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Tuberculosis infection in children who are contacts of immigrant tuberculosis patients

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ABSTRACT: The present study aimed to determine what proportion of children who are in close contact with immigrant tuberculosis (TB) patients are infected with *Mycobacterium tuberculosis*.

For 1.5 yrs, 14 municipal health services in the Netherlands collected data from all non-Dutch TB patients and their contacts. Close contacts aged <16 yrs received a tuberculin skin test (TST). A positive TST was defined as an induration of ⩾10 mm among nonvaccinated children, and ⩾16 mm among bacille Calmette–Guérin-vaccinated children.

In total, 244 patients had 359 close contacts aged <16 yrs. Nine out of the 359 (2.5%) had TB. A TST test was given to 298 out of the 359 (83%). Of the 115 contacts of 44 extrapulmonary TB patients, three (3%) had a positive TST. Of the 186 contacts of 58 positive pulmonary TB patients, 30 (16%) had a positive TST. Contacts of sputum smear-positive patients significantly more often had a positive TST (25%), compared with the contacts of sputum smear-negative patients (7%). Children born abroad significantly more often had a positive TST (20%) than children born in the Netherlands (5%).

In conclusion, the prevalence of active tuberculosis and latent tuberculosis infection among children who are close contacts of immigrant tuberculosis patients is high and warrants an expansion of contact investigation.

KEYWORDS: Infection control, infectious lung diseases, tuberculosis control, tuberculosis epidemiology, tuberculosis in childhood, tuberculosis infection

In the Netherlands, 70% of tuberculosis (TB) patients are immigrants [1]. TB control measures among immigrants include radiographic screening for 2 yrs after entry, contact tracing of TB patients and vaccination of the 6-month-old children of immigrants. In spite of these control measures, TB incidence in immigrants remains high for ⩾10 yrs after immigration [2–4]. One of the possible reasons may be low coverage and yield of contact tracing. In the Netherlands, contacts who are not bacille Calmette–Guérin (BCG) vaccinated are usually investigated by means of tuberculin skin test (TST) to identify a possible infection, while BCG-vaccinated contacts are only investigated by means of chest radiography to identify possible active disease [5].

It is important to assess the yield of contact tracing among immigrants, since they may have a different risk of infection and progression of disease than the local population [4, 6]. To the current authors' knowledge, there is no report on the prevalence of latent tuberculosis infection (LTBI) in children of immigrant TB patients. The index patient being an immigrant was a risk factor for infection in contacts, and immigrants were more often infected than the local population [7, 8].

Most studies that report the infection prevalence in children who are close contacts of sputum smear-positive pulmonary tuberculosis (PTB) patients are from decades ago and in settings with a high background infection risk [9, 10]. There are only a few recent studies conducted in low-incidence areas, and none specifically in immigrants [11–13].

The objectives of the present study were to determine what proportion of BCG-vaccinated and nonvaccinated children who are close contacts of immigrant TB patients have a positive TST, and to identify risk factors for a positive TST. In order to assess the background prevalence of a positive TST in young contacts of immigrants, contacts of PTB patients were compared with contacts of extrapulmonary tuberculosis (EPTB) patients.

MATERIALS AND METHODS

Study subjects

This study was part of a larger study on the effectiveness of screening among immigrants.

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The study was ethically approved by the medical committee for research in humans (CWOM) in Nijmegen, the Netherlands.

Between September 2000 and July 2002, 14 Municipal Health Services (MHSs) in the Netherlands collected data on all immigrant TB patients (presumed index cases) and their contacts. Patients who were born in the Netherlands from non-Dutch parents were also included. The 14 MHSs were representatives for all 40 MHSs in the Netherlands, with respect to geographical location and urban/rural distribution. Both asylum seekers and other immigrants were included.

Contact tracing was performed according to the ''stone in the pond'' principle, in which rings are distinguished based on their closeness of contact [10, 14]. The first ring only included children aged <16 yrs, defined as young close contacts who have regular (at least 4 times per week) contact with the index patient.

Study design

All included contacts in the study received a TST irrespective of BCG vaccination. TST was performed using 2 TU purified protein derivative RT23 with Tween-80 (Statens Serum Institut, Copenhagen, Denmark), and the induration was read after 3–4 days. Indurations >0 mm were usually read by two TST technicians. Contacts of sputum smear-positive PTB patients usually received the TST ~3 months after diagnosis. Contacts of EPTB patients generally received the TST within 5 weeks of diagnosis. In MHSs where TST after BCG was not part of the policy, parents of contacts and contacts aged >12 yrs were asked for informed consent.

