Tuberculosis control among immigrants
Mulder, Christiaan

Citation for published version (APA):
Mulder, C. (2013). Tuberculosis control among immigrants

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
Chapter 1

Introduction
Tuberculosis (TB) is a bacterial infectious disease caused by *Mycobacterium tuberculosis*. The World Health Organization (WHO) estimated that there were 8.8 million new patients with TB and 1.5 million deaths from TB in 2010 (1), making it the second leading cause of death due to an infectious agent after HIV (2). It is further estimated that one-third of the world population is infected with *Mycobacterium tuberculosis* (3). TB primarily affects populations in low- and middle-income countries since poor living conditions are highly associated with TB (1). The incidence of TB is further driven by the HIV epidemic in regions where access to antiretroviral therapy is inadequate. HIV-infected individuals have strongly increased rates of progression from infection to disease (4). Diabetes mellitus (DM) is another risk factor for TB (5). Concerns have been raised about the merging epidemics of TB and DM given that the global burden of DM is expected to rise (6). In high-income countries TB primarily affects certain marginalized risk groups, including immigrants from low- and middle-income countries (7).

In approximately 70% of the patients with TB the lungs are affected (7). TB can also present as extrapulmonary, affecting for example bones and joints (e.g. of the spine), lymph nodes, meninges, or the urinary tract. The clinical symptoms of pulmonary TB include productive cough, fever, night sweats, weight loss, breathlessness and haemoptysis. Diagnosis of active TB relies on microscopic examination and culture of sputum, radiology by chest X-ray (CXR), as well as molecular assays (e.g. Gene Xpert). A positive culture is the gold standard for the diagnosis of TB. The most infectious patients are those with acid fast bacilli in their sputum smears which can be detected either via Ziehl-Neelsen staining or fluorescence microscopy (8-9). The standard antibiotic treatment for TB consists of two months daily isoniazid, rifampicin, ethambutol and pyrazinamide, followed by four months of isoniazid and rifampicin. The emergence of multidrug-resistant TB, that is an *M. tuberculosis* strain resistant at least to isoniazid and rifampicin, is challenging TB control in Eastern Europe and Asia, but could be a threat in high-income countries as well if TB control programs are not adequate (10). Treatment of multidrug-resistant TB is more extensive, more expensive and has poorer treatment outcomes compared to treatment of drug-sensitive TB (11).

*M. tuberculosis* is transmitted through inhalation of aerosols of droplets nuclei containing the bacillus produced by individuals with pulmonary TB through coughing, sneezing, talking, or otherwise exhaling. Following exposure to *M. tuberculosis*, some individuals eliminate the bacillus by an innate or acquired immune response. Others develop latent infection with *M. tuberculosis* (LTBI), a state in which the host immune system controls the replication of the bacillus to the extent that the progression to TB is prevented (12-13). The risk of infection increases with the number of infectious patients in the community, the duration and frequency of exposure, and if exposure occurs in small, dark, and poorly ventilated areas (14). Approximately 10% of the infected individuals who are HIV-negative will progress to TB disease during lifetime (15-16), with the highest risk of progression...
within the first five years after infection (17). Progression to TB after this period in
the absence of exogenous reinfection is defined as endogenous reactivation. Risk of
progressing to TB is related to the virulence of the \textit{M. tuberculosis} strain (18), to the
susceptibility of the host (e.g. HIV, poverty) (19) and to the interaction between bacterial
factors and the host (20-21). Age is a strong determinant of TB disease but differs per
setting. In contrast to in low-income countries, in high-income countries the annual risk
for \textit{M. tuberculosis} infection has declined steeply over the past decades. Therefore, in
the indigenous population in high-income countries, TB is primarily prevalent among the
elderly as a result of reactivation of LTBI (22), whereas in low-income countries, TB is
prevalent among the reproductive and economically active age group as a result of recent
infection (23).

