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Role of Quantiferon-TB Gold In-Tube in screening new immigrants for tuberculosis infection

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Abstract

This study aimed to estimate the risk of progression to active tuberculosis within two years after entry in newly arriving immigrants who were screened with the QuantiFERON®-TB Gold In-Tube assay (QFT-GIT).

In a case-base design, we determined the prevalence QFT-GIT positives among a representative sample of immigrants aged ≥18 years who arrived between April 2009 and March 2011 (the base cohort). Active TB patients (cases) within two years post-arrival of 2005, 2006, or 2007 were extracted from the Netherlands Tuberculosis Register. The risk of progression to active TB was estimated using Bayesian analyses to adjust for the sensitivity of QFT-GIT.

Among the base cohort, 20% of 1,468 arrived immigrants were QFT-GIT positive. Stratified by TB incidence in person's country of origin as low (<100/100,000), intermediate (100-199/100,000) or high (≥200/100,000), the risk of progression to active TB per 100,000 arriving immigrants if QFT-GIT positive was 456 (95% CI: 307-589), 590 (397-762), and 386 (259-499), respectively, compared to 18 (0-46), 38 (0-97), and 28 (0-71) if QFT-GIT negative.

Screening newly arriving immigrants with QFT-GIT contribute to detect those at high risk of subsequent TB reactivation within two years after entry, which offers opportunities for prevention by targeted interventions.

Keywords: immigration, screening, latent tuberculosis, tuberculosis

Introduction

As in most western countries, the incidence of tuberculosis (TB) in the Netherlands is decreasing among the native Dutch population in contrast to first generation immigrants (persons born outside the Netherlands) (1). In 2009, 73% of all TB patients were diagnosed in first generation immigrants (1), and this percentage is estimated to increase (2).

TB incidence in the Netherlands will not decrease further without specific interventions targeted at first generation immigrants. Entry screening for active TB by chest X-ray (CXR) is mandatory for all immigrants aged >12 years from primarily non-Western countries who intend to stay longer than three months (3). Immigrants from high incidence countries (≥200/100,000) are offered voluntary follow-up screening by CXR at six months intervals for two years. This strategy is not effective in terms of lowering the TB incidence among first generation immigrants (4-5). TB in this group is largely due to reactivation of latent tuberculosis infection (LTBI) acquired in the country of origin (6). Screening immigrants at entry for LTBI and providing those infected with prophylactic treatment is a potentially important strategy to reduce the incidence of TB (7-8), but not implemented in the Netherlands because of the low specificity of the tuberculin skin test (TST).

The QuantiFERON®-TB Gold In-Tube assay (QFT-GIT) identifies cellular production of interferon gamma in response to the *M. tuberculosis* specific antigens ESAT-6, CFP10 and TB7.7. Previous research has shown that compared to TST, the QFT-GIT has a higher specificity in measuring LTBI since it is independent of previous Bacille Calmette-Guérin vaccination or infection with most atypical mycobacteria, two factors that are often present in an immigrant population (9).

Whether screening with QFT-GIT and treatment of LTBI in immigrants is an effective intervention depends on its discriminatory ability to identify those at high risk of progression to active TB. The risk of progression to active TB stratified by QFT-GIT result has been assessed among several populations, but never among newly arriving immigrants (10). The objective of this study was to estimate the proportion of newly arrived immigrants with a positive QFT-GIT and to assess the risk for developing active TB within two years after entry given the QFT-GIT result at entry.

Methods

Design

The study used a case-base design. We assessed the prevalence of QFT-GIT positives in a representative sample of newly arriving immigrants at seven Public Health Services (PHSs) between April 2009 and March 2011, denoted as 'base cohort'. This prevalence was projected on three cohorts of immigrants who were registered in the Monitoring for Screening of Immigrants (MSI), and were screened at arrival in 2005, 2006, or 2007 at the same seven PHS, denoted as 'case source cohort'. In the MSI, the PHSs register the results of screening activities. From the case source cohort we extracted the immigrants who developed TB within two years after arrival, denoted as 'cases', by matching the MSI with the Netherlands Tuberculosis Register (NTR).

