Epidemiology of HIV-infection and drug resistance among tuberculosis patients in the Netherlands
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Chapter 1

Introduction
This thesis includes studies on the epidemiology of HIV infection and drug resistance among tuberculosis (TB) patients in the Netherlands. A general introduction is given on tuberculosis as a public health problem, epidemiology of TB, HIV/AIDS and drug resistance, and the organisation of TB control and HIV-testing policy in the Netherlands.

**TUBERCULOSIS AS A PUBLIC HEALTH PROBLEM**

**TB around the world**

TB remains a major global health problem. The WHO estimates that about one third of the world population is infected with *Mycobacterium tuberculosis*. TB is the world’s second commonest cause of death from infectious diseases, after HIV/AIDS. It has been estimated that TB caused 9.2 million new victims in 2006, of whom 709,000 (8%) were HIV-positive. The countries that rank first to fifth in terms of absolute numbers of cases are India, China, Indonesia, South Africa and Nigeria, while Africa has the highest incidence rate per capita: 363/100,000 population, linked to HIV. The African continent hosts 12 of the 15 countries with the highest TB incidence rates. The lowest incidence is found in the European region (49/100,000) and in North America (39/100,000). There were an estimated 1.7 million deaths due to TB in 2006, of which 0.2 million were among People Living With HIV/AIDS (PLWHA), and 14.4 million prevalent TB cases. These staggering figures contrast sharply with the TB situation in the Netherlands, a country with one of the lowest TB incidence and prevalence figures around the world. TB notification rate in the Netherlands has decreased from 150/100,000 in 1950 to about 10/10.000 in the last two decades, with the lowest ever recorded incidence in 2006 of 6.2/100,000. TB mortality rates declined a thousand fold in one century.

**History**

In the second half of the 20th century, the incidence of TB has declined in most developed countries. This is partly attributable to the natural course of the epidemic, partly to improved socio-economic circumstances, and partly to the introduction of effective anti-TB therapy.
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. Thereafter, the number of TB cases increased slowly up to 11.8/1000.000 in 1994. This increase was mainly the result of increasing migration from Morocco and Turkey and increasing numbers of asylum seekers. Since 1994 TB incidence in the Netherlands declined again. Nowadays TB has become mainly a disease of older people and specific risk groups \(^6\)^. In 2007, 960 TB patients were diagnosed in the Netherlands. Almost two thirds of them were among foreign-born persons (figure 1).

In developing countries the incidence was stable or slightly increasing during most of the twentieth century, until the 1980s. In the 1990s the epidemic of Human Immunodeficiency Virus (HIV) caused an enormous increase in many countries \(^1\)^. At the same time, the number of patients with Multi Drug Resistance (MDR) TB increased dramatically in countries with poor TB control.

**Figure 1. Number of tuberculosis patients among native Dutch, 1st generation immigrants and 2nd generation immigrants.**
EPIDEMIOLOGY

Infection and disease

*M. tuberculosis* is transmitted mainly by coughing aerosols containing bacteria. Persons with prolonged and frequent contact have a high risk to inhale the bacteria and become infected. The asymptomatic stage, without clinical or radiological symptoms, is referred to as latent TB infection (LTBI). Only 10% of people infected with *M. tuberculosis* ever develop active TB; the lifetime risk of developing TB is estimated at around 10% in hosts without apparent immunodeficiency. The highest risk of so-called breakdown is within the first two years after infection. TB occurring later is attributed to reactivation. Breakdown is mainly determined by failed cell-mediated immunity. Risk factors for breakdown include genetic factors, environmental factors (alcohol, smoking, malnutrition), some medical conditions (silicosis, cancer, diabetes) and pregnancy. Currently the largest risk factor is HIV infection. In HIV infected people the risk on breakdown to overt TB is estimated around 10% per year.