Methods

Staff of the MHS visited each patient to encourage investigation of contacts. They registered the following information: date of birth; sex; country of origin; relationship to patient; frequency of contact with patient; household member of patient; ring assigned; date of BCG (if vaccinated); duration of stay in the Netherlands; prior TST results; current date of TST; and induration in mm. Prior BCG vaccination was assessed both by looking for a scar and asking the parent or guardian for vaccination history. Data from contact investigation were linked to the Netherlands Tuberculosis Register to obtain age, sex, country of origin, duration of stay in the Netherlands, date of diagnosis, patients' and doctors' delay, method of case finding (by screening or by self reporting with symptoms, *i.e.* passively), location of TB, and sputum smear and culture results of the index patients. The sputum smear test was performed with Ziehl Neelsen staining. Patients having both PTB and EPTB were assigned PTB.

Analysis

A positive TST in children without BCG vaccination was defined as having a TST induration of ⩾10 mm. Since there was no experience with using the TST in BCG-vaccinated children in the Netherlands, the cut-off point for a positive TST in those children was decided after studying the induration distribution.

In order to assess risk factors for infection, children with a positive TST and their index patients were compared with children with a negative TST and their index patients by univariate and multivariate logistic regression analysis.

RESULTS

TB patients and their contacts

During the study period, the 14 MHSs diagnosed 416 immigrant TB patients. The contacts of 244 (59%) patients were investigated. The main reasons given for no contact tracing were the patient: 1) being detected at entry screening (n=37; 22%); 2) having EPTB (n=33; 19%); 3) having moved (n=24; 14%); 4) being sputum smear negative (n=20; 12%); 5) being an asylum seeker living in an asylum seekers' centre where half-yearly screening takes place (n=17; 10%); and 6) being a contact of another patient (n=10; 6%). For 20 patients, other less common reasons were given and for 10 patients the reason was unknown. In total, 3,085 contacts of the 244 patients (mean 11; range 1–135 per patient) were investigated.

TB among contacts

Out of 3,085 TB contacts, 19 had TB themselves (0.7%). For brevity, close contacts aged <16 yrs in the first ring were referred to as young contacts. Of the 359 young contacts, nine had TB (2.5%). All nine cases were contacts of seven PTB patients, of whom five were sputum smear positive, one sputum smear negative and one had an unknown sputum smear result. All were family members, except one who was a close friend living in the same house. Four of seven index patients were from Somalia.

TST among young contacts

Out of 359 young contacts, 300 underwent a TST (83%) and 298 of these showed up for reading (table 1). Reasons for no TST

TABLE 1 Selection of young contacts of immigrant tuberculosis (TB) patients

Characteristics of contacts	Contacts n	Index patients involved n
Total patients	3085	416
PTB		261 (63)
EPTB		155 (37)
Belong to patients with contact tracing	3085	244 (59)
Contact aged <16 yrs	591[#]	151
First ring	373[¶]	121 (50[+])
Visit MHS	359	119
Undergo TST	300	101
TST read	298 (83[§])	100 (84[f])
First ring contacts aged <16 yrs with TB but no TST	3	3[##]
Total included	301 (84[§])	102 (84[f,¶¶])

Data are presented as n or n (%). PTB: pulmonary TB; EPTB: extrapulmonary TB; MHS: municipal health service; TST: tuberculin skin test. [#]: 565 contacts age unknown; [¶]: 51 contacts ring unknown; [+]: percentage of index patients with contact tracing; [§]: percentage of contacts who visited MHS; [f]: percentage of index patients who visited the MHS; [##]: one out of three is also in 100 patients whose contacts had TST read; [¶¶]: two HIV-positive patients.

were as follows: 1) refusal of the parents or child (n=7); 2) time constraints at the MHS (n=13); 3) investigated at a MHS not involved in the study (n=5); 4) reporting a previous positive TST (n=3); 5) asylum seeker without family nearby (n=3); 6) feeling ill (n=1); 7) radiograph already showing active TB (n=1); and 8) unknown (n=26). Three out of the nine contacts who had active TB had no TST performed, and they were assumed to have a positive TST result. In total, 301 children were included in the study. They belonged to 102 index patients, who had, on average, three contacts (median 2; maximum 18).

