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Predictive value for progression to tuberculosis by IGRA and TST in immigrant contacts

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ABSTRACT

The authors determined the positive predictive value (PPV) for progression to tuberculosis (TB) of two IGRA, QuantiFERON-TB Gold in-tube (QFT-GIT) and T-SPOT.*TB* and the tuberculin skin test (TST) in immigrants contacts.

Immigrant close contacts of sputum smear-positive TB patients were included when ≥16 years and their TST result was ≥5 mm at zero or three months after diagnosis of the index patient. Contacts were followed during the next two years for development of TB disease.

Of 339 immigrant contacts with TST ≥5 mm, 324 and 299 had valid results of QFT-GIT and T-SPOT.*TB*, respectively. Nine contacts developed active tuberculosis. One patient had not been tested with TST, while another patient had not been tested with QFT-GIT and T-SPOT.*TB*. The PPV for progression to TB during this period was 9/288=3.1% (95% CI; 1.3-5.0) for TST ≥10 mm, 7/184=3.8% (95% CI; 1.7-5.9) for TST ≥15 mm, 5/178=2.8% (95% CI; 1.0-4.6) for QFT-GIT and 6/181=3.3% (95% CI; 1.3-5.3) for T-SPOT.*TB*. Sensitivity was 100%, 88%, 63% and 75%, respectively.

The predictive values of QFT-GIT, T-SPOT.*TB* and TST for progression to TB disease among immigrant close contacts were comparable.

INTRODUCTION

Interferon-gamma release assays (IGRA) have emerged as an alternative for the tuberculin skin test (TST) for the diagnosis of a latent tuberculosis (TB) infection (LTBI). Currently, two commercial IGRA are available: QuantiFERON-TB® Gold in-tube (Cellesis, Carnegie, Australia) and T-SPOT.*TB*® (Oxford Immunotec, Abingdon, UK). These IGRA measure the immune response to *M. tuberculosis*-specific antigens. IGRA results are not affected by previous BCG-vaccination and most infections of nontuberculous mycobacteria (1). Furthermore, repeated testing does not influence later test results, in contrast to the boosting effect that can be observed when the TST is repeated over time (2). Several countries incorporated the IGRA as a diagnostic test for LTBI in their guidelines and recommend its use as a confirmative test after a positive TST (3, 4) or as an alternative to the TST (4-6). However, more direct evidence from studies with follow-up of untreated latently infected subjects would lend scientific support to the implementation of these guidelines (1, 7).

So far, few prospective studies assessed progression of TB among contacts of infectious pulmonary TB patients in relation to IGRA results (8-12). While one study showed that the QuantiFERON-TB Gold in-tube (QFT-GIT) was a more accurate indicator for progression to active disease than the TST at a cut-off of 5 mm (9), two other studies found that the in-house ELISPOT and TST both missed some of the contacts who progressed to TB disease. It is unclear if these different outcomes can be attributed to the different IGRA used, the type of contacts included in these studies, or to differences in the infection prevalence.

In the current study we assessed the positive predictive value for TB disease of QFT-GIT, T-SPOT.*TB* and TST in immigrant individuals in The Netherlands who were recently exposed to infectious pulmonary TB patients. To our knowledge this is the first longitudinal study that describes the predictive value of both commercially available IGRA in a population with high risk of recent infection, a high lifetime risk of previous infection and a low risk of re-infection after inclusion.

MATERIAL AND METHODS

Study subjects

Between April 2005 and July 2007, close contacts of sputum-smear positive pulmonary TB patients when ≥16 years old and born in a TB endemic country (see list, appendix A) were recruited shortly after the diagnosis of the index patient. Furthermore, we included Dutch-born individuals when at least one of their parents was born in a TB endemic country and they were BCG-vaccinated, since their TST results may be false positive due to their BCG-status. Recruitment took place at 15 municipal health services (MHSs) throughout the Netherlands. We excluded contacts with known conditions associated with an increased risk of progression to disease (including diabetes and HIV infection) and individuals who were given preventive treatment.

Data collection

Screening of close contacts in a contact investigation is performed in two rounds in the Netherlands, first shortly after the diagnosis of the index patient and secondly 8-12 weeks later.

At the time of recruitment all contacts underwent a chest X-ray (CXR) to exclude the presence of active TB disease. Additionally a TST was administered (2 TU, PPD RT23 in Tween-80, Statens Serum Institute, Copenhagen, Denmark) and read after 48-72 hours. Contacts with TST results ≥5 mm were interviewed and blood was obtained for T-SPOT.*TB* and QFT-GIT. If TST was <5 mm in the first round it was repeated at the second round and only followed by IGRA testing if ≥5 mm. Individuals who underwent their first TST during the second round of the contact investigation were tested once. Known past TST responders (TST ≥10 mm) did not undergo TST testing, but were immediately tested with IGRA. Characteristics of the cohort and factors related to positive test outcomes are described elsewhere (13).

