Evaluating the effectiveness of interventions for the prevention of tuberculosis in a low-incidence setting
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Citation for published version (APA):

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Chapter 1 Introduction
Tuberculosis

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis*. It presents most commonly as a respiratory infection, but it can also affect other parts of the body. The classic symptoms are cough, sometimes with blood-containing sputum, fever, night sweats, and weight loss. When other organs are affected a wide range of symptoms can occur. Tuberculosis is transmitted through the air, typically when people suffering from pulmonary TB cough or sneeze. When inhaled, the bacteria are engulfed by alveolar macrophages and bronchial dendritic cells which try to kill the bacteria. When they fail to do so, bacteria replicate and kill the macrophage through apoptosis and necrolysis, releasing the bacilli and cytokines and chemokines, substances that attract other immune-effector cells and trigger a complex delayed type hypersensitivity reaction. A granuloma develops and bacilli can spread to the hilir lymph nodes and disseminate through the body. The host immune response may clear the bacilli or induce a low metabolic and slowly replicative ‘dormant’ state of the bacilli(1). Currently, *Mycobacterium tuberculosis* infection is viewed as a continuous spectrum extending from sterilizing immunity to subclinical active disease through to fulminant active disease(2). In the absence of diagnostic possibilities to detect bacilli contained in a inactive form, latent tuberculosis infection (LTBI) is defined by immunological evidence of sensitization against mycobacterial proteins in the absence of clinical signs and symptoms of active disease. Based on cohort studies(3-5) it is postulated that the life time risk to develop active TB after infection is 5-12%, but children younger than 2 years and immune incompetent individuals have a higher risk(6).

Epidemiology

Tuberculosis has been a major cause of disease and death for many ages. In the early 20th century TB was the major cause of death among young adults in western industrialized countries. Nowadays worldwide TB is causing more deaths than HIV and malaria each. The World Health Organization (WHO) estimated 9 million people suffering from TB in 2014 and 1.5 million deaths caused by TB(7). Fueled by the HIV epidemic, poverty and poor access to health services and adequate diagnosis, the occurrence of TB in sub-Saharan Africa is comparable to the rates observed in western countries around 1900. In the Netherlands the incidence of TB declined steadily to 5.1/100,000 in 2015. The steady decline observed since the start of the TB surveillance in 1950 came to a halt in the late eighties when there was a rise in the influx of immigrants from countries where TB was still endemic. Since then, the TB incidence in the native Dutch population decreased faster than the incidence in the immigrant population. Hence the proportion of TB among immigrants increased. In the 2015, the incidence of TB among the foreign born population was 26 times higher than among the Dutch born population and 72% of the TB patients were foreign born (Figure 1).
Preventive measures against TB were not undertaken until the late 19th century when Robert Koch identified the TB bacillus and insight was gained in the mode of transmission. Even then, options for prevention and control were limited to cough hygiene, sunlight and ventilation to reduce aerogenic transmission. Options for antibiotic treatment were limited too, until streptomycin and isoniazid were discovered after the Second World War. Until that time persons suffering from TB were admitted in dedicated sanatoria for prolonged periods and subjected to a regime of rest, fresh air and a protein rich diet to strengthen their immune systems. When TB drugs became available, early case finding became a sensible thing to do: it was recognized that treatment of TB patients in an early stage improved the chances of recovery and reduced risk of the transmission of the disease to others. In the Netherlands, annual radiologic screening of the professional workforce and screening of schoolchildren using the tuberculin skin test was continued until the late 1960s, when TB incidence had decreased to less than 20 cases per 100,000 population. Careful assessment and screening of close (household) contacts of infectious TB patients is still common practice and generally regarded as the most effective measure to prevent TB(8-10), through early case finding as well as treatment of contacts diagnosed with LTBI.
The emergence of drug resistance immediately after introduction of the first antibiotic (streptomycin) used in TB treatment required therapy consisting of several drugs for a fixed period with good adherence to treatment. Styblo showed in Tanzania in the 1980s that this could be achieved by directly observed treatment (DOT): standardized short course treatment administered under daily observation of a health care worker(11). DOTS (DOT combined with bacteriological confirmation of the diagnosis) was recommended by the WHO as the main strategy to fight to TB, with objectives of detecting and treating at least 70% of the new TB cases and of 85% of patients completing the treatment(12).

