Royal Tropical Institute

Tuberculosis in the Netherlands

An assessment of risk factors and treatment completion among migrants and native Dutch

Maarten Borg
15-2-2023

The Netherlands
Year of presentation: 2023

Title: Tuberculosis in the Netherlands,
An assessment of risk factors and treatment completion among migrants and the native Dutch population.

A thesis submitted in partial fulfillment of the requirement for the degree of Master of Science in Public Health

by
Name Participant: Maarten Borg

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Master of Science in International Health (MIH)

15 february 2023

KIT (Royal Tropical Institute)/Vrije Universiteit Amsterdam
Amsterdam, The Netherlands
September 2023

Organised by:
KIT (Royal Tropical Institute)
Amsterdam, The Netherlands

In cooperation with:
Vrije Universiteit Amsterdam (VU)
Amsterdam, The Netherlands

Abstract:

I*ntroduction*

Tuberculosis is an infectious disease that annually affects over 10 million people worldwide and kills over 1.5 million people yearly.

Effectively addressing the tuberculosis epidemic requires good quality treatment and facilitating accessibility of care. The disease is curable with an intensive 6 months course of antibiotic treatment; however up to 50% of patients do not complete their treatment.

Most patients live in low and middle income countries with a high incidence of tuberculosis.

In the Netherlands – a low incidence country for tuberculosis- tuberculosis yearly affects hundreds of people, mostly vulnerable groups like migrants, refugees and prisoners

Methodology

In order to assess accessibility of health services and quality of care, a retrospective analysis of surveillance data concerning Dutch patients with tuberculosis was conducted. All included patients were stratified according to 3 strata: undocumented migrants, documented migrants and the native Dutch population in order to compare results among migrants with the native Dutch population.

Extensive literature research followed by baseline analysis including risk factors, patient delay and treatment outcomes in a cohort of 12546 patients was performed. Multivariate logistic regression analysis was conducted to assess effect of treatment interventions and other risk factors among which legal status on treatment completion.

Results

Treatment completion reached over 80 %, undocumented migrants had a longer patient delay and legal status was not significantly associated with treatment completion.

Discussion

Treatment support was the most important intervention for improving treatment completion. Policies should aim to improve accessibility of health services for hard to reach groups.

Key Words:

Tuberculosis, Undocumented Migrant, Treatment Outcome, Regression Analysis, Time to Treatment.

Wordcount: 11321 words

Table of contents

List of abbreviations

2HRZE2HR:	2 months Isoniazid, Rifampicin, Pyrazinamide, Ethambutol, continued by 4 months of Isoniazid and Rifampicin
BAL:	Broncho Alveolar Lavage
BCG:	Bacille Calmette Guerin
COA:	Central Organ for Asylumseekers
COPD:	Chronic Obstructive Pulmonary Disease.
COVID-19:	Corona Virus Disease 2019
CVZ:	Institute for Healthinsurances
CXR:	Chest X-ray
DM:	Diabetes Mellitus
DOT:	Direct Observed Therapy
EU:	European Union
ETB:	Extrapulmonary Tuberculosis
HIV:	Human Immunodeficiency Virus
IGRA:	Interferon Gamma Release Assay
KNCV:	National
IND:	Immigration Naturalization Service
MDR:	Multi Drug Resistance
MtB:	Mycobacterium Tuberculosis
NAAT:	Nucleic Acid Amplification Test
NTR:	National Tuberculosis Register
OR:	Odds Ratio
aOR:	Adjusted Odds Ratio
PTB:	Pulmonary Tuberculosis
PCR:	Polymerase Chain Reaction
PHSs:	Public Health Services
TB:	Tuberculosis
TBI:	Tuberculosis Infection
TNF	Tumor Necrosis Factor

TST:	Tuberculin Skin Test
UK:	United Kingdom
WHO:	World Health Organization
ZN:	Ziehl Neelsen

Acknowledgments

I want to express my gratitude to the people from the National Tuberculosis Foundation in The Hague for all the help they provided; without them this study could not have been conducted.

In particular I want to thank my supervisors who helped with collecting the necessary data, gave me suggestions about research domains and who were always willing to help me structure my thoughts about the research topic. I also wish to acknowledge the help of the technical and IT staff for providing me with all the tools needed to bring the thesis to a good end.

I also want to express my gratitude to my academic supervisor of the Royal Tropical Institute who was always ready to give me helpful suggestions and help me find a good direction in this project

Introduction

As a primary healthcare physician I have always been intrigued by how diseases affect all kinds of people, and in particular infectious diseases.

In 2017 I started with the core course in Tropical Medicine at the Royal Tropical Institute as part of my

Master programme, as I wanted to learn more about health in a broader context, apart from my daily work in the consultation room.

It was the best choice I had made in years, as I experienced a whole new world opened up for me in those 4 months of daily tuition. What especially struck me was the realization that in contemporary medicine in our country, most emphasis is on treating diseases by protocol a b or c, whereas rarely underlying drivers of diseases are topic of discussion.

During the Master of International Health programme I got interested in the topic of Tuberculosis(TB), as it is an 'old' disease that still affects millions op people yearly, treatment is possible, but still it exists.

TB is not treated easily as treatment consists of at least 6 months of intensive antibiotic treatment. There are many drivers that make people more susceptible for tuberculosis on side, and many drivers that influence access to care and treatment adherence on the other side.

Accessibility to high quality TB services that address TB is a problem for the people who are most frequently affected by the disease, mostly the poor, homeless, migrants and refugees and other vulnerable groups.

Treatment non-adherence occurs frequently as nearly half of all patients do not complete their treatment, hereby increasing the chances of prolonged infectiousness and drug-resistance.

Therefore the fight against tuberculosis is a real challenge as it needs to address the health needs of the hardest to reach populations, even in a country like the Netherlands.

Still -even in a low incidence country like the Netherlands- it is important to fight tuberculosis, because as an infectious disease it will affect more and more people if no adequate action is taken.

Inspired on this, I decided to assess access to and quality of TB services in the Netherlands in this thesis

I hope this thesis will contribute to the elimination of TB.

Background

Tuberculosis (TB) is a respiratory infectious disease caused by the Mycobacterium tuberculosis complex (*M.tb)* that spreads via *M.tb* containing aerosols, which are released by coughing or sneezing by a patient with infectious pulmonary TB (PTB)(1). TB usually manifests in the lungs (PTB) but may also appear in other parts of the body (extrapulmonary TB (ETB)) and causes generic symptoms such as prolonged cough, night sweats, loss of appetite / weight loss, and fever. Especially persons with ETB may present generic symptoms depending on the location of the disease. The golden standard method for TB diagnosis is conducting a microbial culture. However, a culture is not considered feasible for rapid diagnosis and screening for TB, because it requires a laboratory and takes up to 4-5 weeks before results can be obtained. Therefore, other diagnostics have been used widely such as GeneXpert and molecular testing (Polymerase Chain Reaction)(2, 3). TB can be treated with a six months treatment of multiple antibiotics: 2HRZE4HR (2 months Isoniazid, Rifampicin, Pyrazinamide, Ethambutol, continued by 4 months of Isoniazid and Rifampicin)(4). In absence of TB treatment, approximately 70% of TB patients will die within 10 years(5).

A unique characteristic of the *M.tb* is that it can survive in a viable but dormant state in the human body. This is called tuberculosis infection (TBI). After infection, 5-15% of infected persons will develop TB in their lifetime, of whom 50% will do so in the first 2 years after infection and the other half in the rest of their life, usually due to a weakening immune system(6, 7) . Individual/medical risk factors for the development of TB are -among other risk factors- a compromised immune system (as a result of Human Immunodeficiency Virus infection(HIV), organ transplantation and use of immunosuppressive medication, or malnutrition), diabetes mellitus (DM), smoking tobacco, (excessive) use of alcohol, or vitamin D deficiency(8). The development from TBI to TB can be prevented through identification and treatment of persons with TBI. TBI can be diagnosed by a tuberculosis skin test (TST) and/or serological testing (Interferon Gamma Release Assay(IGRA))(3) after the exclusion of TB through medical examinations (chest radiography (CXR), physical examination and anamnesis).

Globally, TB is the second deadliest infectious disease (after COVID-19). In 2021 an estimated 10.6 million persons developed TB and 1.6 million persons died from TB (WHO Global Tuberculosis Report 2022, (9)). The Netherlands is a low TB incidence country with a TB incidence of 3.6/100,000 persons in 2020 and with 623 reported TB patients in 2020(10). Since the 1990's, the TB epidemiology became highly influenced by the development of TB among migrants: the number of TB patients among the foreign born started to exceed

the TB incidence among the Dutch native population(11) This is a trend also seen in other low-incidence countries(12).

Currently, 75% of the people with TB in the Netherlands is foreign born of whom approximately 3-4% are or were undocumented(13); these numbers are consistent with those found in other low incidence countries(12). Most incident TB patients among the foreign born follow re-activation of TBI acquired in the country of origin(14).
Hence, migrants from high TB incidence countries (many different definitions exist, in this thesis a definition of >50 100.000 persons is used for high incidence countries) are a population of interest for active TB case finding and TB prevention activities in the Netherlands.

In the Netherlands, specialized TB departments of the Public Health Services (PHSs) are responsible for TB care and prevention activities, including TB treatment and support, vaccinations[i],TB source and contact investigations, and screening of high risk TB groups. As migrants from high incidence countries are a population at risk for TB, their screening for TB at entry (of the country) by the PHSs in collaboration with COA (Central Organization for Asylum seekers) and the immigration and naturalization service (IND) is compulsory under the Immigration act.
The Immigration Act mentions that migrants from high incidence countries intending to stay in the Netherlands for longer than 3 months are expected to undergo TB diagnostical testing. The PHSs screen for TB among these immigrants and asylum seekers. Furthermore, immigrants and aylum seekers from countries with an incidence of >200/100.000 are offered biannual follow-up screening through chest radiography during the first 2 years after arrival.
However, undocumented migrants are not routinely screened as a logical consequence of their status; they are usually diagnosed with TB after seeking medical help because of health complaints. They are then either diagnosed in the hospital by a pulmonologist or referred to the PHSs where a TB physician will diagnose them with TB.