About 70% of all TB patients suffer from pulmonary TB (PTB). The others suffer from extra-pulmonary forms (EPTB), such as TB of bone and joints, lymph nodes, urinary tract and TB meningitis. Symptoms related to PTB are productive and prolonged cough, haemoptysis, fever, night sweats, weight loss and fatigue. Limited information is available on the possible role of strain virulence. Children under the age of five and adults over the age of 15 have a higher risk of breakdown than school aged children. Males appear to have a higher incidence of TB than females. The proportion of sputum positives among male suspects is higher than among female suspects. In countries with higher rates of HIV infection, women who are aged between 15-24 years make up a higher proportion of TB cases than men. When the epidemic ages the incidence will reduce first in young adults, since the elderly still have a high risk of reactivation. Re-infection with *M. tuberculosis* may lead to re-infection disease.
The main characteristics of TB patients in the Netherlands is summarised in the annual surveillance reports compiled by KNCV Tuberculosis Foundation and in Table 1.

Table 1. Indicators for tuberculosis in the Netherlands, 2007

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annual number of patients</td>
<td>960</td>
</tr>
<tr>
<td>Proportion of patients with pulmonary tuberculosis</td>
<td>60%</td>
</tr>
<tr>
<td>Number of patients who had pulmonary tuberculosis</td>
<td>576</td>
</tr>
<tr>
<td>Incidence rate all forms of tuberculosis (per 100.000 population)</td>
<td>5.9/100.000</td>
</tr>
<tr>
<td>Incidence rate among Dutch born individuals</td>
<td>2.0/100.000</td>
</tr>
<tr>
<td>Incidence rate among foreign-born individuals</td>
<td>36.7/100.000</td>
</tr>
<tr>
<td>Number of tuberculosis patients who are foreign-born</td>
<td>595 (62%)</td>
</tr>
<tr>
<td>Proportion of tuberculosis patients who are HIV positive</td>
<td>3.5%</td>
</tr>
<tr>
<td>Proportion of tuberculosis patients found by active case finding</td>
<td>18%</td>
</tr>
<tr>
<td>Proportion of patients with multidrug resistant tuberculosis among new patients</td>
<td>0.6%</td>
</tr>
<tr>
<td>Proportion of patients with isoniazid resistant tuberculosis among new patients</td>
<td>4.0%</td>
</tr>
<tr>
<td>Outcome 2006 cohort</td>
<td></td>
</tr>
<tr>
<td>Successfully treated</td>
<td>81%</td>
</tr>
<tr>
<td>Died</td>
<td>10%</td>
</tr>
</tbody>
</table>

Effect of HIV

HIV-infected people who have been or become infected with *M. tuberculosis* have a significantly higher risk (7-10% per year) to develop active TB. They also have a higher risk of recurrent TB after standard treatment. HIV infected TB patients also have higher mortality than HIV negative TB patients. Since the increase of HIV-infection in the world, TB rates have increased, particularly in Africa.

It is estimated that in 2000 nine percent of all new TB cases in adults were attributable to HIV infection, although the proportion in the WHO African region was much greater (31%). Eleven percent of all adult AIDS deaths are caused by TB, and 12% of TB deaths are attributable to HIV. The effect of HIV on the TB epidemic in HIV negative people may be limited: some studies show an increasing incidence in HIV negative people but many others do not. As HIV/AIDS alters the clinical presentation of TB in dually infected individuals with considerably more individuals having sputum-smear negative TB, excess mortality could only be reduced in resource-poor settings if diagnostic algorithms include other tests than sputum microscopy.
HIV associated TB can be reduced by more than 80% with introduction of combination-anti-retroviral therapy (cART) 39. Although there are many different guidelines (reviewed in 2006) 39, the general concept is that TB treatment in co-infected individuals should first be installed before cART. cART is usually delayed to avoid the inherent problems with drug toxicity incurred with multiple drug treatment for TB and ART for HIV/AIDS 39. Moreover, there is the danger of developing paradoxical inflammatory reactions during cART, referred to as immune reconstitution inflammatory syndrome 40. Observational data however suggest that delay beyond two months after starting TB treatment is associated with increased risk of death 39,41, especially among those with low CD4 counts (<200 cells/mL).

The increase in number of patients with both HIV infection and TB has raised the potential for increasing transmission of drug-resistant *M. tuberculosis* strains 42. Reports on associations of HIV co-infection and drug-resistance among patients with TB have been contradictory. Some studies found strongly increased risks for MDR TB among patients dually infected with TB and HIV 43-46, whereas other studies found no increased risk 47-50.