Identification of cut-off point for a positive TST in those with and without previous BCG

BCG-vaccinated children had larger indurations than non-vaccinated children (fig. 1). Numbers were too low to assess infection prevalence by mirror or mixture methods [15, 16]. The decision was made to define a positive TST in BCG-vaccinated children as an induration of $\geqslant$16 mm for two reasons. First, in other studies, it was shown that reactions >15 mm were more likely to be due to infection rather than to BCG [17]. Secondly, this was confirmed in the current study in EPTB patients that were considered noninfectious. Out of 67 BCG-vaccinated young contacts of EPTB patients, nine (13%) had an induration ranging 10–15 mm, but only three had an induration of >15 mm (4%; fig. 2). In nonvaccinated contacts, no young contact of any EPTB patients had an induration of >0 mm (fig. 1). Children with unknown BCG status all had a TST with <10 mm induration and were, therefore, probably not infected.

Among children without BCG, the proportion with a TST result of $\geqslant$10 mm was none out of 43 (0%) among contacts of EPTB patients, and six out of 71 (8%) among contacts of PTB patients (fig. 1). Among children with BCG, the proportion with a TST result of $\geqslant$15 mm was three out of 67 (4%) among contacts of EPTB patients (all born outside of the Netherlands), and 20 out of 103 (19%) among contacts of PTB children (fig. 2).

Risk factors for infection

Of the 301 children included, 33 (11%) had a positive TST according to the current authors' criteria (TST $\geqslant$10 mm in nonvaccinated or $\geqslant$16 mm in vaccinated children). Index patient-related risk factors for a positive TST in their contacts were having an index patient with PTB, and among index patients with PTB those who were sputum smear positive (table 2). Sputum smear was not usually performed in 10 patients, since bronchoalveolar lavage was carried out. In 165 out of 301 (55%) children who had information on diagnostic delay of their index patient (n=59), child contacts who had a positive TST were related to index patients with a longer patient delay (n=24 contacts of 15 index patients; mean delay 7.6 weeks; median 6.0 weeks) than child contacts who had a negative TST (n=141 contacts of 54 index patients; mean delay 6.6 weeks; median 4.0 weeks; Mann-Whitney U-test p=0.05). There was no difference between contact children with a positive TST and contact children with a negative TST in doctors' delay nor in total delay (defined as patients' delay plus doctors' delay) of their index patients. Close contacts of Somalian PTB patients had a positive TST more often than other nationalities after adjustment for smear positivity (adjusted odds ratio (OR) 2.65; 95% confidence interval (CI) 1.08–6.5). Contacts of PTB patients detected by screening tended to have a positive TST less often than contacts of PTB patients detected passively, but this difference was not significant (three out of 27 (11%) *versus* 26 out of 131 (20%); OR 0.5; 95% CI 0.1–1.9). ORs were similar when patients instead of contacts were compared, and which patient had at least one contact with a positive TST was assessed.

The only risk factor among children for having a positive TST was being born outside the Netherlands. Having a BCG vaccination was borderline significant and older age showed a nonsignificant trend with the proportion of children having a positive TST (table 3). Household contacts tended to have a positive TST more often than nonhousehold contacts, but this difference was not significant. Among household contacts of

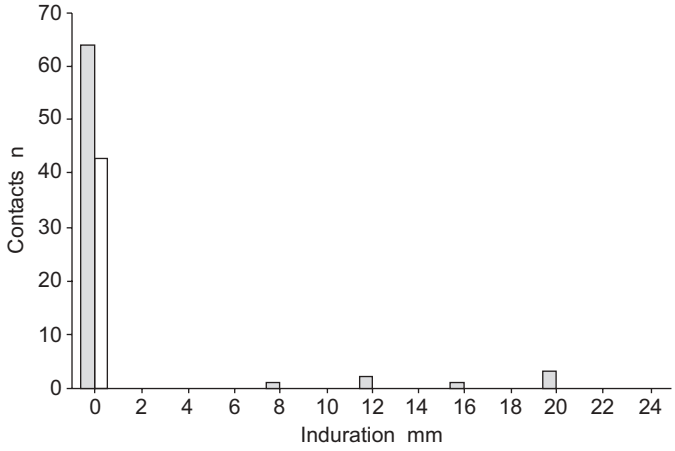

FIGURE 1. Induration size (0=0–1 mm, 2=2–3 mm, *etc.*) of tuberculin skin tests in non-bacille Calmette–Guérin-vaccinated close contacts aged <16 yrs (n=113), by type of tuberculosis (TB) of the index patient (pulmonary TB (■: n=70) and extrapulmonary TB (□: n=43)).