Data collection

For the base cohort, data was collected by trained staff at the seven PHSs located throughout the country. All immigrants ≥18 years, reporting for their entry screening were invited. Asylum seekers were not included because they were not registered in the MSI. Enrolment

continued until 1,500 QFT-GIT outcomes were obtained. This number was needed to determine an assumed prevalence of 30% QFT-GIT positives (11), accounting for an imprecision of 6%, and to be able to stratify analyses. Participants had a structured questionnaire and a QFT-GIT in addition to a routine CXR. Age was categorized as 18-24, 25-34, or ≥35 years. Country of origin was collapsed into region of origin (Europe & Americas, Middle East & North Africa, other Asia, Sub-Saharan Africa, and Other), and tuberculosis incidence in the country of origin (low: <100 cases per 100,000 a year, intermediate: 100-199/100,000, high: ≥200/100,000). Immunocompromised (e.g. HIV-positives) and users of immunosuppressive medication were excluded for QFT-GIT testing. Cases from the base cohort and from the case source cohort who were diagnosed with TB within six months after the entry screening were excluded, because the NTR classified these cases as being detected during entry screening. Ethical approval was obtained from the Netherlands Central Committee on Research involving Human Subjects (CCMO). All participants of the base cohort provided written informed consent.

QFT-GIT (Cellestis LtD, Carnegie, Victoria, Australia) testing was done according to manufacturer's instructions in PHSs' experienced local laboratories. Test results were interpreted according to the manufacturer's provided cut-off values.

Statistical analysis

Demographic data for the base cohort and the case source cohort were compared by Pearson χ^2.

To calculate the risk of progression to TB we adjusted for the sensitivity of the QFT-GIT for detecting the cases, based on published data (12-18). From each of these studies we included

the reported sensitivity and precision for the prediction of TB among QFT-GIT positive individuals in a Bayesian model to obtain a posterior distribution of the sensitivity for the QFT-GIT, from which 20,000 random draws were taken to estimate disease progression and 95% credibility interval (95% CI) per 100,000 population (19). The analyses were stratified for sex, age, and TB incidence in country of origin. See additional information online. Associations were considered statistically significant when $P \leq 0.05$. All analyses were performed in SPSS 17.0 (Chicago, IL, USA) and WinBUGS 1.4.3 (Imperial College and MRC, UK).

Results

Out of the 2,569 newly arrived immigrants 1,570 (61%) gave informed consent, of whom 1,468 had a QFT-GIT result (Figure 1). Compared to non-consenters, the consenters were significantly more often from Sub-Saharan Africa (P=0.001) and countries with high TB incidences (P<0.001). Reasons for individuals not to consent were predominantly a lack of time and fear of having a blood draw.

There were no significant differences between the base cohort and the case source cohort with regards to sex (P=0.086) or age (P=0.982), but moderate differences with regard to country of origin (P=<0.001) and incidence in the country of origin (P=0.006) (Table 1).

Among the base cohort, 296 participants tested QFT-GIT positive (20%), and five had indeterminate results (<1%). The percentage of QFT-GIT positives was lower in the lowest

age category, but similar in the two highest age categories (Table 1). Among immigrants from low incidence countries the prevalence of QFT-GIT positives was lowest, while this was similar for immigrants coming from intermediate or high incidence countries (Table 1).

Among the case source cohort, 30 cases were diagnosed with TB within two years after the entry screening (Table 2). Twenty-five cases (83%) were bacteriologically confirmed by culture, of which 10 cases were clustered (assessed via Variable Number Tandem Repeat) with another TB patient in the NTR. None of these were confirmed to be epidemiologically linked with a case in the Netherlands; suggesting that the cases acquired infection before having arrived into the Netherlands.

Assuming a similar prevalence of QFT-GIT positives in the case source cohort, 5,306 people in the case source cohort would be expected to be QFT-GIT positive, and the positive QFT-GIT would be distributed as shown in Table 2. The median of the posterior distribution of the sensitivity of the QFT-GIT as assessed by Bayesian analyses was 83%, with a 95% CI of 56% to 100%.

