Yield of tuberculosis contact investigations in Amsterdam: opportunities for improvement

Rosa Sloot[1], Maarten F. Schim van der Loeff[2,3], Peter M. Kouw[2] and Martien W. Borgdorff[2,3]

Affiliations: [1]Dept of Clinical Epidemiology, Biostatistics and Bioinformatics, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands. [2]Dept of Infectious Diseases, Public Health Service, Amsterdam, The Netherlands. [3]Center for Infections and Immunity Amsterdam, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands.

Correspondence: Rosa Sloot, Dept of Clinical Epidemiology, Biostatistics and Bioinformatics, Academic Medical Center, PO 22660, 1100 DD Amsterdam, The Netherlands. E-mail: r.sloot@amc.uva.nl

ABSTRACT We aimed to determine the coverage and yield of tuberculosis contact investigation, and compliance with guidelines, and to identify opportunities for improvement.

Data were extracted from records on contacts of pulmonary tuberculosis patients at the Public Health Service (Amsterdam, the Netherlands) from 2008 to 2011. Additional data were obtained from the national tuberculosis register.

Among 3743 contacts of 235 pulmonary tuberculosis index patients, 2337 (62%) were screened for latent tuberculosis infection (LTBI). Those less likely to be screened for LTBI included contacts of sputum smear-negative index patients (adjusted odds ratio (aOR) 0.6, 95% CI 0.4–0.9) and bacille Calmette Guérin (BCG)-vaccinated contacts (aOR 0.06, 95% CI 0.04–0.09). Among BCG-vaccinated contacts, the proportion screened increased from 9% in 2008 to 43% in 2011 (p-value for trend <0.001). LTBI diagnosis among contacts screened was associated with non-Dutch nationality (aOR 2.8, 95% CI 1.9–4.1) and being a close contact (aOR 4.0, 95% CI 1.9–8.3). Of the 254 contacts with LTBI diagnosis, 142 (56%) started preventive treatment. Starting treatment was associated with Dutch nationality (aOR 2.6, 95% CI 1.2–5.4) and being a close contact (aOR 10.5, 95% CI 1.5–70.7). Treatment completion was achieved by 129 (91%) of the 142 contacts who started treatment.

Two areas for improvement were identified: further expanding LTBI screening, particularly among BCG-vaccinated contacts and contacts of sputum smear-negative index patients, and expanding preventive treatment among contacts with LTBI.

@ERSpublications
We need to expand LTBI screening among vaccinated contacts and improve preventive treatment among contacts with LTBI http://ow.ly/yvYdw

Received: Jan 12 2014 | Accepted after revision: June 17 2014 | First published online: July 25 2014

Conflict of interest: None declared.

Introduction

The objective of screening for latent tuberculosis infection (LTBI) during contact investigations in low-incidence countries is to prevent the occurrence of secondary patients through the identification and treatment of contacts after their recent exposure to an index patient with active tuberculosis [1]. Contacts of pulmonary tuberculosis (PTB) patients are identified and graded according to the duration and intensity of exposure [2]. Preventive therapy is indicated if a contact has an increased risk of developing disease and if the benefit of treatment outweighs the risk of side-effects. Thus, the success of contact investigation depends on adequate identification and diagnosis of recently infected contacts at risk of progression to active tuberculosis, provision of preventive treatment and treatment completion. With the introduction of interferon-γ release assays (IGRAs), screening for LTBI has become more specific, especially among bacille Calmette–Guérin (BCG)-vaccinated individuals [3].

The goals of our study were to determine the coverage and yield of contact investigation, to assess compliance with guidelines, and to identify opportunities for improvement.

Methods

Index patients

In the city of Amsterdam, the Netherlands, the diagnosing physician notifies the Public Health Service (PHS) of patients in whom tuberculosis is diagnosed. Demographic information including sex, year of birth, country of origin and being part of a risk group (the homeless and drug users) is recorded by the PHS staff. In addition, clinical and laboratory information is collected, including details on HIV infection, type of tuberculosis (PTB or extrapulmonary tuberculosis), results of sputum smears and sputum culture, results of tuberculin skin tests (TSTs), and chest radiography findings. In order to assess the risk of transmission, a nurse at the tuberculosis control department of the PHS interviews the patient and enquires about persons with whom the patient has had recent contact. The PHS then starts a source and contact investigation.

Contact investigations

The PHS staff investigates recent contacts of PTB index patients, and evaluates duration and frequency of exposure to the index patient during the infectious period. Accordingly, contacts are listed as first-, second-, or third-circle contacts based on national guidelines for contact investigation [4]. Screening for LTBI and tuberculosis starts among first-circle contacts (categorised as close contacts) of PTB patients and, depending on the infection and disease prevalence among first-circle contacts of smear-positive PTB index patients, second-circle and eventually possibly third-circle contacts are also invited for screening (second- and third-circle categorised as casual contacts).

According to national guidelines for LTBI screening, all contacts born after 1945 of sputum smear-positive PTB patients and first-circle contacts born after 1945 of smear-negative PTB patients should be screened for LTBI [5]. LTBI screening starts with a TST and contacts are concurrently screened for tuberculosis by chest radiography. The TST is performed by intradermal injection of 2 U purified protein derivative RT23 on the volar side of the forearm. After 72–96 h, the diameter of the induration at the site of injection is measured in millimetres. If the TST induration is $\geqslant$5 mm, the TST is followed by an IGRA. At the PHS in Amsterdam, QuantiFERON-TB (QFT) (Cellestis, Carnegie, Australia) is used. This assay measures the production of interferon-γ (IFN-γ) after T-cells are exposed *in vitro* to a *Mycobacterium tuberculosis*-specific antigen mix; a QFT is considered positive if the IFN-γ concentration is $\geqslant$0.35 IU·mL^{-1} [6].

