Tuberculosis control among immigrants
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Chapter 8

General discussion
The work presented in this thesis evaluates the effectiveness of selected tuberculosis (TB) control activities among immigrants in the Netherlands. We have assessed the (cost)-effectiveness of screening newly arriving immigrants for latent TB infection (LTBI) using interferon gamma release assays (IGRAs) and the tuberculin skin test (TST). Moreover, we have evaluated the conduct and effectiveness of contact investigations among immigrants. The main findings were that LTBI prevalence at entry was approximately 20% based on IGRA and 40% based on TST, and that IGRA and TST positive individuals were at high risk of progression to TB (approximately 450 and 250 per 100,000 persons, respectively). Screening immigrants for LTBI would be far more cost-effective than the current strategy using chest radiography only. Investigation of contacts of foreign-born index patients was less complete but had higher yield than among contacts of Dutch index patients. Improved national guidelines are needed for the investigation of contacts of immigrant patients. These key findings will be discussed below, followed by recommendations for TB control and further research.

**IMMIGRANT SCREENING PROGRAM**

Immigrants from non-Western countries who newly arrive in the Netherlands and intend to stay for more than three months are currently screened for pulmonary TB by means of a chest X-ray (CXR) (1). This screening strategy has been questioned since the yield of detecting active TB at entry is low (<0.35%) (2-3) and its cost-effectiveness may be below the Dutch willingness to pay threshold (4). TB among immigrants is primarily caused by endogenous reactivation of LTBI. The highest risk of progression to TB is within the first few years after immigration (5-9), but even a decade after arrival in the Netherlands, the incidence among immigrants exceeds the incidence of the Dutch population (9-10). We therefore suspected that screening newly arriving immigrants for LTBI and offer those with LTBI treatment to prevent progression to TB could be a promising strategy to reduce the incidence of TB and curb further transmission in the immigrant population. An additional advantage of screening for LTBI would be the prevention of extrapulmonary TB, a form of TB which is rather common among immigrants (7, 11-12), but generally not detectable on chest radiographs. To determine whether screening for LTBI should be implemented it is important to get insight in the prevalence of LTBI diagnosed at entry, the risk of progression to TB among those with LTBI, and the cost-effectiveness of LTBI screening. Tests which may be used for LTBI screening include the QuantiFERON®-TB Gold In-Tube assay (QFT-GIT), which is one of the two commercially available IGRAs, and the TST. Positive results for both tests were considered as a proxy for LTBI, since an accurate gold standard for LTBI is absent (13).
We assessed the prevalence of positive QFT-GIT and TST results and determined the risk of progression to TB within two years in a representative sample of newly arriving immigrants presenting for mandatory screening in chapter 2 and 3. We showed that 20% of the 1468 immigrants (all ≥18 years and immunocompetent) had a positive QFT-GIT result and were considered to have LTBI. The Netherlands and the United Kingdom are the only two countries that have assessed the prevalence of positive QFT-GIT results on a large sample of newly arriving immigrants derived from multiple centres. Both countries reported a prevalence of 20% (14). We were able to show that this prevalence was representative at the national level since our study population reflected the demographic characteristics of the immigrants who were registered in the Monitoring and Screening Register which contains records of all screened immigrants. We estimated with the use of Bayesian analyses that immigrants with a positive QFT-GIT result at entry had a risk of progression to TB of 467 per 100,000 persons (95% credibility interval: 314-603), whereas for QFT-GIT negatives we found a risk of 25/100,000 (95% CI: 0-64) (chapter 2).

In chapter 3 we showed that 42% of 643 of these immigrants had a positive TST result (≥10 mm induration) and were considered to have LTBI. This higher LTBI prevalence measured by TST reflects the lower specificity due to cross-reaction with the bacille Calmette Guérin (BCG) vaccination (85% was vaccinated) and environmental mycobacteria. We estimated that the risk of progression to TB for TST positives was 242/100,000 (95% CI: 195-275) and for TST negatives this risk was 20/100,000 (95% CI: 0-65) (chapter 3). For both QFT-GIT and TST we found no marked differences in risk of progression to TB by sex, age and incidence in country of origin.