[i] Vaccinations consist of a vaccination with the BCG vaccine(Bacille Calmette Guerin)

Problem statement

Due to globalization, international conflicts and economic reasons, migration leads to increasing numbers of migrants going from low-and middle income countries to high income countries(15).
These migrants may come from countries with a high incidence of TB and may be documented or undocumented.
In the Netherlands, TB is a minor health problem as compared to the total burden of disease, mainly affecting marginalized groups like the homeless and migrants. The TB incidence among foreign-born residents is more than 20 times higher than among the native population(10).
Therefore, appropriate access to TB health services - regardless of people's legal status - is crucial to improve the health status of migrants and prevent the spread of contagious infectious diseases like TB(16). In many European countries, the number of patients with TB among migrants as a part of the total TB burden is increasing each year(17).

The World Health Organization(WHO) published the END TB strategy(18), with the goal to reach elimination of TB worldwide and end the global TB epidemic by 2035.
In concordance with the END TB strategy, a framework towards TB elimination in low incidence countries was developed and published by the WHO(19). One of the most important activities in low-incidence countries to reach elimination is screening for TBI and TB among high risk groups, such as migrants from high incidence countries.
In this framework (towards TB elimination in low incidence countries), an action plan is recommended, by focusing on stimulating integrated patient-centered care and prevention (especially for the most vulnerable and hard-to-reach groups and by addressing the special needs of migrants), applying bold policies and supportive systems and intensified research and innovation.
In concordance with the WHO END TB Strategy and its framework towards TB elimination in low incidence countries the Netherlands developed its END TB programme and aims to reduce its TB incidence by 25% in 2025 and its incidence rate by 90% between 2015 and 2035.

Important bottlenecks in addressing TB in general are access to health services(20) and treatment completion; up to half of all of patients with TB do not complete treatment, which contributes to prolonged infectiousness, drug resistance, relapse, and death(21, 22)
Therefore, accessibility of TB services, rapid initiation of treatment and adherence to and completion of treatment are the essence of high quality TB services.

(Im)Migrants and TB

The risk of TB among migrants is determined by various factors that influence exposure to TB and development of TB. Among these factors are TB epidemiology (incidence and prevalence) in the country of origin, specific factors in the migration phase (e.g. crowded or poorly ventilated modes of transport) and factors related to conditions in the arrival phase (e.g. housing and working conditions) where poverty, homelessness and overcrowding are recognized drivers in the spread of infection(23). Difficulties and challenges faced during and after migration may increase the risk of progression to active disease by compromising immunity(24).

Upon arrival, migrants face challenges including communication issues, discrimination and loss of social support(25), which may lead to poorer mental health, which may lead to progression to active disease among people with TBI, potentially via a negative effect on the host's immune system(26).

Individual factors that are related to physical health as mentioned earlier (malnutrition, DM, chronic kidney disease, vitamin D deficiency, smoking tobacco, use of immunosuppressive drugs, use of alcohol and illicit drug use) and mental health, and inadequate health literacy also increase the risk of developing TB(23).

Misconceptions and cultural beliefs (including stigma) about TB may be factors that lead to delayed healthcare seeking behaviour and increased transmission within migrant communities(24).

Migrants face many barriers with regard to access to healthcare, including transportation difficulties, lack of awareness of the local health system, language barriers and economic barriers. These factors may all lead to delayed access to the healthcare system and possible prolonged infectiousness of people with TB(24).

Concluding, not only individual factors such as comorbidity and epidemiology of TB in the country of origin play a role in the development to active TB among migrants, but socio-economic factors, factors related to migration itself and access to care all contribute to the risk of developing TB.

Undocumented (Im)Migrants and TB

Apart from abovementioned risk factors, undocumented migrants face even higher barriers in accessing the healthcare system due to uncertainty surrounding entitlement to healthcare services. In a survey among undocumented migrants in 11 European countries, performed by Medecins du Monde, it became clear that nearly one third of undocumented migrants were not aware of their right to health coverage(27).

Fear of immigration authorities is another barrier to accessibility of care, since TB patients can be legally deported while receiving ongoing treatment in countries like the United States of America or Australia(28); in

some European countries including the Netherlands there are laws that prevent undocumented migrants from deportation while receiving TB treatment(29).

Social discrimination (lack of health insurance and thus more out-of-pocket expenditures for healthcare), isolation and poverty form extra barriers in access to care for this group(30-32)

Undocumented migrants may also face difficulties with regard to completion of long term TB treatment if they do not have adequate housing or employment and are short-term residents(23, 33). They also may not be willing to provide details about their migration route and contacts, information that may be essential for tracing contacts - an essential part of TB services.

Justification

TB in the Netherlands: the need for looking into (undocumented) migrants

In the Netherlands, TB mostly manifests in marginalized groups like migrants, the homeless, incarcerated people and undocumented people(13).

As a logical consequence of their legal status, undocumented migrants are not routinely screened for TB. Consequently, delayed diagnosis and supposed poorer treatment results (partly because of health illiteracy) in this group may potentially lead to continued transmission of TB.

All undocumented people in the Netherlands have the right to access to care. However, fear of immigration authorities - a well known concept among (undocumented) migrants - and other factors as mentioned above - may lead to delay in healthcare seeking behaviour; it is important to know that the IND can suspend expulsion of a foreign national and his/her family members if they are suspected of having or have been diagnosed with TB. This regulation is known as “artikel 64”. Furthermore, there are financial regulations for undocumented migrants that allow for (partial)reimbursement of healthcare related costs (CVZ regulation(College voor Zorgverzekeringen/institute of healthinsurances))to healthcare providers (34). Housing, health insurance and the costs of living are covered as well during this period(35).

Lack of awareness of regulations like these may form a barrier to healthcare seeking behaviour.

Therefore, both documented and undocumented migrants receive special attention from the PHSs. In fact, an extensive programme -including interventions to improve treatment completion such as treatment support, and directly observed therapy (DOT), - that addresses TB among vulnerable groups has been developed and is being practised by the PHSs. However, up to now, a thorough analysis of the results of this programme has not yet been performed.

In this study, it was hypothesized that access to TB services and start of treatment are delayed among risk groups like documented migrants and undocumented migrants and that their treatment adherence and completion is impaired as compared to the ‘national’/non migrant population.

The objective of this study was to assess patient delay - as a proxy for access to care-, health-system delay(delay until treatment) and treatment completion among undocumented migrants, documented migrants and native Dutch, and to assess effectivity of interventions aimed at treatment completion.

It is important to conduct this study, as accessibility and quality of treatment (short delay and treatment completion) are essential parts of good TB services, so the assessment of these parameters will hopefully allow for finding starting points for improvement of TB services in order to contribute to the elimination of TB in the Netherlands.

Research questions:

-What is patient delay and health system delay among documented and undocumented migrants for TB in The Netherlands as compared to the native Dutch population?
-What is TB treatment adherence and completion among documented and undocumented migrants and the native Dutch population in the Netherlands?
-Which risk factors for TB and which interventions aiming to improve treatment completion are associated with TB treatment completion among documented and undocumented migrants and native Dutch population in the Netherlands?

Methods

Study design and setting:

This study was designed as a retrospective analysis of surveillance data derived from the National Tuberculosis Register (NTR). The dataset that was used contains data of all people diagnosed with TB between 2000 and 2020 in the Netherlands. These data include both patients with TBI and TB (disease). For this study, only data on patients with TB were used.

Initial literature review:

Based on the WHO framework(19) a literature search was conducted to find relevant literature concerning the main objectives of this study. The search was conducted using Pubmed and Web of Science as well as websites from organizations such as the World Health Organization and Doctors without Borders. Articles were eligible for inclusion if they were published from 2000 onwards, were published in English and were either meta-analysis, review articles, systematic review articles, relevant cohort studies, policy documents or (international) guidelines. The search strategy was conducted by using a combination of words that addressed the main domains of this study: Tuberculosis, migrant health, undocumented migrants, treatment completion, accessibility. For the Pubmed search, free text terms were used in combination with Medical Subject Heading (MeSH) terms.

Literature with relevance to answer the study questions was selected and most priority was given to meta analyses, guidelines, and large population-based studies.

The literature review was used to describe the population of TB patients, particularly the variables that are associated with TB (21, 36, 37) to provide input into the retrospective analysis of NTR data.

Many variables were found to be associated with TB; and the following variables were selected from the NTR and they were divided in categories.

1. Baseline characteristics: gender, age, country of birth, comorbidity, HIV status, BCG vaccination status, reason of examination, previous diagnosis of TB.
2. Diagnosis and treatment related variables: type of TB (PTB/ETB or both), patient delay, health system delay, diagnostic features (microscopy/PCR/culture), treatment features (treatment outcome, treatment completion, side effects, submission to clinical institution, treatment support, DOT) legal aspects (article 64) and financial aspects
(health insurance and financial support).

Ethical considerations:

Permission to use the NTR data for this study was obtained from the NTR registration committee. Only anonymised data were provided to the researcher for the analysis. In the Netherlands, ethical approval is not needed for the use of anonymised data from the NTR.

Participants and statistical methods:

In the period 2000-2020, data of in total 21693 patients with TB disease were logged in the database. Since many important data – for example diagnostic variables - were logged starting from 2007 onwards, only patients that were diagnosed in 2007 and later were included in this study, yielding data from 12546 patients with TB.

All patients were stratified according to their legal status(undocumented migrant, documented migrant and native Dutch) to be able to compare the target population (undocumented migrants and migrants) with the native Dutch population. The composition of these strata is explained further.

First, baseline characteristics and diagnostic and treatment characteristics among all 12546 patients were analyzed in a baseline analysis and some important variables (age, gender, comorbidity, patient and health system delay and treatment outcomes) were tested for significant differences between strata, using a chi-square test.

In order to test effectiveness of treatment interventions, a univariate and multivariate logistic regression analysis was performed (among 9796 patients, after deleting cases with missing/unknown data) with treatment completion as a dependent variable and treatment associated variables(side effects, submission to clinical institution, treatment support and DOT) and and legal status, age, gender and comorbidity as independent variables.

The regression analysis was performed both for the whole cohort of 9796 patients and for each stratum apart, in order to assess effectiveness of interventions for the whole cohort as well as for each stratum.

The intervention-variables were chosen based upon their relevance found in relevant literature(38-40) and availability of these variables in the NTR and baseline characteristics such as legal status, age, gender and comorbidity were analyzed as well to correct for confounding.