Contacts with a high risk of progression to active tuberculosis after recent infection, in particular those younger than 5 years of age or HIV-infected contacts, are screened for active tuberculosis irrespective of the duration and frequency of contact with their index case. If a tuberculosis diagnosis is made, the tuberculosis control physician gives the patient antituberculosis treatment. Contacts with an LTBI diagnosis are offered preventive treatment (either 3 months of isoniazid and rifampicin, 6 months of isoniazid or 4 months of rifampicin) or, if contraindicated, follow-up of contacts at risk of progression to tuberculosis is proposed.

Study population

Index patients

Data for our study were obtained from the Netherlands Tuberculosis Register (NTR). This database combines mandatory tuberculosis notification data with voluntary input of other relevant information by PHSs. It contains information on virtually all tuberculosis patients in the Netherlands, including: HIV status; whether the patient belongs to a risk group; and drug sensitivity of the infecting *M. tuberculosis* strain. All sputum smear-positive and sputum smear-negative PTB index patients reported to the PHS in Amsterdam from 2008 through 2011 were eligible for study inclusion. Subsequently, index patients were excluded if no contact could

be linked to the index patient, if all contacts of a sputum smear-negative index patient were casual contacts, if all contacts had coprevalent tuberculosis or if contacts were born before 1945.

Contacts of index patients

The Tuberculosis Information System, an electronic tuberculosis patient and client registration system at the PHS in Amsterdam, was used to identify all contacts who were traced and examined in the course of contact investigations around PTB index patients during the study period. Some individuals were a contact in more than one contact investigation during the study period and these individuals were included multiple times. Data on treatment initiation and treatment completion from contacts who started with preventive therapy were extracted from the section of the NTR in which records of newly diagnosed LTBI patients are notified to the register by the PHSs.

Definitions

Contacts eligible for analysis were classified according to their TST and IGRA results based on the guidelines for LTBI screening and LTBI diagnosis (table 1). TST and IGRA results of contacts were included if the date of the result was $\leqslant$180 days after the first contact of the PHS with an index patient, which constitutes the actual start of any source and contact investigation. If active TB was diagnosed $\leqslant$180 days after tuberculosis diagnosis of the index patient, contacts were considered coprevalent tuberculosis cases.

Screening for LTBI

A contact was considered to have been screened for LTBI if an IGRA result was available or if the TST was performed and an intermediate TST induration of 5–<15 mm was followed by an IGRA. As the national guideline for the use of the IGRA is ambivalent regarding the additional value of the IGRA with a TST induration of $\geqslant$15 mm, contacts were considered screened if the TST induration was $\geqslant$15 mm, irrespective of an IGRA result. Children without BCG vaccination below the age of 5 years with a TST induration of $\geqslant$10 mm and HIV-infected contacts with a TST induration of $\geqslant$5 mm were also considered screened if the TST was not followed by an IGRA. Other contacts were considered not screened if neither a TST nor IGRA were done, or when a TST induration of 5–<15 mm was not followed by an IGRA.

LTBI diagnosis

Contacts were regarded as having LTBI if the IGRA was positive or if their TST induration was $\geqslant$15 mm. For contacts below the age of 5 years, who were not BCG-vaccinated and had a TST induration $\geqslant$10 mm, an IGRA was considered redundant; these contacts were diagnosed with LTBI. HIV-infected contacts with a TST induration of $\geqslant$5 mm were diagnosed with LTBI irrespective of an IGRA result.

TABLE 1 Indication for screening, diagnosis and preventive treatment of latent tuberculosis infection (LTBI) of contacts of patients with tuberculosis, according to guidelines [4, 5]

Criteria for LTBI screening
First-circle contacts and contacts with high risk of active tuberculosis, born after 1945, of PTB patients, are investigated for LTBI and tuberculosis by the combination of a TST and chest radiography, irrespective of BCG status
If the TST induration is 5–<15 mm and active tuberculosis is excluded by chest radiography, the TST is followed by an IGRA; if the TST induration is $\geqslant$15 mm, an IGRA is not indicated
In contacts where the TST result might be less reliable, an IGRA may be used instead of a TST
Depending on the infection prevalence among first-circle contacts, second- and eventually possibly third-circle contacts of sputum smear-positive PTB patients are investigated for LTBI similar to that described for first-circle contacts
Criteria for LTBI diagnosis
Contacts are diagnosed with LTBI if the IGRA is positive or if TST induration is $\geqslant$15 mm
Contacts have indeterminate outcome for LTBI if neither IGRA nor TST are performed, or if the TST induration is 5–<15 mm is not followed by the IGRA
In contacts below the age of 5 years, who were not BCG-vaccinated and who have a TST induration $\geqslant$10 mm, LTBI is diagnosed irrespective of the IGRA result
HIV-positive contacts with an induration of TST $\geqslant$5 mm are diagnosed with LTBI irrespective of the IGRA result
Criteria for starting preventive LTBI treatment and treatment completion
All contacts diagnosed with LTBI are eligible for preventive treatment except for contacts of index patients with MDR-TB
Contacts are regarded as having completed treatment if the prescribed amount of medication has been taken or if, in case of treatment interruption, 80% of the prescribed medication has been taken

PTB: pulmonary tuberculosis; TST: tuberculin skin test; BCG: bacille Calmette–Guérin; IGRA: interferon-γ release assay; MDR-TB: multidrug-resistant tuberculosis.