The design we used to estimate the risk of progression to TB deserves some discussion. We decided not to design a prospective study because it was expected that the risk of immigrants progressing to TB would be relatively low. Hence if we would have followed immigrants prospectively this would have required a very large study. Instead, we designed a case-base study, which is also known as a case-cohort study (15). In our case-base design, we measured exposure (prevalence of LTBI) in a representative group of controls, which were the immigrants who arrived during 2009-2011. We extrapolated this LTBI prevalence to the population of whom the cases originated, which were immigrants who arrived during 2005-2007. The cases were those immigrants who progressed to TB within two years after immigration. This way we were able to estimate what number of infected individuals progressed to TB within two years per 100,000 persons. The risk of progression to TB we have estimated in this manner might have been overestimated. We assumed that all immigrants who progressed to TB were already infected at entry and could therefore be detected. However, they could have been infected after immigration, either in the Netherlands, or in their country of origin if they travelled after entry. We
determined that none of the cases were epidemiologically linked with another TB patient in the Netherlands, and therefore the risk of infection in the Netherlands was assumed very low. We had no data to adjust for travel history of the cases, whereas travelling to the country of origin is a known risk factor for getting TB (16-19). We assumed that the risk related to travelling to the country of origin in our study was limited because we assessed progression to TB within two years after entry. The risk of progression to TB could also have been underestimated because immigrants who progressed to TB could have returned to their country of origin instead of seeking healthcare in the Netherlands. We assumed no difference in remigration rates between immigrants who progressed to TB within two years and the ones who remained healthy (non-differential misclassification). Furthermore, the sensitivity of QFT-GIT and TST to detect those who progress to disease is lower than 100% (20-29). We accounted for this with the use of Bayesian analyses.

The prognostic value of the QFT-GIT and the TST has been studied primarily in contacts of TB patients and in healthcare workers (30-31). We were the first to present the risk of progression to TB for newly arriving immigrants. This risk was high, but considerably lower than among contacts. This was not an unexpected finding, given that due to the high annual risk of TB infection in their countries of origin (32), positive QFT-GIT and positive TST results in our population likely reflect old infections for which the risk of progression to TB is relatively low. Moreover, our findings confirm that the QFT-GIT and the TST in screening immigrants have a high negative predictive value (NPV) for progression to TB (31). A high NPV indicates that restricting offering chemoprophylactic therapy to test-positives in a screening program only would be appropriate.

**Cost-effectiveness**

The findings from chapter 2 and 3 were used to determine the cost-effectiveness of screening newly arriving immigrants for LTBI (chapter 4). We compared the cost-effectiveness of three LTBI screening strategies compared to the current strategy of screening by chest radiography and not to screen at all in four hypothetical cohorts of 10,000 immigrants (stratified by incidence in country of origin) over a period of 20 years. These LTBI screening strategies were screening with QFT-GIT, TST, or screening according to a two-step strategy which we defined as first testing by TST and if positive followed by the QFT-GIT. In the LTBI screening strategies, active TB was ruled out and preventive therapy was offered if the test for LTBI was positive. We showed that screening newly arriving immigrants for LTBI by any of these methods was superior to the current screening strategy in terms of cost-effectiveness. Screening with the two-step strategy was most cost-effective (€50,000 - €71,000 per QALY gained), except among immigrants coming from countries with an incidence of 350/100,000 or more, for which screening with the TST was most
cost-effective (€43,000 per QALY gained). Although cost-effective, screening for LTBI will not result in cost savings (chapter 4).

Decision making in healthcare is increasingly based on cost-effectiveness considerations. Cost-effectiveness studies are however difficult to compare because the outcomes are highly dependent on the populations studied, input parameter values used, the screening strategies compared, the modelling strategies used and the choice of outcome measures. Among contacts of TB patients and among healthcare workers screening for LTBI by IGRA have been shown to be most cost-effective if the two-step strategy is used (33). So far, few studies estimated the cost-effectiveness of LTBI screening among newly arriving immigrants. In the United States and the United Kingdom screening with QFT-GiT was considered most cost-effective (14, 34), whereas in Canada screening with CXR was considered most cost-effective (35). The main reasons for the divergent finding in Canada was that in contrast to the other studies, the investigators assumed better performance of the CXR and almost no difference in costs between CXR screening and no to screen at all.

