Tuberculosis control among immigrants
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Chapter 5

Missed opportunities in tuberculosis control in the Netherlands due to prioritisation of contact investigations

Christiaan Mulder, Connie G. M. Erkens, Peter M. Kouw, Erik M. Huisman, Wieneke Meijer-Veldman, Martien W. Borgdorff, Frank van Leth

ABSTRACT

Background: The Dutch contact investigation guidelines stipulate that Public Health Services should examine contacts around all pulmonary tuberculosis patients to prevent disease and further transmission. Our objective was to assess to what extent these guidelines were applied and whether patient characteristics were associated with having contacts investigated.

Methods: We extracted the records of all reported pulmonary tuberculosis patients from the nationwide surveillance register covering 2006 to 2007. Patient characteristics associated with having contacts investigated were assessed by multivariable logistic regression analysis.

Results: Out of the 1236 pulmonary tuberculosis patients reported, 909 (74%) patients were eligible for analysis, since 133 (11%) patients had incomplete records, and 194 (16%) patients were registered by Public Health Services whom did not report contact investigation results. For 710 (78%) out of the 909 patients contacts were investigated. Compared to Dutch patients, contacts were significantly less often investigated around immigrant patients (84% versus 75%, OR: 0.60; 95%CI: 0.40-0.92). Contacts were significantly more often investigated for smear positive patients (OR: 3.52; 95%CI: 2.23-5.55) and culture positive patients (OR: 2.71; 95%CI: 1.76-4.16), compared to smear negative and culture negative patients, respectively.

Conclusion: Initiating contact investigations appear to be prioritised based on the infectiousness, but also on the ethnicity of pulmonary tuberculosis patients. By not investigating the contacts of 25% of the immigrant patients, there is a risk of missing a significant number of infected and diseased contacts, since the incidence in this group is markedly higher than in the Dutch population.
INTRODUCTION

Eliminating tuberculosis (TB) in the Netherlands will not be reached during the coming decades mostly due to continuing immigration of individuals from countries with a high burden of tuberculosis (1). Since the incidence in the Netherlands is low, 7.0 cases per 100,000 individuals in 2009, the TB control strategy focuses on identifying tuberculosis infection or disease in high risk groups including immigrants, the homeless, and contacts of tuberculosis patients.

Public Health Services (PHSs) in the Netherlands are responsible for contact investigations. According to the national guidelines, contacts around each newly diagnosed patient with a pulmonary TB (PTB) component should be examined for TB and/or latent tuberculosis infection (LTBI) (2). The extent of these contact investigations depend on the infectiousness of the index case and the probability of the contacts being exposed to the bacterium. The nurse practitioner with or without the assistance of a medical doctor, assesses for each identified contact this probability based on frequency, intimacy and setting of exposure, and on the vulnerability of the contact. The investigations follow the stone-in-the-pond principle irrespective whether a patient belongs to a risk group or not (3). Screening for infection starts in the most exposed contacts and continues to the less exposed contacts until the infection prevalence resembles the background prevalence of infection in the community, which was estimated in 2005 to be 2.40%, or until all identified contacts are screened. This background prevalence is estimated from the risk of TB infection, which is estimated in the Netherlands since 1910 (4).

Screening contacts of PTB patients is considered as a key element in the prevention of disease and further transmission (5). It is unknown to what extent the national guidelines are followed and whether specific patients are less likely to have their contacts examined. Signals from surveillance data show differences in size and yield of contact investigations between Dutch and immigrants. This suggests that the prioritisation of investigating contacts is based on other criteria than those recommended in the guidelines. The purpose of this study was therefore to answer the following questions. 1) For which proportion of pulmonary tuberculosis patients are the contacts investigated? 2) Which demographic and clinical characteristics of pulmonary tuberculosis patients associate significantly with having contacts investigated? This will give an indication on how the national guidelines are implemented in every-day patient care, since it reflects the unknown prioritisation processes. Furthermore, this will give insight for which groups of patients contact investigations currently work inadequately. In this study we focused on differences between Dutch and immigrant patients because we have the impression that the process of investigating contacts between both patient groups differs. Since it is estimated that the
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proportion of immigrant patients in the Netherlands will increase the coming decades (1), it is essential to get more insight in the adequacy of preventive strategies in the immigrant patient population.

METHODS

Study population
In the Netherlands we have a comprehensive nationwide case-based TB register, the Netherlands Tuberculosis Register (NTR). Since 1993, the PHSs voluntarily report electronically all newly diagnosed TB patients through a web-based system. On national level the data are validated and any inconsistencies are discussed with the PHSs. Since 2006 most of the PHSs also report aggregated data on the size and the yield of contact investigations for each TB case per exposure group. We extracted the records of all registered cases with pulmonary tuberculosis in 2006 and 2007 from the NTR. Because PHSs do not regularly investigate contacts around patients with extrapulmonary TB (due to an assessment of low-risk of transmission), we only included those patients who had a pulmonary component, hereafter referred to as index cases.

