Predictive Value of the Tuberculin Skin Test among Newly Arriving Immigrants

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Abstract

Rationale: Screening and treating newly arriving immigrants for latent tuberculosis infection (LTBI) in low-incidence countries could be promising to reduce the tuberculosis incidence among this population. The effectiveness of screening with the tuberculin skin test (TST) is unknown.

Objectives: To estimate the risk of progression to tuberculosis within two years after entry, stratified by TST result at entry.

Methods: In a case-base design, we determined the prevalence of TST positives (10 mm and 15 mm) among a representative cohort of immunocompetent immigrants (n = 643) aged ≥18 years who arrived between April 2009 and March 2011 in the Netherlands (base cohort). Immigrants who progressed to tuberculosis within two years after arrival in 2005, 2006 or 2007 were extracted from the Netherlands Tuberculosis Register (case source cohort). The prevalence of TST positives from the base cohort was projected on the case source cohort to estimate the risk of progression to active tuberculosis by using Bayesian analyses to adjust for the sensitivity of the TST and Poisson regression analyses to take into account the random error of the number of extracted cases.

Results: The prevalence of TST positives was 42% and 23% for a cut-off value of 10 mm and 15 mm, respectively. The overall risk of progression to tuberculosis if TST positive was 238 per 100,000 population (95% CI 151–343) and 295 per 100,000 population (95% CI 161–473) for a cut-off value of ≥10 mm and ≥15 mm, respectively. The corresponding risk for TST negatives was 19 (95% CI 0–59) and 58 (95% CI 25–103).

Conclusion: The TST has the discriminatory ability to differentiate between individuals at low and high risk of disease.

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Introduction

In countries with a low-incidence of tuberculosis (TB), TB is primarily prevalent among first generation immigrants. In the Netherlands, 73% of the new patients with TB in 2010 were first generation immigrants, corresponding to an incidence of 43.6 per 100,000 persons, whereas this incidence was 1.6/100,000 for the native population [1]. Immigrants from high incidence countries have a high risk of developing TB in the first five years after immigration [2]. From the Netherlands Tuberculosis Register (NTR) it appeared that in 2010, 12% of the first generation immigrants with TB were diagnosed at entry, while another 25% were diagnosed with TB within 2.5 years after entry [1]. Furthermore, the majority of immigrants with TB had a unique strain of Mycobacterium TB (MTB), and the ones who belonged to a cluster (patients with identical DNA-fingerprint isolates) were often not epidemiologically linked [1]. These data suggest that immigrants acquire TB infection in their country of origin and that incident TB is a consequence of reactivation of latent TB infection (LTBI).

All immigrants aged >12 years from high-incidence countries intending to stay more than three months in the Netherlands, currently only undergo a mandatory screening for TB by chest x-ray (CXR) [3]. Immigrants are not screened for LTBI because the specificity of the tuberculin skin test (TST) is considered limited, due to cross-reactivity with bacille Calmette-Guérin (BCG) vaccination and environmental mycobacteria [4].

Interferon gamma release assays (IGRAs) were developed to improve the diagnosis of LTBI. These are based on identifying cellular production of interferon gamma (IFN-γ) in response to MTB specific antigens and do therefore not react on BCG and most environmental mycobacteria. One of those IGRAs is the QuantiFERON®-TB Gold In-Tube (QFT-GIT). In a recent study we have shown that immigrants with a positive QFT-GIT at entry had a considerable higher risk of progression to active TB within two years compared to immigrants with a negative QFT-GIT at
entry [5]. This implies that targeted testing for LTBI, at least with the QFT-GIT, and subsequently offering preventive therapy, might contribute to decrease the incidence of TB.

The effectiveness of using the TST in screening immigrants for LTBI is still unknown since it has never been used in the Dutch setting. Several studies found that, among immigrant contacts of TB patients, the TST and QFT-GIT were both indicative in predicting the risk of developing TB [6,7]. Kik et al. found a similar positive predictive value (PPV) for QFT-GIT and TST, irrespective whether a cut-off value for the TST of 10 mm or 15 mm was used. Also the negative predictive values of both tests were comparable [6]. The TST therefore might also have potential in screening immigrants for LTBI at entry, especially since the TST is relatively cheap, easy to administer, and extensively used in routine practice for many years. Whether the TST would be useful depends on its discriminatory ability in comparison with the QFT-GIT. The objective of this study was to predict the risk of progression to TB within two years after entry given the TST result at entry.