The heterogeneity of the cost-effectiveness estimates of the different studies underscores the difficulty for policy makers in deciding what screening strategy would be favourable. In a few other low-incidence countries with high immigration rates, LTBI screening of immigrants has been implemented. Policies vary widely with respect to location of screening (before, at, or after entry), selection criteria (dependent on age and TB incidence in country of origin), and diagnostics used (36-39). Context specific cost-effectiveness studies are essential to generate realistic estimates. We have used context specific input with respect to LTBI prevalence at arrival and the subsequent risk of progression to TB. However, we also had to estimate many parameter values since we modelled the effects over a period of 20 years. The sensitivity analysis nevertheless indicated that our initial parameter assumptions were fairly robust. The cost-effectiveness estimates of LTBI screening are considered conservative for two reasons. First, immigrants who decided to leave the Netherlands were no longer followed in our model which means that healthy life years were missed, whereas the costs of screening and offering preventive therapy at arrival were included in the cost-effectiveness estimates. Second, we did not account for future transmission outside the modelled cohort of immigrants.

**Recommendations for TB screening among new immigrants**

We showed that the risk of progression to TB for immigrants who tested positive was well above the Dutch risk group definition of 50/100,000. This indicates that this group can be classified as a new risk group that warrants active screening in Dutch TB control. Our cost-effectiveness analysis showed that LTBI screening with any given strategy was within the Dutch willingness to pay threshold of €80,000 per quality adjusted life year (QALY)
gained. In contrast, the current screening strategy of CXR screening for pulmonary TB was well above this threshold, in the order of €120,000 – 760,000 per QALY gained. We therefore recommend a revision of the screening program for newly arriving immigrants by incorporating screening for LTBI. Several programmatic aspects have to be decided on before mass LTBI screening could be implemented. These will be discussed in the next paragraphs and include eligibility, diagnostics, acceptability of testing and preventive treatment, and costs.

Decisions have to be made regarding which immigrants would be eligible for LTBI screening. Should this be restricted to those immigrants who currently undergo the mandatory entry screening? In our view, LTBI screening should be offered to those immigrants who have a subsequent risk of progression to TB, are able to complete screening, and who can complete a course of chemoprophylactic therapy of 3 to 4 months. We have provided evidence that this should include the immigrants who apply for a residence permit and migrate either for family, work or study purposes. An implementation study should explore whether it will be feasible to screen and treat those coming for work and study purposes because of their short duration of stay in general, and whether those immigrants accept screening and treatment. Further decisions have to be made whether LTBI screening should be offered to all age groups. Based on current evidence there is no reason to exclude specific age groups. In the US, LTBI screening is offered to all age groups (40), whereas in the UK LTBI screening is only offered to those who are ≤35 years of age due to the low risk of progression to disease and concerns about side effects of preventive therapy in older persons (41). Closely monitoring preventive treatment in older persons would limit the risk of severe side effects. Evidence regarding the role of IGRAs in newly arriving immigrant children is limited. Among young contacts a high prognostic value of the IGRA for progression to TB has been reported (42). TB in children always reflects a recent infection and given the high risk of progression to (severe) TB disease (43), testing and treating them should be a priority. Nevertheless, indeterminate IGRA results have been associated with younger age (44), harming the efficiency of IGRA screening among children. Cost-effectiveness studies concerning screening newly arriving immigrant children for LTBI should be conducted to support policy makers in determining the optimal age cut-off for screening if any.