Study definitions
For each reported index case in the NTR the PHSs recorded whether contacts were investigated. If this was unknown we assumed that no contacts were investigated.

We examined the following variables of the index cases for associations with having contacts investigated: sex, age, urban residence, ethnicity, smear positivity, cavitary TB, culture positivity, case finding and risk group. To reflect best the data as reported in the NTR we generated four age groups, 0-14, 15-34, 35-64 and ≥65 years. Urban index cases were those cases who lived in one of the four largest cities of the Netherlands.

We referred the first and second generation immigrants as the immigrant population and the autochthonous population as the Dutch population. Only index cases were included of whom the ethnicity was known. The TB incidence amongst second generation immigrants in the Netherlands mimics more the incidence amongst the autochthonous population and is therefore much lower than the incidence of the first generation immigrants. In a sensitivity analysis, we therefore assessed how the association changed between ethnicity and having a contact investigation performed if the second generation immigrant index cases were pooled with the autochthonous index cases instead of with the first generation immigrants.
Index cases were categorised as sputum smear positive when either Ziehl Neelsen (ZN) microscopy of sputum or bronchial alveolar lavage (BAL) was positive. When smear status was unknown, we considered it as negative. Index cases were classified as having cavitary TB when this was recorded in the diagnosis, and as culture positive if the diagnosis was bacteriologically confirmed by culture. Index cases with unknown culture results (2%) we considered as culture positive. In daily practice, PHSs consider patients as potentially infectious unless the culture results proof otherwise. Actively found index cases were those cases who were found by (periodically) screening. Passively found index cases were those cases who contacted a health care facility by themselves. When it was unknown how cases were found (4%), we considered them as passively found. Index cases who belonged to a risk group were: contacts, refugees, asylum seekers, illegal residents, homeless persons, prisoners, drug addicts, health care workers, previously diagnosed patients, travellers (>3 months to endemic area), sailors and others.

Ethical approval was not deemed necessary since retrospective surveillance data was used without the possibility of linking patients’ records to patients’ personal data.

**Statistical analysis**

Characteristics of the index cases are presented stratified by the ethnicity of the index cases. Associations between the characteristics of the index cases and having contacts investigated were assessed by logistic regression analysis. By using a forward stepwise procedure, starting with ethnicity as the basis for the model, we determined which variables explained best the overall variance in having a contact investigation performed by assessing the log-likelihood ratio for consecutive nested models. The significance of a variable within a model was assessed by the Wald test. We first included the demographic variables in the model and continued with the clinical variables. We checked for interaction between ethnicity and all explanatory variables in the association with having contacts investigated. For the sensitivity analysis for ethnicity the identical multivariable regression method was used. Associations were considered statistical significant when p-values were ≤0.05, for interaction terms p-values of ≤0.1 were used. All analyses were performed in SPSS 17.0 (Chicago, IL, USA).

**RESULTS**

The extracted data from the NTR yielded 1236 index cases over 2006 and 2007 (Figure). Of these, 909 (74%) index cases were eligible for analysis, since 98 (8%) index cases had incomplete records, 194 (16%) index cases were registered by PHSs who did not participate in the data collection of contact investigation results, and for 35 (3%) index
cases the ethnicity was unknown. More than two-third of the eligible index cases was immigrant.

Compared to Dutch index cases, immigrant index cases were relatively younger, more often actively found, more often from a risk group and more often from an urban area (Table 1). Two hundred and eighty three (46%) of the immigrants were part of a risk group, of these 67 (24%) were asylum seeker and 41 (14%) were illegal residents.

For 710 (78%) of the index cases the contacts were investigated (Table 2). No contacts were investigated for 8% of the smear positive and 17% of the culture positive index cases. The majority of these index cases were immigrant males from rural areas. Six out of the 33 (18%) smear positive index cases without having contacts investigated were asylum seekers. For the culture positive index cases without having contacts investigated 22% (26/130) was asylum seeker.
Table 1. Baseline characteristics of Dutch and immigrant index cases