Materials and Methods

Ethics Statement

Ethical approval was obtained from the Netherlands Central Committee on Research Involving Subjects.

Design

This study is a post-hoc analysis of data derived from the study assessing the relationship between QFT-GIT result and risk of active TB in immigrants within two years of time of entry screening [5]. A case-base design was used, also labelled as ‘case-cohort’ design [8]. A representative group of controls is selected from which the cases originated, regardless of future disease status. A case-base design was used, because in a prospective design we would have needed a very large sample to obtain accurate risk estimates given the relatively low risk of progression to active TB [9]. The prevalence of TST positives (≥10 mm and ≥15 mm) was assessed in a representative sample of newly arriving immigrants at seven Public Health Services (PHSs) between April 2009 and March 2011, denoted as ‘base cohort’ (Figure 1). We projected this prevalence on a cohort of immigrants who were screened for active TB at arrival in 2005, 2006, or 2007 at the same seven PHS and were registered in the Monitoring for Screening of Immigrants (MSI), denoted as ‘case source cohort’. From this cohort the immigrants who developed TB within two years after arrival were extracted, denoted as ‘cases’, by matching the MSI with the NTR by sex, country of birth and date of birth. The TST status of the case source cohort was therefore “assessed indirectly” by assuming a similar distribution of TST test results as directly assessed in the base cohort. As a matter of fact, since the immigrants from the case source cohort were not tested for LTBI at entry, none of them were offered a course of preventive therapy.

All immigrants aged ≥18 years who visited the PHS for their entry screening, reported to be immunocompetent and provided written informed consent, were eligible for enrolment in the base cohort. We excluded immigrants who were diagnosed with active TB within six months after entry, because in the NTR these are reported as detected at entry screening and not during follow-up. Regarding the sample size, in our previous study 1570 immigrants consented. Out of these, 643 received a TST. The sample of 643 gave us enough power to find a prevalence of TST positives (≥10 mm and ≥15 mm) was assessed in a representative sample of newly arriving immigrants at seven Public Health Services (PHSs) between April 2009 and March 2011, denoted as ‘base cohort’ (Figure 1). We projected this prevalence on a cohort of immigrants who were screened for active TB at arrival in 2005, 2006, or 2007 at the same seven PHS and were registered in the Monitoring for Screening of Immigrants (MSI), denoted as ‘case source cohort’. From this cohort the immigrants who developed TB within two years after arrival were extracted, denoted as ‘cases’, by matching the MSI with the NTR by sex, country of birth and date of birth. The TST status of the case source cohort was therefore “assessed indirectly” by assuming a similar distribution of TST test results as directly assessed in the base cohort. As a matter of fact, since the immigrants from the case source cohort were not tested for LTBI at entry, none of them were offered a course of preventive therapy.

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Statistical Analyses

To calculate the risk of progression to active TB per 100,000 population we used a Bayesian approach with non-informative priors. The numerator (number of cases identified from the case source cohort) was modelled using the Poisson distribution to allow for uncertainties in the number of identified patients. The denominator (number of immigrants with positive/negative TST) took into account differences in sensitivity of the TST reported in the published data [6,10,11,12,13,14]. The Bayesian model provided a posterior distribution for the risk of progression to active TB from which 20,000 random samples were drawn to arrive at a point estimate and 95% credibility interval (CI). We estimated the risk stratified by sex, age and incidence in country of origin (see Text S1 for more details).

The risk estimates of progression to active TB enabled us to calculate the numbers needed to treat (NNT), and the numbers needed to screen (NNS) to prevent one TB patient within two years, for TST $\geq 10$ mm and TST $\geq 15$ mm. We assumed a 60% efficacy rate of the preventive treatment [15].

