Tuberculosis transmission in the Netherlands: the role of immigration and travel
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Chapter 1

General introduction
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Tuberculosis (TB), does it still occur? When I told people that I was studying TB in The Netherlands, many were amazed to hear that this disease is still present in a country like The Netherlands. They relate the disease with poor African countries with weak health systems.

With an estimated one-third of the world population infected and approximately 1.7 million deaths in 2006 attributed to TB world-wide, TB remains a major public health concern today (1). Although The Netherlands belongs to the countries with the lowest rates of TB, it has not yet been eliminated in The Netherlands, with approximately 1000 new patients occurring every year. In this introduction I provide some background on TB and its transmission, the disease and infection. This is followed by an overview of the global epidemiological situation and the epidemiology and control of TB in The Netherlands. Lastly, I will discuss the aims of this thesis.

Tuberculosis transmission
TB is caused by an infection with Mycobacterium tuberculosis (2). M. tuberculosis is transmitted by patients with infectious pulmonary TB who spread the disease to others by coughing or sneezing droplets containing M. tuberculosis (2, 3). Individuals who inhale these airborne droplet nuclei can become infected. A susceptible person needs to be exposed to an infectious TB patient to become infected and may later develop the disease. The majority of individuals (90%) infected with M. tuberculosis will remain asymptomatic, and will never develop clinical disease. These individuals have a latent TB infection (LTBI). Approximately 10% of infected individuals develop TB during their life. The risk of progression to active disease declines steeply with time since infection. About 50-80% of the individuals who develop TB disease will do so within the first 2-5 years after infection (4-6). When individuals develop active TB more than 2-5 years after infection this is called reactivation. The risk of development of TB given infection depends on factors related to the host (such as the immunologic and medical condition, genetics, behavior, including smoking), and factors associated with the mycobacteria, such as virulence of the strain (7-11). The most important risk factor for disease progression is co-infection with the human immunodeficiency virus (HIV). The risk of progression to active TB after infection among individuals who are co-infected with HIV is estimated to be 10% per year (12, 13).

To distinguish between different TB strains, the sputum isolates of TB patients may be subjected to DNA fingerprinting (14). If a patient with infectious pulmonary TB has transmitted the disease to another patient, the mycobacteria in their isolates will generally have an identical DNA fingerprint pattern. Patients who have an identical fingerprint pattern of their isolates form a cluster. Clusters represent recent or ongoing transmission whereas unique DNA fingerprint patterns are attributed to reactivation of old
infections or recent transmission from patients outside the observed period or area (15, 16).

**Tuberculosis disease**
The symptoms of active TB are not very specific and depend on the localization of the disease. TB most commonly manifest in the lungs (pulmonary TB), but can affect other organs such as the lymph nodes, the spine, the pleura, bones, abdomen or meninges (extrapulmonary TB). The most common symptoms for pulmonary TB include productive cough, weight loss, fever (night sweats), hemoptysis and breathlessness (17). A chest-X-ray (CXR) is usually performed when individuals are suspected to have pulmonary TB. The gold standard for the diagnosis of TB is growth of *M. tuberculosis* on a culture plate. In 37-75% of the culture-confirmed pulmonary TB patients mycobacteria are detected in their sputum smear by Ziehl-Neelsen staining (18, 19). These patients are considered to be the most infectious.