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Dutch n (%)</th>
<th>Immigrant n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>294</td>
<td>615</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>178 (61)</td>
<td>368 (60)</td>
</tr>
<tr>
<td>Female</td>
<td>116 (39)</td>
<td>247 (40)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-14</td>
<td>6 (2)</td>
<td>27 (4)</td>
</tr>
<tr>
<td>15-34</td>
<td>43 (15)</td>
<td>290 (47)</td>
</tr>
<tr>
<td>35-64</td>
<td>123 (42)</td>
<td>235 (38)</td>
</tr>
<tr>
<td>65+</td>
<td>122 (41)</td>
<td>63 (10)</td>
</tr>
<tr>
<td>Region</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>55 (19)</td>
<td>191 (31)</td>
</tr>
<tr>
<td>Rural</td>
<td>239 (81)</td>
<td>424 (69)</td>
</tr>
<tr>
<td>Smear positive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>153 (52)</td>
<td>326 (53)</td>
</tr>
<tr>
<td>Yes</td>
<td>141 (48)</td>
<td>289 (47)</td>
</tr>
<tr>
<td>Cavitary TB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>231 (79)</td>
<td>487 (79)</td>
</tr>
<tr>
<td>Yes</td>
<td>63 (21)</td>
<td>128 (21)</td>
</tr>
<tr>
<td>Culture positive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>52 (18)</td>
<td>96 (16)</td>
</tr>
<tr>
<td>Yes</td>
<td>241 (82)</td>
<td>519 (84)</td>
</tr>
<tr>
<td>Case Finding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Passive</td>
<td>255 (87)</td>
<td>441 (72)</td>
</tr>
<tr>
<td>Active</td>
<td>39 (13)</td>
<td>174 (28)</td>
</tr>
<tr>
<td>Risk group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>190 (65)</td>
<td>332 (54)</td>
</tr>
<tr>
<td>Yes</td>
<td>104 (35)</td>
<td>283 (46)</td>
</tr>
</tbody>
</table>

The univariable regression analysis revealed that, except for sex and age, all explanatory variables were significantly associated with whether contacts were investigated.

In the multivariable analysis, contacts were significantly less often investigated around immigrant index cases (OR: 0.60; 95%CI: 0.40-0.92) compared to Dutch index cases. Contacts were significantly more often investigated for smear positive index cases (OR: 3.52; 95% CI: 2.23-5.55) and culture positive index cases (OR: 2.71; 95%CI: 1.76-4.16), compared to smear negative and culture negative index cases, respectively. Contacts were significantly less often investigated around actively found index cases compared to passively found index cases (OR: 0.38; 95%CI: 0.26-0.57), and around index cases who belonged to a risk group compared to index cases who did not (OR: 0.44; 95%CI: 0.30-0.65). Compared to index cases without cavitations, contacts of index cases with cavitations were more likely to be examined, although this difference was not statistically
significant (OR: 1.65; 95%CI: 0.89-3.06). Contacts of rural index cases were less often examined, although not statistically significant, compared to contacts of urban index cases (OR: 0.72; 95%CI: 0.47-1.10).

None of the explanatory variables showed interaction on the association of ethnicity and having contacts investigated.

In the sensitivity analysis we found that contacts of first generation immigrants index cases were less likely to be investigated compared to contacts of the group consisting of second generation immigrants and Dutch index cases, and that the association found (OR: 0.55; 95%CI: 0.37-0.82) was similar to our initial analysis.
DISCUSSION

This study shows that contacts were not investigated for 22% of the TB patients with a pulmonary component in the Netherlands over 2006 and 2007. This could lead to potentially missed opportunities in identifying individuals with LTBI or active disease. The results of our study suggest that both demographic and clinical characteristics of infectiousness associate significantly with having contacts investigated. Our data indicate that contacts were significantly less often investigated when the index cases were either immigrants, sputum smear negative, culture negative, actively found or member of a risk group. These findings give direction on how the national contact investigation guidelines are implemented in daily practice.

Contacts of immigrant index cases were significantly less often investigated compared to contacts of Dutch index cases. For a quarter of the immigrant index cases no contacts were investigated for TB or LTBI. The potential public health consequence for this is evident. Two-third of the index cases of our study population was immigrant, and it is assumed that this proportion in the Netherlands will increase to 85% during the coming decades (1). Taking into consideration that the proportion of Dutch patients with TB attributable to transmission from an immigrant index case increased from 29% in 1995 to 50% in 2005 (6), this highlights that all immigrant index cases are marked sources for ongoing TB transmission, and that efforts should be undertaken to investigate contacts of immigrant index cases.

There are several possible reasons why contacts of immigrant index cases were less often investigated. One explanation might be, as supported by our data, that immigrant index cases were relatively more often diagnosed through active case finding. TB might be, for example, diagnosed by chest X-ray during the mandatory entry screening for immigrants from non-Western countries who are intending to stay longer than 3 months in the Netherlands (7). Close contacts, like the family members, have most likely undergone the entry screening at the same moment. Therefore repeating the chest X-ray in the context of contact investigation would be deemed as unnecessary. Additional screening for LTBI in the context of contact investigation is seen as unnecessary. According to the guidelines screening of contacts for LTBI is restricted to persons and situations where the difference between the expected prevalence of infection and the background prevalence in the population is large enough to guarantee a reliable positive predictive value for recent infection. In practice this means that screening for LTBI is restricted to persons born in the Netherlands after January 1st, 1945 and persons born in endemic areas younger than 12 years. Nevertheless, our multivariable model showed that ethnicity remained significantly associated when adjusted for the way of case finding. Other factors might have played a role, like the unwillingness of immigrant index cases to name their contacts.
or a limited capacity of PHSs to keep track of immigrant index cases. It is suggested that compared to Dutch patients, immigrants more often do not have or do not report any contacts. In all these cases PHSs might report in the surveillance register that no contact investigation was performed, despite the efforts made of making a list of eligible contacts.