Eligible patients could have 1 of 3 reasons for not being included in the present study. First, they could not have consented to participate in the original study; second, they did participate but did not want to have a TST administered, or third, they had a TST administered but there was no available result (test failure or no return for test reading). Given the post-hoc analysis, there is a need to carefully check for selection bias at each of these instances. We therefore compared the baseline characteristics of the base cohort with the case source cohort, the non-consenters and the participants without a TST result by Pearson $\chi^2$. Baseline characteristics were sex, age (18–24 years, 25–34 years and $\geq 35$ years), region of origin (Europe & the Americas, North Africa & Middle East, Asia, Sub-Saharan Africa, Unknown), incidence of TB in country of origin (< 100 (low), 100–199 (intermediate) and $\geq 200$ (high) per 100,000 population), BCG vaccination (yes if BCG-scar was present and/or participant indicated being vaccinated), previous diagnosis of TB (yes/no), smoking (yes if ever smoked/no) and time in the Netherlands before screening (yes if $\leq 3$ months in the Netherlands before screening/no). Associations were considered statistically significant when $p$-values were $\leq 0.05$. Statistical analyses were conducted using SPSS 17.0 (Chicago, IL, USA) and WinBUGS 1.4.3 (Imperial College and MRC, UK).

Results

During the study period, 2,569 immigrants were approached for study enrolment at the seven PHSs. Out of 1,570 consenters, 1,559 were eligible for TST testing since 11 were excluded because they were HIV-positive ($n = 4$), used immunosuppressives ($n = 5$), or were diagnosed with active TB within 6 months ($n = 2$) (Figure 2).
In 753 (48.3%) immigrants, out of those eligible, a TST was administered because others refused the TST due to a lack of time for the second visit. Out of these, 82 did not return for the reading of the TST, and in 25 the TST result was unknown because it was not registered. Three participants with no data on country of origin were excluded from all analyses, resulting in 643 (41%) immigrants with a TST result. The consenters were significantly more often from high-incidence countries than non-consenters (20% versus 14%, data not shown). Compared to the case source cohort, there were significantly more females (57% versus 52%), more immigrants from Asia (45% versus 41%), and more immigrants from high-incidence countries (23% versus 19%) in the base cohort (Table 1). The immigrants in the base cohort were significantly more often BCG-vaccinated (85% versus 76%) and

| Table 1. Baseline characteristics for base cohort, case source cohort and participants without TST result. |
|---------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|
| **Base cohort** | **Case source cohort** | **Base cohort compared with case source cohort** | **No TST result** | **Base cohort compared with no TST result** |
|-----------------|-----------------|------------------------------------------|-----------------|------------------------------------------|
| **N (%)** | **N (%)** | **P-value** | **N (%)** | **P-value** |
| **Total** | 643 (100%) | 26,317 (100%) | – | 913 (100%) | – |
| **Sex** | | | | | |
| Female | 370 (57%) | 13,766 (52%) | 0.020 | 488 (54%) | 0.110 |
| Male | 273 (43%) | 12,504 (48%) | | 425 (47%) | |
| Unknown | – | 47 (0.2%) | | – | |
| **Age** | | | | | |
| 18 to 24 years | 180 (28%) | 7,877 (30%) | 0.173 | 284 (31%) | 0.072 |
| 25 to 34 years | 306 (48%) | 12,797 (49%) | | 449 (49%) | |
| ≥35 years | 157 (24%) | 5,643 (21%) | | 180 (20%) | |
| **Region of birth** | | | | | |
| Europe & the Americas | 156 (24%) | 7,647 (29%) | 0.014 | 245 (27%) | 0.048 |
| North Africa & Middle East | 93 (15%) | 3,680 (14%) | | 133 (15%) | |
| Asia | 291 (45%) | 10,849 (41%) | | 428 (47%) | |
| Sub-Saharan Africa | 103 (16%) | 3,894 (15%) | | 102 (11%) | |
| Unknown | – | 247 (1%) | | 5 (0.5%) | |
| **Incidence in country of origin** | | | | | |
| 0–99 | 302 (47%) | 13,799 (52%) | 0.001 | 470 (52%) | 0.040 |
| 100–199 | 195 (30%) | 7,231 (28%) | | 277 (30%) | |
| ≥200 | 146 (23%) | 5,040 (19%) | | 161 (18%) | |
| Unknown | – | 247 (1%) | | 5 (0.5%) | |
| **BCG vaccination** | | | | | |
| Yes | 549 (85%) | – | – | 695 (76%) | <0.001 |
| No | 94 (15%) | – | | 59 (7%) | |
| Unknown | – | | | 159 (18%) | |
| **Previous diagnose of TB** | | | | | |
| Yes | 7 (1%) | – | – | 12 (1%) | 0.881 |
| No | 622 (97%) | – | | 879 (96%) | |
| Unknown | 14 (2%) | – | | 22 (3%) | |
| **Ever smoked** | | | | | |
| Yes | 190 (30%) | – | – | 262 (29%) | 0.390 |
| No | 450 (70%) | – | | 641 (70%) | |
| Unknown | 3 (0.5%) | – | | 10 (1%) | |
| **Time in NL before screening ≥3 months** | | | | | |
| Yes | 591 (92%) | – | – | 840 (92%) | 0.502 |
| No | 50 (9%) | – | | 65 (7%) | |
| Unknown | 2 (0.3%) | – | | 8 (1%) | |