Although many baseline characteristics other than legal status, age, gender and comorbidity were available for this regression analysis, only these were selected as these they did not have too many missing data; e.g. HIV status or patient delay could have been selected however these variables had too many missing data which would have negatively affected the sample size too much.

For both statistical analyses (chi square and regression analysis) a significance level of $p<0.05$ was defined as significant.

Glosssary of Terms

High incidence/Low incidence	Many different definitions of high/low incidence of TB are used in the literature. In this study an incidence of >50/100.000 was defined as high incidence. An incidence of<50/100.000 was defined as low incidence(NTR).
Treatment Completion	At the end of the treatment the prescribed amount of medication has been taken, or when it is estimated that at least 80% of the prescribed amount of medication has been taken and when the results of a sputum culture are unknown (NTR).
Curation	At the end of treatment, the prescribed amount of medication has been taken, or it is estimated that at least 80% of the prescribed amount of medication has been taken and there is a negative sputum culture (NTR). In this study both treatment completion and curation were logged as 1 variable.
Treatment discontinuation	A treatment has been interrupted more than 2 months, or when it is estimated that no more than 80% of the prescribed amount of medication has been taken, or when a standard treatment of 6 months has not been completed within 9 months, or when a standard treatment of 9 months has not been completed within 12 months (NTR).
Patient delay	The time between the onset of symptoms until first contact with the healthcare system (NTR).
Health system delay	The time between first contact with the healthcare system until the start of treatment (NTR).
Undocumented Migrant	A person who has been born abroad with the absence of a legal residence status at time of first investigation concerning TB or at time diagnosis-irrespective of duration of stay in the Netherlands. This group includes asylum seekers and refugees, after having been denied a legal residence status. Per definition all undocumented migrants are migrants from outside the EU region.
Documented Migrant	A person who has been born abroad with a legal residence status at time of first investigation concerning TB or at time of diagnosis, e.g. a foreign student, asylum seeker or refugee or working migrant.
Native Dutch	A person with Dutch nationality at time of diagnosis, including incarcerated people, homeless people, people with a drug addiction, healthcare professionals, travelers to endemic area's as long as they were not classified as a migrant
Asylum seeker	An 'asylum seeker' was defined as a person who seeks safety from persecution or serious harm in a country other than his or her own and awaits a decision on the application for refugee status(41).
Refugee	A 'refugee' was defined as a person who has been forced to flee his or her country because of persecution, war or violence and seeks protection in another country(41)
Article 64	Based upon this article in the dutch law, undocumented patients cannot be forced to leave the country while receiving treatment for TB.
CVZ applied	This refers to a financial regulation that partially reimburses healthcareproviders for healthcosts made for a patient without healthcare insurance and reimburses patients for housing and living costs while receiving treatment.

Attention: On the next page a table will be displayed explaining all variables used in this study

Legal status	Patients with TB were stratified according to their legal status; in this manner 3 strata were created: undocumented migrants, documented migrants and the native Dutch population.
Age	Age was reported in age-categories: 0-14, 15-24, 25-34, 35-44, 45-54 and 55+ and frequencies were logged
Gender	Patients were either noted as male or female and frequencies were logged
Comorbidity with increased risk to develop TB	Many of these factors have been logged in the NTR; in this study we used the variable "comorbidity with increased risk to develop TB", which includes: malignancy, kidney insufficiency/dialysis, organ transplantation, diabetes mellitus, COPD, silicosis, malabsorption syndrome, inflammatory bowel disease, rheumatoid arthritis, congenital immunodeficiency syndromes, malnutrition/underweight, Zinc deficiency, vitamin D deficiency, recent pregnancy, other immunodeficiency conditions, immunomodulation medications/cytostatics, systemic corticosteroids, Tumor Necrosis Factor(TNF) alfa inhibitors/ other biologicals, other immunosuppressive medications. This variable was logged as either yes or no or unknown depending on the existence of 1 or more risk factors. Tobacco use was not included in this list, and HIV was listed as a separate variable.
Patient delay	Patient delay was logged as a baseline characteristic and was measured in timeblocks of 4 weeks: (0-4, 5-8, 9-12 and 13+ weeks). Definition of patient delay is explained in the glossary of terms.
Health system delay	Health system delay was logged as a baseline characteristic and was measured in timeblocks of 4 weeks: (0-4, 5-8, 9-12 and 13+ weeks) Definition is mentioned in glossary of terms.
Country of origin	Countries of origin were logged as a baseline characteristic; the top 10 of countries of origin with the highest absolute numbers of patients with TB were listed. All listed countries except the Netherlands have a high burden of TB.
Reason of migration	During the transit phase, migrants move from their place of origin to their place of destination or interception location . During this stage, risk of TB transmission and disease is dependent on the type of migration channels used: in general, migrants who planned their migration through regular channels have a lower risk of infectious disease exposures during transit than irregular migrants(24) Asylumseekers and refugees tend to migrate through irregular channels where as other migrants such as students or expats usually travel through regular channels; therefore the reason of migration is associated with TB exposure. In this study several reasons of migration were assessed: work, family migration, internship/au-pair, asylum/refugee, study or tourism.
BCG status	BCG(Bacille-Calmette Guerin) vaccination currently is the only vaccine that gives protection against disseminated forms of TB(miliary TB) and TB meningitis in infants(42) In this study BCG vaccination was logged as either yes or no or unknown at time of diagnosis.
HIV status	HIV infection without proper treatment affects the host's immune system negatively and makes the host more susceptible to opportunistic infections like tuberculosis. In fact, it is the single most well known riskfactor for the development of TB-both by increasing the risk of rapid progression to active disease as well as by increasing the reactivation of TBI(43) HIV status was logged as either yes, no or unknown
Previous diagnosis of TB Previous treatment of TB Completion of previous treatment	One of the well known factors related to TB is a previous episode of TB and status of treatment completion of a previous episode of TB. (44) These parameters were either logged as yes, no or unknown
Type of TB	Patients were either diagnosed with PTB, ETB or both
Reason TB examination	This parameter was logged according to the following categories: Health complaints, source/contact investigation, screening of a risk group, chest X-ray after diagnosis of TBI, other and unknown.
Type of diagnostical test	<u>Microscopy</u> In this study Ziehl-Neelsen (ZN) positivity after sputum smear or Broncho Alveolar Lavage(BAL) was used as diagnostic variable. This is a bacteriological staining method used to identify acid fast bacilli like the Mtb and can be seen under a microscope. Smear positive individuals are more infectious to other people than smear negative individuals and the concentration of bacilli is positively correlated with infectivity of the TB patient(45) <u>Culture</u> Confirmation of the diagnosis by culture was used as another diagnostic parameter; as mentioned earlier this can be a time consuming process and therefore other more rapid tests are usually applied like molecular testing. <u>Molecular testing</u> Polymerase Chain Reaction(PCR) is a Nucleic acid amplification test (NAAT) that allows to detect TB particularly in patients with low bacterial load as this test detects TB more accurately than microscopic tests or culture(3) In fact, some molecular tests allow for (drug)susceptibility testing like GeneXpertbut these data were not logged in the NTR database. All patients included in the analysis were diagnosed with TB and diagnosis was made by either molecular testing (PCR), microscopy showing acid-fast bacilli or culture
Treatment Outcome	This variable was subdivided in the following subvariables: treatment completion, treatment discontinuation, deceased during treatment, treatment continued abroad, treatment failure and unknown treatment outcome.
Side Effects	Side effects were logged as either yes or no

Submission to clinical institution	This parameter relates to patients with TB being hospitalized or admitted to a sanatorium or hospital for clinical treatment, and was either logged as yes, no or unknown
Treatment support	Treatment support was defined as social/mental support after the intake/time of diagnosis to the patient by the TB nurse and by interventions aimed at improving therapy compliance. This parameter was either logged as yes, no or unknown
Direct Observed Therapy(DOT)	DOT was defined as any use of tuberculostatic medication administered/taken under direct observation of a nurse/designated person This parameter was either logged as yes, no or unknown and DOT by whom was also logged: by a nurse, a third person or by both a nurse and third person
Healthinsurance/financial regulations	Health insurance status was logged from 2014 onwards and was noted as either yes, no or unknown. If status was no, , it was noted how many patients were applied for article 64 or a special financial regulation(CVZ)(see definition of terms in table above)

In the following sectio the relevance of variables that were used to answer the study questions are further explained:

Age

TB affects people of all ages, however especially children under the age of 5 are more likely to develop TB(probably because of an immature immune system). Older age is a risk factor as well, as this is usually linked to a weakened immunesystem, predisposing for an increased susceptibility of developing TB. Among migrants somehow a different age pattern is visible, probably due to migration related reasons(46).

Gender

Men are more likely to be diagnosed with TB than women, with a male-to-female ratio of 1.6:1.0, globally. In both native and migrant populations, males are more frequently reported with TB. Overall, in the EU in 2010, the male:female gender ratio was 2.0:1.0 for native TB patients and 1.5:1.0 for foreign-born patients(17).

Comorbidity with increased risk to develop TB:

Many individual comorbidities have been associated with an increased risk of developing TB as discussed earlier in the problem statement. All variables that were logged in the variable comorbidity are mentioned in the table above.

Patient delay

Patient delay is a bottleneck in addressing TB as patients can be infectious for a long time before they enter the healthcare system and addressing patient delay can have an important impact on breaking the chain of infectious TB(20).

Health system delay

Health system delay can be regarded as a proxy for quality of TB services; a prolonged delay can prolong infectiousness of a patient with TB(20).

TB treatment completion

Treatment completion is essential for patients with TB as this decreases the chance of developing drug resistance and prolonged infectiousness. This variable was assessed in baseline analysis, and it was used as a dependent variable in univariate and multivariate logistic regression analysis in order to assess the association of risk factors and treatment-interventions with treatment completion.

Side effects:

The negative influence of side effect-ranging from neurological or psychological symptoms to hepatitis- of tuberculosis treatment on treatment completion has been reported earlier(21) This variable was assessed in baseline analysis and used in the regression analysis to assess its association with treatment completion.

Submission clinical institution

There can be many reasons for submission ranging from severity of disease to problems related to homelessness(48, 49); submission is used as an intervention to improve treatment outcome(39).

Treatment support:

TB treatment is intensive and usually lasts for at least several months; support is known to increase treatment compliance and improve treatment outcomes/completion(40) Therefore this variable was used as an independent variable in the regression analysis to assess its association with treatment completion.