The overall associated risk of disease progression for QFT-GIT positives was markedly higher compared to QFT-GIT negatives, 467 (314-603) vs. 25 (0-64) per 100,000 population, respectively (Table 2). The risk of progression to TB with a positive QFT-GIT did not differ between males and females, nor between the different age groups. Irrespective of incidence in country of origin, the risk of progression to TB was markedly higher in QFT-GIT positives compared to QFT-GIT negatives.

Discussion

The present study shows that one fifth of a representative sample of newly arriving immigrants in the Netherlands had LTBI as measured by QFT-GIT. The estimated risk of progression to TB within two years for QFT-GIT positives was substantial and, irrespective of immigrants' sex, age, and incidence in the country of origin, significantly higher than the risk of progression among QFT-GIT negatives. The risk was significantly higher than the Dutch risk-group definition of an incidence of 50 per 100,000 population, based on a tenfold higher incidence of TB compared to that in the autochthonous population. This indicates that in this study we have identified a new risk group, being newly arriving immigrants with a positive QFT-GIT result. This finding suggests that using QFT-GIT might be of value in immigrant entry screening programs.

The observed prevalence of QFT-GIT positivity of 20% among newly arriving immigrants is representative at national level, because there were no marked differences in demographic characteristics between the base cohort and the case source cohort. Other European countries reported a similar LTBI prevalence among newly arriving immigrants measured by IGRA, but in general among asylum seekers, and only at regional level (18, 20).

The high risk of progression to TB among immigrants originating from intermediate incidence countries might be explained by a high prevalence of risk factors associated with progression to TB. We did not observe risk differences based on sex and age. Because we determined the risk of progression to TB of QFT-GIT positive immigrants in a screening setting, as opposed to a setting with actual recent documented exposure, we found lower risk estimates compared to those of previous studies (10).

We excluded 22 cases who developed TB within six months after entry screening. Of these, only three were identified passively which can be considered as a result of reactivation. The exclusion of such a small number of cases leads to a slight underestimation of the risk of progression to TB. Given that most cases diagnosed with TB within six months were detected actively (by entry screening) the role of QFT-GIT for the first six months would have been limited.

The usefulness of screening newly arriving immigrants for LTBI is continuously debated, and differs from the screening for active TB. While active TB can be a serious immediate threat to public health, LTBI in the short term is not. Wilson and Jungner proposed several criteria to fulfil before a screening program could be implemented (21). According to these criteria, prerequisites are the use of an accurate diagnostic test which can diagnose a health state which is curable according to a comprehensive and acceptable treatment regimen. Translating these criteria to this specific setting, screening newly arriving immigrants for infection should only be considered if the program is well organized, resources are sufficient for initiating such a strategy, and there is a willingness to treat. Up to now, the available diagnostic test (TST) was deemed insufficient, and the need for treatment was disputed, while programmatic limitations were envisioned (22).

We have shown that QFT-GIT seems to have the discriminatory ability to classify individuals for low and high risk of progression to active TB within two years. It is currently unknown whether the development of active TB beyond two years post-immigration is also associated with QFT-GIT results at the time of immigration. If such association is strong, then targeted treatment of all QFT-GIT positive immigrants could have a significant impact on the overall number of active TB in immigrants. Molecular data from the NTR suggest that the majority of

immigrants who progress to TB several years post-immigration are due to remote infections which would increase the expected effectiveness of entry screening for LTBI (1).

To what extent QFT-GIT distinguishes recent from remote infection is unclear, but can have implications whether to start preventive therapy. Recently infected individuals are considered to be at greater risk for progressing to disease compared to individuals with a remote infection (23). Among newly arriving immigrants a high proportion of remote infections has to be expected, which cannot be distinguished from recent infections. Until new technologies are designed for distinguishing recent from remote infection, for example by further developing tests for measuring promising latency antigens (24), we should consider all newly arriving immigrants with a positive QFT-GIT to have a substantial risk of progressing to TB.