Contacts with TST results ≥5 mm were invited for follow-up visits at 6, 12, 18 and 24 months after inclusion and were interviewed and investigated for signs and symptoms suggestive of TB disease. Contacts who did not show up for their follow-up visit after several invitations were, if possible, interviewed by telephone.

Ethics

Ethical approval for this study was obtained from the Netherlands Central Committee on Research Involving Human Subjects (CCMO, P04.1214C) and all participants provided oral and written informed consent. Contacts with possible LTBI in our study did not received preventive treatment, in accordance with the common practice in the Netherlands. The justification for this policy is that among adults with a high likelihood of remote (instead of recent) infection and the possibility of false-positive TST results due to previous BCG-vaccination the benefit of preventive therapy may not outweigh the risks related to the chemotherapy.

Incident TB cases

Contacts diagnosed with TB at least 3 months after the diagnosis of the index patient were considered to be incident cases, whereas TB cases diagnosed within the first 3 months after the diagnosis of the index patient were considered to be co-prevalent and excluded from the analysis. The diagnosis of TB disease was based on CXR, symptoms, smear and/or culture results.

Laboratory procedures

Both IGRA were performed according to the instructions of the manufacturers (14, 15), and tested in a single laboratory (Leiden University Medical Center, The Netherlands), as described earlier (13). For QFT-GIT (two-tube format) a positive test was defined as ≥0.35 IU/ml. Interpretation of T-SPOT.*TB* results was according to the latest criteria defined by the manufacturer.

When available, *M. tuberculosis* isolates from the incident cases and their index patients were subjected to *IS6110* restriction fragment length polymorphism (RFLP) typing (16) and if less than 5 bands additionally sub-typed using the polymorphic GC-rich sequence as a probe (17), to determine if the RFLP patterns were identical. Molecular typing was done at the National Institute of Public Health and the Environment.

Predictive values

In our primary analysis we determined the positive predictive value (PPV), negative predictive value (NPV), sensitivity and specificity of the different tests among our cohort of contacts who by definition had a TST ≥5 mm. Development of active TB was used as the 'disease outcome' in these calculations; thus we determined sensitivity and specificity of the test result for progression to TB disease. The PPV was calculated as: number of incident TB cases with a positive test

outcome / total number of contacts with a positive test outcome. Since the cumulative number of TB cases, and therefore the PPV, is dependent on the duration of follow-up and not all of our contacts could be followed for 2 years, we performed a secondary analysis to determine test parameters for progression to disease within the first 12 months of follow-up. Not all contacts attended the follow-up visits. Therefore we performed an even more strict sensitivity analysis in which we determined the test parameters for disease progression among contacts who attended the follow-up up to at least 12 months.

Follow-up time

The date of start of follow-up was defined as 3 months after the diagnosis of the index patient, or the date of blood collection for those who had IGRA testing >3 months after the diagnosis of their index patient. Follow-up time was calculated from the start of follow-up up to 24 months, the date of TB diagnosis, the date of death or emigration out of the Netherlands, whichever occurred first.

To ascertain that we did not miss any incident cases, we performed a search in the Netherlands Tuberculosis Register (NTR) and assessed if any of the included contacts was registered with TB up to August 1st 2008. Since the NTR is an anonymous register the search was based on the date of birth, gender and country of birth and MHSs were asked to confirm if the matches between the study database and the NTR database were indeed the same person. Although we excluded contacts with TST <5 mm from follow-up, the same search strategy in the NTR was performed to assess if any of them was registered with TB afterwards.

Statistical analysis

Poisson regression was used to estimate incidence rates and 95% confidence intervals (CI) for progression to TB per 1000 person-years. For the primary analysis we constructed Kaplan-Meier curves. The equality of the survival distributions were compared by the Gehan-Breslow-Wilcoxon-test that weighs the time points by the number of cases. Statistical analyses were conducted using SPSS version 16.0 for Windows (SPSS, Inc., Chicago, IL).