DOT

DOT is recognized as a way of improving treatment adherence and completion(39) This variable was assessed in baseline analysis and used as an independent variable in the regression analysis to assess its association with treatment completion.

Results

Characteristics of study population

Tables A, B and C(see below) describe the baseline characteristics and diagnostic and treatment details of the study population (for most variables n=12.546).

Most patients included in the analysis were documented migrants (n=8.794, 70.1%), followed by the native Dutch population (n=3.427, 27.3%) and the number of undocumented migrants was only small (n=325, 2.6%).

Table A

Baseline characteristics	Total		Undocumented Migrants		Documented Migrants		Native Dutch	
	n	(column%)	n	(column %)	n	(column %)	n	(column %)
Total	**12546**	**100**	**325**	**100**	**8794**	**100**	**3427**	**100**
Gender								
Male	7309	58.3	234	72	4991	56.8	2084	60.8
Female	5236	41.7	91	28	3802	43.2	1343	39.2
Unknown	1	0	0		1		0	
Age (years)								
0-14	590	4.7	4	1.2	220	2.5	366	10.7
15-24	2055	16.4	57	17.5	1603	18.2	395	11.5
25-34	3141	25	140	43.1	2535	28.8	466	13.6
35-44	2022	16.1	76	23.4	1574	17.9	372	10.9
45-54	1616	12.9	25	7.7	1162	13.2	429	12.5
55+	3122	24.9	23	7.1	1700	19.3	1399	40.8
Country of birth (top 10)								
Afghanistan	227	1.8	1	0.3	226	2.6	N.A.	
Eritrea	733	5.8	11	3.4	722	8.2	N.A.	
Ethiopia	236	1.9	6	1.8	230	2.6	NA	
India	408	3.3	17	5.2	391	4.4	N.A.	
Indonesia	515	4.1	28	8.6	487	5.5	N.A.	
Morocco	1124	9	39	12	1085	12.3	N.A.	
Netherlands	3420	27.3	3	0.9	0	0	3417	
Somalia	1592	12.7	19	5.8	1573	17.9	N.A.	
Suriname	452	3.6	5	1.5	447	5.1	N.A.	
Turkey	376	3	6	1.8	370	4.2	N.A.	
Other	3463	27.6	190	58.5	3273	37.2	N.A.	
Reason of migration(reported ≥2017)	**9119**							
Work	327	3.6	7	2.2	320	3.6	N.A.	
Asylum/Refugee	746	8.2	23	7.1	723	8.2	N.A.	
Family Migration	190	2.1	0	0	190	2.2	N.A.	
Study	73	0.6	0	0	73	2.2	N.A.	
Au pair	4	0	2	0.6	2	0	N.A.	
Tourism	15	0.2	1	0.3	14	0.2	N.A.	
Other reason	108	1.2	13	4	95	1.1	N.A.	
Not applicable(stays>5yr in NL)	759	8.3	19	5.8	740	8.4	N.A.	
Unknown	1	0	1	0.3	0	0	N.A.	
Uknown - diagnosis before 2017	6896	75.6	259	79.7	6637	75.5	N.A.	
BCG vaccination status								
No	2888	23	32	9.8	746	8.5	2109	61.5
Yes	3678	29.3	109	33.5	3264	37.1	305	8.9
Unknown	5987	47.7	184	56.6	4784	54.4	1013	29.6
HIV-status								
Negative	6424	51.2	192	59.1	4810	54.7	1422	41.5
Positive	398	3.2	27	8.3	307	3.5	64	1.9
Unknown	5724	45.6	106	32.6	3677	41.8	1941	56.6
Comorbidity increasing the risk for TB								
No	8269	65.9	193	59.4	5915	67.3	2161	63.1
Yes	1963	15.6	51	15.7	1254	14.3	658	19.2
Unknown	2314	18.4	81	24.9	1625	18.5	608	17.7
Previous diagnosis of TB								
No	10976	87.5	274	84.3	7670	87.2	3032	88.5
Yes	783	6.2	26	8	492	5.6	265	7.7
Unknown	787	6.3	25	7.7	632	7.2	130	3.8
Previous treatment completed(n=783)	**783**		26		492		265	
No	341	43.6	11	42.3	233	47.4	97	36.6
Yes	151	19.3	7	26.9	120	24.4	24	9.1
Unknown	291	37.2	8	30.8	139	28.3	144	54.3

Table B

Diagnostic characteristics and delay	Total		Undocumented Migrants		Documented Migrants		Native Dutch	
	n	(column %)	n	(column %)	n	(column%)	n	(column%)
Total	**12546**	**100**	**325**	**100**	**8794**	**100**	**3427**	**100**
Type of tuberculosis								
PTB	5553	44.3	160	49.2	3588	40.8	1805	52.7
ETB	5451	43.4	123	37.8	4110	46.7	1218	35.5
PTB & ETB	1542	12.3	42	12.9	1096	12.5	404	11.8
Reason TB examination								
Health Complaints	9877	78.7	265	81.5	6969	79.2	2643	77.1
Source / contact investigation	812	6.5	6	1.8	325	3.7	481	14
Screening of risk group	1341	10.7	46	14.2	1247	14.2	48	1.4
Chest X-ray after TBI diagnosis	67	0.5	0	0	27	0.3	40	1.2
Other	408	3.3	8	2.5	199	2.3	201	5.9
Unknown	41	0.3	0	0	27	0.3	14	0.4
Patient delay								
0-4 weeks	2008	16	31	9.5	1310	14.9	667	19.5
5-8 weeks	443	3.5	15	4.6	294	3.3	134	3.9
9-12 weeks	260	2.1	11	3.4	177	2	72	2.1
>13 weeks	413	3.3	19	5.8	240	2.7	154	4.5
Unknown	9422	75.1	249	76.6	6773	77	2400	70
Health system delay								
0-4 weeks	3985	31.8	107	32.9	2721	30.9	1157	33.8
5-8 weeks	462	3.7	7	2.2	294	3.3	161	4.7
9-12 weeks	249	2	2	0.6	144	1.6	103	3
>13 weeks	489	3.9	3	0.9	272	3.1	214	6.2
Unknown	7361	58.7	206	63.4	5363	61	1792	52.3
Microscopy ZN/BAL								
Negative	4865	38.8	129	39.7	3538	40.2	1198	35
Positive	3399	27.1	108	33.2	223	2.5	1068	31.2
Not done	3842	30.6	80	24.6	2706	30.8	1056	30.8
Unknown	440	3.5	8	2.5	327	3.7	105	3.1
PCR								
Negative	1996	15.9	43	13.2	1467	16.7	486	14.2
Positive	6712	53.5	197	60.6	4755	54.1	1760	51.4
Not done	2364	18.8	51	15.7	1546	17.6	767	22.4
Unknown	1474	11.7	34	10.5	1026	11.7	414	12.1
Culture								
Negative	1955	15.6	39	12	1352	15.4	564	16.5
Positive	8704	69.4	267	82.2	6291	71.5	2146	62.6
Not done	1267	10.1	11	3.4	724	8.2	532	15.5
Unknown	620	4.9	8	2.5	427	4.9	185	5.4

Table C

Treatment characteristics and interventions	Total		Undocumented Migrants		Documented Migrants		Native Dutch	
Total (row %)	**12546**	**100%**	**325**	**100%**	**8794**	**100%**	**3427**	**100%**
TB treatment outcome								
Completed	11048	88.1	260	80	7817	88.9	2971	86.7
Discontinued	445	3.5	12	3.7	294	3.3	139	4.1
Side effects	*148*	*33.3*	*2*	*0.6*	*73*	*0.8*	*73*	*2.1*
Withdrawal from treatment	*257*	*57.8*	*10*	*3.1*	*198*	*2.3*	*49*	*1.4*
Unknown	*40*	*9*	*0*	*0*	*23*	*0.3*	*17*	*0.5*
Deceased during treatment	539	4.3	6	1.8	249	2.8	284	8.3
Due to TB	*176*	*32.7*	*3*	*0.9*	*86*	*1*	*87*	*2.5*
Not due to TB / Unknown	*363*	*67.3*	*3*	*0.9*	*163*	*1.9*	*197*	*5.7*
Treatment continued abroad	405	3.2	33	10.2	360	4.1	12	0.4
Treatment completed	*34*	*8.4*	*2*	*0.6*	*31*	*0.4*	*1*	*0*
Treatment outcome	*371*	*91.6*	*31*	*9.5*	*329*	*3.7*	*11*	*0.3*
Failed (positive culture ≥5 months)	2	0	0	0	1	0	1	0
Unknown	107	0.9	14	4.3	73	0.8	20	0.6
One or more side effects reported								
No	10930	87.1	290	89.2	7738	88	2902	84.7
Yes	1616	12.9	35	10.8	1056	12	525	15.3
Submission to clinical institution								
No	8411	67	190	58.5	5879	66.9	2342	68.3
Yes	4009	32	131	40.3	2825	32.1	1053	30.7
Unknown	126	1	4	1.2	90	1	32	0.9
TB treatment support								
No	605	4.8	23	7.1	376	4.3	206	6
Yes	11908	94.9	299	92	8395	95.5	3214	93.8
Unknown	33	0.3	3	0.9	23	0.3	7	0.2
Direct Observed Therapy(DOT)								
No	8971	71.5	128	39.4	6215	70.7	2628	76.7
Yes	3453	27.5	191	58.8	2486	28.3	776	22.6
Unknown	122	1	6	1.8	93	1.1	23	0.7
Insurance for healthcost (reported ≥2	5012		122		3626		1264	
No	512	10.2	104	85.2	333	9.2	75	5.9
Art 64 requested	*97*	*18.9*	*76*	*73.1*	*21*	*6.3*	*0*	*0*
Not honored	*1*	*0*	*1*	*0.8*	*0*	*0*	*n.a.*	
Honored	*95*	*1.9*	*74*	*60.7*	*21*	*0.6*	*n.a.*	
Unknown	*1*	*0*	*1*	*0.8*	*0*	*0*	*n.a.*	
CVZ for no insurance applied	*24*	*4.7*	*11*	*10.6*	*13*	*3.9*	*0*	*0*
No art 64 or CVZ	*112*	*21.9*	*13*	*1.3*	*89*	*2.7*	*10*	*13.3*
Unknown	*279*	*54.5*	*4*	*3.8*	*210*	*63.1*	*65*	*86.7*
Yes	4352	86.8	16	13.1	3173	87.5	1163	92
Unknown	148	3	2	1.6	120	3.3	26	2.1

Description of the baseline analysis:

Patient delay:

For most patients, patient delay was not reported. However: Undocumented migrants had a significantly less frequent patient delay of 0-4 weeks as compared to documented migrants and native Dutch patients. Between 5-12 weeks of delay, no significant differences were reported between the 3 groups. Both undocumented migrants and native Dutch had significantly more often a patient delay of more than 13 weeks than documented migrants.