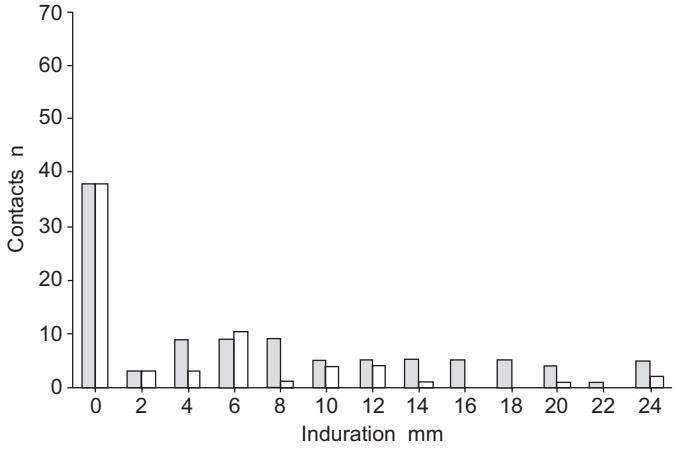

FIGURE 2. Induration size (0=0–1 mm, 2=2–3 mm, *etc.*) of tuberculin skin test in bacille Calmette–Guérin-vaccinated close contacts aged <16 yrs (n=170), by type of tuberculosis (TB) of the index patient (pulmonary TB (■: n=103) and extrapulmonary TB (□: n=67)).

TABLE 2 Risk factors among patients for infection in their close young contacts[#]

Patient characteristics	Patients n	Child with close contacts with TST n	Young contacts with positive TST n (%)	Crude OR (95% CI)
Age yrs				
0–24	25	93	11 (12)	1
25–34	33	78	6 (8)	0.62 (0.22–1.76)
35–44	27	86	13 (15)	1.33 (0.56–3.15)
⩾45	17	44	3 (7)	0.55 (0.14–2.06)
Sex				
Male	42	131	15 (12)	1.09 (0.53–2.26)
Female	60	170	18 (11)	1
Country of origin				
Morocco	15	49	3 (6)	0.42 (0.12–1.50)
Turkey	8	26	2 (8)	0.53 (0.12–2.47)
Somalia	36	126	17 (14)	1
Other African country	10	31	2 (7)	0.44 (0.10–2.02)
Asia	26	58	6 (10)	0.74 (0.28–1.99)
Other	7	11	3 (27)	2.40 (0.58–9.97)
Type of immigrant				
Asylum seeker	57	171	23 (13)	1.53 (0.66–3.59)
Other immigrant	37	87	8 (9)	1
Unknown	8	43	2 (5)	
Location of TB				
PTB	58	186	30 (16)	7.2 (2.1–24.1)*
EPTB	44	115	3 (3)	1
Sputum smear[¶]				
Positive	25	88	22 (25)	5.2 (1.69–16)*
Negative	23	54	4 (7)	1
Unknown	10	44	4 (9)	
Culture[¶]				
Positive	40	123	22 (6)	NA
Negative	5	15	0	
Unknown	13	48	8 (17)	
Born abroad[+]				
Yes	95	259	32 (12)	1
No	7	42	1 (2)	0.17 (0.02–1.30)
Duration of stay in the Netherlands yrs				
<2.5	27	175	19 (11)	1
⩾2.5	64	69	11 (16)	1.56 (0.70–3.47)
Unknown	11	57	3 (5)	
Method of case detection				
Screening	15	29	4 (14)	1.26 (0.41–3.90)
Passive	83	249	28 (11)	1
Contact tracing	4	23	1 (4)	
Total	102	301	33 (11)	

Data are presented as n or n (%), unless otherwise stated. TST: tuberculin skin test; OR: odds ratio; CI: confidence interval; TB: tuberculosis; PTB: pulmonary TB; EPTB: extrapulmonary TB; NA: not available. [#]: n=301, unless otherwise stated; [¶]: PTB n=56; [+]: *i.e.* outside the Netherlands. *: $p<0.05$.

sputum smear-positive PTB patients, 16 out of 52 children (31%) had a positive TST.

In a multivariate analysis including patient and child factors, only being born outside the Netherlands was significant (table 4). Children with a positive TST who were contacts of EPTB patients were all born outside the Netherlands. When repeating the analysis within young contacts of PTB patients, being born abroad was the significant risk factor (OR 3.52; 95% CI 1.12–11.0), and also after adjustment for sputum smear positivity (OR 3.26; 95% CI 1.01–11). When adding Somalia as the country of origin of the patient into this analysis, it did not contribute to the model.