RESULTS

Participants and test results

During the study period, 380 contact investigations were conducted at the participating MHSs. Of 812 immigrant close contacts aged ≥16 years, 433 (53%) fulfilled the inclusion criteria and gave informed consent (Figure 1). Details on the comparison between contacts who were included and those who were not asked or refused participation are described elsewhere (13). Out of 433, 339 (78%) contacts were eligible for follow-up since they either had TST results ≥5 mm (n=322) or were known positive TST responders in the past (n=17). TST results were ≥10 mm in 288/339 (85%), and ≥15 mm in 184/322 (57%). Blood collection for IGRA failed in 12 contacts. At recruitment 178 (54%) of 327 remaining individuals had a positive QFT-GIT result. For 28 individuals no valid T-SPOT.*TB* result was available due to insufficient blood collection (n=19), inconclusive test result (n=5) or technical failure (n=4). T-SPOT.*TB* was positive in 181 (61%) of the remaining 299 individuals. Characteristics of the study population are given in Table 1.

Incident cases

Nine contacts developed TB disease >3 months after the diagnosis of the index patient. All were registered in the NTR and had been BCG vaccinated (Table 2). None of the participants with TST

<5 mm and none of the participants who did not attend all follow-up visits matched with any of the TB-cases notified in the NTR. One incident case was not tested with TST at recruitment and in another incident case blood collection for IGRA had failed. All eight IGRA tested patients had TST results ≥10 mm and seven (88%) had results ≥15 mm. T-SPOT.*TB* was positive in 6/8 (75%) (all >30 spots), while QFT-GIT was positive in 5/8 (63%) TB patients (4/5 were >10 IU/ml). The two patients with negative T-SPOT.*TB* results were also negative in the QFT-GIT. Six patients (including all three TST positive/IGRA negative) were confirmed by culture, and RFLP fingerprinting of the isolates of these six patients were identical to those of the corresponding index case.

None of the three incident patients with at least one negative IGRA result at recruitment were known to be HIV positive or to have any other immune suppressive disorder. Furthermore, none of them reported to have traveled to a TB endemic country or have been exposed to another TB case in the period between their inclusion and diagnosis. All had IGRA results far below the threshold of a positive test (QFT-GIT results: -0.24, 0.02 and 0.04 IU/ml; T-SPOT.*TB* results: 0 and 1 spot). Contacts were tested with IGRA between 4 to 200 days after the diagnosis of the index case (median 37 days, IQR; 15-117). The three contacts who developed TB and who had at least one negative IGRA results were tested relatively early, at 5, 19 (not negative in T-SPOT.*TB*) and 34 days after diagnosis of the index patient.

Survival analysis

No significant difference was observed between the incidence of TB in IGRA positive and IGRA negative contacts (QFT-GIT; Gehan-Breslow-Wilcoxon-test p-value=0.718, T-SPOT.*TB*; p-value=0.443) (Figure 2). Using a cut-off of 15 mm, the difference between the incidence of TB

among contacts who were TST positive or negative was not statistically different (p-value=0.081).

Predictive values

The 339 contacts were followed for a median follow-up time of 1.83 year (IQR=1.30-2.00). This corresponded with an incidence rate of 16/1000 person-years (95% CI; 7.3-30.5). The PPV for progression to TB was 3.1% (95% CI; 1.3-5.0) for TST ≥10 mm, 3.8% (95% CI; 1.7-5.9) for TST ≥15 mm, 2.8% (95% CI; 1.0-4.6) for QFT-GIT and 3.3% (95% CI; 1.3-5.3) for T-SPOT.*TB*, and sensitivity for TB disease was 100%, 88%, 63% and 75%, respectively (Table 3). Specificity of the tests in this group of contacts with TST ≥5 mm (or known positive result), was highest for QFT (46%), followed by TST (cut-off 15 mm) (44%), T-SPOT.*TB* (40%) and lowest for TST (cut-off 10 mm) (15%).

Five contacts were excluded in the secondary analysis, since their follow-up started less than 12 months before August 1st 2008. The incidence rate during the first 12 months was 21/1000 persons-years (95% CI; 8.6-44.2). The PPV in the first 12 months was again not better for QFT-GIT (1.7%, 95% CI 0.3-3.1) or T-SPOT.*TB* (2.2%, 95% CI 0.6-3.9%) than for the TST using a cut-off of 10 mm (2.5%, 95% CI 0.8-4.1) or 15 mm (3.3%, 95% CI 1.4-5.2).

Restricting the analysis to contacts who attended the follow-up visits, the IGRA did not have a higher PPV compared to the TST either at a cut-off of 10 or 15 mm, although all PPVs were slightly increased.