Health system delay:

For most patients it is unknown how much health system delay was; delays were not reported significantly more often among Undocumented migrants and documented migrants as compared to native Dutch.

For native Dutch, a health system delay of 0-4 weeks and 5-8 weeks was reported significantly more frequent as compared to health system delay for documented migrants. Delays of 9-12 and >13 weeks were reported significantly more often for native Dutch as compared to delays for documented and undocumented migrants.

Treatment outcomes:

Treatment was completed(in the Netherlands and abroad combined) significantly less often among undocumented

migrants(80.6%) than among the native Dutch(86.7%) and documented migrants(93.4%)and significantly more often

among documented migrants(93.4%) than amongthe native Dutch.

Discontinuation because of side effects was reported more frequent among native Dutch(2.1%) as compared to

documented migrants(0.8%) and undocumented migrants(0.6%) and only the difference between native Dutch and

documented migrants was significant. Among native Dutch, significantly more patients died during treatment(8.3%)

than among the undocumented(1.8%) and documented migrants(2.8%).

Withdrawal from treatment was reported significantly more frequent among documented migrants(2.3%) than among native Dutch(1.4%), although undocumented migrants also reported higher frequencies of withdrawal3.1%) as

compared to documented migrants and native Dutch, though this difference was not significant.

Hardly any treatment failure was reported. Significantly more unknown treatment results were reported among undocumented migrants than among documented migrants and native Dutch.

Gender:

In the group of undocumented migrants, significantly more males were present than in the group of documented migrants and native Dutchs. And in the group of documented migrants, significantly less males were present than in the group of native Dutch.

Significantly fewer females were present in the group of undocumented migrants and native Dutch as compared to the group of documented migrants.

Age:

Native Dutch had significant higher frequencies of children aged 0-14 with TB as compared to undocumented migrants and documented migrants. Age between 15-24, 25-34 and 35-44 was reported with significantly higher frequencies for undocumented migrants and documented migrants as compared to native Dutch.

Age of 45-54 was reported significantly less frequent among undocumented migrants than among documented migrants and native Dutch

Age of 55+ was reported significantly more frequent among native Dutch and documented migrants than among undocumented migrants the percentage of those aged 55+ among native Dutch was also significantly higher than among documented migrants.

Comorbidity increasing the risk for TB:

Significantly more native Dutch patients had comorbidity as compared to documented migrants and native Dutch also had higher frequencies of comorbidity than undocumented migrants though not significantly. For 18.4% of all selected patients, comorbidity status was unknown.

Countries of origin were listed in a top 10 ranking according to absolute numbers of patients with TB; most patients originated from Morocco, Somalia and the Netherlands. All countries in the top 10 are countries with a high burden of TB (except from the Netherlands) .

Reasons of migration:

For the majority of patients, it was unclear what the reasons of migration were; this parameter was only registered from 2017 onwards and most patients were diagnosed before this year. Seeking asylum or being a refugee were reported most frequently.

BCG vaccination status:

Over one third of both undocumented and documented migrants had had a BCG vaccination at time of diagnosis of TB as compared to around 9% among native Dutch; a significant difference. For nearly half of all migrants and one third of Dutch natives, BCG vaccination status was unknown.

HIV status:

Among undocumented migrants, HIV positivity percentages were significantly higher than among documented migrants and native Dutch; among documented migrants these percentages were also significantly higher than among native Dutch. However for a large percentage, HIV status was unknown among all strata.

Previous diagnosis of TB:

For native Dutch a previous diagnosis of TB had been made significantly more frequent than among documented migrants. Undocumented migrants also reported a higher frequency of previous episodes of TB,lthough not significantly more than the other 2 strata. Of those who had a previous episode of TB ,undocumented migrants and documented migrants UDMs and DMs had been treated significantly more often than native Dutch. Of those who had been treated for a previous episode of TB, treatment had been completed significantly more often among undocumented migrants and documented migrants than among native Dutch.

Unknown data about previous treatment and treatment completion were reported significantly more often among native Dutch than among undocumented migrants and documented migrants.

Type of TB:

Documented migrants had PTB significantly less often than did undocumented migrants and native Dutch. On the contrary, ETB was reported significantly more often among documented migrants than among undocumented migrants and native Dutch. ETB and PTB combined was reported without significant differences between all strata.

Reason of TB exam;

Documented were examined significantly more frequently because of health complaints as compared to native Dutch. Undocumented migrants had higher frequencies of health complaints as compared to documented migrants and native Dutch but no significant differences were found. Both undocumented migrants and documented migrants had significantly fewer frequencies of source/contact investigations as reason for TB examination as compared to the native Dutch. Equal proportions among documented migrants and undocumented migrants were reported as result of screening of risk populations and these proportions were significantly higher than among native Dutch.

Microscopy/PCR/culture:

Undocumented migrants and native Dutch had significantly more often sputum/BAL positive smears as compared to documented migrants. Significantly higher proportions of undocumented migrants and documented migrants were diagnosed by PCR as compared to native Dutch. Significant higher proportions of undocumented migrants and documented migrants had a positive sputum culture as compared to native Dutch.

Side effects were reported less frequently among undocumented migrants than among documented migrants and native Dutch and only the difference between documented migrants and native Dutch was significant.

Submission to a clinical institution was reported significantly more frequent among undocumented migrants than among documented migrants and native Dutch.

Treatment support was reported significantly more often among documented migrants than among undocumented migrants and native Dutch.

DOT:

DOT was applied significantly more frequent among undocumented migrants than among documented migrants and native Dutch. DOT was also applied more frequently by nurses among undocumented migrants than among documented migrants and native Dutch. DOT was applied significantly more often by a third person among documented migrants and native Dutch than among undocumented migrants.

Health insurance status was monitored since 2014:

Most TB patients(86.8%) had health insurance at time of diagnosis, however among undocumented migrants this percentage(13.1%)was significantly lower. For most undocumented migrants article 64 was requested and honored; this means they could not be forced to leave the country during treatment of TB. For 14% of the uninsured undocumented migrants, a special regulation for reimbursement of health costs associated with TB treatment was applied; this percentage is higher than among documented migrants and native Dutch but a small percentage overall.

Variables associated with treatment completion

In order to assess associations between some baseline characteristics, treatment interventions and TB treatment completion, a univariate and multivariate logistic regression analysis was performed.

As legal status was hypothesized to be associated with treatment completion, this variable was tested for its association with treatment completion.

Other variables such as clinical submission, treatment support and DOT are interventions known to positively affect treatment completion; these variables were used to test their association with treatment completion in the population in this study.

The association of these intervention variables was corrected for age, gender, comorbidity and side effects of treatment.

The results of univariate and multivariate logistic regression analysis for the whole cohort(n=9796) are shown in table D.

Table D

Univariate and multivariate logistic regression analysis	TB Treatment completion					
	No (%)	Yes (%)	OR (95%CI)	p-value	aOR (95%CI)	p-value
Total (n=9796)	**734 (7.5%)**	**9062 (92.5%)**			**Method=enter**	
Status						
Undocumented migrant	13 (6.2%)	198 (93.8%)	1		1	
Documented migrant	407 (6.0%)	6409 (94.0%)	1.03 (0.59-1.83)	0.91	0.98(0.53-1.78)	0.94
Dutch-native	314 (11.3%)	2455 (88.7%)	0.51 (0.29-0.91)	0.02	0.64(0.35-1.18)	0.16
Gender						
Male	475 (8.4%)	5196 (91.6%)	1		1	
Female	259 (6.3%)	3866 (93.7%)	1.37 (1.17-1.60)	<0.00	1.27(1.07-1.52)	0.007
Age (years)						
0-14	13(2.70%)	474(97,3%)	1		1	
15-24	68(4.20%)	1554(95.80%)	0.63 (0.34-1.14)	0.13	0.56(0.30-1.06)	0.073
25-34	107(4.40%)	2309(95.60%)	0.59 (0.33-1.06)	0.08	0.54(0.29-0.998)	0.049
35-44	60(3.80%)	1515(96.20%)	0.69 (0.38-1.27)	0.24	0.76(0.40-1.44)	0.398
45-54	87(6.90%)	1180 93.10%)	0.37 (0.21-0.67)	0.001	0.47(0.25-0.88)	0.018
55+	399(16.40%)	2030(83.60%)	0.14 (0.08-0.25)	<0.001	0.22(0.12-0.39)	<0.001
Comorbidity increasing the risk for TB						
No	435(5.5%)	7494(94.5%)	1		1	
Yes	299(16%)	1568(84%)	0.30(0.26-0.36)	<0.001	0.64(0.53-0.77)	<0.001
Side effects						
No	508(6%)	8000(94%)	1		1	
Yes	226(17.5%)	1062(82,5%)	0.30(0.25-0.35)	<0.001	0.32(0.26-0.38)	<0.001
Submission to clinical institution						
No	310(4.7%)	6309(95,3%)	1		1	
Yes	424(13.3%)	2753(86,7%)	0.32(0.27-0.37)	<0.001	0.55(0.46-0.66)	<0.001
TB treatment support						
No	155(51,7%)	145(48,3%)	1		1	
Yes	579(6,1%)	8917(93,9%)	16.5(12.9-21.0)	<0.001	15.3(11.7-20.0)	<0.001
Direct Observed Therapy						
No	445(6.30%)	6671(93.70%)	1		1	
Yes	289(10.80%	2391(89.20%)	0.56(0.47-0.65)	<0.001	0.59(0.48-0.71)	<0.001

In univariate logistic regression analysis, for native Dutch the odds that they completed their treatment were significantly lower than among undocumented migrants but in multivariate analysis, there was no significant difference in the odds for treatment completion between all strata.