BCG: bacille Calmette-Guérin; NL: the Netherlands. TST: tuberculin skin test.

1Sample of newly arriving immigrants at seven Public Health Services (PHSs) between April 2009 and March 2011.

*Three cohorts of immigrants who were screened at arrival in 2005, 2006 or 2007 and were registered in the Monitoring for Screening of Immigrants (MSI).

1Chi² test.

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from high incidence countries (23% versus 18%) than the immigrants without a TST result. Although the base cohort and the case source cohort differed in demographics a bit, we consider the base cohort representative for the case source cohort.

Overall, 273 out of 643 (42%) were TST positive when the cut-off value was set at 10 mm and 145 (23%) when the cut-off value was set at 15 mm (Table 2).

In the case source cohort we identified 30 immigrants who developed active TB within two years. Ten cases were clustered, but none were epidemiologically linked to a TB patient in the Netherlands according to the registries. When the TST cut-off value was set at 10 mm, the expected number of TST positives in the case source cohort based on the prevalence found among the base cohort, was 11,173 (42%) (Table 3). The median sensitivity of the TST was estimated at 90% (95% CI 72%–100%). The overall risk of progression to TB for TST positives was 238 per 100,000 population (95% CI 151–343) (Table 3) and 58 per 100,000 population (95% CI 25–103) for TST negatives.

For both cut-off values of the TST, no marked differences in risk of progression to TB were estimated between the males and females, while minor differences were seen with respect to strata of age (15 mm) or TB-incidence in country of origin (10 mm and 15 mm) (Tables 3, 4).

The NNT and NNS to prevent one TB patient within two years after entry for a TST cut-off value of 10 mm were 700 and 1649, respectively. The corresponding NNT and NNS for a TST cut-off value of 15 mm were 565 and 2505, respectively.

**Discussion**

This study shows that the TST had the discriminatory ability to identify high and low risk groups for progression to active TB among newly arriving immigrants. This ability was irrespective of the cut-off value of 10 mm or 15 mm, but did not apply for the highest age group (if cut-off value 15 mm) and highest incidence category with respect to country of origin (for both cut-off values).