DISCUSSION

In this prospective cohort study including recently exposed immigrant close contacts with TST results ≥5 mm who were followed without preventive treatment, we found that the positive predictive values of QFT-GIT and T-SPOT.*TB* for subsequent development of TB disease during the first two years after a contact investigation were comparable to that of the TST irrespective of the TST cut-off (10 or 15 mm). Our results differ from those in other populations in low incidence settings (9) that showed that the QFT-GIT may be a good predictor for development of active TB. In our study over half of the tested immigrant close contacts were QFT-GIT or T-SPOT.*TB* positive. When we assume that contacts with TST <5 mm whom we had excluded from IGRA testing would have been IGRA negative, still 42-46% of the contacts would be IGRA positive. This high proportion of positive tests found among recently exposed immigrant contacts is probably not only attributable to recently acquired infections (13).

So far five other contact studies assessed progression to disease in contacts tested with an IGRA (8-12) in different populations. Diel *et al*. (9) found 6 TB patients among 41 QFT-GIT positive contacts. The PPV of the QFT-GIT in this study (14.6%) was significantly higher than when a TST cut-off of 5 mm was used (PPV=2.3%, p=<0.003), although not at a cut-off of 10 mm (PPV=5.6%, p=0.10). In contrast, two studies assessing the ELISPOT in household contacts in Gambia (11) or in child contacts in Turkey (8), reported a similar prediction of TB cases by ELISPOT compared to the TST. Similar to our findings in the latter two studies (8, 11) the IGRA missed some of the contacts who progressed to disease. It is unclear if discrepancies between these studies may be explained by differences in the type of IGRA that was used. Direct comparison between the QFT-GIT and T-SPOT.*TB* showed that discrepancies occur, and T-SPOT.*TB* seemed to be slightly more sensitive than QFT-GIT (13, 18-21). Probably of more importance are the differences in the populations studied and the TB incidence in these countries.

In contrast to our expectations, three incident cases had a negative IGRA result. Re-infection and co-morbidity were unlikely explanations for the negative IGRA results. We performed the IGRA only once and usually shortly after the diagnosis of the index patient. Although the time to positivity after infection may be shorter for IGRA than for the TST (22), it is possible that we tested our contacts too early and the IGRA was not yet positive in contacts who later progressed to disease. On the contrary, reversions of previously positive IGRA results have also been reported (23, 24). More studies are needed to determine the optimal moment for IGRA testing after infection to develop new diagnostic algorithms for LTBI.

While the immigrant contacts in our study were all recently exposed, we observed previously that positive IGRA results may also be associated with remote infection (13). The implementation of IGRA in clinical practice in high TB endemic settings or among individuals with a high likelihood of previous exposure as recommended by some (25) is therefore debatable (26, 27). Nevertheless, the incidence rate among the recently exposed immigrant contacts was relatively high (16/1000) compared to estimations of others who assessed close contacts, ranging between 3.2-12.5/1000 (8, 11, 28, 29). Based on these results it may be recommendable to incorporate the use of preventive therapy or other preventive measures in the Dutch setting for the screening of immigrant close contacts of sputum smear-positive TB cases, as is already the practice in many other low incidence countries (3-5, 30). The choice of the diagnostic test to be used may be based on their cost-effectiveness.

Our study had some shortcomings. Firstly, we determined the IGRA and followed contacts actively only when TST ≥5 mm. The exclusion of contacts with TST results <5 mm may have

influenced our PPV and sensitivity estimations only to a limited extent. Few contact studies reported the percentage of positive IGRA results among contacts with TST <5 mm but found this to be less than 10% (9, 18, 19, 31, 32). Moreover, their risk of progression to disease is negligible (33) and we did not observe any case of TB in this subgroup upon checking the NTR. When one would assume that none of the immigrants with TST <5 mm would be IGRA positive, and indeed no TB cases occurred in this group, by definition this would result in the same PPV and sensitivity as estimated here. However, we may have underestimated the specificity and NPV when tests would be used directly as a single test (instead of after TST ≥5 mm). Secondly, we did not have complete follow-up data for all contacts. Although it is likely that contacts who stopped attending the follow-up visits were less likely to have developed TB disease, since they would otherwise have been notified to the NTR, we do not know this with certainty. Nevertheless, when the analysis was restricted to contacts followed for at least 12 months, we found the same pattern of PPVs as in our primary analysis, implying that non-participation in the follow-up visits will have had limited effect on our findings. Furthermore, our sample size was too small to determine superiority of one of the tests over the others. More longitudinal studies are needed to reveal in which persons which test will predict disease progression best.

In conclusion, we observed a high incidence rate of TB disease among immigrant close contacts during the subsequent two years of follow-up. The PPV for progression to TB among immigrant close contacts of both IGRA was not better than that of the TST. The incidence found among the study population justifies active preventive measures in this group.