DOI: 10.1183/09031936.00009114

Treatment initiation and completion

All contacts diagnosed with LTBI were considered eligible for treatment, except for contacts of multidrug-resistant tuberculosis index patients. For these contacts, treatment regimen and initiation was dependent on the susceptibility pattern of *M. tuberculosis* cultured from the index patient. Contacts were regarded as having completed treatment if the prescribed amount of medication had been taken or if, in case of treatment interruption, 80% of medication prescribed had been taken.

Analysis

This study had four outcomes of interest: 1) the coverage of LTBI screening among listed contacts; 2) the proportion of contacts screened with an LTBI diagnosis; 3) the proportion of LTBI cases starting LTBI treatment; and 4) the proportion of contacts who completed treatment. Demographic, laboratory and clinical determinants (both index patient and contact related) were identified using logistic regression. In order to adjust for correlated data (multiple contacts belonging to the same contact investigation), generalised estimating equations were used. Variables that were associated with the outcome in univariate analysis at $p<0.2$ were included in a model, and variables were subsequently eliminated from the model if they did not have an independent association with the outcome and their exclusion did not substantially affect the estimates of the other variables. Sex and age, of both index and contact, were kept in the models *a priori* and the level of significance in all analyses was $p<0.05$.

Results

Study population

Index patients

From 2008 to 2011, 292 PTB index patients were reported to the PHS in Amsterdam and registered in the NTR. 57 (20%) patients were excluded from further analysis for the following reasons: no contact investigation was performed (n=17); it was not possible to link any contact to the index patient (n=27); or all contacts of a sputum smear-negative index patient were casual contacts, all contacts had coprevalent

TABLE 2 Characteristics of index patients with pulmonary tuberculosis reported to the Public Health Service (Amsterdam, the Netherlands) from 2008 to 2011

	Included	Excluded	p-value[#]
All	235 (80)	57 (20)	
Sex			
Males	146 (80)	37 (20)	0.697
Females	89 (82)	20 (18)	
Age median (IQR)	42 (28–58)	39 (27–53)	0.573[+]
0–14 years	2 (100)	0	0.403
15–34 years	91 (78)	26 (22)	
35–54 years	73 (78)	20 (22)	
⩾55 years	69 (86)	11 (14)	
Country of birth			
The Netherlands	63 (89)	8 (11)	0.044
Outside the Netherlands	172 (78)	49 (22)	
At risk[¶]			
No	220 (81)	51 (19)	0.263
Yes	15 (71)	6 (29)	
Sputum smear status			
Positive	154 (94)	9 (6)	<0.001
Negative	81 (63)	48 (37)	
MDR-TB			
No/unknown	233 (81)	55 (19)	0.172
Yes	2 (50)	2 (50)	
HIV status			
Negative	98 (75)	33 (25)	0.076
Positive	18 (90)	2 (10)	
Unknown	119 (84)	22 (16)	

Data are presented as n (%), unless otherwise stated. IQR: interquartile range; MDR-TB: multidrug-resistant tuberculosis. [#]: Chi-squared test or Fisher's exact test, unless otherwise stated; [¶]: the homeless and drug users; [+]: Mann–Whitney U-test.

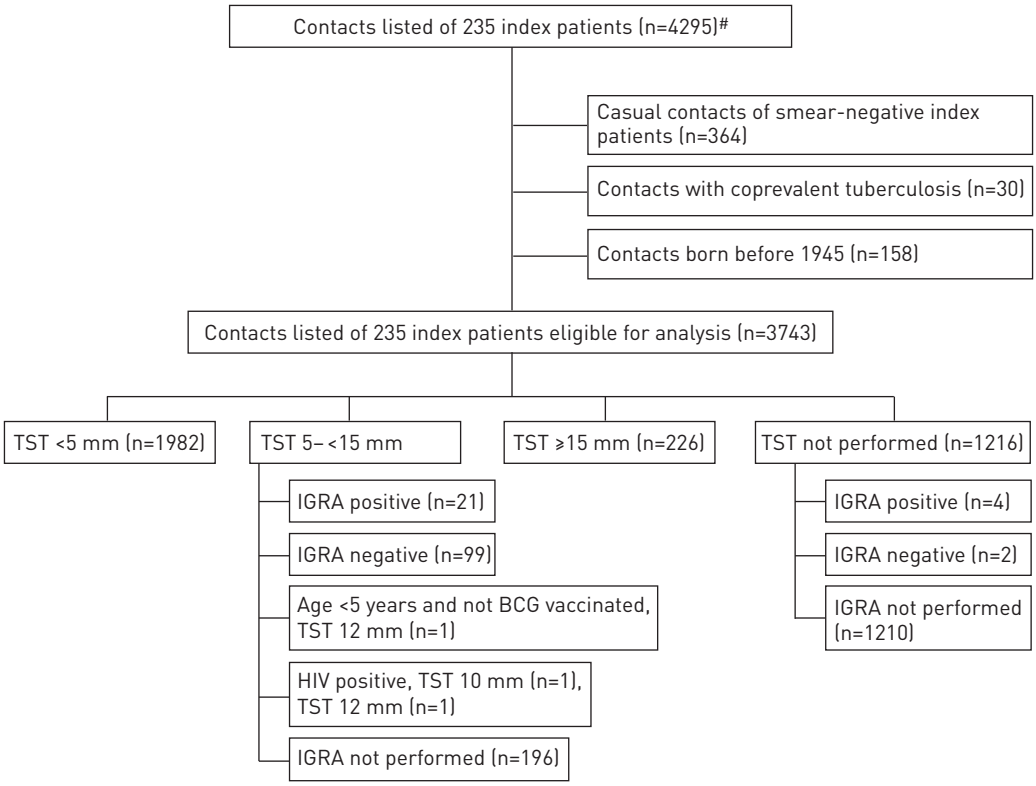

FIGURE 1 Flow chart of study inclusion of contacts of 235 patients with pulmonary tuberculosis reported to the Public Health Service in Amsterdam, the Netherlands, from 2008 to 2011. TST: tuberculin skin test; IGRA: interferon-γ release assay; BCG: bacille Calmette–Guérin. #: 4242 individuals.