Being a female patient was significantly positively associated with treatment completion in multivariate analysis (aOR= 1.27(confidence interval (CI):1.07-1.52), p <0.001 as compared to being a male patient.

Patients of young age (0-14) completed their treatment in 97.3%. Compared to this group in multivariate analysis, patients between the ages 25-34, 45-54 and 55+, had significantly lower odds of completing their treatment.

Having comorbidity increasing the risk for TB was negatively associated with treatment completion as compared to patients without comorbidity in multivariate analysis (p<0.001).

The same counts for patients who experienced side effects during their treatment; having side effects was negatively associated with treatment completion as compared to patients who did not experience side effects (p<0.001).

Being submitted to a clinical institution was negatively associated with treatment completion as compared to not being submitted to a clinical institution (p<0.001) in multivariate analysis.

Treatment support was positively associated with treatment completion as compared to patients who did not receive treatment support (p<0.001) in multivariate analysis.

Receiving DOT was negatively associated with treatment completion as compared to patients who did not receive DOT in multivariate analysis (p<0.001).

Although legal status was not significantly associated with treatment completion in this multivariate regression analysis, a subgroup analysis was performed in order to identify factors that were either positively or negatively associated with treatment completion per stratum, as the focus of this study was to assess treatment results (and associated factors) among documented migrants and undocumented migrants.

Both a univariate and multivariate logistic regression analysis was performed and the results are shown in tables E, F and G.

Table E

Univariate and multivariate logistic regression analysis	Treatment Completion Undocumented Migrants(n= 211)					
	No (%)	Yes (%)	OR (95%CI)	p-value	aOR (95%CI)	p-value
Total	**13 (6.2%)**	**198 (93.8%)**			**Method=enter**	
Gender						
Male	9 (6.1%)	139 (93.9%)	1		1	
Female	4 (6.4%)	59 (93.7%)	0.96 (0.28-3.22)	0.94	0.86(0.24-3.31)	0.86
Age (years)						
0-14	0 (0.0%)	2 (100.0%)	n.a.		high	
15-24	4 (10.8%)	33 (89.2%)	1.77 (0.35-8.95)	0.49	1.94(0.32-11.9)	0.48
25-34	4 (4.6%)	83 (95.4%)	4.45 (0.90-22.0)	0.07	5.14(0.92-28.8)	0.06
35-44	1 (2.0%)	49 (98.0%)	10.5 (1.01-109.0)	0.05	10.3(0.96-111)	0.06
45-54	1 (5.6%)	17 (94.4%)	3.64 (0.34-39.01	0.29	4.12(0.37-46.0)	0.35
55+	3 (17.6%)	14 (82.4%)	1		1	
Comorbidity increasing the risk for TB						
No	11 (6.6%)	155 (93.4%)	1		1	
Yes	2 (4.4%)	43 (95.6%)	1.53 (0.33-7.15)	0.59	1.83(0.33-10.2)	0.49
One or more side effects reported						
No	10 (5..4%)	174 (94.6%)	1		1	
Yes	3 (11.1%)	24 (88.9%)	0.46 (0.12-1.79)	0.26	0.41(0.10-1.72)	0.22
Submission to clinical institution						
No	7 (6.0%)	109 (94.0%)	1		1	
Yes	6 (6.3%)	89 (93.7%)	0.95 (0.31-2.94)	0.93	1.05(0.29-3.73)	0.95
TB treatment support						
No	0 (0.0%)	4 (100.0%)	1		1	
Yes	13 (6.3%)	194 (93.7%)	N.A.		0	0.99
Direct Observed Therapy						
No	4 (5.1%)	74 (94.9%)	1		1	
Yes	9(6.8%)	124 (93.2%)	0.75 (0.22-2.50)	0.63	0,76(0.19-3.11)	0.72

Within the group of undocumented patients (n=211), no variables were significantly associated with treatment completion (in multivariate regression analysis), however some trends were noticeable.

For instance, being male was positively associated with treatment completion as compared with the female gender, though not significantly.

All age-groups had a positive association with treatment completion as compared to the age group of 55+, though not significantly.

All 4 patients who did not receive treatment support completed their treatment as compared to 93.7% of patients who did receive treatment support, so based on these small numbers (as compared to the other subgroups/strata) treatment support was negatively associated with treatment completion, though not significantly.

Comorbidity and submission to a clinical institution were positively associated with treatment completion, though not significantly. Side effects and DOT were both negatively associated with treatment completion though not significantly.

The results of the regression analysis for treatment completion of the subgroup of documented migrants(n=6818) are shown in table F:

Table F

Univariate and multivariate logistic regression analysis	Treatment Completion Documented Migrants(n= 6816)					
	No (%)	Yes (%)	OR (95%CI)	p-value	aOR (95%CI)	p-value
Total	**407(6.0%)**	**6409(95%)**			**Method=enter**	
Gender						
Male	273(7.10%)	3559(92.90%)	1		1	
Female	134(4.50%)	2850(95.5%)	1.63(1.32-2.02)	<0.001	1.70(1.34-2.13)	<0.001
Age (years)						
0-14	5(2.80%)	172(97.20%)	5.00(2.03-12.3)	<0.001	3.13(1.21-8.08)	0.02
15-24	49(3.90%)	1209(96.10%)	3.59(2.59-4.98)	<0.001	2.47(1.71-3.57)	<0.001
25-34	82(4.20%)	1862(95.80%)	3.3(2.51-4.34)	<0.001	2.33(1.71-3.16)	<0.001
35-44	46(3.80%)	1177(96.20%)	3.72(2.66-5.21)	<0.001	3.03(2.11-4.37)	<0.001
45-54	58(6.50%)	841(93.50%)	2.11(1.54-2.88)	<0.001	1.93(1.38-2.70)	<0.001
55+	167(12.70%)	1149(87.30%)	1		1	
Comorbidity increasing the risk for TB						
No	259(4.60%)	5375(95.40%)	1		1	
Yes	148(12.50%)	1035(87.50%)	0.34(0.27-0.42)	<0.001	0.64(0.50-0.82)	<0.001
One or more side effects reported						
No	281(4.70%)	5702(95.30%)	1		1	
Yes	126(15.10%)	708(84.90%)	0.28(0.22-0.35)	<0.001	0.27(0.21-0.35)	<0.001
Submission to clinical institution						
No	181(3.90%)	4414(96.10%)	1		1	
Yes	226(10.20%)	1996(89.80%)	0.36(0.30-0.44)	<0.001	0.70(0.54-0.89)	<0.001
TB treatment support						
No	72(42.40%)	98(57.60%)	1		1	
Yes	335(5.00%)	6312(95.00%)	13.8(10.0-19.1)	<0.001	13.6(9.55-19.5)	<0.001
Direct Observed Therapy						
No	224(4.60%)	4686(95.40%)	1		1	
Yes	183(9.60%)	1724(90.40%)	0.45(0.37-0.55)	<0.001	0.53(0.41-0.67)	<0.001

All variables were significantly associated with treatment completion ($p<0.05$).

Younger age (<55) and the female gender were positively associated with treatment completion as was treatment support, that showed a very high adjusted odds ratio in multivariate logistic regression analysis. Comorbidity, side effects, submission to a clinical institution and DOT were all significantly negatively associated with treatment completion.

The results of the regression analysis for treatment completion of the subgroup of native Dutch(n=2769) are shown in Table G:

Table G

Univariate and multivariate logistic regression analysis	Treatment Completion Native Dutch (n= 2769)					
	No (%)	Yes (%)	OR (95%CI)	p-value	aOR (95%CI)	p-value
Total	**314(11,3%)**	**2455(88,7%)**			**Method=enter**	
Gender						
Male	193(11.40%)	1498(88.60%)	1		1	
Female	121(11.20%)	957(88.80%)	1.02(0.80-1.30)	0.88	0.83(0.63-1.10)	0.2
Age (years)						
0-14	8(2.60%)	300(97.40%)	9.91(4.484-20.3)	<0.001	5.392(2.48-11.7)	<0.001
15-24	15(4.60%)	313(95.40%)	5.51(3.22-9.44)	<0.001	3.467(1.93-6.25)	<0.001
25-34	21(5.50%)	364(94.50%)	4.58(2.88-7.28)	<0.001	2.895(1.73-4.85)	<0.001
35-44	13(4.30%)	289(95.70%)	5.87(3.31-10.4)	<0.001	4.101(2.24-7.52)	<0.001
45-54	28(8.00%)	322(92.00%)	3.04(2.01-4.59)	<0.001	2.588(1.64-4.09)	<0.001
55+	229(20.90%)	867(79.10%)	1		1	
Comorbidity increasing the risk for TB						
No	165(7.70%)	1965(92.30%)	1		1	
Yes	149(23.30%)	490(76.70%)	0.28(0.22-0.35)	<0.001	0.63(0.47-0.84)	<0.001
One or more side effects reported						
No	217(9.30%)	2125(90.70%)	1		1	
Yes	97(22.70%)	330(77.30%)	0.35(0.27-0.45)	<0.001	0.37(0.27-0.50)	<0.001
Submission to clinical institution						
No	122(6.40%)	1786(93.60%)	1		1	
Yes	192(22.30%)	669(77.70%)	0.24(0.19-0.30)	<0.00	0.38(0.28-0.51)	<0.001
TB treatment support						
No	83(65.90%)	43(34.10%)	1		1	
Yes	231(8.70%)	2412(91.30%)	20.2(13.6-29.8)	<0.00	21.2(13.5-33.3)	<0.001
Direct Observed Therapy						
No	217(10.20%)	1911(89.80%)	1		1	
Yes	97(15.10%)	544(84.90%)	0.64(0.49-0.82)	<0.00	0.72(0.52-0.99)	0.43

In the subgroup of native Dutch, all variables but gender and DOT were significantly associated with treatment completion.. Being female and receiving DOT were negatively associated with treatment completion, though not significantly. Comorbidity, side effects and submission to a clinical institution were all significantly negatively associated with treatment completion.

Younger age and receiving treatment support were both significantly positively associated with treatment completion.

Discussion

The Netherlands is a country with low incidence of TB; most patients diagnosed with TB are those with a migration background; and the data that were analyzed in this report are consistent with this statement.

In order to adequately address the burden of TB in low incidence countries, among other interventions, the WHO advises that TB services should be focused on high-risk groups such as migrants, undocumented people, the homeless and other marginalized groups.