| Table 2. Prevalence of TST positives for cut-off value ≥10 mm and ≥15 mm. |
|--------------------------|--------------------------|--------------------------|
|                          | Total | Number of TST positives if ≥10 mm (% of total) | Number of TST positives if ≥15 mm (% of total) |
| Total                    | 643   | 273 (42)                                      | 145 (23)                                      |
| Sex                      |       |                                               |                                               |
| Female                   | 370   | 153 (41)                                      | 83 (22)                                       |
| Male                     | 273   | 120 (44)                                      | 62 (23)                                       |
| Age (yr)                 |       |                                               |                                               |
| 18–24                    | 180   | 50 (28)                                       | 20 (11)                                       |
| 25–34                    | 306   | 148 (48)                                      | 86 (28)                                       |
| ≥35                      | 157   | 75 (48)                                       | 39 (25)                                       |
| Region of origin         |       |                                               |                                               |
| Europe & Americas        | 156   | 64 (41)                                       | 30 (19)                                       |
| North Africa & Middle East| 93    | 40 (43)                                       | 25 (27)                                       |
| Other Asia               | 291   | 114 (39)                                      | 55 (19)                                       |
| Sub-Saharan Africa       | 103   | 55 (53)                                       | 35 (34)                                       |
| Incidence in country of origin |       |                                               |                                               |
| <100                     | 302   | 120 (40)                                      | 58 (19)                                       |
| 100–199                  | 195   | 82 (42)                                       | 44 (23)                                       |
| ≥200                     | 146   | 71 (49)                                       | 43 (29)                                       |
| BCG-vaccinated           |       |                                               |                                               |
| Yes                      | 549   | 249 (45)                                      | 128 (23)                                      |
| No/unknown               | 94    | 24 (26)                                       | 17 (18)                                       |
| Ever treated for TB      |       |                                               |                                               |
| Yes                      | 7     | 5 (71)                                        | 3 (43)                                        |
| No/unknown               | 636   | 268 (42)                                      | 142 (22)                                      |
| Ever smoked              |       |                                               |                                               |
| Yes                      | 190   | 95 (50)                                       | 45 (24)                                       |
| No/unknown               | 453   | 178 (39)                                      | 100 (22)                                      |
| ≤3 months in NL before screening |       |                                               |                                               |
| Yes                      | 591   | 255 (43)                                      | 138 (23)                                      |
| No/unknown               | 52    | 18 (35)                                       | 7 (14)                                        |

BCG: bacille Calmette-Guerin; NL: the Netherlands; TST: tuberculin skin test. doi:10.1371/journal.pone.0060130.t002
The estimated risks for TST positives to progress to TB within two years were considerably higher than the incidence of 50/100,000 which is used in the Netherlands as a cut-off value to define a risk group. Appropriate preventive interventions to lower the incidence of TB among newly arriving immigrants should therefore be undertaken.

In a previous study [5] we found that the risk of progression to active TB within two years per 100,000 population was 467 (95% CI 314–603) among QFT-GIT positive individuals whereas the risk of progression to active TB among QFT-GIT negatives was 25 (95% CI 0–64). It appears therefore that the discriminatory ability of QFT-GIT is slightly better than that of the TST using either a 10 mm or 15 mm cut-off value. The discriminatory ability of TST was somewhat lower than of QFT-GIT, probably because of the, in general, lower specificity (cross reactions attributable to BCG and environmental mycobacteria) and, when using a 15 mm cut-off value.

### Table 3. Risk of progression to TB within two years after entry screening for TST ≥10 mm.

| Case source cohort | TB within two years | Incidence of TB within two years per 100.000 population | Expected TST positive at entry | Estimated risk of progression to TB per 100,000 population |
|--------------------|---------------------|----------------------------------------------------------|-------------------------------|----------------------------------------------------------|
| N                  | N                   | N (%)                                                   | TST-positive                  | TST-negative                                              |
| Overall            | 26,317              | 30                                                      | 11,173 (42)                   | 238 (151–343)                                            | 19 (0–59)                                                 |
| Sex                |                      |                                                         |                               |                                                          |
| Female             | 13,766              | 15                                                      | 5,692 (41)                    | 233 (120–373)                                            | 17 (0–57)                                                 |
| Male               | 12,504              | 15                                                      | 5,621 (45)                    | 241 (122–388)                                            | 20 (0–66)                                                 |
| Age (yr)           |                      |                                                         |                               |                                                          |
| 18–24              | 7,877               | 6                                                       | 2,188 (28)                    | 237 (75–472)                                             | 9 (0–36)                                                  |
| 25–34              | 12,797              | 16                                                      | 6,189 (48)                    | 228 (122–364)                                            | 22 (0–74)                                                 |
| ≥35                | 5,643               | 8                                                       | 2,696 (48)                    | 258 (99–476)                                             | 24 (0–89)                                                 |
| TB incidence in country of origin |          |                                                         |                               |                                                          |
| <100               | 13,799              | 12                                                      | 5,483 (40)                    | 193 (90–322)                                             | 13 (0–46)                                                 |
| 100–199            | 7,231               | 12                                                      | 3,041 (42)                    | 346 (163–581)                                            | 26 (0–89)                                                 |
| ≥200               | 5,040               | 119                                                     | 2,451 (49)                    | 212 (68–418)                                             | 20 (0–79)                                                 |

**TB:** tuberculosis; **TST:** tuberculin skin test.

*Based on surveillance data from the MSI & NTR.
1 Number estimated based on prevalence positive TST ≥10 mm in base cohort.
2 Based on a median (95% CI) sensitivity for TST ≥10 mm of 90% (72–100%).

