy-three (83%) children had a known TB source that had been diagnosed within 3 years. In 44 cases (60%), the known source case was a household contact, and the majority of household contacts were parents (Table 2). In 29 (40%) children, the suspected source case was a non-household contact, often a family member, though 16 (55%) non-household contacts were not further specified. Sixty-six (75%) of the children with TB disease were classified as part of epidemiological clusters (Table 2). There were no significant differences between age groups and source cases found in and outside the household (p = 0.7).

Information on Mtb genotypes was available for all except one of the children with culture-confirmed TB, of which 35% belonged to cluster C2/1112-15. We identified nine (26%) genotype matches between children with TB disease and corresponding culture positive parent, the majority among the youngest children (Table 3). When combining epidemiological and microbiological data and exploring genotype links in the municipality of the index child we identified another eight children with potential source cases. Only five of the eight potential cases matched fully on genotype, outbreak number and municipality of child and source case (Fig., Supplemental Digital Content 1, http://links.lww.com/INF/D230 which demonstrates all source cases). For three of the 34 genotyped children, source cases remained unknown and for four other source cases we found no further matches and could not specify the relation more than unnamed household or non-household contact.
Discussion

In this study, we show that TB transmission persistently occurs among Danish children who are primarily infected by their parents. Almost all children with TB disease acquired TB in Denmark with Danish Mtb genotypes. The vast majority were part of epidemiological clusters. The burden of disease was heaviest for the youngest children.

The identified source cases to our children with TB disease had a recent TB diagnosis and the majority were household contacts, most often a parent. In Denmark according to national guidelines, all children less than five years who has known TB exposure, in terms of close family, should be treated as having latent tuberculosis infection, regardless of TST and interferon-γ release assay results once active TB has been ruled out. In cases of TB disease all children are treated with standard anti-tuberculosis drug regimen. In our population of children with TB disease, the most commonly identified non-household source cases were relatives or contacts from day-care-centres, but in 55% of non-household cases the source contacts were classified as unspecified, which was quite surprising. Even though we searched for potential source cases in the municipality of a TB child case by genotype or epidemiological cluster match, several source cases remained unidentified. The proportion of undetected TB source cases may contribute to further spread of disease in the community (17), which is worrying.

The most contagious TB cases are cases with smear positive pulmonary TB. Interestingly, in the adult population in Denmark more Danes (69%) are sputum smear positive when diagnosed with pulmonary TB compared to foreign-borns (53%) (18). This might be explained by physicians working in Denmark being more prone to suspect TB in foreign-borns than in Danes, thereby possibly introducing a detection bias causing delayed diagnosis (doctor’s delay) leading to increased risk of
infectiousness. On top of this, there may be an element of patient’s delay. A Norwegian review found factors such as low educational level, poverty, alcoholism and drug abuse to be important risk factors in delaying the diagnosis and treatment of TB disease (19). With an estimated incidence of 6.9 per 1 000 000 Danish children under 15 years of age, TB is not a common disease among Danish children but still important not to miss.

Contact tracing and outbreak management are important components of TB prevention and control strategies. In our study, we investigated both notification data and information on genotypes in culture-positive cases and we explored potential associations to children with TB disease in the municipality. In spite of this effort, it was not possible to identify source cases to all children with TB disease, which is a shortcoming that needs to be addressed by relevant authorities in the years to come. It is worrying that Denmark compared with other Scandinavian countries seems to have a larger degree of recent TB transmission and less effective TB prevention and control as remarked in a recently published study (20). Earlier identification of adults with TB disease may prevent transmission or allow for preventive treatment before progression to disease (21). Diagnosing TB in children is challenging as TB may mimic other diseases due to unspecific and atypical clinical signs (22) and as children often have paucibacillary infections causing difficulties with isolation and verification of Mtb in specimens from children (7). About 40% of the children in our study had culture-confirmed TB, indeed substantially more than the 19% reported in 2009 in the European Union (4). Among the culture positive children in our study, the most dominant Mtb genotype was C2/1112-15. This genotype is frequently seen in socially marginalized people, e.g. individuals who are homeless or have alcohol or drug abuse, especially among men with pulmonary TB in the capital of Denmark (13). When
genotyping was introduced as routine diagnostic tool in 1992 in Denmark, C2/1112-15 accounted for 5.8% culture-confirmed TB cases among Danes (23) increasing up to 30% in 2011 (24). This genotype is now generally the most distributed among Danes in Denmark. Transmission of genotype C2/1112-15 has not been interrupted and the genotype now also appears to be the most dominant among Danish children. There is a well-known strong association between low socioeconomic status and the risk of TB (25). As 35% of our children with TB disease belonged to cluster C2/1112-15, we suspect that these cases occurred among similarly socioeconomically marginalized Danish families, though this warrants future research.