A possible intervention in QFT-GIT positive newly arriving immigrants is to offer prophylactic treatment. The Dutch prophylactic treatment regimen was recently revised from six months daily isoniazid (6H) to either 6H or three months daily isoniazid plus rifampicin (3HR) for HIV-negative individuals who are suspected to be recently infected and have a CXR without TB-related abnormalities. Preventive therapy is not considered among individuals who are suspected to have a remote infection. In a meta-analysis it was shown that 3HR was comparable to standard therapy with 6H or 12H in terms of efficacy, the proportion of severe side effects, and mortality, while treatment adherence was equal or greater among patients receiving 3HR (25). Up to now, only a limited number of individuals have been treated with the new 3HR regimen in the Netherlands, but completion rates seem promising (1). A meta-analyses showed that the median (95%CI) hepatotoxicity rate, defined by elevated hepatic aminotransferases and/or symptoms of hepatitis, for individuals aged <35 years treated with 6-9H was 0.2% (0.1-0.3) (26). Offering preventive therapy to newly

arriving immigrants who are QFT-GIT positive is therefore expected to be possible without major hepatotoxicity problems, especially since the majority is aged <35 years. However, the prevalence of chronic viral hepatitis is significant in certain regions and can therefore be expected to be higher among immigrants than among native Dutch individuals, with an associated increase in the risk of hepatotoxicity.

The efficacy of prescribing prophylactic treatment to newly arriving immigrants with a positive QFT-GIT result is directly related to the prevalence of multidrug resistant TB (MDR-TB) in the countries of origin. Although a threat to the efficacy of preventive therapy, we believe this will not be a major issue in newly arriving immigrants given that between 2006-2009 the prevalence of MDR-TB among all notified patients in the Netherlands was around 1% (1). However, when active TB develops in an immigrant who has received treatment for LTBI, the risk of MDR-TB should be suspected from the outset and empirical treatment should include that possibility.

Numbers needed to treat to prevent 1 case of TB within two years, given a positive QFT-GIT and an efficacy of 60% of prophylactic treatment, will be around 350. The corresponding number needed to screen (NNS) will be around 1,800. This NNS is comparable to the NNS found for other mass screening programs in the Netherlands.

An alternative for preventive therapy is to actively follow-up QFT-GIT positive immigrants by periodical CXR screening. The coverage of the current voluntary six-monthly follow-up screening for a period of two years offered to immigrants from high incidence countries is dropping as low as 34% (4). Furthermore, half of the cases in our case source cohort were diagnosed with extrapulmonary TB (ETB) and would not have been detected by CXR.

Offering active follow-up to QFT-GIT positive immigrants, even if mandatory, is therefore unlikely to be effective. Another alternative to treatment is to rely on a well-established contact tracing strategy in the Netherlands. However, analyses of routine data have shown that in the group of first-generation immigrants, this strategy works suboptimal compared to native Dutch TB patients (27-28).

The public health benefit of screening newly arriving immigrants for LTBI depends highly on the organization of the program. Menzies et al. highlighted that in screening programs fewer than 40% of the participants who could have benefited from preventive therapy actually did so (7). Reasons were no participation in the initial screening, no show for medical evaluation of positive tests, but also non-compliance of physicians to follow treatment recommendations leading to non-compliance or refusal of therapy among individuals diagnosed with LTBI. There is some recent evidence that these negative indicators can be improved upon by using QFT-GIT compared to the conventional TST (29-30). In depth research is needed to get insight in barriers and facilitators of a successful treatment program. Based on the data collection at the seven PHSs we are convinced that screening newly arriving immigrants for LTBI by QFT-GIT is achievable without major logistical difficulties.

Our work had several limitations. The estimates for risk of progression to TB were not derived in a prospective manner. We therefore had to assume that the cases were already infected at entry. Being infected in the Netherlands after entry was considered unlikely as none of the cases in our study were epidemiologically linked with other patients diagnosed in the Netherlands. The risk of progression to TB could have been attributed to travelling to the country of origin after the initial screening, but we had no data to incorporate this.