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Legends to figures

Figure 1. Cohort profile of recruited contacts

Definition of abbreviations: TST= tuberculin skin test; QFT-GIT=QuantiFERON TB Gold in tube; TB=tuberculosis pos= positive; neg= negative; n.r.=no result, y=years, IQR=inter quartile range.

* No T-SPOT.*TB* result of 28 individuals because of technical failure (n=4), inconclusive test results (n=5) or insufficient blood collected to perform the test (n=19).

† Known positive TST results were all considered to be at least 10 mm (the regular cut-off for a positive TST result in the Netherlands), but were excluded from the analysis that used 15 mm as a cut-off since no exact indurations were known.

Figure 2. Kaplan-Meier curves showing the proportion of TB free contacts with a positive or negative result in QFT-GIT (a), T-SPOT.*TB* (b), TST at a cut-off of 10mm (c), TST at a cut-off of 15mm(d).

Persons at risk, figure 2a

Follow-up time (months)	**0**	**3**	**6**	**9**	**12**	**15**	**18**	**21**
QFT-GIT positive	178	176	175	174	163	135	116	95
QFT-GIT negative	149	146	144	144	140	113	96	87

Persons at risk, figure 2b

Follow-up time (months)	**0**	**3**	**6**	**9**	**12**	**15**	**18**	**21**
T-SPOT.*TB* positive	181	178	176	175	165	140	121	101
T-SPOT.*TB* negative	118	116	115	115	111	84	71	64

Persons at risk, figure 2c

Follow-up time (months)	0	3	6	9	12	15	18	21
TST ≥10 mm	288	282	279	278	265	216	187	134
TST 5-9 mm	51	51	51	51	48	39	32	30

Persons at risk, figure 2d

Follow-up time (months)	0	3	6	9	12	15	18	21
TST ≥15 mm	184	180	178	177	166	132	111	92
TST 5-14 mm	138	136	135	135	131	107	97	87

† Follow-up time was calculated from the date of start of follow-up (the date 3 months after the diagnosis of the index patient, or the date of blood collection for those who had IGRA testing >3 months after the diagnosis of their index patient) up to 24 months, the date of TB diagnosis, the time of emigration or death of the subject, or at the 1st of August 2008, whichever data came first.