tuberculosis or contacts were born before 1945 (n=13). Excluded index patients did not differ significantly from the 235 included index patients, except for country of birth (p=0.044) and smear status (p<0.001) (table 2). Culture status was known for 227 out of 235 included index patients and of these, 211 (93%) were culture positive.

Contacts listed among index patients

The 235 PTB index patients had 4295 listed contacts. Casual contacts of sputum smear-negative PTB index patients (n=364, 9%), contacts with coprevalent tuberculosis (n=30, 1%) and contacts born before 1945 (n=158, 4%) were excluded from further analysis (fig. 1).

Of 30 contacts with coprevalent tuberculosis, 17 (57%) were female, 19 (63%) were first-circle contacts, 14 (47%) had evidence of BCG vaccination and their median age was 23 years (interquartile range (IQR) 6–43 years).

Of the 3743 contacts eligible for analysis, 2337 (62%) were screened for LTBI and included: contacts with a TST induration of <5 mm (n=1982) and of ⩾15 mm (n=226), contacts with an intermediate TST followed by an IGRA (n=120), contacts without TST but with an IGRA result (n=6), and three other contacts (two HIV-infected and one below the age of 5 years without BCG vaccination) (fig. 1). The remaining 1406 (38%) contacts were not screened for LTBI: for 196 contacts, an intermediate TST result was not followed by IGRA and for 1210 contacts neither TST nor IGRA were done. Among 2337 contacts screened for LTBI, 254 (11%) were diagnosed with LTBI.

Among the 226 contacts with an induration ⩾15 mm, 82 (36%) were also investigated by IGRA; 38 (46%) of these had a negative IGRA.

LTBI screening among eligible contacts

In the multivariable analysis, contacts of younger index patients were more likely to be screened for LTBI and contacts of sputum smear-negative index patients were less likely to be screened for LTBI (adjusted odds ratio (aOR) 0.6, 95% CI 0.4–0.9) (table 3).

DOI: 10.1183/09031936.00009114

TABLE 3 Characteristics of 3743 contacts of pulmonary tuberculosis patients in relation to being screened for latent tuberculosis infection (LTBI) at the Public Health Service in Amsterdam (the Netherlands) from 2008 to 2011

Factor	Screened	Not screened	Crude OR	Adjusted OR
All	2337 (62)	1406 (38)		
Index factors				
Sex				
Males	1323 (60)	886 (40)	1	1
Females	1014 (66)	520 (34)	1.1 (0.8–1.5)	1.3 (0.9–1.9)
Age				
0–14 years	105 (81)	25 (19)	4.9 (3.4–7.0)	10.6 (4.9–23.1)
15–34 years	963 (67)	479 (33)	1.7 (1.2–2.3)	1.4 (1.0–2.1)
35–54 years	871 (64)	499 (36)	1.3 (0.9–1.9)	1.0 (0.7–1.6)
⩾55 years	398 (50)	403 (50)	1	1
Country of birth				
The Netherlands	923 (68)	434 (32)	1	
Outside the Netherlands	1414 (59)	972 (41)	0.4 (0.3–0.6)	
At risk[#]				
No	2231 (64)	1272 (36)	1	
Yes	106 (44)	134 (56)	0.8 (0.4–1.3)	
Sputum smear status				
Positive	2096 (64)	1203 (36)	1	1
Negative	241 (54)	203 (46)	0.5 (0.3–0.7)	0.6 (0.4–0.9)
Contact factors				
Sex				
Male	1206 (63)	717 (37)	1	1
Female	1078 (61)	676 (39)	1.0 (0.9–1.2)	1.1 (0.9–1.4)
Age				
0–4 years	184 (80)	45 (20)	4.0 (2.5–6.2)	7.0 (3.6–13.7)
5–14 years	152 (66)	77 (34)	2.1 (1.4–3.1)	3.2 (1.8–5.6)
15–34 years	854 (64)	484 (36)	1.3 (1.0–1.9)	1.3 (0.9–1.9)
35–54 years	868 (59)	600 (41)	1.0 (0.8–1.3)	1.0 (0.7–1.4)
⩾55 years	275 (58)	198 (42)	1	1
Nationality				
Dutch	1507 (65)	827 (35)	1	
Other	213 (35)	388 (65)	0.3 (0.2–0.4)	
Unknown	617 (76)	191 (24)	1.2 (0.8–1.7)	
Type of contact				
First circle	1067 (66)	557 (34)	1.0 (0.7–1.4)	
Second circle	934 (60)	636 (41)	1.0 (0.7–1.5)	
Third circle	276 (61)	175 (39)	1	
Unknown	60 (61)	38 (39)	1.7 (0.9–3.4)	
Year of contact investigation				
2008	396 (52)	370 (48)	1	
2009	915 (66)	480 (34)	1.1 (0.7–1.6)	
2010	471 (61)	300 (39)	1.1 (0.7–1.7)	
2011	555 (68)	256 (32)	1.4 (0.9–2.1)	
BCG				
No evidence of vaccination/unknown	2069 (80)	530 (20)	1	1
Evidence of vaccination	268 (23)	876 (77)	0.08 (0.05–0.1)	0.06 (0.04–0.09)

Data are presented as n (%) or OR (95% CI). BCG: bacille Calmette–Guérin. [#]: the homeless and drug users.