Data regarding remigration within two years after the entry screening was lacking, and therefore the direction of potential bias was unknown. However, because the observed risk for QFT-GIT positive immigrants to progress to active TB was around tenfold higher than the level used for the Dutch risk group definition (50/100.000), it is unlikely that preferential mass remigration of immigrants without active TB underlay the observed findings.

Another limitation is that the results cannot be extrapolated to newly arriving immigrant children (<18 years). Nationwide, this group accounts for approximately one sixth of the total number of patients diagnosed with TB within two years after entry (1). Compared to adults, the risk of progression to TB in children is higher indicating that the use of QFT-GIT for detection and targeted treatment of LTBI in children might thus be even more effective (31).

In conclusion, the findings of this study among newly arriving immigrants to the Netherlands provide evidence that screening by QFT-GIT detects those at high risk of subsequent TB reactivation and that targeted interventions might lower the TB incidence among first generation immigrants. The next step will be to incorporate these findings in a cost-effectiveness analysis including several alternative entry screening strategies as well as alternative strategies for TB control, such as contact investigation. This will give evidence to reconsider the national immigrant screening program.

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Figure 1. Study flow diagram of base cohort

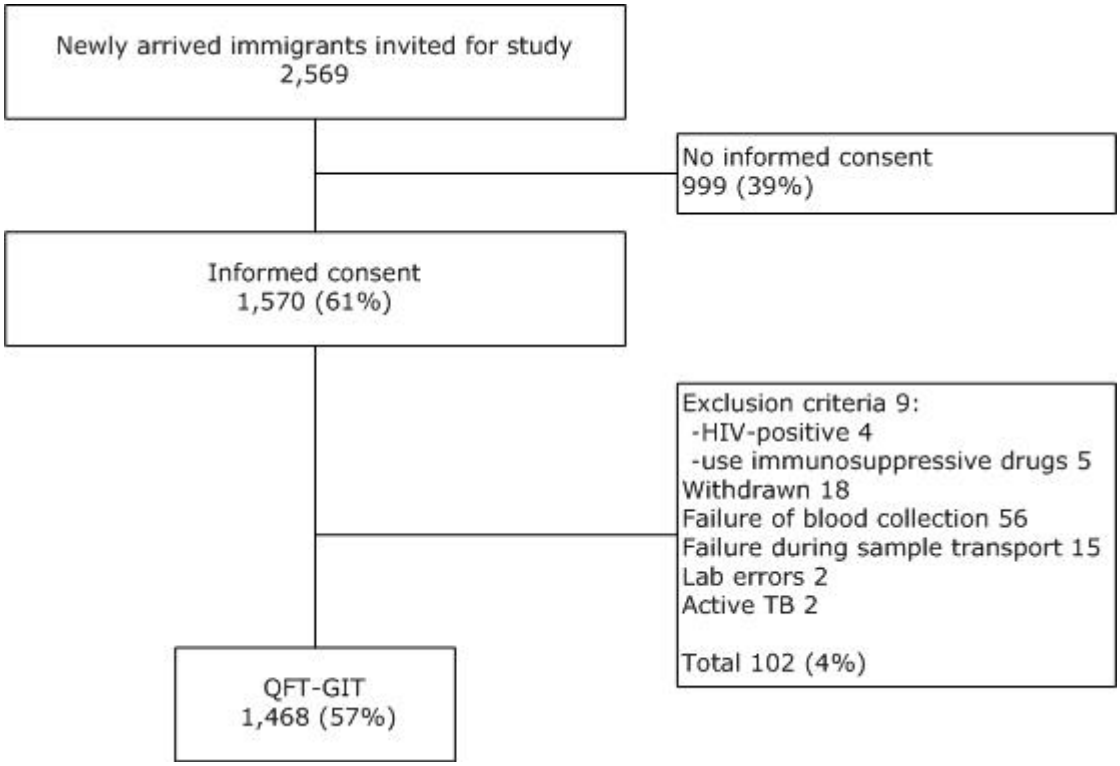

Table 1. Baseline characteristics of the case source cohort and the base cohort including the number of QFT-GIT positives.