Figure 1. Cohort profile of recruited contacts

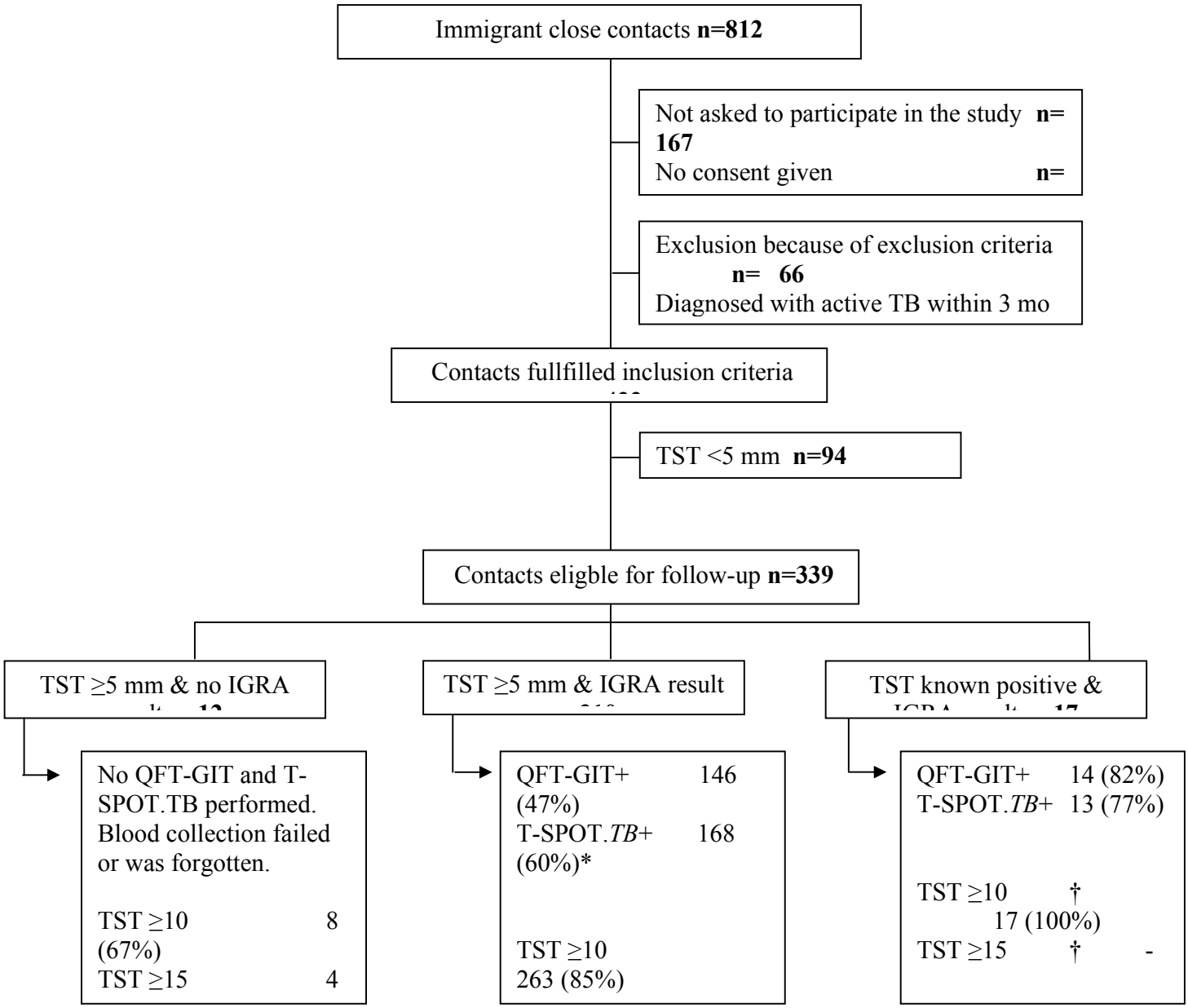

Figure 2. Kaplan-Meier curves showing the proportion of TB free contacts with a positive or negative result in QFT-GIT (a), T-SPOT.*TB* (b), TST at a cut-off of 10mm (c), TST at a cut-off of 15mm(d).