**TB control policy in the Netherlands**

The pillars of Dutch TB control policy are based on the DOTS strategy recommended by WHO: political commitment with increased and sustained financing; case detection through quality-assured bacteriology; standardized treatment, with patient supervision and support; effective drug supply and management system, and a monitoring and evaluation system, including impact measurement. In addition a risk group approach is pursued, to enhance case finding and case holding in vulnerable and risk populations(13). This approach was chosen in the early 1980s when, in accordance with WHO recommendations, population-based screening programs were abolished(14) (15). The objective of the risk group approach is to reduce morbidity and mortality as well as transmission of TB through early detection of patients suffering from TB, and to prevent TB disease in persons with a high risk of progression to active TB when infected. In 1995, the Committee for Practical TB Control (CPT) and the National Health Council defined a risk group for TB as a (sub)population with an incidence of >50 per 100,000 population, ~10 times the rate in the general Dutch population(16). Interventions for high-risk groups focused mainly on active case finding through radiological screening among contacts of infectious TB patients, new immigrants and asylum seekers from TB endemic areas, prisoners and drug users or homeless persons. Screening for tuberculosis is mandatory for asylum seekers and for new immigrants from non-western countries intending to stay longer than 3 months. Until 2007 a biannual follow-up screening for a period of 2 years was offered to all newly arriving migrants. In addition to active case finding, population groups at risk for exposure to TB are targeted for screening for LTBI and preventive treatment. Target groups include TB contacts, health workers and other professionals working with unscreened risk groups for TB, and long-term travelers to countries where TB is endemic. In the clinical health sector, patients with a high risk to develop TB when infected, such as HIV-infected individuals and persons receiving immunosuppressant treatment are also targeted for LTBI screening.

**Organization**

The Public Municipal Health Services (PMHSs) have a pivotal role in TB control. PMHSs have been performing prevention and control of TB in the Netherlands since 1993 when they took over this responsibility from the local TB consultation bureaus as defined in the public health legislation(17) and from 2008 onwards the Public Health Act(18). Health providers and laboratories are required by law to notify TB patients nominally to the local PMHSs and take appropriate measures to prevent further transmission. TB public health physicians and dedicated TB nurses in the PMHSs offer support to the TB patient while on treatment, provide health education to the patient and the public and offer advice on the necessary measures for infection control and contact investigation. In addition, PMHSs offer (primary) preventive treatment to TB contacts with TB infection identified in
contact investigation, perform active case finding through screening of new immigrants and other high risk groups for TB, and provide BCG-vaccination of new-born children with a parent born in a country with estimated TB incidence >50 per 100,000 population. PMHSs provide information, advice and guidance to local authorities, medical professionals, individuals and the public on a range of TB issues related to diagnosis, screening, treatment, risk of transmission and need for preventive measures. They also contribute to the understanding of the epidemiological TB situation through maintaining the Netherlands TB register and submit anonymized data on TB and LTBI cases to the national TB register. Policy development is coordinated at national level by the CPT consisting of professionals active in TB control in the PMHSs, other public health institutions and professional organizations. CPT guideline development and policy development relies on epidemiological information derived from surveillance data, as well as scientific evidence based on the analysis of monitoring and evaluation data into the effectiveness of interventions.

**TB surveillance and monitoring of effectiveness of screening**

In the Netherlands notification of infectious diseases to the Health Inspectorate has been mandatory since 1865, but notification of tuberculosis was not mandatory until 1980, when TB became less stigmatized(19). In the late 1980s it became apparent that the nominal information collected by the Health Inspectorate did not render sufficient information to identify population groups at risk for TB, and that it would be advisable to continue the systematic data collection performed by the TB consultation bureaus(20). Moreover, it was perceived necessary to monitor the implementation of WHO recommendations for standardized treatment regimens and DOTS in view of the worldwide emerging problem of drug resistance (21). In 1993, PMHSs and KNCV Tuberculosis Foundation started the Netherlands Tuberculosis register (NTR), supplementary to the mandatory notification of nominal data to the Health Inspectorate. The goals of the NTR are: i) TB disease and LTBI surveillance, ii) providing information for regional and national policy development, iii) providing information for scientific research and training, iv) support quality control of TB preventive interventions(22). Anonymized data on the diagnosis and treatment outcome for new and recurrent TB patients and persons diagnosed with latent TB infection were initially collected through a paper questionnaire. Data collection for TB as well as LTBI cases has encompassed anonymized case-based demographic information, method of case finding, treatment regimen and treatment outcome. For TB cases, disease location, risk factors, co-morbidity, laboratory and DNA-fingerprint results, occurrence of serious adverse events, treatment supervision and adherence, and results of the contact investigation are additionally recorded. In 2005 the paper NTR questionnaires were integrated in the official central web-based notification system for infectious disease notification and surveillance ‘Osiris’, hosted by the National Institute for Public Health and the Environment (RIVM). Annually RIVM publishes in cooperation with KNCV Tuberculosis Foundation an annual description of the TB situation and the yield of active case finding in the surveillance report ‘Tuberculose in Nederland’.