Another group of immigrants considered for LTBI screening are asylum seekers. Asylum seekers were not evaluated in our study, whereas they account for almost 20% of all TB patients among immigrants in the Netherlands. Evidence on the risk of progression to TB among asylum seekers is scarce. In Norway, 29% of the asylum seekers were IGRA positive (26) and a positive IGRA had a positive predictive value of 3.3% for progression to TB (45). This is a much higher risk than we have found for legal immigrants in Chapter 2. It would be an organizational challenge to invite asylum seekers for participation and to treat them
adequately since they move between asylum centres. We recommend that results should be awaited of the implementation study on screening legal immigrants for LTBI before considering screening asylum seekers for LTBI. We recommend the same for immigrants who are currently not obligated to undergo entry screening. They account annually for 5-10% of all TB patients in the Netherlands (7), and come mainly from Surinam, Poland, Romania, Bulgaria and Portugal. Some of these countries have a rather high TB incidence such as Surinam (135/100,000 in 2009) and Romania (125/100,000 in 2009). According to our cost-effectiveness findings screening them for LTBI would be within the Dutch willingness to pay threshold. Immigrants currently have to undergo mandatory screening if their country is on a list which is based on historical grounds, rather than on epidemiological grounds. Instead, immigrants could be invited for screening based on TB incidence in the country of origin. Our cost-effectiveness findings suggest that a threshold of 100/100,000 could be considered. This would imply a reduction of around 40% of immigrants who have to undergo the mandatory entry screening (46), making it feasible to reconsider the groups being invited without overburdening the health service.

Based on our cost-effectiveness estimates there would be no preference for one test over the other. Using the QFT-GIT as a screening tool for LTBI rather than the TST would nevertheless be advantageous. In BCG-vaccinated individuals, such as most newly arriving immigrants, the specificity of the QFT-GIT is higher and therefore the numbers needed to treat to prevent one TB patient would be lower (13). Furthermore, QFT-GIT testing would only require a single visit to the public health service (PHS). We further showed that the acceptance for TST testing was low and that not everyone returned for TST-reading (chapter 3). We recommend the use of the three tube protocol of the QFT-GIT, which includes a mitogen control to check for immunocompetency. Severe immunosuppression with low CD4 counts has been significantly associated with indeterminate QFT-GIT results (24, 47-48). Given the potential risk of progression to TB in individuals with low CD4 counts, for example because of comorbidity with HIV (49), adequate follow-up should be offered to those with an indeterminate test result.

Programmatic constraints might limit the public health impact of LTBI screening. In a review of studies conducted in the US and Canada, Menzies et al. pointed out that fewer than 40% of the individuals who could have benefitted from preventive therapy actually did so (50). Reasons for this low public health impact were no participation in the initial screening, not returning for TST-reading or follow-up evaluations, not commencing or adhering of preventive therapy and non-compliance of physicians with the recommendation to prescribe treatment. Interaction between healthcare workers and patients is strongly associated with treatment adherence (51). The preference of physician specialists for one test over the other could therefore have impact on the programmatic outcomes of interventions, but findings have been conflicting (52-53). In estimating cost-effectiveness
we have assumed that physicians and newly arriving immigrants had a 100% screening participation, 76% uptake of preventive treatment with a 77% adherence. Our sensitivity analyses showed that varying these percentages had no major impact on the findings. Nevertheless, in chapter 2 we assessed that almost 40% of the invited immigrants did not consent to be tested for LTBI (chapter 2). Although non-consent is inherent to research, this high rate illustrates that the acceptability of being tested for LTBI in a future immigrant screening program might be low if it will be implemented on a voluntary basis. Implementing LTBI screening on a mandatory basis, which in some countries already is the case (39), needs further discussion and would require ethical and legislative considerations. A low acceptance rate for testing and starting preventive therapy could seriously harm the effectiveness of screening newly arriving immigrants for LTBI on a programmatic level. How to overcome these issues should be further studied. An implementation study is recommended to determine the barriers and facilitators for accepting LTBI screening and preventive treatment, to determine treatment outcomes, and to get insight into the interaction between healthcare workers and patients to determine the preferred screening algorithm.

Since screening for LTBI will not result in cost savings, its implementation will depend on the resources policy makers are willing to spend. The role of health insurance companies with respect to reimbursing costs for LTBI tests and treatment may need some discussion, given that it is likely that the majority of immigrants will not have a Dutch health insurance at arrival. Financial barriers could constrain adequate testing and treatment (51). Solutions for these financial constraints should be solved at national level to assure equity access to health service delivery throughout the country.