Key for improving TB services is monitoring and evaluation. Assessing TB services in terms of quality, is one way of addressing this topic. To assess quality of TB services in the Netherlands, a quantitative analysis of risk factors for TB, patient delay, health system delay and treatment completion was conducted in this study for patients diagnosed with TB (stratified by legal status).

After a thorough literature research aimed at finding variables that are associated with TB diagnosis, relevant variables from a large surveillance database were analyzed among all TB patients diagnosed with TB from 2007-2020 (stratified by legal status), yielding the baseline characteristics in tables A-C in which risk factors for TB are shown as well as diagnostical features and treatment related results.

The framework of the WHO was helpful in such a way that it helped to identify certain groups at risk and inspired the investigator to stratify patients according to legal status. Stratification to these strata allowed for comparing risk factors for TB and other TB related variables and the quality of TB services among different strata.

Discussion of the Main Results:

The assessment of risk factors and diagnostic characteristics will be discussed here, after which more focus will be on discussing the multivariate analysis of treatment completion.

Age, gender, comorbidity, HIV status, BCG status, country of origin and previous episode of TB all are risk factors for developing TB. These risk factors were unevenly distributed among the different strata.

Male gender was more frequently observed among undocumented migrants and native Dutch, making these groups more prone for TB. However, for the undocumented migrants, this observation may also be explained by the fact that females have more problems accessing the healthcare system because of shame, fear or a lack of health literacy as reported by Schoevers et al. (33). Hence, possibly the actual number of female TB patients-and especially undocumented females- might be higher than reported in this study.

The age distribution among the different strata resembles the distribution as described in literature, with relatively younger ages among migrant populations and older age among nationals (46). Odone et al. (17) described that this difference is mainly due to a different age structure of migrants and natives, but might also be linked to a different natural history of TB in these different populations.

Most comorbidity was observed among native Dutch, possibly explained by the age distribution in this stratum with significantly more older patients, hence predisposing them for comorbidity. Another explanation might be that this group also represents hard to reach populations like the homeless, incarcerated people and people addicted to drugs, who have a higher risk of comorbidity(36).

HIV was observed most frequently among documented and undocumented migrants, probably a reflection of a higher incidence of HIV in their country of origin. The finding that migrants have a disproportionate vulnerability to have a HIV-TB co-infection as compared to national (host country) populations has also been described in a systematic review (50). Although nearly one third of all migrants had had a BCG vaccination, this did not protect them from developing TB; this finding probably reflects the fact that BCG vaccination is mostly effective in protecting children from TB meningitis. There are indications that BCG vaccination has limited efficacy in some migrants' home countries, even when there is a good BCG coverage (51). This may cause an increased prevalence of TBI among migrants, even when vaccinated with BCG (23).

Most patients diagnosed with TB were migrants, either documented or undocumented. The top 10 countries listed in table A are all countries with a high incidence of TB However, this does not mean that these migrants had TB while migrating. Pareek et al. (14) found that the majority of migrants with (active) TB

developed TB following arrival in the UK rather than patients migrating with active TB , and in a meta-analysis it was reported that only 0.35% of immigrants had active TB upon arrival (52), implying that migration-related factors contribute to the development of active TB.

Undocumented migrants and native Dutch had a previous episode of TB more frequently than did documented migrants. Of those who had been previously diagnosed with TB, the highest percentage of treatment was in the group of migrants as compared to native Dutch, and completion of previous treatment was also higher among migrants than among native Dutch, although percentages of treatment completion were very low (see table A). Reasons for non-completion of previous treatment were not available.

Most patients with TB were examined because of health complaints; migrants more frequently than native Dutch. Migrants were less frequently examined as result of source and contact investigations; this may reflect migrant's fear of authorities, especially among undocumented migrants. Examination because of health complaints may also reflect that migrants may have had longer patient delay than the native Dutch population, possibly due to impaired health literacy, fear of authorities or stigma, as has been reported elsewhere (27, 40).

PTB was reported more frequently among undocumented migrants and native Dutch. This finding is consistent with the fact that among these patients higher frequencies of a positive sputum smear were reported, meaning that these patients had open (infectious) TB. These data may reflect that these groups were diagnosed with TB at a later stage of their disease, also reflected by a higher percentage of patient delay of >13 weeks among these patients.

Patient delay and health system delay:

Although patient delay and health system delay both were not logged for more than half of all patients in the NTR, some trends were noticeable and due to the nature of the data collection, exact time of patient delay could not be calculated. Among undocumented migrants, a short patient delay of 0-4 weeks was reported significantly less frequent than among the other strata, and patient delay of 13 weeks and more was reported significantly more frequent among undocumented migrants and native Dutch than among documented migrants. This means that for undocumented migrants there was a trend of longer patient delay compared to the other strata. This means that especially undocumented migrants with PTB may have been infectious to other people for a longer time due to increased patient delay. The finding that undocumented migrants have a longer patient delay - although possibly not a correct reflection of reality

due to many missing data - is in concordance with findings in literature about access to care in 11 European countries (27).

Patient delay is often linked to accessibility of health services and health seeking behaviour of patients. Accessibility of health services among migrants is a bottleneck in achieving universal health coverage and can be attributed to many underlying factors such as stigma, fear of authorities, health illiteracy and socio economic status (40). In optimizing TB services, it is important to assess and address these underlying factors. Although very important, this topic was not analyzed further in this study, as this requires a more qualitative approach and no qualitative data were available in the NTR.

Assessing health system delay showed some interesting results as well, and here exact time of health system delay could not be calculated either. Here many data were missing as well and reasons for longer or shorter health system delay were not logged.

A 'short' delay of 0-4 weeks was reported slightly but significantly more frequent among native Dutch than among documented migrants, and also more frequent but not significantly than among undocumented migrants. Longer health system delay was also reported significantly more frequent among native Dutch than among undocumented migrants and documented migrants.

A shorter/longer health system delay may mean a shorter/longer period of infectiousness. Among undocumented and documented migrants, longer health system delay percentages nearly approached 0, meaning that once 'in the system', after the first 4 weeks, hardly any delay of treatment was observed.

Although differences were relatively small, a trend of longer health system delay among native Dutch was noticeable. One of the explanations for this difference in health system delay is that among the native Dutch population, tuberculosis may not be the first diagnosis doctors think of, so time until diagnosis and hence start of treatment may be prolonged. Active screening programmes among migrant populations may also have contributed to faster diagnosis and start of treatment for migrants. Similar results have been observed in the UK, were UK born patients experienced longer delay until start of treatment than foreign born patients (53).

Treatment completion:

In the baseline analysis (table C), treatment completion was observed most frequently among documented migrants and significantly more frequent than among undocumented migrants and native Dutch. These findings are partly similar to those reported in a UK study among migrants and UK-born people, where it was

shown that TB treatment completion was actually marginally higher in migrants (85%) than the UK-born (81%) (54), however in this study undocumented migrants were not mentioned specifically. In another study among nationals and TB in the UK (55), it was observed that many national born TB patients were homeless, drug-users and prisoners and frequently lost to follow up, so these factors may have negatively influenced frequency of treatment completion among this group, as may have been the case in the present study. For nearly all patients who continued their treatment abroad, treatment results were unknown.

In multivariate logistic regression analysis however, legal status was not found to be significantly associated with treatment completion - and the hypothesis of impaired treatment completion among migrants could not be demonstrated. In fact, the odds for treatment completion were highest among undocumented migrants in the multivariate logistic regression analysis, even higher than among native Dutch patients, though not significantly.

In multivariate logistic regression analysis of all strata combined as shown in table D other variables were tested for association with treatment completion as well. Female gender, younger age and treatment support were found to be significantly positively associated with treatment completion. Male gender, older age (especially 45-54 and 55+), comorbidity, side effects, clinical submission and DOT were found to be significantly negatively associated with treatment completion.

These findings are partly in concordance with those reported in a systematic review of risk factors concerning non-adherence of treatment of TB patients (56), in which it was concluded that among other factors, undocumented immigration status and older age were consistently correlated with non-adherence to treatment and ethnicity, sex and level of education were non consistently correlated to non-adherence.

A striking difference is that undocumented immigration status in this review paper (56) was correlated with nonadherence to treatment, whereas in our study these results could not be reported in the multivariate regression analysis.

The review article(56) mentions that nonadherence among undocumented migrants may largely be explained by the fact that many undocumented migrants were ‘sent back home’ and were lost to follow up. This in contrast to the Dutch situation where due to ‘Article 64’ undocumented migrants have the right to stay in the country while on treatment, thereby allowing for better treatment adherence.

Older age as a factor negatively influencing treatment adherence might be explained by reduced mobility negatively affecting ability to visit health facilities (21). Comorbidity (such as mental illness or diabetes) and side effects have been described to negatively affect treatment completion in other reports as well (39, 57).

In the multivariate logistic regression analysis, side effects were significantly negatively associated with treatment completion, with the exception of the undocumented migrants group in which no significant association was found. Side effects have been described as negatively associated with treatment adherence and completion, although most side effects are usually reported when treating patients for multi drug resistant (MDR) TB (21). Unfortunately, data about resistance patterns of TB were not logged in the NTR.

Clinical submission has been reported to improve treatment adherence in other reports (39), especially among hard to reach populations, however in this study this effect could not be demonstrated. A possible explanation may be that clinical submission may not have lasted long enough to complete treatment, but further research is needed to address this yet unclear finding.

DOT has been described widely as an intervention that contributes to treatment adherence and completion (39), however this effect could not be demonstrated in this study. A possible explanation might be found in arguments as mentioned in a qualitative analysis of the effect of treatment interventions; DOT being perceived as imprisoning and forming a barrier to work responsibilities might negatively affect treatment adherence (39, 49).

Female gender was positively associated with treatment completion; this finding was also demonstrated in the review article(56). While some studies report 'higher motivation' among females to positively affect treatment adherence, much remains unclear on this topic, as reported in a systematic review of qualitative research related to patient adherence to tuberculosis treatment (21).

Treatment support was positively associated with treatment completion; this finding is in concordance with findings in other publications (39). Feeling cared for, understood and supported by nurses who address patient's needs are the main reasons for the positive effect on treatment completion (21, 39).