LTBI screening was associated with contact age groups 0–4 years (aOR 7.0, 95% CI 3.6–13.7) and 5–14 years (aOR 3.2, 95% CI 1.8–5.6) as compared with age ⩾55 years. BCG-vaccinated contacts were less likely to be screened for LTBI (aOR 0.06, 95% CI 0.04–0.09) (table 3).

Figure 2 shows coverage of LTBI screening among contacts by year of contact investigation and BCG status. The proportion of BCG-vaccinated contacts screened for LTBI increased over time from 9% in 2008 to 43% in 2011 (Chi-squared test for trend, $p<0.001$). The proportion of contacts screened for LTBI among non-BCG-vaccinated contacts remained relatively constant over the 4-year study period at an average of 79% (Chi-squared test for trend, $p=0.225$) (fig. 2).

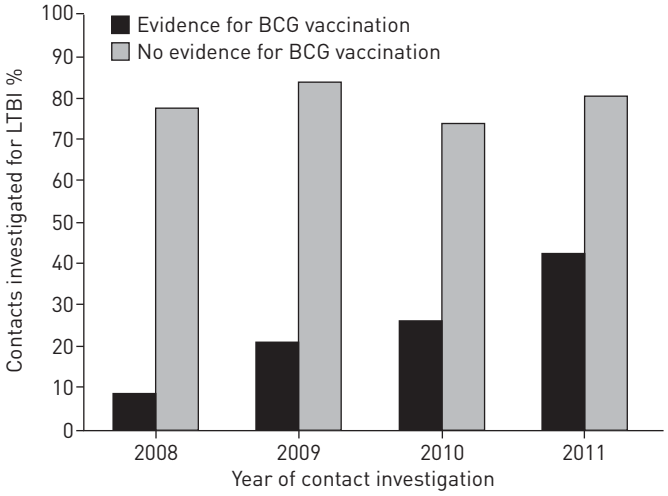

FIGURE 2 Coverage of screening for latent tuberculosis infection (LTBI) among 3743 contacts of pulmonary tuberculosis patients in contact investigations at the Public Health Service in Amsterdam (the Netherlands) from 2008 to 2011 by bacille Calmette–Guérin (BCG) status and year of investigation.

LTBI diagnosis among examined contacts

Contacts of sputum smear-negative index cases were less likely to be diagnosed with LTBI in multivariable analysis (aOR 0.3, 95% CI 0.1–0.7) (table 4). Contacts with index age group 15–34 years were more likely diagnosed with LTBI as compared with age ⩾55 years (aOR 2.1, 95% CI 1.2–3.6).

Contact factors associated with LTBI diagnosis were: non-Dutch nationality as compared with Dutch nationality (aOR 2.8, 95% CI 1.9–4.1); being a first-circle contact as compared with a third-circle contact (aOR 4.0, 95% CI 1.9–8.3); and BCG vaccination (aOR 4.4, 95% CI 2.9–6.6) (table 4). Female contacts were less likely to be diagnosed with LTBI (aOR 0.6, 95% CI 0.5–0.9). Younger age was associated with lower odds for LTBI.

Treatment of contacts diagnosed with LTBI

Of the 254 contacts diagnosed with LTBI, 142 (56%) started LTBI treatment. In the multivariable analysis, contact age groups 0–14 years and 15–34 years were associated with starting preventive LTBI treatment as compared with age ⩾55 years (aOR 8.5 (95% CI 2.1–34.6) and 4.0 (95% CI 1.3–12.4), respectively) (table 5). Other contact factors associated with starting treatment were Dutch nationality as compared with non-Dutch nationality (aOR 2.6, 95% CI 1.2–5.4) and being a first-circle contact as compared to a third-circle contact (aOR 10.5, 95% CI 1.5–70.7) (table 5).

Treatment completion

Of the 142 contacts who started preventive treatment: 129 (91%) completed treatment; 10 (7%) did not complete treatment; and for three (2%), it was unknown whether they completed treatment. Reasons for not completing treatment were: unknown (n=7); side-effects (n=2); and treatment of active tuberculosis (n=1). The median age of contacts not completing treatment was 25 years (IQR 23–45 years) and median age of contacts completing treatment was 32 years (IQR 19–47 years). The distribution of these ages did not differ significantly (p=0.883).

Discussion

Over a third of the contacts of PTB patients reported to the PHS in Amsterdam from 2008 through 2011 were not screened for LTBI. Contacts of sputum smear-negative PTB patients and BCG-vaccinated contacts were less likely to be screened for LTBI. The proportion of BCG-vaccinated contacts screened for LTBI over time increased significantly. Nearly half of the contacts diagnosed with LTBI did not start treatment. However, among contacts who started treatment, 90% completed it.