**Latent tuberculosis infection**
Detection and treatment of individuals with LTBI is a key component for achieving TB elimination (20). Among individuals with LTBI, development of the disease can effectively be prevented by the intake of a preventive treatment course (21). Nevertheless, preventive treatment can have side effects (22). It is therefore usually only offered to individuals who benefit most from this treatment, such as individuals with an impaired immunity and those who are thought to be recently infected. The diagnosis of LTBI relied until some years ago on the tuberculin skin test (TST). Early studies had shown that individuals, who were known to be exposed to *M. tuberculosis*, reacted when tested with tuberculin. Furthermore, it was found that individuals with an induration on the TST subsequently had a higher risk of developing active TB compared to those without an induration (5, 21, 23). Consequently, the TST was adopted as a diagnostic test for the detection of a LTBI infection. However, the TST is not a perfect test. Among individuals who have been vaccinated with the bacille Calmette-Guérin (BCG) the TST may give false positive reactions. This is especially the case during the first 10 years after vaccination (24). Moreover, infections with mycobacteria other than TB can also give rise to a (false) positive TST. This is due to the crude mixture of antigens from *M. tuberculosis* present in the tuberculin fluid used for TST. Many of these antigens are shared among *M. tuberculosis*, *M. bovis* BCG and several non-tuberculous mycobacteria (NTM).

In the last decade, new blood tests have been developed that offer an alternative for the TST for the diagnosis of a LTBI. These T-cell based assays measure the production of interferon-gamma (IFN-γ) upon stimulation of antigens specific to *M. tuberculosis*, such as the early secretory antigenic target 6 (ESAT-6) and culture filtrate protein 10 (CFP-10).
These proteins, encoded by genes located in the region of difference 1 (RD1) of the *M. tuberculosis* genome, are not shared with any BCG strain and most NTM (25, 26). Two commercial interferon-gamma release assays (IGRA) are currently available on the market: T-SPOT.TB® (Oxford Immunotec, Abingdon, UK) and QuantiFERON-TB® Gold In-Tube (Cellestis, Carnegie, Australia) (QFT-GIT). Both assays measure IFN-γ production. The T-SPOT.TB is based on an enzyme-linked immunospot (ELISPOT) method enumerating IFN-γ producing lymphocytes. The QFT-GIT uses an Enzyme-Linked Immuno Sorbent Assay (ELISA) format, measuring IFN-γ production in whole blood. Nowadays, the IGRA are used in several countries in addition to or as an alternative for the traditional TST (27-30).

**Global epidemiology of tuberculosis**

Worldwide, TB is after HIV/AIDS the second leading cause of death due to an infectious agent. The World Health Organization (WHO) estimated that there were 9.2 million new TB patients in 2006 (1). Although the majority of the patients occur in the most populous countries of Asia, the incidence rates are highest in the African continent (31). Due to the HIV-epidemic in Africa and the high susceptibility of HIV-positive individuals to TB, the incidence of TB in African countries has more than doubled between 1990 and 2006 (1, 32). Out of the 1.7 million estimated deaths due to TB in 2006, 0.2 million were among HIV-positive people (1).

In 2000, world leaders adopted the United Nations Millennium development Goals. These goals form a plan to reduce extreme poverty and setting out time-bound targets with a deadline of 2015. One of these goals is to combat HIV/AIDS, malaria and other diseases including TB (33). The global target for TB control is to halt and reverse the incidence of TB by 2015. The Stop TB partnership, an international network of 500 organizations working together to realize the common vision of a world free of TB, has translated this into the following two targets: 1) to halve the prevalence and death rates by 2015 compared to their level in 1990 and 2) to detect at least 70% of new smear-positive cases and to successfully treat at least 85% of detected cases. Moreover the Stop TB partnership aims to reach a global incidence of <1 case of active TB per million population per year by the year 2050 (1, 34). In order to reach these targets, the WHO advocates its Stop TB strategy that consists of the following 6 main components: 1) pursue high-quality DOTS expansion and enhancement, 2) address TB/HIV, multidrug resistant TB, and other challenges, 3) contribute to health system strengthening, 4) engage all care providers, 5) empower people with TB and communities and 6) enable and promote research (35).

While the most important aspects of TB control in high-burden countries focus on the detection and treatment of all TB patients, a broader spectrum of interventions is available and feasible for TB control in low-incidence counties that are approaching the elimination phase of TB. In many European countries the number of TB cases decreased
among the autochthonous population. However, TB re-emerged and became a more prominent problem among the foreign-born populations entering these countries (36). Interventions in these countries include 1) ensuring early detection of TB patients and their treatment until cure and preventing avoidable deaths from TB; 2) reducing the incidence of infection by risk group management and prevention of transmission of infection in institutional settings and 3) reducing the incidence of TB through outbreak management and provision of preventive therapy for specified groups and individuals (37).