In the subgroup regression analysis similar trends were observed. However, in the group of undocumented migrants, no significant association between treatment interventions or risk factors and treatment completion could be observed, possibly because of the smaller sample size. Males tended to have a positive association with treatment completion as was observed among native Dutch, a trend that is in contrast with observations among documented migrants in which the female gender was positively associated with treatment completion. A possible explanation for the gender difference among undocumented migrants may be that female undocumented migrants in the Netherlands have a lower health care utilization as reported earlier by Schoevers et al. (33).

Among undocumented migrants comorbidity and clinical submission also had a slight but not significant positive association with treatment completion, as opposed to findings in the other strata. Further research is needed to better understand these findings.

The paradoxical negative association of treatment support to treatment completion among undocumented migrants can probably be attributed to the small sample size and the fact that all 4 patients who did not receive treatment support, still completed their treatment.

Discussion of the Broader Context

Currently, migrants from countries with high TB incidences are screened for active TB soon after arrival in the Netherlands, one of the important pillars of TB prevention. However, to complement these activities, that only consider the higher incidence of TB in the country of origin, more attention can be paid to policies addressing risk factors (such as socio-economic inequity, stigma, comorbidities or housing problems) which make migrants more susceptible for reactivation of TBI after arrival in the Netherlands in the first place.

Apart from assessing factors related to treatment completion, some legal and social factors influencing accessibility of TB services have not been the main focus of this study but will be discussed here.

In the Netherlands, many regulations exist that support patients with TB(I) not only financially, but also legally. This study has shown that only for a small percentage of migrants, financial regulations were applied for the undocumented group, of which 85.2% did not have health insurance at time of diagnosis, meaning that in the period that was studied (from 2014 until 2020 for these parameters), healthcare providers possibly were not aware of reimbursement regulations, which may have negatively affected treatment adherence.

Since 2014, universal health coverage policies and regulatory frameworks for TB notification have been recommended by the WHO end-TB strategy. In this recommendation, it is mentioned that TB diagnosis and treatment must be free of charge for all migrants, irrespective of their legal status (12). It must be mentioned that the Netherlands is the only country in which documented migrants have to pay (via their health insurance) for diagnostic/therapeutic measures regarding TB(I). This may impede access to TB services and thereby result in prolonged infectiousness among TB patients.

Article 64 as a legal regulation was applied for 74 patients out of the 76 undocumented migrants for whom the request was made, meaning that almost all undocumented migrants were allowed to complete their treatment in the Netherlands during the period that was observed (2014-2020).

In multivariate regression analysis, the odds for treatment completion among the native Dutch population were lower than among the other strata; this finding sheds an interesting light on this group. Where the vulnerability of migrants has been discussed extensively in this report, probably a considerable number of patients within the native Dutch population is also vulnerable and has risk factors for non-adherence to treatment.

For instance, the homeless are a population that is hard to reach, even in a high income country as the Netherlands, a risk factor that was not corrected for in the regression analysis. Factors like these may have contributed largely to non-adherence in this group, but were not investigated separately because no specific data about the composition of the stratum of native Dutch was available in the NTR.

Strengths and limitations of this study

One of the strengths of this study is that it reflects results from a large database, and although a selection of data from 2007 onwards was made, data from a large cohort of 12546 patients could be analyzed. This study has retrospectively assessed 4 domains related to TB in the Netherlands:

-an overview of risk factors for TB.

-assessment of patient delay as a proxy of healthcare seeking behaviour/accessibility of TB services.

-assessment of health system delay as an indicator of diagnostic and treatment delay and thereby quality of TB services.

-assessment of treatment completion and associated factors.

By doing so, a comprehensive overview of TB services in the Netherlands has been made available.

Weaknesses must be mentioned as well:

Only a univariate baseline analysis was conducted; conducting a multivariate baseline analysis would give a more detailed insight into the weight and interlinked-ness of the risk factors and diagnostic and treatment associated variables.

Assessment of variables such as patient delay was susceptible to bias; in this study patient delay was defined as time from onset of symptoms until first contact with the healthcare system. However in this phase there are actually 2 phases; the first phase is characterized by start of symptoms and realization of them, the second phase is about time from realization of symptoms until first contact with the health system through healthcare seeking behaviour. The assessment of patient delay -in toto- does not assess these 2 different aspects.

Results regarding treatment completion may have been confusing to the reader; treatment completion was significantly lower among the undocumented in the baseline analysis, however the odds for treatment completion in multivariate logistic regression analysis were the highest for this group. These findings are different because of the selection process and deleting of missing data, before regression analysis could be conducted.

Although data from many patients could be used, many data had not been logged consistently in the NTR and therefore it made them difficult to interpret. For example, data concerning patient delay, an important variable, were unknown for more than half of all patients. Important baseline characteristics like HIV status,

BCG status had many unknown data as well; therefore only 2-3 baseline characteristics were selected for multivariate logistic regression analysis and results from this analysis have only been corrected for a few confounding baseline characteristics (age, gender, comorbidity) and side effects.

Data about antibiotic resistance patterns had not been retracted from the NTR; these data are frequently used in analysis of surveillance data. Treatment of MDR is associated with increased occurrence of side effects; this may have confounded the results. However, multidrug resistance and extended drug resistance is a phenomenon that does not occur frequently in the Netherlands.

It would have been interesting to assess the evolution of risk factors and treatment associated variables in the course of time, however this analysis was not conducted in this study. This analysis would-for instance-have allowed for a more accurate interpretation of effectivity of treatment interventions.

Patient delay has been discussed earlier. It reflects healthcare seeking behaviour and has been topic of much qualitative research as patient delay forms the bottleneck in access to health services. However, in this study, accessibility to health services could only be assessed in a quantitative way, no means were calculated and many data were missing, so the conclusions drawn from this analysis have to take that into account.

Study results are always prone to a selection bias as they only reflect data from patients who have -in this setting-accessed the healthcare system. Probably more patients from a hard-to-reach population such as especially the undocumented migrants are ‘under the radar’ and may not get their needs met. This may have lead to a lower number of included patients, especially among the undocumented.

Conclusion and recommendations

TB affects people worldwide, especially the vulnerable such as migrants, the homeless, incarcerated people and other hard to reach groups. A combination of policies and action plans as stated in the END TB strategy of the WHO aims to break the chain of transmission of TB and reach elimination. Based on the action framework for low incidence countries, this study aimed to assess accessibility of TB services and quality of treatment among documented and undocumented migrants and compare these with the native Dutch population (three strata).

Risk factors for TB and other diagnosis and treatment related variables were observed to be unevenly distributed among the different strata and not only patients from migrant populations had risk factors; the native Dutch population was also vulnerable in terms of risk factors.

It is recommendable to conduct a more thorough (and multivariate) analysis of risk factors among the different strata in order to be able to distinguish (and address) the most important risk factors that make patients more susceptible to TB in the first place (Recommendation for research 1) .

While patients were stratified in 3 strata; each stratum could be divided into more strata. For example, the group of the native Dutch consists of homeless, incarcerated patients and other hard-to-reach populations. In order to be better able to identify groups at risk, it would be good to further analyse these substrata (Recommendation for research 2).

In this study, it was hypothesized that access to TB services and start of treatment are delayed among documented and undocumented migrants and that treatment adherence and completion of these migrants is impaired as compared to the 'national'/non-migrant population.

Although exact patient delay and health system delay were not calculated in this study, some trends were noticeable. Undocumented migrants tended to have longer patient delays than the patients in the other strata, probably reflecting difficulties in access to care. This finding supports the hypothesis of delayed access to care for this vulnerable group. Possible explanations have been suggested in this study, however due to the available data and quantitative nature of this study no exact causes of this delay can be mentioned here. Although much research has been conducted to assess and address accessibility problems, accessibility is still a problem for vulnerable groups.

Improving access to TB services remains a very important factor in breaking the chain of transmission of TB. Therefore, policies addressing accessibility of TB services should focus on both patient related barriers - such

as health literacy - and structural barriers such as stigma, and on creating action plans supporting access to care (Recommendation for policy 1).

The hypothesis of a higher health system delay among migrants could not be fully supported in this study; a trend of longer health system delay among the native Dutch population was observed. Possible explanations have been suggested, and again no exact causes can be mentioned here. Once having 'entered the healthcare system' hardly any delay in start of treatment was noticed among migrants. Therefore, policies and action plans should have more focus on shortening health system delay among the native Dutch population. Creating more awareness about TB among healthcare providers by better education can be a measure that will lead to earlier diagnosis and start of treatment (Recommendation for education 1).

Assessment of treatment completion was conducted in two separate ways: In the baseline analysis, treatment completion was reported significantly less often among undocumented migrants than among the patients of the other strata, and native Dutch also had lower percentages of treatment completion than documented migrants. This finding supports the hypothesis of impaired treatment uptake by undocumented migrants.

However, in the multivariate logistic regression analysis, risk factors for TB and treatment intervention variables showed a different pattern; no significant associations between legal status and treatment completion were found when corrected for confounders such as age, gender, comorbidity and side effects. The native Dutch population had the lowest odds of treatment completion and for the whole cohort the male gender, older age (especially 45-54 and 55+), comorbidity, side effects, clinical submission and DOT were all found to be negatively associated with treatment completion. These impaired treatment results among the native Dutch population were not in line with the hypothesis.

Treatment support was the only intervention that showed a positive association with treatment completion in all groups and probably reflects the effect of high quality patient centered care. Clinical submission and DOT were not consistently associated with improved treatment results. More research is needed to assess reasons why some of these interventions have not reached their goals (Recommendation for research 3). Furthermore, action plans should be patient centered and address the (perceived) barriers that impair the effectiveness of these interventions. (Recommendation for action 1).

Apart from the abovementioned interventions, it was observed that the Article 64 regulation was applied frequently. Financial regulations that reimburse both healthcare providers and patients with healthcare related costs were not observed to be applied frequently. More patient-and healthcare provider-centered

education should be provided the ministry of Health to increase the application of financial regulations and improve treatment adherence (Recommendation for education 2).

Further research should be conducted to measure the effectiveness of application of both legal and financial measures on treatment completion (Recommendation for research 4).

A last recommendation that relates to the global burden of TB is that - in accordance with the WHO guidelines - national policies should continue to support organisations such as the KNCV in their efforts to contribute to TB programme implementation worldwide and to conduct international research concerning TB. This will not only positively influence TB incidence and prevalence abroad, but - in a world where migration is increasing each year - also indirectly in the Netherlands (Recommendation for policy 3).

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