\textbf{LATENT TUBERCULOUS INFECTION}

Given that one-third of the world population is assumed to be infected with TB, there is
a huge reservoir for subsequent progression to TB. In high-income countries, in addition
to case detection and treatment, TB is controlled by identifying and offering preventive
treatment to individuals who are latently infected with \textit{M. tuberculosis}. Once identified
with LTBI, individuals can be effectively treated with either six to nine months of isoniazid
or three months isoniazid in combination with rifampicin. Patients appear to adhere
better to the latter regimen, while the efficacy, and proportion of severe side effects
seem comparable with six months isoniazid (24). Because of possible side effects, such
as hepatotoxicity (25), preventive treatment is only offered to those individuals who
are at highest risk of progression to disease such as individuals with impaired immunity
and individuals who are thought to be recently infected. Diagnosing LTBI is however
challenging because individuals with LTBI are asymptomatic and no live mycobacteria can
be extracted (26). Therefore, LTBI diagnosis is based on the adaptive immune response
against \textit{M. tuberculosis}. For more than hundred years the tuberculin skin test (TST) was the
only available test to measure this immune response. It measures an \textit{in vivo} cell-mediated
immune response to tuberculin, a purified protein derivative (PPD) of \textit{M. tuberculosis}. The
TST reaction is measured by the transverse diameter of induration, 48–72 hours after
antigen injection. PPD is a mixture of antigens, many of which are shared by \textit{M. tuberculosis},
\textit{M. bovis}, \textit{M. bovis bacilli Calmette-Guérin} (BCG) and other environmental mycobacteria.
As a result, the specificity of the TST is low in populations with a high prevalence of BCG
vaccination and infection with environmental mycobacteria. This applies to many people
from low- and middle-income countries.
In the early 2000s blood tests have been developed to improve the diagnosis of LTBI. These are interferon gamma release assays (IGRAs). They are based on the principle that T-cells of individuals infected with \textit{M. tuberculosis} produce IFN-γ when these are sensitized with \textit{M. tuberculosis} specific antigens (ESAT-6, CFP-10 and TB 7.7) (27). The IFN-γ production in response to these specific mycobacterial antigens is assumed to be indicative of infection with \textit{M. tuberculosis}. Two IGRAs are currently commercially available, the QuantiFERON®-TB Gold In-Tube assay (QFT-GIT) and the T-SPOT.TB. The QFT-GIT measures the IFN-γ production in whole blood via the method of Enzyme Linked Immuno Sorbent Assay (ELISA), whereas the T-SPOT.TB is based on an enzyme-linked immunospot (ELISPOT) method enumerating the IFN-γ producing T-cells. An advantage of these \textit{in vitro} tests is the possibility of adding a positive control (mitogen stimulus) to discriminate true negative responses from anergy.

Both IGRAs are used in clinical practice and have shown to be more specific than the TST in BCG-vaccinated populations while the sensitivity seems similar (28). The T-SPOT.TB is reported to be most sensitive among immunocompromised individuals (28), whereas the QFT-GIT may be preferable in screening settings since this test is cheaper (29). Both IGRAs have the advantage of a single patient visit. The TST and the IGRAs cannot differentiate between recent or old LTBI, nor between LTBI and active TB.