### INVESTIGATION OF CONTACTS OF FOREIGN-BORN INDEX CASES

Systematically evaluating the contacts of pulmonary TB patients is considered a cornerstone in controlling TB in low-incidence countries (54). National guidelines recommend that for each pulmonary TB patient (index case) the contacts should be evaluated to prevent further transmission by diagnosing early stage TB and test and treat for LTBI (55). It was unknown whether the effectiveness of contact investigations (CIs) among immigrants differed from the effectiveness of CIs in the native Dutch population. Surveillance data regarding the programmatic outcomes of CIs are available since 2006. These data gave an opportunity to determine the effectiveness of CIs among Dutch and immigrant pulmonary TB patients. In chapter 5 we showed that CIs were initiated in 78% of the index cases diagnosed in 2006-2007 in the Netherlands. In 84% of the Dutch index cases a CI was
initiated, whereas this was 75% for immigrant index cases which was significantly less. We further showed in chapter 6 that once a CI was initiated, close contacts of immigrant index cases were less likely to be tested for TB and for LTBI than close contacts of Dutch index cases, while the yield of TB and LTBI was higher in the contacts of immigrant index cases. The findings of chapter 5 and 6 reveal that CIs for immigrant index cases could be more effective if CIs for all pulmonary TB patients were initiated and if all their eligible contacts would be screened for TB and/or LTBI.

In chapter 7 we explored in a multiple case-study the challenges public health nurses (PHNs) experienced in conducting CIs involving immigrant contacts. These CIs were conducted less efficiently and uniformly than desired. The challenges were a result of the ambiguity of the national guidelines on CI, and of the tendency of PHNs to work from an individual-health perspective rather than a population-health perspective. This practice was not per se beneficial for the individuals involved (e.g. overdiagnosis), nor for the community as such (inefficient use of resources). We showed that applying the stone-in-the-pond principle was difficult when immigrant contacts were involved. The guidelines lack estimates of the background LTBI prevalence for immigrant populations, whereas it is recommended to compare the observed LTBI prevalence with background prevalence estimates before deciding to scale up the CI. This study showed that the national guidelines for CI should be updated and tailored to the daily practice by including explicit recommendations and contextual information. Implementing revised guidelines successfully would require a comprehensive dissemination strategy.

It would be relevant to know how our findings relate to international standards. In 2010, a European consensus document was published in which five key indicators and their objectives were proposed to enhance the effectiveness of CIs (54) (Table). These indicators were based on guidelines on CI written by the Centers of Disease Control and Prevention (56). From the studies presented in this thesis we can conclude that the performance of the Dutch program did not reach the proposed international standards (Table). Especially the performance of CIs around immigrant index cases was poor. We did not study the two indicators regarding preventive therapy, but surveillance data suggest that the objective of starting preventive therapy was not reached, while the objective of treatment completion was reached. Data is lacking to determine whether at least 80% of the CIs were finished within 4 months. In our multiple-case study (chapter 7) we assessed that only 4 out of the 14 CIs were finished within 4 months. Therefore, this objective perhaps was also not reached on national level. Considering the five key indicators, the effectiveness of CIs in the Netherlands should be optimized since only the level of completing preventive therapy was according to international standards. Our studies further reveal that especially around immigrant index cases the effectiveness of CIs should be improved.
To identify opportunities for improving the effectiveness of CIs among immigrants we need to analyse which factors might have hampered conducting CIs around immigrant index cases. First, the low coverage of LTBI testing among contacts of immigrant index cases was likely explained by the content of the national guidelines for CI which were published in 2007. These guidelines recommended not to test contacts for LTBI if they originated from endemic countries, because of the high a-priori risk of having LTBI and because the specificity of the TST was considered limited (55). Since 2011, the use of the more specific IGRAs is recommended. All contacts, irrespective of prior BCG-vaccination or country of birth, should be screened for LTBI in a two-step approach with initial TST testing followed by IGRA if an induration of \( \geq 5 \) mm is measured. IGRAs seem to correlate better with intensity, duration and proximity of exposure to the index case compared to the TST (31, 52), and may have a higher positive predictive value for progression to TB (57), but conflicting findings have been reported (21). National surveillance data showed that IGRAs are beginning to be widely implemented; in 2006 only 2% of all LTBI among contacts was diagnosed by IGRAs while this increased to 43% in 2010 (7). Second, challenges were reported in deciding when to scale up a CI if immigrant contacts were involved because the guidelines lack the background prevalence of LTBI in immigrant populations (chapter 7). Third, it is suggested that the willingness of immigrant index cases to name their contacts is low due to the fear of being stigmatized (58-59). In chapter 7 we described that the PHNs indeed sometimes had difficulties with capturing contact information, but this was not restricted to immigrant index cases. Finally, PHNs experienced difficulties to capture exposure information in immigrant index cases due to cultural and language barriers. This hampered an adequate identification of all their contacts and their level of exposure and therefore an effective CI and adequate TB control (60).