DISCUSSION

The present study has shown that the prevalence of a positive TST among close young contacts of immigrant TB patients was

TABLE 3 Risk factors among children who are close contacts for infection#

Contact characteristics	Children infected*	Univariate OR (95% CI)
Age yrs		
0–5	11/132 (8)	1
6–10	7/76 (9)	1.12 (0.41–3.01)
11–15	15/93 (16)	2.12 (0.92–4.84)
Sex		
Male	19/159 (12)	1.23 (0.59–2.56)
Female	14/141 (10)	1
Unknown	0/3	
Country of origin		
Netherlands	11/87 (13)	1
Morocco	1/32 (3)	0.22 (0.03–1.80)
Turkey	2/14 (14)	1.15 (0.23–5.85)
Somalia	12/90 (13)	1.06 (0.44–2.56)
Other African country	0/16 (0)	
Asia	5/47 (11)	0.82 (0.27–2.53)
Other	0/8	
BCG		
Yes	25/172 (15)	2.30 (1.00–5.29)
No	8/116 (7)	1
Unknown	0/14	
Time since BCG yrs¶		
0–5	5/50 (10)	1
>5	7/51 (14)	1.43 (0.42–4.85)
Unknown	13/71 (18)	
Born abroad+		
No	5/96 (5)	1
Yes	15/75 (20)	4.55 (1.57–13.2)*
Unknown	113/117 (11)	
Living in the same house		
Yes	26/199 (13)	1.95 (0.82–4.67)
No	7/98 (5)	1
Unknown	0/4	
Relationship to patient		
Family	27/248 (11)	1
Friends	3/17 (18)	1.75 (0.47–6.50)
School	2/30 (7)	0.58 (0.13–2.59)
Other	1/6 (17)	
Frequency of contact		
Daily	31/271 (11)	1
Not daily	2/15 (13)	1.19 (0.26–5.53)
Unknown	0/5	
Total	33/301 (11)	

Data are presented as n/N (%), unless otherwise stated. OR: odds ratio; CI: confidence interval; BCG: bacille Calmette–Guérin. #: n=301, unless otherwise stated; ¶: n=172; +: *i.e.* outside the Netherlands. *: $p<0.05$.

16% among contacts of PTB patients, and 3% among contacts of EPTB patients. The prevalence among young contacts of sputum smear-positive PTB patients was 25% and among sputum smear-negative PTB patients 8%. The only risk factor for having a positive TST among young contacts was being born abroad.

The prevalence of a positive TST among young contacts of sputum smear-positive PTB patients was lower than the prevalence found in high-incidence countries [18–21], and older studies in other countries during decades with medium or high TB incidence [9, 10, 22]. The main reason is probably that, in high-incidence settings, infection in contacts is often attributable to casual contact with others rather than the index patient, due to a higher infection pressure [23]. The prevalence of a positive TST in young contacts of smear-positive PTB patients found by the current authors was also lower than in low-incidence settings in Spain (61%), but similar to those in France (22%) and Alaska (35%) [11–13].

The main risk factor among index patients was having sputum smear-positive PTB, as was reported previously [10, 12, 13]. Young contacts of EPTB patients were probably not infected by their index patient, but by another patient. Young contacts of Somalian PTB patients had a positive TST more often than contacts of Moroccan patients. The present authors could not confirm other risk factors among index patients for a positive TST in the contacts, such as younger age, which was found by others [13]. This was possibly due, in part, to the small number of immigrant patients that had young contacts, and low prevalence of a positive TST that gave the study less power.

The apparent protective effect of screening for PTB on a positive TST in contacts was slightly larger in size (56%) than was estimated in earlier studies [24, 25]. However, this difference was not significant. Only a few patients had contacts that were identified by screening. Furthermore, most people that were identified by screening reported few contacts since they had been <2 yrs in the country, or their contacts were also in the screening programme. The significant effect of a longer patient delay on a positive TST among child contacts was another indication that screening for active TB may reduce secondary infections among contacts.

The current authors found only one risk factor for a positive TST among the young contacts. Children that were born abroad had, as expected, a positive TST more often. Although older children had a positive TST more often, as was found in other studies, this was not significant [6]. Older contacts have had a higher accumulated risk on contact with other TB patients. Even in those children that were born in the Netherlands, not all may be infected by the presumed index case, since return visits to the home region or country may be frequent and affect the risk of infection [26]. No effect of living in the same household or frequency of contact, as others had found, could be ascertained, probably since only close contacts were included in the present study [11, 18].