**TUBERCULOSIS EPIDEMIOLOGY IN THE NETHERLANDS**

From the beginning of the twentieth century the incidence of TB in the Netherlands steadily declined, presumably as a result of improved socio-economic conditions. In the second half of the century this decline accelerated with the introduction of anti-TB chemotherapy. From 1984 onwards however, this decline halted as a result of increased immigration from countries with a high TB incidence. Elimination of TB, defined as an incidence of <1 smear-positive patient per million population, and/or an overall prevalence of LTBI in the general population <1% (30), is a stated goal of the United States (US) and European Union public health policies (31-32). In the Netherlands, it has been estimated that in the indigenous population the prevalence of LTBI could be less than 1% before 2030 (33). An incidence of less than 1 smear-positive patient per million population however is estimated not to be reached in the coming decades (33-34). The main reason for not reaching TB elimination is that the incidence of TB in the Netherlands, as well as in other high income countries, is largely determined by the incidence of TB among first generation immigrants (hereafter referred to as immigrants) (Figure) (7, 35-37). In 2010, 73% of the total 1,073 TB patients in the Netherlands were immigrants (35), while this is expected to be 85% in 2030 (34). After migration, the risk of progression to TB is highest during the first few
years (35, 38-39). Nevertheless, the incidence of TB among immigrants remains high even many years after immigration (40). This is a result either of reactivation of LTBI or because of (re)infection during travel to their country of origin or in the Netherlands. Molecular epidemiological studies are consistent with TB among immigrants being mainly the result of reactivation of LTBI (41). The proportion of Dutch patients with TB attributable to transmission from an immigrant patient increased from 29% in 1995 to 50% in 2005 (42) and is expected to increase to 60% in 2030 (33). In surrounding countries this proportion was lower (43-44), perhaps explained by differences in immigrant populations and different patterns of social mixing.

TUBERCULOSIS CONTROL AMONG IMMIGRANTS

TB control in the Netherlands is carried out by Public Health Services (PHSs). The National Institute for Public Health and the Environment (RIVM) is responsible for national surveillance, KNCV Tuberculosis Foundation contributes to guideline development, training and quality control, while the Health Care Inspectorate is responsible for safeguarding the quality of services. Most foreign-born TB patients in the Netherlands are diagnosed
by the regular health service; around 20% are detected actively by the PHSs. The strategy specifically targeted for controlling TB among the immigrant population and preventing its transmission is the mandatory entry screening for active TB. Another important strategy to early diagnose TB and or infection and prevent subsequent transmission is the systematically evaluation of the contacts of a pulmonary TB patient. The persistently higher incidence of TB among immigrants reveals that these TB control activities might be less effective than desired. A critical evaluation of current TB control activities among the immigrant population is therefore warranted.

**Immigrant screening program**

In the Netherlands, TB screening among immigrants from high incidence countries has been conducted since 1966. The objectives of screening immigrants from high-incidence countries are to identify and treat those with active TB and prevent further transmission into the community. Entry screening is mandatory for immigrants from non-Western countries intending to stay longer than three months in the Netherlands; currently this includes all countries except countries of the European Union, Australia, Canada, Iceland, Israel, Japan, Liechtenstein, Monaco, New Zealand, Norway, Surinam, Switzerland and the USA. Immigrants applying for a residence permit in the Netherlands are referred by the Immigration Department to the PHSs for radiologic screening for pulmonary TB. A voluntary follow-up screening by CXR every six months for a period of two years was offered before 2008 to all immigrants; since 2008 this has been restricted to immigrants from countries with an incidence of ≥200/100,000 population given the limited yield and coverage among immigrants from other countries (45). All individuals with any abnormalities on CXR are subject to sputum microscopy and culture. Individuals with suspected extrapulmonary TB are usually referred to hospital services for diagnosis.

TB screening of asylum seekers and other immigrants at entry is common practice in many other low-incidence countries, but policies vary (46). The effectiveness and the cost-effectiveness of the current strategy to screen TB in immigrants are controversial (47-48). A lot of TB among immigrants is not detected by the current screening strategy. This is a result of reactivation of LTBI after the initial entry screening (45), and because extrapulmonary TB is not screened for while this form of TB is increasingly diagnosed among immigrants (35, 49-50).

LTBI screening is currently not conducted among immigrants in the Netherlands because the specificity of the previously only available test, the TST, was considered too low. Given the availability of the more specific QFT-GIT, the question was raised whether this test could be used to effectively screen immigrants for LTBI and contribute to TB control among immigrants. This depends in principle on the ability of the QFT-GIT to predict progression
to active TB. Previous studies showed that in recently exposed individuals, such as contacts of an infectious patient, the TST and the QFT-GIT both discriminated who was at risk of progressing to TB (51-52). However, conflicting results have been reported whether IGRAs could better predict progression to active TB compared to TST (52-55). For recent immigrants the role of the QFT-GIT and their added value over the TST were unknown. We therefore designed a study to determine the ability of QFT-GIT and TST to predict progression to TB and determine the cost-effectiveness of these tests in the immigrant screening program.