**Thesis aim and objectives**

In general, good public health practice requires systematic monitoring and evaluation the effectiveness of screening programs in order to inform policy development and prioritize risk groups and to safeguard appropriate use of public resources(23). The well-coordinated national TB control policy development, combined with a longstanding tradition of collecting epidemiological and
operational data to monitor TB control interventions, offers a unique opportunity to study the effectiveness of internationally recommended TB control policies in low incidence settings. Thus the studies included in this thesis were aimed at determining the effectiveness of specific TB control interventions and screening algorithms in risk groups, and at identifying specific target groups with a higher risk for TB or to progress to disease when infected with M. *tuberculosis*.

**Specific objectives**

**Screening of immigrants**

In the 1980s and 1990s immigrants from non-western countries and asylum seekers were targeted for radiographic TB screening upon entry and bi-annual follow-up screening during the two years after entry. TB screening of asylum seekers and other immigrants at entry was common practice in other low-incidence countries (24-31), but few countries performed follow-up screening among immigrants with a normal chest X-ray(29, 32). The effectiveness, in broad sense, of TB screening in immigrants and asylum seekers has been disputed(25, 33-35). Particular concerns are cost-effectiveness, the substantial resources required, the need for adequate access to diagnosis and care and the assurance of continuum of care for all migrants. However, it has been shown that screening contributes to reduction of severity of disease and duration of infectiousness, as well as to decreased transmission potential (36).

In The Netherlands immigrants and asylum seekers have been regarded as distinct risk groups for two reasons: i) asylum seekers undergo a different process for TB screening: they reside in the dedicated reception facilities and are screened shortly after arrival. Whereas immigrants are required individually to report to the PMHSs within 3 months after arrival in The Netherlands for TB screening; ii) in the literature it was reported that asylum seekers are likely to be exposed to a higher risk of infection after their departure from the country of origin(37). In 1993, a study estimated a yield of the entry screening among asylum seekers in The Netherlands of 300-400 cases of TB disease per 100,000 persons screened(38). This rate was lower than the rate observed among asylum seekers and refugees in other low incidence countries(24, 29-31, 39, 40). The rate was highest among persons from Somalia and Yugoslavia. From this finding the question arose if the screening could be targeted to specific high-risk groups. Data on the yield of the TB screening of immigrants were not known. Stimulated through a government research grant from ZonMW(41), KNCV Tuberculosis Foundation and PMHSs started the Monitoring Screening of Immigrants (MSI) project in 1996, and set up a national system to periodically assess the effectiveness of the Dutch immigrant screening policy. The objective of the study using MSI data described in Chapter 2 was to assess the prevalence, coverage and yield of the entry and follow-up screening and the risk to develop TB in the first two years after entry, and to describe associated factors and characteristics of immigrants detected with active TB disease or with a higher risk to develop active TB in order to identify risk groups to which screening can be targeted.

**Diagnostic algorithm for LTBI**

Until 2007, the tuberculin skin test (TST) was used in the Netherlands for the diagnosis of latent TB infection. In daily practice the TST has many limitations: the positive predictive value is low when used in populations with a low likelihood of infection as well as in BCG-vaccinated populations.
Before 2007, skin tests with crude antigens of common nontuberculous mycobacteria were often used in addition to TST to confirm LTBI. Moreover, varying cut-offs for the size of the TST-reaction defining LTBI were recommended: a low cut-off of 5 mm and more for ‘vulnerable’ populations where a high sensitivity was required, a cut-off of 10 mm and more for BCG-naïve populations, and a high cut-off of 15 mm and more for BCG-vaccinated populations and other populations in which a high specificity was required. Since 2000, interferon-gamma release assays (IGRA) came on the market(42): blood tests based on ex-vivo stimulation of T-lymphocytes by specific antigens of Mycobacterium tuberculosis. IGRA were claimed to have an equal sensitivity, but higher specificity than the TST, especially in BCG-vaccinated populations(43, 44). In addition, IGRA had several operational advantages over the TST: i) for the TST specific dexterity and experience is needed to administer the test and interpret the reaction; ii) the TST-reaction needed to be measured within 72-96 hours. However, the cost of the two available commercial IGRA and laboratory handling were considerably higher than the cost of the TST. Cost-effectiveness studies supported the use of IGRA in high-income countries, with TST followed by an IGRA being the more cost-effective strategy(45). It was not clear if this strategy would be the most cost-effective strategy for the Dutch setting, where the majority of the target population for LTBI screening was not vaccinated with BCG and the operational costs for IGRA were considerably higher than the cost for TST. Therefore, to guide the choice for the optimal diagnostic algorithm for the Dutch TB control setting, it was decided that IGRA would be recommended as confirmatory test after TST and the added value of IGRA in terms of numbers needed to treat and incremental costs would be evaluated prospectively after the introduction for routine use by the PMHSs. The results of this evaluation are described in Chapter 3.