The guideline for LTBI screening with the TST was expanded to include BCG-vaccinated individuals in contact investigations in the Netherlands in November 2004 [7, 8]. Screening for LTBI among BCG-vaccinated contacts was further expanded with the introduction of the IGRA. The Netherlands, like several other countries, has implemented IGRAs in LTBI screening programmes [9, 10]. Similar to the British guidelines [10], the Dutch guideline indicates that the IGRA should be used to validate a positive TST result [5]. A study by MULDER *et al.* [11] showed that LTBI screening was less often conducted among people likely to have a high prevalence of BCG vaccination and risk of previous TB exposure. With the introduction of the IGRA, an LTBI diagnosis is more likely to indicate actual recent infection than a positive TST result

DOI: 10.1183/09031936.00009114

TABLE 4 Characteristics of 2337 contacts of pulmonary tuberculosis patients in relation to latent tuberculosis infection (LTBI) diagnosis at the Public Health Service in Amsterdam (the Netherlands) from 2008 to 2011

Factor	Contacts diagnosed with LTBI	Contacts without LTBI diagnosis	Crude OR	Adjusted OR
All	254 (11)	2083 (89)		
Index factors				
Sex				
Males	164 (12)	1159 (88)	1	1
Females	90 (9)	924 (91)	0.8 (0.5–1.4)	0.9 (0.5–1.4)
Age				
0–14 years	3 (3)	102 (97)	0.6 (0.1–4.8)	0.6 (0.2–1.8)
15–34 years	157 (16)	806 (84)	2.0 (1.1–3.5)	2.1 (1.2–3.6)
35–54 years	60 (7)	811 (93)	0.9 (0.5–1.7)	1.2 (0.6–2.3)
⩾55 years	34 (9)	364 (91)	1	1
Country of birth				
The Netherlands	76 (8)	847 (92)	1	
Outside the Netherlands	178 (13)	1236 (87)	1.5 (0.9–2.4)	
At risk[#]				
No	242 (11)	1989 (89)	1	
Yes	12 (11)	94 (89)	0.6 (0.1–2.5)	
Sputum smear status				
Positive	245 (12)	1851 (88)	1	1
Negative	9 (4)	232 (96)	0.4 (0.2–0.8)	0.3 (0.1–0.7)
Contact factors				
Sex				
Male	158 (13)	1048 (87)	1	1
Female	96 (9)	982 (91)	0.6 (0.5–0.8)	0.6 (0.5–0.9)
Age				
0–4 years	8 (4)	176 (96)	0.3 (0.1–0.6)	0.1 (0.1–0.3)
5–14 years	21 (14)	131 (86)	0.7 (0.4–1.3)	0.4 (0.2–0.8)
15–34 years	88 (10)	766 (90)	0.5 (0.3–0.7)	0.3 (0.2–0.5)
35–54 years	93 (11)	775 (89)	0.6 (0.5–0.8)	0.6 (0.4–0.8)
⩾55 years	44 (16)	231 (84)	1	1
Nationality				
Dutch	153 (10)	1354 (90)	1	1
Other	78 (37)	135 (63)	4.0 (3.0–5.5)	2.8 (1.9–4.1)
Unknown	23 (4)	594 (96)	0.2 (0.1–0.7)	0.3 (0.1–0.7)
Type of contact				
First circle	158 (15)	909 (85)	6.1 (2.7–13.7)	4.0 (1.9–8.3)
Second circle	79 (8)	855 (92)	3.0 (1.3–6.6)	2.1 (1.0–4.5)
Third circle	11 (4)	265 (96)	1	1
Unknown	6 (10)	54 (90)	3.2 (1.0–9.6)	2.3 (0.8–6.8)
BCG				
No evidence of vaccination/unknown	154 (7)	1915 (93)	1	1
Evidence of vaccination	100 (37)	168 (63)	6.2 (4.3–9.0)	4.4 (2.9–6.6)

Data are presented as n (%) or OR (95% CI). BCG: bacille Calmette–Guérin. [#]: the homeless and drug users.

[3, 12, 13]. Our study showed that indeed more contacts of PTB patients were screened for LTBI in each year following the introduction of the IGRA guidelines and that this positive trend was mainly observed among BCG-vaccinated contacts. However, LTBI screening among BCG-vaccinated contacts should be further expanded as 57% remained untested for LTBI at the end of the 4-year study period. As 11% of contacts screened for LTBI were diagnosed with LTBI, an estimated 155 LTBI diagnosis may have been missed among the contacts who were eligible for LTBI screening but were not screened for LTBI. Absence of LTBI screening was also evident among contacts of sputum smear-negative PTB patients. A previous study, conducted in the Netherlands on data from 2006–2007, found that contact investigations were less likely to be started around sputum smear-negative patients than around smear-positive patients [14]. Even though different outcome measures were used, these observations indicate a lack of improvement since 2007. Although sputum smear-positive patients are known to be more infectious than smear-negative patients, it has been shown that 13% of tuberculosis transmission in the Netherlands is attributable to smear-negative, culture-positive patients [15]. Yet, in our study, the proportion of contacts diagnosed with LTBI was

TABLE 5 Characteristics of 254 contacts of pulmonary tuberculosis patients in relation to starting latent tuberculosis infection treatment at the Public Health Service in Amsterdam (the Netherlands) from 2008 to 2011