The estimated risks for TST positives to progress to TB within two years were considerably higher than the incidence of 50/100,000 which is used in the Netherlands as a cut-off value to define a risk group. Appropriate preventive interventions to lower the incidence of TB among newly arriving immigrants should therefore be undertaken.

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### Table 4. Risk of progression to TB within two years after entry screening for TST ≥15 mm.

| Case source cohort | TB within two years | Incidence of TB within two years per 100.000 population | Expected TST positive at entry | Estimated risk of progression to TB per 100,000 population |
|--------------------|---------------------|----------------------------------------------------------|-------------------------------|----------------------------------------------------------|
| N                  | N                   | N (%)                                                   | TST-positive                  | TST-negative                                              |
| Overall            | 26,317              | 30                                                      | 5,934 (23)                    | 295 (161–473)                                            | 58 (25–103)                                               |
| Sex                |                      |                                                         |                               |                                                          |
| Female             | 13,766              | 15                                                      | 3,088 (22)                    | 281 (130–492)                                            | 55 (21–105)                                               |
| Male               | 12,504              | 15                                                      | 2,840 (23)                    | 306 (139–538)                                            | 61 (23–116)                                               |
| Age (yr)           |                      |                                                         |                               |                                                          |
| 18–24              | 7,877               | 6                                                       | 875 (11)                      | 388 (108–830)                                            | 33 (7–75)                                                 |
| 25–34              | 12,797              | 16                                                      | 3,057 (24)                    | 257 (122–447)                                            | 68 (26–130)                                               |
| ≥35                | 5,643               | 8                                                       | 1,402 (25)                    | 325 (114–643)                                            | 72 (21–157)                                               |
| TB incidence in country of origin |          |                                                         |                               |                                                          |
| <100               | 13,799              | 12                                                      | 2,650 (19)                    | 261 (110–475)                                            | 42 (15–83)                                                 |
| 100–199            | 7,231               | 12                                                      | 1,632 (23)                    | 423 (178–773)                                            | 83 (30–166)                                               |
| ≥200               | 5,040               | 6                                                       | 1,483 (29)                    | 228 (64–486)                                             | 64 (14–149)                                               |

**TB:** tuberculosis; **TST:** tuberculin skin test.

*Based on surveillance data from the MSI & NTR.
1 Number estimated based on prevalence positive TST ≥15 mm in base cohort.
2 Based on a median (95% CI) sensitivity for TST ≥15 mm of 59% (37–82%).

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having a slight overrepresentation of immigrants originating from high incidence countries in the base cohort might be that we have overestimated the overall prevalence of TST positives, and thereby underestimated the overall risk of progression to disease. Thirdly, we had to assume that the immigrants who progressed to disease within two years were already infected at entry. The absence of clustering and the absence of confirmed contact among clustered cases are consistent with reactivation of LTBI. Fourthly, we could not adjust for potential bias as a result of differential drop-out of immigrants during the two year passive follow-up. In other words, from the surveillance data we could not determine whether deceased individuals were more prone to (re)migrate or stay in the host country. Finally, our findings cannot be translated to newly arriving immigrant children (<10 years).

In conclusion, in this study we found that newly arriving immigrants with a positive TST result at entry were at considerable risk of progression to active TB, whereas for TST negatives this risk was limited. Nevertheless, the discriminatory ability of the TST was somewhat lower than that of the QFT-GIT. This suggests that the QFT-GIT, either used alone or in combination with the TST, is the favorable diagnostic tool for screening newly arriving immigrants coming to low-incidence countries. Further study is needed with respect to the cost-effectiveness for the TST and the QFT-GIT in the immigrant screening program to gain further evidence for considering screening immigrants for LTBI.

Supporting Information

Text S1 Calculation of the risk of progression to tuberculosis. (DOC)

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Author Contributions

Conceived and designed the experiments: CM BM FvL. Analyzed the data: CM BM MWB FvL. Wrote the paper: CM BM MWB FvL.

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