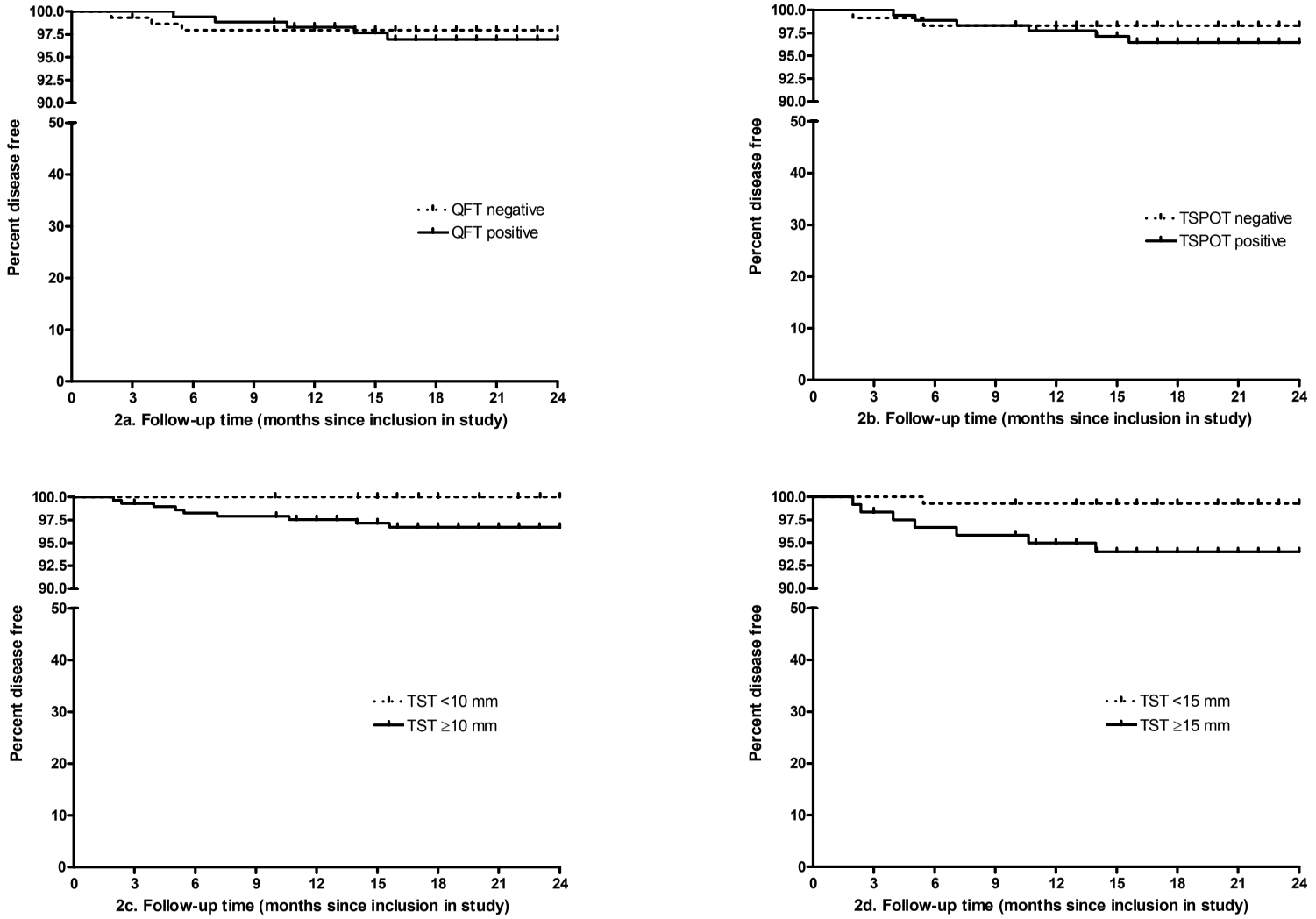

Table 1. Description of the study population; immigrant close contacts with a TST result of at least 5 mm (n=339)

	Study population	
	N	**%**
Total	**339**	**100**
Gender		
Male	189	55.8
Female	147	43.4
Unknown	3	0.9
Age (years)		
16-24	53	15.6
25-34	80	23.6
35-44	115	33.9
≥ 45	91	26.8
Continent of birth		
Europe, North America	27	8.0
South America	27	8.0
Asia	123	36.3
Other Africa	98	28.9
Sub-Saharan Africa	59	17.4
Unknown	5	1.5
Recent close contact		
Non-household contact	185	54.6
Household contact	115	33.9
Unknown	39	11.5
BCG scar		
Yes	274	80.8
No	43	12.7
Unknown	22	6.5
QFT-GIT result		
Negative	149	44.0
Positive	178	52.5
Not done	12	3.5
T-SPOT.*TB* result		
Negative	118	34.8
Positive	181	53.4
Not done/no valid result*	40	11.8
TST result (mm)		
5-9	51	15.0
10-14	87	25.7
≥ 15	184	54.3
Known TST responder	17	5.0

Definition of abbreviations: TST= tuberculin skin test; QFT-GIT=QuantiFERON TB Gold in tube.
* No T-SPOT.*TB* result because blood collection failed (n=12), technical failure (n=4), inconclusive test results (n=5) or insufficient blood collected to perform the test (n=19)

Table 2. Characteristics of contacts that developed TB disease during follow-up

Nr	Sex	Age group (y)	Region of birth	Time in NL (y)	HH contact	TST 1st round (mm)	TST 2nd round (mm)	QFT-GIT (IU/ml)	T-SPOT.*TB* (max spot count minus nill)	Reactive panel (T-SPOT.*TB*)‡	Time until IGRA testing (d) ll	Time to TB (mo)**	Type of TB	Culture	Case finding††
1	M	16-24	Asia	6	Yes	15	ND	Neg (0.02)	Neg (0)	None	34	4	ETB	Pos†	Passive
2	M	16-24	sS-Africa	5	Yes	ND	21	Pos (>10)	Pos (>100)	AB	137	4	PTB	Neg	Active
3	F	25-34	sS-Africa	9	No	18	ND	ND	ND	ND	-	5	PTB &ETB	Pos†	Passive
4	F	35-44	sS-Africa	3	Yes	17	ND	Neg (-0.24)	Pos (11)	B	19	6	ETB	Pos†	Active
5	M	16-24	O-Africa	3	No	10	ND	Neg (0.04)	Neg (1)	None	5	8	PTB	Pos†	Passive
6	F	16-24	O-Africa	9	Yes	15	ND	Pos (>10)	Pos (47)	AB	8	9	PTB	Neg	Active
7	F	≥45	S-America	13	Yes	25	ND	Pos (0.88)	Pos (68)	B	44	12	PTB	Neg	Passive
8	M	35-44	S-America	15	Yes	ND	18	Pos (>10)	Pos (>100)	AB	92	13	PTB	Pos†	Active
9	F	35-44	S-America	14	Yes	*ND	*ND	Pos (>10)	Pos (>100)	AB	28	18	PTB	Pos†§	Passive

Definition of abbreviations: TST= tuberculin skin test; NL=Netherlands; HH=household; QFT-GIT=QuantiFERON TB Gold in tube; F=female; M=male; pos=positive; neg=negative; ND=not done; S=South; sS=sub-Saharan; O=other; d=days; mo=months; y=years; NA=not applicable; FU=follow-up.