Effectiveness of TB control efforts in children
The WHO’s DOTS and StopTB strategies have focused mainly on improving detection and treatment of infectious cases(46, 47). Recently it was recognized that as a consequence of this approach the prevention and management of TB in children has been neglected by national TB programs(48, 49). Although children with TB disease are generally considered non-infectious, TB infection and disease in a child can be regarded as a sentinel event for ongoing transmission. In addition, young children are more susceptible than adults to progression from TB infection to active disease and may suffer severe TB-related morbidity and mortality. BCG vaccination, active case-finding of children in contact with adults with TB and isoniazid preventive therapy to prevent progression of latent TB are the basic elements of TB prevention in children and have been practiced in the Netherlands since several decades, but the effectiveness of this approach had not been evaluated before. The objectives of the study described in Chapter 4 were to analyze trends and characteristics of TB and LTBI among children, to identify risk factors for delayed case finding of active TB in children and to explore opportunities where TB prevention can be further improved.

Effectiveness and impact of LTBI diagnosis and treatment
Randomized clinical trials have demonstrated the safety and effectiveness of preventive chemotherapy to reduce the risk of tuberculosis among persons with latent infection(50). In these trials various preventive treatment regimens were shown to reduce the development of incident TB by approximately 40-50%. However, under operational circumstances the effectiveness of preventive treatment programs is influenced by other factors such as treatment acceptance and treatment completion rates. In 2014, the World Health Organization (WHO) launched the End TB
Strategy to step up efforts for the elimination of tuberculosis worldwide. For low-incidence countries, screening and providing preventive treatment for LTBI in populations at high risk for TB is recommended as a key intervention (51-53). In its guidelines for LTBI management WHO recommends routine monitoring and evaluation for initiation and completion of treatment, occurrence of adverse events and development of active TB during and after the completion of treatment for latent TB. Thus far few countries have routinely practiced LTBI treatment at scale, and data on evaluation of LTBI management programs are sparse (34, 54). With the studies in Chapter 5 and 6 we aimed to evaluate the effectiveness of LTBI screening and preventive treatment performed in the public health sector in the Netherlands, in terms of the annual number of cases identified with LTBI in different target groups for LTBI screening, to determine factors associated with treatment acceptance, successful outcome of preventive treatment and the occurrence of (severe) adverse events and to assess the impact of the intervention in the different target groups.

Outline of the thesis and research questions:
In summary the overall aim of the thesis is to determine the effectiveness of specific TB control interventions and screening algorithms and to further identify and prioritize target groups for the interventions.

Specific study questions addressed this thesis are:

1. What is the yield and effectiveness of the screening of new immigrants to the Netherlands in terms of coverage, numbers and prevalence of cases detected, and proportion of the cases in the target group detected through screening, and which groups should be prioritized for screening? (Chapter 2)
2. What is the added value of interferon gamma release assays (IGRA) used as a confirmatory test after tuberculin skin test (TST) in terms of numbers needed to treat in specific target groups for LTBI screening in the Dutch setting, and what are the (incremental) costs and the cost-effectiveness? (Chapter 3)
3. What is the burden of TB disease among children in the Netherlands, what proportion of childhood TB cases is detected early through active case finding, how many children are successfully targeted for preventive treatment, and what are the further opportunities for prevention? (Chapter 4)
4. What is the performance of LTBI management in the public health sector in the Netherlands, in terms of numbers of cases diagnosed, treatment acceptance, treatment completion and the occurrence of severe adverse events? (Chapter 5)
5. What is the observed incidence of TB in different target groups for LTBI screening and in groups receiving different treatment regimens and for which groups should LTBI screening be prioritized? (Chapter 6)

The general discussion in Chapter 7 discusses the main conclusions, lessons learned and policy implications of the studies for TB control in the Netherlands, the overall strengths and limitations of these studies utilizing TB surveillance data and recommendations for future research.
References