Contact investigation

The objectives of evaluating the contacts of a patient with pulmonary TB are to identify and treat patients with tuberculosis and LTBI, in order to reduce transmission through early case detection and reduce tuberculosis incidence through offering preventive therapy to those with LTBI. Approximately 7% of all TB patients in the Netherlands are detected via a contact investigation, making it the second most important active case finding strategy with respect to the number of TB patients detected (35). Public health nurses are primarily responsible for contact investigations under the supervision of a TB specialist. National guidelines recommend that for each patient with pulmonary TB a contact investigation is initiated and that contacts are tested according to the stone-in-the-pond principle. According to this principle screening for TB and/or LTBI starts among the most exposed contacts and expands to less exposed contacts until the infection prevalence resembles the background prevalence of infection in the community, or until all identified contacts have been screened (56). In contrast to Dutch contacts, foreign-born contacts were recommended to be only screened for active TB. Foreign-born contacts were considered to have a high a-priori risk of infection and it was therefore deemed not possible to determine recent transmission. Additionally, the specificity of the TST to detect LTBI was considered low due to cross-reaction with BCG. These qualitative arguments were not quantified. Moreover, the availability of the IGRAs might overcome the problem of limited specificity of the TST.

According to a literature review, contact investigations were conducted heterogeneously across countries, making it difficult to use for aggregate data-analyses (57). It was further shown that the LTBI yield among foreign-born contacts was high which highlighted the opportunity for intensifying TB control. In the Netherlands, the effectiveness of contact investigations around immigrant patients and their contacts was unknown, because these data were not registered. Since 2006 the PHS routinely reported electronically to the Netherlands Tuberculosis Register (NTR), which registers all TB cases, whether a contact investigation for a TB patient was initiated and what the outcomes were. These national
surveillance data offered an opportunity for determining the effectiveness of contact investigations in the immigrant population.

Heterogeneity regarding the process of contact investigations was reported in the US (58-59). The adherence to national guidelines was poor which harmed the programmatic outcomes of contact investigations. Little was known about the process of how contact investigations were conducted in the Netherlands. We therefore considered it relevant to gain insight in this process, and explored to what extent public health nurses adhered to the national guidelines and which factors were associated with non-adherence.

**SCOPE AND OUTLINE OF THIS THESIS**

The general objective of this thesis was to contribute to improved effectiveness of TB control activities among immigrants by 1) assessing the (cost-)effectiveness of screening newly arriving immigrants for LTBI using QFT-GIT and TST, and by 2) evaluating the conduct and effectiveness of contact investigations among immigrants.

**Entry screening**

Chapter 2 describes a case-base study in which almost 1500 newly arriving immigrants were enrolled to assess the prevalence of infection in this population as measured by the QFT-GIT, and to determine the risk of progression to TB within two years after entry given the QFT-GIT result at entry. In chapter 3, a subset of these 1500 newly arriving immigrants was analyzed to assess the prevalence of infection as measured by the TST, and to determine the risk of progression to TB within two years after entry given the TST result at entry. In chapter 4, the cost-effectiveness analyses of alternative immigrant screening strategies, including screening for LTBI, are presented.

**Contact investigation**

In chapter 5, we use national surveillance data of 2006-2007 to investigate whether contact investigations were initiated among all patients with pulmonary TB and which determinants were associated with (not) having a contact investigation initiated. In chapter 6, we compare the coverage and yield of contact investigations between immigrant and Dutch patients by using national surveillance data of 2006-2007. In chapter 7, the adherence of the public health nurses to the national contact investigation guidelines is assessed in a multiple-case study.

In chapter 8 the main findings are discussed and recommendations for TB control and further research are outlined.
REFERENCES