TB in young children indicates recent transmission and missed opportunities for TB prevention (26, 27). Of particular interest are possibilities for improvements of current surveillance and contact tracing systems. As suggested by the World Health Organization, future surveillance should include multilinked data including information on demographics, clinical, genotypes and socioeconomic data (28). It may improve the Danish surveillance data to introduce electronic notification with disease specific entries and the possibility to better ensure the completeness of the data before submission is allowed. Another possible improvement would be to integrate the Danish national microbiology database in the surveillance system, as this database contains results on all microbiological specimens tested, regardless of the result. This could improve the sensitivity of the surveillance system, since it would also pick up microscopy or PCR positive cases, which may not have had samples sent for culturing. Repeated cross-linkage with the Danish Patient Registry may also be used to identify possible clinical-only cases not known by the reference laboratory or to the notification database.
To our knowledge, this is the first study to evaluate TB transmission in ethnic Danish children. The strengths of the study are its nationwide design and long study period. Furthermore, data was retrieved from comprehensive and detailed registers and we were able to include information on genotypes for the whole period though there was a shift in the genotyping method from RFLP to MIRU-VNTR. The study was limited by the retrospective design, small population size and the fact that we did not review medical records. Our main findings were that TB transmission in Danish children especially occurs within the households but also that for many children source cases remained unknown, which underlines a need for improved contact tracing and increased focus on risk groups in the future.
References


### TABLE 1. Characteristics of Danish children with tuberculosis in Denmark from 2000-2013

<table>
<thead>
<tr>
<th>Study population</th>
<th>All children</th>
<th>Culture-positive</th>
<th>Culture-negative*</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>88 (100%)</td>
<td>35 (40%)</td>
<td>53 (60%)</td>
<td></td>
</tr>
</tbody>
</table>

**Sex**
- Male: 50 (57) / 22 (63) / 28 (53) 0.35
- Female: 38 (43) / 13 (37) / 25 (47)

**Age**
- 0-4 yrs: 42 (48) / 17 (49) / 25 (47) 0.22
- 5-9 yrs: 28 (32) / 13 (37) / 15 (28)
- 10-14 yrs: 18 (20) / 5 (14) / 13 (25)

**Disease site**
- Pulmonary: 70 (80) / 25 (71) / 45 (85) 0.13
- Extrapulmonary**: 18 (20) / 10 (29) / 8 (15)
  - TB meningitis: 7 (39) / 5 (50) / 2 (25) 0.17
  - Lymphatic TB: 5 (28) / 1 (10) / 4 (50)
  - Other: 6 (33) / 4 (40) / 2 (25)

**Positive diagnostic tests**
- Microscopy: 5 (1) / 3 (9) / 2 (4)
- PCR: 12 (14) / 9 (26) / 3 (6)
- TST: 18 (20) / 5 (14) / 13 (25)
- IGRA: 7 (8) / 0 (0) / 7 (13)
- Chest X-ray: 28 (32) / 1 (1) / 27 (51)
- Histology: 1 (1) / 0 (0) / 1 (2)

*Abbreviations: yrs = years, PCR: polymerase chain reaction, TST: tuberculin skin test, IGRA: interferon gamma release assay

The Chi-square test was used to evaluate differences between culture-positive and culture-negative children, p<0.05 was considered statistically significant.
* 20 children did not have cultures performed.

* *For these three subgroups, percentages are calculated out of the number of extrapulmonary TB cases. "Other" covers few cases of miliary TB, pleural and one unknown.
**TABLE 2:** Identified source cases to 88 Danish children with tuberculosis, stratified by age, Denmark, 2000-2013.

<table>
<thead>
<tr>
<th>Source cases</th>
<th>Children by age group</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-4 yrs</td>
<td>5-9 yrs</td>
</tr>
<tr>
<td>Household</td>
<td>44 (60)</td>
<td></td>
</tr>
<tr>
<td>Parents</td>
<td>16</td>
<td>10</td>
</tr>
<tr>
<td>Siblings</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Others</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td><em>Part of epidemiological</em></td>
<td>20</td>
<td>13</td>
</tr>
<tr>
<td>Non-household</td>
<td>29 (40)</td>
<td></td>
</tr>
<tr>
<td>Family</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Day-care-centre</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Unspecified</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td><em>Part of epidemiological</em></td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>Total identified</td>
<td>73 (83)</td>
<td></td>
</tr>
<tr>
<td>Un-Ident.</td>
<td>6</td>
<td>5</td>
</tr>
</tbody>
</table>

Abbreviations: yrs = years, N = number

In the subgroup of “Others” in the household source cases were e.g. grandmother, au pair or unspecified.

In the subgroup of “Unspecified” in the non-household source cases the precise relation to the child with TB was not known or for other reasons not notified to the authorities.
**TABLE 3**: Number of genotype matches between household- and non-household source cases and culture-positive Danish children with tuberculosis, stratified by age group, Denmark 2000 -2013.

<table>
<thead>
<tr>
<th>Source cases</th>
<th>Children by age group</th>
<th>Total</th>
<th>N = 34 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-4 yrs</td>
<td>5-9 yrs</td>
<td>10-14 yrs</td>
</tr>
<tr>
<td>Household</td>
<td>5</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Non-household</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Potential</strong></td>
<td>5</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

Abbreviations: yrs = years, N = number

* Potential matches are matches between children with TB disease and potential source cases on genotype, outbreak number and municipality.