Factor	Treatment	No treatment	Crude OR	Adjusted OR
All	142 (56)	112 (44)		
Index factors				
Sex				
Males	89 (54)	75 (46)	1	1
Females	53 (59)	37 (41)	1.1 (0.5–2.1)	1.1 (0.5–2.6)
Age				
0–14 years	1 (33)	2 (67)	0.8 (0.3–1.8)	0.1 (0.1–0.7)
15–34 years	98 (62)	59 (38)	3.3 (1.3–8.4)	1.8 (0.5–6.0)
35–54 years	30 (50)	30 (50)	1.7 (0.6–4.6)	1.0 (0.2–3.8)
⩾55 years	13 (38)	21 (62)	1	1
Country of birth				
The Netherlands	43 (57)	33 (43)	1	
Outside the Netherlands	99 (56)	79 (44)	1.0 (0.5–2.0)	
At risk[#]				
No	135 (56)	107 (44)	1	
Yes	7 (58)	5 (42)	0.8 (0.2–3.6)	
Sputum smear status				
Positive	139 (57)	106 (43)	1	
Negative	3 (33)	6 (67)	0.3 (0.8–1.5)	
Contact factors				
Sex				
Male	89 (56)	69 (44)	1	1
Female	53 (55)	43 (45)	0.8 (0.5–1.4)	0.8 (0.5–1.4)
Age				
0–4 years	8 (100)	0		
5–14 years	16 (76)	5 (24)	10.5 (2.6–41.5)[¶]	8.5 (2.1–34.6) [¶]
15–34 years	57 (65)	31 (35)	4.1 (1.3–12.7)	4.0 (1.3–12.4)
35–54 years	48 (52)	45 (48)	2.4 (1.0–5.8)	2.3 (0.8–5.9)
⩾55 years	13 (29)	31 (71)	1	1
Nationality				
Dutch	98 (64)	55 (36)	1.7 (0.8–3.6)	2.6 (1.2–5.4)
Other	40 (51)	38 (49)	1	1
Unknown	4 (17)	19 (83)	0.2 (0.1–0.5)	0.4 (0.1–1.1)
Type of contact				
First circle	99 (63)	59 (37)	10.6 (1.7–63.2)	10.5 (1.5–70.7)
Second circle	39 (49)	40 (51)	5.3 (0.8–34.7)	5.3 (0.7–37.1)
Third circle	2 (18)	9 (82)	1	1
Unknown	2 (33)	4 (67)	2.8 (0.4–16.7)	1.5 (0.2–11.8)
BCG				
No evidence of vaccination/unknown	89 (58)	65 (42)	1	
Evidence of vaccination	53 (53)	47 (47)	0.7 (0.4–1.3)	

Data are presented as n (%) or OR (95% CI). BCG: bacille Calmette–Guérin. [#]: the homeless and drug users; [¶]: age categories 0–4 and 5–14 years were combined to calculate the odds ratio.

considerably lower among contacts of smear-negative index patients than among contacts of smear-positive patients. A cost-effectiveness analysis may indicate whether enhancement of screening among first-circle contacts of smear-negative index patients is indeed cost-effective.

Especially in low-incidence countries, preventive treatment of LTBI is an important component of tuberculosis control strategies. However, almost half of the contacts diagnosed with LTBI did not start on preventive treatment. A study conducted in Sydney, Australia, by DOBLER *et al.* [16] showed that physicians' decisions to offer LTBI treatment may be correlated with factors associated with an increased risk of developing tuberculosis, such as young age and being a close contact of an index case. Unfortunately we were not able to determine whether these contact factors influenced physicians' decisions on treatment or whether patients' refusal was associated with starting treatment. Although contacts with non-Dutch nationality were more likely to be diagnosed with LTBI, they were less likely to start preventive treatment. LTBI diagnosis among non-Dutch contacts might be due to remote past infection, which makes LTBI

DOI: 10.1183/09031936.00009114

treatment seem less beneficial. However, it has been demonstrated that non-native tuberculosis contacts have a higher risk of developing active tuberculosis [17, 18], indicating LTBI treatment should be offered to this group as well. Our study showed that most of those who started treatment also completed treatment. Thus, a great deal is to be gained from offering preventive treatment among contacts diagnosed with LTBI, in particular among non-Dutch contacts.

Screening for LTBI among recently exposed contacts of PTB patients has become more specific since the introduction of the IGRA [3]. This was also apparent in our study, as 82% of the intermediate TST outcomes followed by an IGRA resulted in a negative IGRA result. Interestingly, even among contacts in whom a TST induration $\geqslant$15 mm was followed by an IGRA, a high proportion (46%) had a negative IGRA result.

The association found between BCG vaccination and LTBI diagnosis is probably attributable to three phenomena. First, there may be false positive TSTs following BCG vaccination. Second, a selection effect; BCG vaccination is more likely among immigrants from high-burden countries who are also more likely to have LTBI [19]. A third explanation might be selection bias, as BCG-vaccinated contacts were less likely to be screened for LTBI and BCG-vaccinated contacts who were screened might have been exposed to a more infectious index patient.

This study had three limitations, mainly attributable to routine data collection. First, in order to investigate treatment initiation among contacts diagnosed with LTBI, records had to be extracted from the NTR, where each contact diagnosed with LTBI in the Netherlands is registered. This might have resulted in an unknown proportion missing due to nonmerging of data and could have led to a slight underestimation of the proportion of contacts who started preventive treatment. Furthermore, we might have underestimated the proportion diagnosed with LTBI if diagnosis was based on other factors than TST or IGRA result. For example, a low TST cut-off for the clinical diagnosis of LTBI may be used for immune disorders like HIV. For most contacts, HIV status was unknown and HIV-positive contacts with a TST induration of $\geqslant$5 mm should, according to the guidelines, be diagnosed with LTBI irrespective of an IGRA result. However, as the prevalence of HIV among tuberculosis patients in Amsterdam is about 6% [20], unknown HIV among PTB contacts is not expected to have resulted in a significant underestimation of LTBI diagnosis in our study. Third, as the positive predictive value of a TST $\geqslant$15 mm is high if background infection prevalence is $>$10%, an IGRA might not be of additional value and therefore contacts with a TST $\geqslant$15 mm were considered screened irrespective of an IGRA result [5]. This might have influenced our results in two ways. The TST in 82 (36%) out of 226 contacts with a TST $\geqslant$15 mm was followed by an IGRA, of which 38 (46%) tested negative. However, in 64% of the contacts with a TST $\geqslant$15 mm, no IGRA was performed. If these contacts would not have been considered to have been screened for LTBI, we would have concluded that an even larger proportion of contacts had not been screened.