### Table

Key indicators and their objectives for determining the effectiveness of contact investigations (54), and performance in the Netherlands stratified by ethnicity of the index case.

<table>
<thead>
<tr>
<th>Key indicator</th>
<th>Objective</th>
<th>Dutch</th>
<th>Immigrant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of infectious patients with at least 1 contact listed</td>
<td>90%</td>
<td>84%*</td>
<td>75%*</td>
</tr>
<tr>
<td>Proportion of high-priority contacts evaluated for TB and LTBI</td>
<td>90%</td>
<td>75%¶</td>
<td>50%¶</td>
</tr>
<tr>
<td>Proportion of infected contacts who begin preventive therapy</td>
<td>85%</td>
<td>75%†</td>
<td>76%†</td>
</tr>
<tr>
<td>Proportion of contacts completing preventive therapy</td>
<td>75%</td>
<td>86%†</td>
<td>84%†</td>
</tr>
<tr>
<td>Proportion of CIs concluded within 3-4 months</td>
<td>80%</td>
<td>No data</td>
<td>No data</td>
</tr>
</tbody>
</table>

*Chapter 5
¶Chapter 6
†Based on surveillance data between 2006-2011
Recommendations for contact investigations around foreign-born index cases

Since immigrants are expected to be overrepresented among TB patients in the coming decades (61) priorities in CIs should shift to immigrant patients and their contacts. A first step would be to improve the guidelines on CI with explicit recommendations with respect to diagnostics and the process. With respect to diagnostics, the national recommendations of using IGRAs should be incorporated in the guidelines for CI. This would likely increase the coverage for LTBI testing among immigrants. With respect to the process, we showed that current guidelines lack clear recommendations with respect to the background LTBI prevalence among immigrant communities. As a consequence, heterogeneous and inefficient decisions were made in applying the stone-in-the-pond principle. The LTBI prevalence reported in this thesis as measured by QFT-GIT could be incorporated in the revised guidelines.

Implementing LTBI screening for newly arriving immigrants would yield relevant information for CIs involving immigrants. First, for each immigrant tested at entry a baseline value with respect to LTBI will be available. That means if a conversion will be measured during a CI in which the person is involved this likely will reflect recent infection and preventive treatment should be offered. It further means that if LTBI would be detected during entry screening and someone would receive preventive therapy, retesting during a CI would be non-informative because test results are likely to remain positive since reversion rates after preventive treatment are low (62). In this way, resources could be used more efficiently. Second, on a programmatic level, screening for LTBI will give estimates of the LTBI prevalence for specific immigrant populations. These would add to the LTBI prevalence estimates we presented in chapter 2. This would be helpful in applying the stone-in-the-pond principle adequately. Ideally, LTBI prevalence estimates are used stratified by age and incidence in country of origin. From our data we suggest a background LTBI prevalence lower than 20% among immigrants coming from countries with an incidence of <100/100,000 population, whereas the background LTBI prevalence for others is between 20-30%. We do not have prevalence data for children (<18 years), but we assume this would be lower than 20% (63). Additional modelling studies would be helpful in determining how screening newly arriving immigrants and conducting CIs could interact with each other most effectively.