**(M/X)DR tuberculosis**

The incidence of drug resistance has increased since the first drug treatment for TB was introduced in 1943 51. The emergence of MDR-TB followed the widespread use of rifampicin since the 1970s. Although its causes are microbial, clinical and programmatic, drug-resistant TB is essentially a man-made phenomenon 52-55. From a microbiological perspective, most of the resistance is caused by a genetic mutation that makes a drug ineffective against the mutant bacilli. An inadequate or poorly administered treatment regimen allows a drug-resistant strain to become the dominant strain in a patient infected with TB 69.

Short-course chemotherapy for patients infected with drug-resistant strains may create even more resistance to the drug in use. This has been termed the “amplifier effect” of short-course chemotherapy. Ongoing transmission of established drug-resistant strains in a population is also a significant source of new drug-resistant cases.

MDR strains are by definition resistant to isoniazid and rifampicin. XDR strains have additional resistance against the most effective second-line therapeutic drugs used commonly to treat MDR TB: one or more fluoroquinolones and at least one of
three injectable second-line drugs used to treat TB (amikacin, kanamycin, or capreomycin).

MDR and XDR tuberculosis was found in every country surveyed \(^49\). In 2000, the proportion of new tuberculosis cases with an MDR strain was globally about 3.2% (figure 2) \(^26-57\). The highest rates are found in Eastern Europe, but high rates are also found in other areas such as China \(^48\). The proportion MDR TB among retreatment cases is even higher, e.g. up to 60% in Uzbekistan \(^49\). Since MDR patients are infectious for a longer period of time compared to patients harbouring drug-sensitive bacilli, they may infect more people, and therefore aggravate the epidemic \(^58-70\). However, fitness estimates of \textit{M. tuberculosis} strains are quite heterogeneous and this variation may preclude our ability to predict future trends of this pathogen \(^60\).

MDR can be prevented by adequate standardized first-line treatment under appropriate management conditions. Once MDR has emerged, second-line treatment under excellent management conditions maybe required to control it \(^61\). HIV may generate a higher number of MDR patients in hospital settings, but not necessarily in community settings \(^56\).

**Mortality**

TB can be cured and with proper treatment mortality is less than 5%. Without the proper treatment about 50% of TB patients will die \(^7\). The highest number of TB deaths occur in adults, the economically active group, although TB case fatality ratio is highest in children and the elderly \(^7, 62\). Immuno-compromised patients are at high risk of death. Those patients with HIV who are properly treated for TB, death is mainly caused by co-morbidity and related to low CD4 counts reflecting late diagnosis and severe disease progression \(^39, 63-65\). The mortality rate among MDR patients is high because effective treatment is either not available in time or not available at all, especially in poor-resource settings \(^56\). Mortality rates among patients with XDR TB are similar to those of TB patients in the pre-antibiotic era because of the limited responsiveness of XDR TB to available antibiotics \(^67-68\), especially so in the dually HIV and TB infected \(^59\).
MDR-TB among new TB cases
1994-2007

* Sub-national coverage in India, China, Russia, Indonesia.

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dates lines on maps represent approximate border lines for which there may not yet be full agreement.

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Figure 2. MDR-TB among new TB cases, 1994-2007
(http://www.who.int/tb/features_archive/mdr_map_new_cases.pdf)

ORGANISATION OF TUBERCULOSIS CONTROL IN THE NETHERLANDS

The Netherlands have no national TB control program. The national policy has been determined by the Committee for Practical Tuberculosis control (CPT) for over 50 years. The CPT is supported by KNCV Tuberculosis Foundations, an organisation that has existed over a 100 years. TB control is carried out by Municipal Health Services (MHSs), with a compulsory reporting system that also captures patients detected and treated in a hospital.
**Vaccination**
The cornerstones of TB control are early case detection, and ensuring treatment compliance usually by directly observed therapy (DOT) 72. The role of vaccination with Bacille Calmette-Guerin (BCG) for TB control is uncertain. BCG vaccination is usually given at birth. The effectiveness of BCG to prevent TB has varied greatly in different studies 72-75. However, in most studies BCG proves to prevent disseminated TB in children, such as meningitis and miliary TB 76. Therefore BCG vaccination reduces childhood TB mortality. Together with the USA, the Netherlands is one of the few countries that have never included BCG in the national vaccinations program for the population at large, as the impact on the TB transmission remains unproven, while the protective effect of BCG vaccination is at best weak, and short-lived 77.