In conclusion, LTBI screening among contacts of PTB patients should be further expanded, in particular among BCG-vaccinated contacts and close contacts of smear-negative PTB patients. Furthermore, future efforts should focus on enhanced treatment initiation among contacts diagnosed with LTBI, especially among non-Dutch contacts. Accordingly, identification of factors associated with the uptake of preventive therapy for both physicians and patients should be further explored.

Acknowledgements

We would like to thank Annet Reusken, Carolien Moree and Wieneke Meijer (all Dept of Infectious Diseases, Public Health Service, Amsterdam, the Netherlands) for advice on the practice of contact investigations in Amsterdam and data preparation.

References

1 Erkens CGM, Kamphorst M, Abubakar I, *et al.* Tuberculosis contact investigation in low prevalence countries: a European consensus. *Eur Respir J* 2010; 36: 925–949.
2 Veen J. Microepidemics of tuberculosis: the stone-in-the-pond principle. *Tuber Lung Dis* 1992; 73: 73–76.
3 Diel R, Nienhaus A, Lange C, *et al.* Tuberculosis contact investigation with a new, specific blood test in a low-incidence population containing a high proportion of BCG-vaccinated persons. *Respir Res* 2006; 7: 77.
4 KNCV Tuberculosis Foundation. Landelijke Coördinatie Infectieziektebestrijding. Richtlijn Tuberculose-contactonderzoek [Tuberculosis contact investigation]. Juni 2007. The Hague, KNCV, 2007.
5 KNCV Tuberculosis Foundation. IGRA-werkgroep Commissie voor Praktische Tuberculosebestrijding. Richtlijn Interferon Gamma Release Assays bij de diagnostiek van Tuberculose [Guideline Interferon Gamma Release Assays for tuberculosis diagnostics]. December 2010. The Hague, KNCV, 2007.
6 European Centre for Disease Prevention and Control. Use of interferon-gamma release assays in support of TB diagnosis. March 2011. Stockholm, ECDC, 2011.
7 Lambregts-van Weezenbeek CS, Cobelens FG, Mensen EA, *et al.* De tuberculinetest in Nederland: nieuw beleid voor een oude test; richtlijn van de Commissie voor Praktische Tuberculosebestrijding [The tuberculin skin test in the Netherlands: new policies for an old test; guideline from the Netherlands Tuberculosis Control Policy Committee]. *Ned Tijdschr Geneeskd* 2003; 147: 543–546.
8 KNCV Tuberculosis Foundation. Commissie voor Praktische Tuberculosebestrijding. Interpretatie tuberculine-huidtest [Interpretation tuberculin skin test]. November 2004. The Hague, KNCV, 2004.

9 Centers for Disease Control and Prevention. Guidelines for the investigation of contacts of persons with infectious tuberculosis. Recommendations from the National Tuberculosis Controllers Association and CDC. *Morb Mortal Wkly Rep* 2005; 54: 1–47.
10 The National Collaborating Centre for Chronic Conditions, Tuberculosis. Clinical diagnosis and management of tuberculosis, and measures for its prevention and control. London, Royal College of Physicians, 2006.
11 Mulder C, van Deutekom H, Huisman EM, *et al.* Coverage and yield of tuberculosis contact investigations in the Netherlands. *Int J Tuberc Lung Dis* 2011; 15: 1630–1637.
12 Brodie D. Use of an interferon-γ release assay to diagnose latent tuberculosis infection in foreign-born patients. *Chest* 2008; 133: 869–874.
13 Diel R, Goletti D, Ferrara G, *et al.* Interferon-γ release assays for the diagnosis of latent *Mycobacterium tuberculosis* infection: a systematic review and meta-analysis. *Eur Respir J* 2010; 37: 88–99.
14 Mulder C, Erkens CGM, Kouw PM, *et al.* Missed opportunities in tuberculosis control in The Netherlands due to prioritization of contact investigations. *Eur J Public Health* 2011; 22: 177–182.
15 Tostmann A, Kik SV, Kalisvaart NA, *et al.* Tuberculosis transmission by patients with smear-negative pulmonary tuberculosis in a large cohort in The Netherlands. *Clin Infect Dis* 2008; 47: 1135–1142.
16 Dobler CC, Luu Q, Marks GB. What patient factors predict physicians' decision not to treat latent tuberculosis infection in tuberculosis contacts? *PLoS ONE* 2013; 8: e76552.
17 Geng E, Kreiswirth B, Driver C, *et al.* Changes in the Transmission of Tuberculosis in New York City from 1990 to 1999. *N Engl J Med* 2002; 346: 1453–1458.
18 Cain KP, Haley CA, Armstrong LR, *et al.* Tuberculosis among foreign-born persons in the United States: achieving tuberculosis elimination. *Am J Respir Crit Care Med* 2007; 175: 75–79.
19 Berkel GM, Cobelens FG, de Vries G, *et al.* Tuberculin skin test: estimation of positive and negative predictive values from routine data. *Int J Tuberc Lung Dis* 2005; 9: 310–316.
20 GGD Amsterdam. Jaarverslag 2012 Tuberculosebestrijding. Oktober 2013. [Annual report 2012 Tuberculosis control. October 2013.] Amsterdam, GGD Amsterdam, 2013.

DOI: 10.1183/09031936.00009114