Tuberculosis epidemiology and control in The Netherlands

Since the national recording of the annual TB cases in The Netherlands, the incidence of TB per 100,000 inhabitants decreased every year from 184.7 in 1948 to 8.2 in 1987. This decline may be the result of improved socio-economic conditions during these years and the introduction of anti-TB therapy. Thereafter, the number of new TB cases increased slowly up to 11.8/100,000 in 1994. This increase was mainly the result of the increasing migration from Morocco and Turkey and increasing numbers of asylum seekers which

**Figure 1a. Number of tuberculosis patients among native Dutch, 1st generation immigrants and 2nd generation immigrant.**
reached a maximum of 52,600 in 1994 (38). Since 1994 TB incidence in The Netherlands declined again. Nowadays, TB is concentrated in specific risk groups. In 2007, 960 TB patients were diagnosed in The Netherlands. Almost two thirds of them were among foreign-born persons (Figure 1a) (39). Since cities contain a large proportion of the risk groups for TB, TB is more common in the four largest cities (>250,000 inhabitants) in The Netherlands than elsewhere. In 2007, 36% of TB incidence occurred in the cities Amsterdam, Rotterdam, The Hague and Utrecht. In these urban areas the TB incidence is on average four times higher (15.8/100,000) than in rural areas (4.3/100,000) (Figure 1b) (39). Table 1 provides indicators for the TB situation in The Netherlands.

While the TB incidence in The Netherlands is among the lowest worldwide (1, 40, 41), it has not yet reached the elimination target of less than 1 sputum smear-positive patient per 1,000,000 inhabitants. Under the current circumstances it is expected that elimination in The Netherlands will not be reached. It is estimated that the TB incidence rate will
decline to an estimated number of 832 patients yearly in The Netherlands (42, 43). By that time first generation immigrants will probably account for 85% of the TB cases nationally (43).

Table 1. Indicators for tuberculosis in The Netherlands, 2007

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence rate all forms of tuberculosis (per 100,000 population)</td>
<td>5.9</td>
</tr>
<tr>
<td>Incidence rate among Dutch-born individuals</td>
<td>2.0</td>
</tr>
<tr>
<td>Incidence rate among foreign-born individuals</td>
<td>36.7</td>
</tr>
<tr>
<td>Incidence rate all forms of TB in urban areas</td>
<td>15.8</td>
</tr>
<tr>
<td>Incidence rate all forms of TB in rural areas</td>
<td>4.3</td>
</tr>
<tr>
<td>Incidence rate all forms of TB among Moroccans</td>
<td>48</td>
</tr>
<tr>
<td>Incidence rate all forms of TB among Turkish individuals</td>
<td>21</td>
</tr>
<tr>
<td>Incidence rate all forms of TB among Surinam individuals</td>
<td>18</td>
</tr>
<tr>
<td>Incidence rate all forms of TB among Somalian individuals</td>
<td>62.7</td>
</tr>
<tr>
<td>Proportion of tuberculosis patients found through active case finding</td>
<td>18%</td>
</tr>
<tr>
<td>Proportion active case finding among Dutch-born TB patients</td>
<td>17%</td>
</tr>
<tr>
<td>Proportion active case finding among foreign-born TB patients</td>
<td>18%</td>
</tr>
<tr>
<td>Proportion of tuberculosis patients who were clustered (according to the DNA fingerprint pattern of their sputum isolate)</td>
<td>35%</td>
</tr>
<tr>
<td>Proportion of patients with multidrug resistant tuberculosis (among new patients)</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