A consensus document was published in an attempt to make the conduct of CIs uniform within the European Union (54). Adopting the recommendations from this document in the revised Dutch guidelines could improve the uniformity, effectiveness and efficiency of the conduct of CIs, but some challenges will remain. First, other than the current prioritization of contacts, it is proposed to define contacts as having high-, medium- or low-priority.
These definitions should be based on the level of exposure to the index case, but to a large extent also on the vulnerability of the contact (e.g. children and immunocompromised individuals are most vulnerable). As we showed in chapter 7, potentially vulnerable contacts were missed because their immune status was often unknown since it was only asked when they showed up for testing. Second, we showed that not following the guidelines with respect to identifying and prioritizing contacts and scaling up a CI was primarily related to the intention of the PHN to protect individual health of the contacts by acting on their demands (chapter 7). Dealing with healthcare workers who work from an individual health perspective is inherent to the challenges involved in implementing public health guidelines (64). Guidelines are not intended to make work processes stringent, they rather should accommodate a smooth and efficient practice. Revising guidelines with explicit recommendations could assist in achieving this efficient practice, but the TB workforce should be actively involved in developing and disseminating these guidelines to enhance their implementation (65). Implementation should be further stimulated by training PHNs about transmission of TB, how to reassure contacts without testing them and how to deal with ambiguities in the guidelines.

**FURTHER RESEARCH**

This thesis presents recommendations for optimizing the two major current interventions which aim to reduce the incidence of TB among immigrants; screening newly arriving immigrants and evaluating the contacts of infectious TB patients. Other strategies to reduce the incidence of TB among immigrants should be studied further. The most important new method which might contribute to TB control among immigrants in the future would be a new vaccine. Twelve vaccine candidates are now studied in clinical trials (66). Depending on the efficacy of these vaccines, their safety, acceptability and cost-effectiveness, newly arriving immigrants could be offered a vaccine to prevent progression to TB rather than treating them with preventive therapy. A vaccine could even make screening programs for immigrants unnecessary.

Further research is needed into biomarkers which can predict progression to disease, can differentiate between an old and a recent TB infection, and can be used as a point of care test. The dynamics of biomarkers need to be determined in relation to exposure, disease development and curative treatment. With respect to the IGRAs, more research is needed whether the test accuracy can be improved by modification in testing methods, application of different interpretation criteria (67), or inclusion of additional antigens (68-69).
For the diagnosis of active TB some new tools were endorsed by the WHO (70), for example the Gene Xpert MTB/RIF assay (71). This test has not been evaluated yet among newly arriving immigrants, but given the low yield of active TB at arrival and the relatively high costs of the test, in its current form it will likely not become a candidate for implementation in this screening setting. The Electronic Nose (E-Nose) is another innovative approach that is currently in development (72). Its potential value in screening newly arriving immigrants for active TB needs to be studied. Comparative programmatic implementation studies from different settings should contribute to tailor recommendations of these new tests (73).

The current Dutch treatment regimen to prevent progression from LTBI to TB, 3 months of isoniazid in combination with rifampin, seems adequate (74-75). Nevertheless, surveillance data showed that around 5% of the immigrant patients had a *Mycobacterium* TB strain resistant at least to isoniazid (INH) which reflected the level of INH-resistance in their country of origin (7). Offering preventive therapy to immigrants latently infected with a resistant strain would increase the risk of progression to multidrug resistant TB (MDR-TB). No randomized clinical trials have been published on the efficacy of preventive treatment combinations for individuals infected with a resistant strain (76). Further research should therefore be conducted to improve prophylactic treatment regimens which account for potential drug resistance. Trials to treat those exposed to drug resistant patients are ongoing (74).

**CONCLUSIONS**

The results in this thesis suggest a revision of the Dutch immigrant screening program. Screening for LTBI rather than screening for TB only will be most cost-effective and within the Dutch willingness to pay threshold. We provided evidence that the QFT-GIT could be a useful tool in this respect, but also the TST could perform well. The effectiveness of contact investigations involving immigrant contacts was limited and should be optimized. Guidelines should be updated with explicit recommendations and contextual information should be taken into account by actively involving the TB workforce. Future developments will further target these TB control activities and could contribute to a decline in TB incidence among immigrants.
REFERENCES