* TST known positive, due to previous TB episode
† RFLP pattern of isolate was identical to that of the index case.
‡ A=ESAT-6, B=CFP-10.
§ Isolate was not identical to the RFLP pattern of that of the previous TB episode of this case.
ll Number of days between diagnosis of the index patient and blood collection for IGRA determination
** Number of months between diagnosis of the index patient and diagnosis of TB of the contact
†† Passive case finding=cases reported spontaneously, active case finding=cases were found during a screenings visit

Table 3. Sensitivity, specificity and predictive values for development of tuberculosis disease for QuantiFERON-TB Gold in tube, T-SPOT.*TB* and TST among immigrant contacts

Time point	Number of contacts	Number of incident TB cases	Incident TB cases		Other contacts		Sens (95% CI)*	Spec (95% CI)*	PPV (95% CI)*	NPV (95% CI)*
			Test + (n)	Test - (n)	Test + (n)	Test - (n)				
PRIMARY ANALYSIS										
All contacts with TST ≥5 mm. Test parameters determined with follow-up until 1st August 2008.										
TST ≥10 mm	339	9‡	9	0	279	51	100 (100-100)	15 (12-19)	3.1 (1.3-5.0)	100 (100-100)
TST ≥15 mm	322	8‡	7	1	177	137	88 (84-91)	44 (38-49)	3.8 (1.7-5.9)	99.3 (98.4-100)
QFT-GIT	327	8	5	3	173	146	63 (57-68)	46 (40-51)	2.8 (1.0-4.6)	98.0 (96.5-99.5)
T-SPOT.*TB*	299	8	6	2	175	116	75 (70-80)	40 (34-45)	3.3 (1.3-5.3)	98.3 (96.8-99.8)
SECUNDARY ANALYSIS										
Contacts with TST ≥5 mm, who started follow-up at least 12 months before August 1st 2008.										
Test parameters are determined after 12 months follow-up.										
TST ≥10 mm	334	7	7	0	278	49	100 (100-100)	15 (11-19)	2.5 (0.8-4.1)	100 (100-100)
TST ≥15 mm	317	7	6	1	176	134	86 (82-90)	43 (38-49)	3.3 (1.3-5.3)	99.3 (98.3-100)
QFT-GIT	323	6†	3	3	173	144	50 (45-55)	45 (40-51)	1.7 (0.3-3.1)	98.0 (96.4-99.5)
T-SPOT.*TB*	295	6†	4	2	175	114	67 (61-72)	39 (34-45)	2.2 (0.5-3.9)	98.3 (96.8-99.8)
SENSITIVITY ANALYSIS										
Contacts with TST ≥5 mm, who were actively followed for at least 12 months.										
Test parameters determined after 12 months follow-up.										
TST ≥10 mm	203	7	7	0	165	31	100 (100-100)	16 (11-21)	4.1 (1.4-6.8)	100 (100-100)

TST ≥15 mm	191	7	6	1	107	77	86 (81-91)	42 (35-49)	5.3 (2.1-8.5)	98.7 (97.1-100)
QFT-GIT	201	6†	3	3	112	83	50 (43-57)	43 (36-49)	2.6 (0.4-4.8)	96.5 (94.0-99.1)
T-SPOT.*TB*	186	6†	4	2	114	66	67 (60-73)	37 (30-44)	3.4 (0.8-6.0)	97.1 (94.6-99.5)

Definition of abbreviations: TST= tuberculin skin test; QFT-GIT=QuantiFERON TB Gold in tube; TB=tuberculosis += positive; - = negative; sens=sensitivity; spec=specificity; PPV=positive predictive value; NPV=negative predictive value, CI=confidence interval.
* Sensitivity, specificity, positive and negative predictive value for development of tuberculosis disease are determined in immigrant close contacts with TST ≥5 mm.
† IGRA was not performed in 1 incident TB case
‡ TST was known positive (≥10 mm) in 1 incident TB case and not determined at recruitment of the study. This case was excluded form the analysis of TST ≥15 mm.

Appendix A

List of birth countries considered *not* to be high endemic for this study

Australia
Austria
Belgium
Canada
Czech Republic
Cyprus
Denmark
Estonia
Finland
Germany
Greece
Hungary
Iceland
Ireland
Israel
Italy
Japan
Latvia
Lithuania
Luxembourg
Malta
Monaco
New Zealand
Norway
Poland
Portugal
Slovakia
Slovenia
Spain
Sweden
Suriname *(if the individual has not received a BCG vaccination in Suriname during childhood)*

Switzerland
United Kingdom
USA