The study had two limitations. First, the cut-off point that was chosen for a positive TST in BCG-vaccinated contacts was arbitrary. Since 15 mm was chosen as a cut-off point, the infection prevalence in BCG-vaccinated contacts may have been underestimated. Most of the studies in high-incidence countries, and the study in Spain, used a cut-off point of 10 mm in BCG-vaccinated subjects [11, 13, 19]. However, the current authors may also have overestimated the infection prevalence in BCG-vaccinated children, for following reasons: 1) positive TST reactions due to *Mycobacteria* other than TB could not be excluded; and 2) the effect of BCG on the result of

TABLE 4 Risk factors among index patients and contacts themselves for infection in young contacts[#]

Characteristics	Patients n	Child close contacts with TST n	Young contacts with positive TST n (%)	Multivariate OR (95% CI)
Location of TB and sputum smear index				
PTB smear positive	25	88	22 (25)	22.6 (5.8–88.9)*
PTB smear negative	23	54	4 (7)	2.5 (0.5–12.0)
PTB smear unknown	10	44	4 (9)	4.4 (0.9–21.7)
EPTB	44	115	3 (3)	1
Contact born abroad[¶]				
No	NA	96	5 (5)	1
Yes		75	15 (20)	10.0 (2.9–34.8)*
Unknown		117	113 (11)	1.8 (0.6–5.6)
Total	102	301	33 (11)	

Data are presented as n or n (%), unless otherwise stated. TST: tuberculin skin test; OR: odds ratio; CI: confidence interval; TB: tuberculosis; PTB: pulmonary TB; EPTB: extrapulmonary TB; NA: not applicable. [#]: n=301; [¶]: *i.e.* outside the Netherlands. *: $p<0.05$.

the TST test may be stronger for BCG given at 6 months (as happens in children of immigrants in the Netherlands) than for BCG given at birth (as usual in most countries) [17]. This may have been the reason why BCG-vaccinated contacts seemed to have a positive TST more often than nonvaccinated ones, although this was not significant after adjustment for being born abroad. The appropriateness of the cut-off point of the TST for measuring infection prevalence may also be affected by reading errors and reversions [27].

The second limitation of the study was the low number of contacts included, limiting the power of the study to find risk factors for infection. Although not the main objective of the study, the present authors learned that both the proportion of immigrant TB patients where contact tracing takes place (40%), and the number of contacts investigated (average 11), were less than expected. Coverage of contacts among immigrants may be low, since only a few contacts may be indicated due to social stigmatism [8]. Also, contact tracing is less intensive for patients detected at entry screening and asylum seekers who are living in an asylum seekers' centre, since they undergo half-yearly screening by chest radiography. Therefore, contacts may have been missed.

The current study had the following policy implications. First, the high TB disease and positive TST rate among close contacts show the importance of contact tracing for disease and infection among immigrants. Recently, the Dutch guideline which advised not giving a TST to BCG-vaccinated subjects was changed to ''In contact tracing a history of BCG vaccination is no longer a contra-indication for LTBI screening'' [5]. The present study supports this decision. Children with a LTBI, who are close contacts of a pulmonary tuberculosis patient, may be offered preventive treatment, since they are likely to be recently infected. The choice depends on, among other things, the age of the child and the size of the TST. The risk of breakdown after infection varies strongly with age. It is highest among children aged <2 yrs, lowest among children of school age, and increases again during adolescence [28, 29]. The size of the TST may predict the risk of disease within 2 yrs [30–32].

The results of all immigrant PTB patients in the Netherlands were extrapolated to assess how many close young contacts should be offered LTBI treatment per year. In 2002, there were 862 non-Dutch patients, of whom 527 had PTB [33]. Therefore, the annual number of infected close young contacts of PTB patients can be estimated as the proportion of infected contacts (0.16), multiplied by the annual number of PTB patients (n=527), multiplied by the number of young contacts in the first ring (n=373), and divided by the number of index patients in the study (n=416), which equals 76. It should be feasible to offer these close young contacts preventative treatment.

Lastly, among immigrants, there may be the need for techniques to expand contact investigation. More contacts of immigrants need to be investigated than is current practice. In order to improve the contact tracing of immigrants, it may be helpful to have tuberculosis nurses of the same language and culture as the patients. The cost-effectiveness of offering preventative therapy to casual young contacts needs to be investigated [34, 35].

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