**Case detection**
Case detection in low incidence countries focuses on passive and active case finding. Passive case finding reflects a policy where case detection depends on patients spontaneously reporting to the health system. Affluent countries use chest X-ray and often sputum smear microscopy and culture for the diagnosis in individuals reporting with suspected TB.
Main methods of active case finding are contact tracing and the screening of high risk groups 78. Active case finding aims not only at finding patients with active TB but also finding recently infected people with LTBI who may benefit from preventive therapy 79.

**Screening and contact tracing**
Currently the largest risk groups that are screened in most low-incidence countries are asylum seekers and other immigrants 78-80. Screening is often limited to a chest X-ray at entry, although some countries also screen for infection 78-80. Most low-incidence countries have a post-entry screening, that is often mandatory 80-82-85. In most of the countries it is practically not possible to screen all immigrants, since they use different ways of entry. Illegal immigrants are the most difficult target group 84. Since 1996, screening in the Netherlands has been limited to asylum seekers and other immigrants from high-prevalence countries, health workers, prisoners, drug-users and homeless, travellers and sailors 87.
The MHSs in the Netherlands are also responsible for contact tracing. Shortly after a new diagnosis of TB, individuals who have been in close contact with the index patient are screened. Typically, contact tracing is conducted according to the ‘stone in the pond’ principle. First only the close contacts around the patient are examined. If contacts test positive with active TB or LTBI, a second circle of contacts will be screened. The proportion of contacts that are infected or have TB will decrease with each ring further away from the patient. Non-BCG-vaccinated contacts usually receive a tuberculin skin test (TST) to find LTBI while excluding active TB. In BCG vaccinated people (most immigrants) contact tracing is limited to screening for active TB by chest X-Ray.

**Notifications and treatment outcome**

**Treatment**

In the Netherlands, LTBI is generally treated with six to nine months of isoniazid, which has an efficacy between 70 and 90% or for a shorter period by a combination of isoniazid with rifampicin. It is only useful to give preventive therapy for LTBI when the infection is recent, since old infections have a low risk of reactivation, and preventative therapy may have side effects. Preventive therapy for LTBI in persons with a high risk of breakdown, such as people with LTBI and HIV co-infection is widely recommended.

The standard short course TB treatment of new smear positive patients consists of an intensive phase of two months isoniazid, rifampicin, pyrazinamid and ethambutol, followed by a continuation phase of four months of isoniazid and rifampicin (2HRZE/4HR). The WHO policy is to directly observe the treatment (DOT) to ensure adherence to therapy. The six-month treatment regimen of fully drug-sensitive TB has high cure rates with only 1-2% relapses.

**MDR /XDR tuberculosis: individualised versus standardised treatment regimens**

Treatment of drug-resistant TB is expensive and complex because it necessitates the use of second-line TB drugs, which are associated with a greater incidence of adverse reactions and require longer treatment duration than first-line drugs. However, comprehensive programmes have shown the efficacy of MDR TB treatment and mathematical models have suggested that this therapy is cost-effective, even in resource-poor settings.
Nevertheless, current guidelines for MDR TB management are largely based on expert opinion and case series, rather than on the results of clinical trials. Guidelines in different countries are based on variable health-system approaches to MDR TB treatment. Some programmes use second-line drug susceptibility testing to design individualised treatment regimens for patients with MDR TB, minimising amplification of resistance and sparing patients from otherwise toxic drugs. Other programmes use standardised drug regimens based on population surveys of local drug-susceptibility patterns in the context of limited laboratory capacity or pharmaceutical access (such as lack of participation in the WHO Green Light Committee programme, which provides countries with access to quality-assured second-line drugs at substantially reduced prices).

Programmes differ in their use of strategies to promote adherence such as directly observed therapy (DOT). Some treatment programmes use only self-administered therapy, some use DOT only for the intensive phase and others incorporate DOT throughout treatment. MDR TB treatment programmes also vary in other characteristics, including the size of drug regimens, duration of treatment, definitions of cure, and follow-up protocols.