	Case source cohort*	Base cohort¶		Case source cohort compared with base cohort
	n (%)	n (%)	QFT-GIT positive n (% of base cohort)	p-value
Total	26,317	1,468	296 (20)	
Sex				
Female	13,766 (52)	799 (54)	152 (19)	0.086
Male	12,504 (48)	669 (46)	144 (22)	
Unknown	47 (0)	0 (0)	0 (0)	
Age, years				
18-24	7,877 (30)	436 (30)	58 (13)	0.982
25-34	12,797 (49)	716 (49)	163 (23)	
≥35	5,643 (21)	316 (22)	75 (24)	
Region of origin				
Europe, Americas	7,647 (29)	376 (26)	48 (13)	<0.001
Middle East, North Africa	3,680 (14)	219 (15)	54 (25)	
Other Asia	10,849 (41)	679 (46)	141 (21)	
Sub-Saharan Africa	3,894 (15)	188 (13)	52 (28)	
Other	1 (0)	6 (0)	1 (17)	
Unknown	246 (1)	0 (0)	0 (0)	
Estimated TB incidence in country of origin				
<100/100,000	13,799 (52)	725 (49)	116 (16)	0.006
100-199/100,000	7,231 (28)	453 (31)	107 (24)	
≥200/100,000	5,040 (19)	284 (19)	72 (25)	
Unknown	247 (1)	6 (0)	1 (17)	
Ever smoked daily				
No	n.a.	1,025 (70)	207 (20)	
Yes		433 (29)	87 (20)	
Unknown		10 (1)	2 (20)	
Ever treated for TB				
No	n.a.	1,418 (97)	280 (20)	
Yes		17 (1)	9 (53)	
Unknown		33 (2)	7 (21)	
Time between entry and screening				
≤3 months	n.a.	1,353 (92)	278 (21)	
≥4 months		108 (7)	17 (16)	
Unknown		7 (0)	1 (14)	
TB-related abnormalities on CXR				
No	n.a	1,454 (99)	288 (20)	
Yes		14 (1)	8 (57)	

*: three cohorts of immigrants who were registered in the Monitoring for Screening of Immigrants (MSI) and were screened at arrival in 2005, 2006, or 2007; ¶: sample of newly arriving immigrants at seven Public Health Services (PHSs) between April 2009 and March 2011

Table 2. Risk of progression to TB within two years for QFT-GIT positives and negatives

	Case source cohort n	TB within two years	Incidence of TB within two years per 100.000 population	Expected QFT-GIT positive at entry* n (%)	Estimated risk of progression to TB per 100,000 population‡ (95% CI)	
					QFT-GIT positive	QFT-GIT negative
Total	26,317	30	114	5,306 (20)	467 (314-603)	25 (0-64)
Sex						
Female	13,766	15	109	2,619 (19)	473 (318-611)	24 (0-60)
Male	12,504	15	120	2,691 (22)	460 (310-595)	27 (0-68)
Age, years						
18-24	7,877	6	76	1,048 (13)	473 (318-611)	15 (0-39)
25-34	12,797	16	125	2,913 (23)	453 (305-586)	28 (0-72)
≥35	5,643	8	142	1,339 (24)	493 (332-638)	33 (0-83)
TB incidence in the country of origin						
<100/100,000	13,799	12	87	2,208 (16)	456 (307-589)	18 (0-46)
100-199/100,000	7,231	12	166	1,708 (24)	590 (397-762)	38 (0-97)
≥200/100,000	5,040	6	119	1,278 (25)	386 (259-499)	28 (0-71)

*Number estimated based on QFT-GIT positive prevalence in base cohort as presented in table 1

† Based on surveillance data from MSI & NTR

‡ Based on Bayesian statistics for posterior distribution resulted in a median (95%CI) sensitivity for QFT-GIT of 83% (56-100)