Indicators of infectiousness such as smear status of an index case appeared to be an important component for the decision whether to start a contact investigation. For smear negative index cases contacts were investigated significantly less likely compared to smear positive index cases. However, for 8% of the sputum-smear positive index cases no contacts were examined. Although it is well known that smear positive index cases are more infectious compared to smear negative index cases, previous research has indicated that 13% of the TB transmission in the Netherlands is attributed to smear negative, culture positive index cases (8). The Dutch guidelines therefore prescribe that around smear negative index case at least the close contacts should be examined.

Similarly, compared to culture positive index cases we found that for culture negative index cases contacts were significantly less often investigated. The national guidelines prescribe that, in order to prevent further transmission, contact investigations should start as soon as possible irrespective of knowing the culture status of the index case. Therefore, this finding implies that either the national guidelines are used differently in this respect, or that some sort of registration error is made, e.g. by mistakenly reporting that no contact investigation was performed after terminating it because the index case appeared to be culture negative. More in-depth research is needed to clarify how culture status is affecting the initiation and/or termination of a contact investigation and whether specific training is required to enhance the registration process.

Contacts of actively found index cases were three times less likely to be investigated compared to contacts of passively found index cases. Probably most of the contacts of actively found index cases were also part of a contact group suitable for active screening. As a consequence, most of these contacts were screened periodically and therefore initiating a new contact investigation was deemed unnecessary. Similarly, we found that contacts of index cases who belonged to a risk group were less often investigated, probably because they were themselves also part of a risk group and therefore periodically screened.

For the index cases of whom the contacts were investigated, the PHSs reported in the nationwide tuberculosis register on aggregated level how many contacts were identified, how many were screened, how many were diagnosed with TB and how many with LTBI. Presenting the coverage and yield of these contact investigation are beyond the scope of this paper.
PHSs investigate whether there is an epidemiological link between clustered patients, patients with an identical DNA-fingerprint, to get more insight in transmission patterns. Contact investigations are an essential component of assessing these epidemiological links. Van Deutekom et al. showed that many clustered patients were not identified if only contact investigations were conducted (9). This finding suggests that epidemiological links between clustered patients were missed. Not initiating contact investigations could be a reason of missing these epidemiological links.

To our knowledge, our study is the first that gives insight into the prioritising process in terms of assessing which characteristics of index cases are associated with whether contacts are investigated. Moreover, our findings are from nationwide surveillance data. Recently, the Centers for Disease Control and Prevention (CDC) published data which showed that in the United States (US) during 2002-2006 around 92% of the sputum-smear positive TB patients contacts were examined annually (10). This figure is identical to ours. This indicates that not only in the Netherlands, but also in the US, difficulties are faced with organising contact investigations for the most contagious group of index cases. In order to improve this, more insight is needed on why contacts of sputum-smear positive TB patients are not always investigated. Based on our findings we could state that, at least over 2006 and 2007, the Netherlands did not reach the objective of having 90% of the index cases having listed at least one contact, as was proposed by an European expert group (11).

The observed prioritisation in investigating contacts seems to be in general based on valid arguments. Contacts investigated around actively found index cases and index cases from a risk group are not always examined due to existing additional screening policies. Contacts from smear negative and culture negative index cases can be seen as having a very low risk of transmission. However, not investigating contacts around immigrant index cases does not seem to be based on valid arguments and can be seen as a missed opportunity for tuberculosis control.

In conclusion, the outcomes from the nationwide surveillance register about contact investigations showed that not around each index case the contacts were investigated. Index cases appeared to be prioritised for having their contacts investigated not only on indicators of infectiousness but also based on demographic characteristics. We found that contacts of immigrant index cases were significantly less often examined for LTBI and TB compared to contacts of Dutch index cases. This could hamper the effectiveness of TB control in the Netherlands since infected and diseased contacts are potentially missed. Reasons why contacts of immigrant index cases are less often investigated should be further investigated. The daily practice of investigating contacts appeared to differ from...
how it is prescribed in the national guidelines. A thorough evaluation of how the national guidelines are translated into daily practice will give insight on how decisions are made during the process of investigating contacts.

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