Data from 33 studies in 20 countries that included treatment outcomes for a total of 8506 patients receiving second-line drug treatment for MDR TB was recently systematically reviewed. Although the proportion of patients achieving treatment success was better in studies that used individualised treatment regimens as compared to standardised treatment regimens, the difference was not significant. Studies that incorporated both treatment for longer than 18 months and DOT throughout the entire treatment period had a significantly greater proportion of patients achieving treatment success than all other studies (69% ; 95% CI: 64-73%). WHO guidelines for the treatment of MDR tuberculosis encourage a minimum of 18 months of treatment after culture conversion and DOT throughout treatment. The previously mentioned meta-analysis underscores the importance of these particular recommendations and emphasizes their use in combination.
Millenium Development Goals

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 tuberculosis – covered in Millenium Development Goal 6, Target 6.C: have halted by 2015 and begun to reverse the incidence of major diseases like TB, and significantly reduce the incidence, prevalence and death rates associated with tuberculosis. Targets set are to halve the prevalence and death rates by 2015 compared to their level in 1990 and to detect at least 70% of new smear-positive cases and to successfully treat at least 85% of detected cases.

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, MDR 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.

http://www.mdgmonitor.org/goal6.cfm
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 countries that are approaching the elimination phase of TB. In these countries interventions include:

1) ensuring early detection of TB patients and their treatment until cure and preventing avoidable deaths from tuberculosis;

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 tuberculosis through outbreak management and provision of preventive therapy for specified groups and individuals.

**HIV TESTING POLICY**

Before the introduction of cART in the Netherlands, HIV testing policy was only targeted at the known risk groups for HIV-infection: TB patients presenting with uncommon extrapulmonary manifestations, drug users and patients coming from endemic areas.

In the Netherlands cART was available from 1996 onwards, and in 2000, the proportion of HIV-infected patients on cART reached a stable level. With the implementation of cART chances for survival improved immensely. Here we will explore HIV-testing among TB patients over the years 1995-2001. Only recently the national guidelines were changed into the policy that HIV testing should be offered to every TB patient as an integral part of the TB diagnostic process in accordance with WHO/UNAIDS guidelines for Provider Initiated Testing and Counseling (PITC). PITC is voluntarily and informed consent, counseling and confidentiality (3 C’s) have to be respected. Patients have the right to refuse HIV-testing and counseling.
AIM OF THE THESIS AND RESEARCH QUESTIONS

The aim of this thesis is to better understand epidemiological developments in the field of TB in the Netherlands, with special attention to the effect of HIV-infection and drug resistance in a low-prevalence country. The following research questions have been formulated:

- What is the proportion of TB patients infected with HIV?
- What is the proportion of TB patients tested for HIV-infection?
- What is the impact of HIV-infection in TB patients on morbidity and mortality?
- What is the relation of HIV-infection on TB drug resistance?
- What is the proportion of TB patients harbouring MDR *M. tuberculosis* strains
- What is the impact of MDR *M. tuberculosis* strains on morbidity and mortality?

OUTLINE OF THE THESIS

Chapter 2 describes the prevalence and predictive factors of HIV-infection among TB patients in the Netherlands, for the years 1993-2001. In Chapter 3 describes the comparison of the proportions of TB patients tested for HIV infection before and after introduction of 'highly active antiretroviral therapy' (HAART) in the Netherlands. It also describes the predictive factors for performing an HIV-test in this population. In Chapter 4 the effect of HIV infection on mortality and the trend in mortality among notified TB patients in the Netherlands over the period during which HAART was introduced (1993-2001) is presented. Chapter 5 reports on a population-based study of anti-TB drug resistance patterns and associations with HIV infection in the Netherlands during 1993-2001. Chapter 6 describes demographic, clinical and microbiological features of MDR-TB patients in the Netherlands during the period 1998-2008 – it also presents factors associated with treatment outcomes, including in-vitro drug susceptibility, drug treatment and co-infections, as well as the role of surgery. In Chapter 7 the main findings are summarized and discussed in the context of the literature, recommendations for future TB control are given.
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