In The Netherlands, TB control is carried out by Municipal Health Services (MHSs). One of the key components of TB control in The Netherlands includes the performance of source and contact investigation. Shortly after the diagnosis of a new TB patient, individuals who have been in close contact with the patients are screened. When the index patient is considered to be infectious, contacts are screened to find cases who may have been infected by the index patient. If the index patient is not considered to be infectious, contacts are screened to find the source patient who may have infected the index patient. Contact investigation is executed according to the stone in the pond principle; first only contact who had frequent and intensive contact with the patient are assessed (44). Depending on the proportion of infections found in these close contacts, it is decided whether contacts who had less frequent and less intensive contact with the patient need to be assessed. Dutch-born individuals, when screened in a contact investigation, are in principle screened both for the presence of active TB disease by use of chest-X-ray and for the presence of an infection by use of TST. Screening among immigrants who participate in a contact investigation is limited to the screening for active TB. The main reason for this is related to the diagnostic test used for detection of LTBI, the TST. The TST has a limited positive predictive value (PPV) among immigrants due to the high frequency of cross-reactions to BCG vaccination (which many immigrants received in the past) and to infections with atypical mycobacteria (45, 46). It also does not distinguish between recent and remote (i.e. acquired in the past) infection. A high proportion of immigrants has a remote infection and offering preventive therapy to all TST-positive migrants may not be cost-effective because of the possible side effects and the high number needed to treat to
prevent one case. Consequently, immigrants are not routinely screened for LTBI and are not offered preventive treatment in The Netherlands. Due to the growing evidence that the new interferon-gamma release assays may offer a more specific alternative to the TST, these assays are also increasingly used for the detection of LTBI in The Netherlands. Several low-incidence countries nowadays have incorporated the use of the IGRAs in their guidelines and either advise them to be used as an equal alternative to the TST or as a confirmative test after a positive TST is found (27-30). In The Netherlands the evidence on the usefulness of IGRA in populations with a high prevalence of remote infection was considered too limited to change the current guidelines and it was decided to await study results on the predictive value of these tests in this specific group.

Another pillar of TB control is the screening of risk groups (47). Immigrants, who plan to stay in The Netherlands for at least 3 months, undergo entry screening. Up to 2006, the first entry screening was obligatory while the following 4 screening rounds during the next 2 years were voluntary. Recently, this policy has changed because the yield of the follow-up screening among persons from countries with a TB incidence of <200/100,000 was limited. Today, all immigrants still undergo entry screening but only immigrants who originate from countries where the TB incidence is estimated to be ≥200/100,000 are eligible for follow-up screening after entry (48). Based on the local epidemiological situation, other risk groups that are targeted for periodical screening include homeless people, drug addicts and professional contacts of TB risk groups (49).

Outline of this thesis
The first part of this thesis deals with the identification of groups that may need more attention in order to reach elimination of TB in The Netherlands. Chapter 2 describes the prediction of potential outbreaks of TB, based on the characteristics of the first two patients observed in the same DNA fingerprint cluster. In chapter 3 the transmission caused by sputum smear-negative pulmonary TB patients in The Netherlands is quantified. Chapter 4 describes the results the risk of TB among immigrants that is associated with travel to their country of origin, for immigrants from Morocco and Turkey.

The second part of this thesis was, except for chapter 8, based on a large prospective cohort study, the so called PREDICT-study. In this part the use of the IGRAs is assessed as diagnostic and prognostic tests for LTBI and TB disease among immigrants and the associated costs. The PREDICT-study started in 2005 and aimed to determine which diagnostic strategy can best predict TB disease among immigrant contacts. The use of the two IGRA was compared with the TST for detection of a latent tuberculosis infection and prediction of disease. Chapter 5 describes the results of the three diagnostic tests among the contacts included in the PREDICT-study and identifies risk factors associated with a positive test. Chapter 6 presents the ability of the IGRA to predict TB in contrast to the TST. In chapter 7 a cost-effectiveness analysis is presented that compares costs and cost-
effectiveness of different strategies for the detection and treatment of LTBI amongst immigrants. In chapter 8 we describe the costs that immigrant TB patients face and which are the result of their disease.

References


