Tuberculosis in Suriname

Trends in epidemiology, diagnostics and treatment

Fitzgerald Anoep Gopie

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WHATEVER HAPPENED WAS GOOD

WHATEVER IS HAPPENING IS GOOD

WHATEVER WILL HAPPEN WILL ALSO BE GOOD

WHAT HAVE YOU PARTED WITH THAT MAKES YOU CRY?

WHAT DID YOU BRING WITH YOU THAT YOU HAVE LOST?

WHAT DID YOU CREATE WHICH IS NOW DESTROYED?

WHAT YOU HAVE TAKEN, YOU HAVE TAKEN ONLY FROM HERE.

WHAT WAS GIVEN, WAS GIVEN ONLY FROM HERE.

WHAT IS YOURS TODAY, WAS SOMEONE ELSE'S YESTERDAY AND

WILL BE SOMEONE ELSE'S TOMORROW. (Bhagvad Gita)

Front cover	Jacaranda trees, Buenos Aires
Source	Gopie F.A
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List of abbreviations

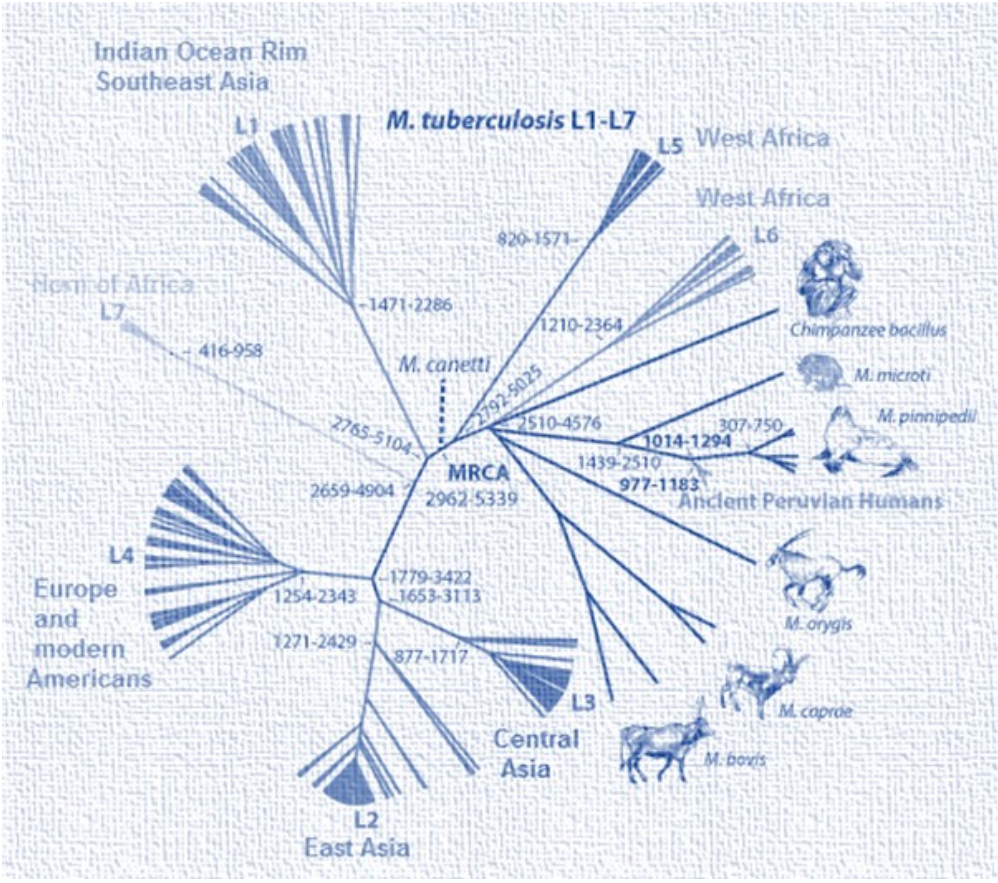
Table 1. Abbreviations (A-N).

AFB	Acid-fast bacilli
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine transaminase
aOR	Adjusted odds ratio
ART	Antiretroviral therapy
Asp/D	Asparagine
AST	Aminotransferase
ATS	American Thoracic Society
BAD	Bureau Alcohol and Drugs
BCE	Before Common Era
BCG	Bacillus Calmette-Guerin
BOG	Bureau voor Openbare Gezondheidszorg
CAREC	Caribbean Epidemiology Center, Trinidad
CE	Common Era
CI	Confidence interval
DM	Diabetes mellitus
DOT	Direct observed therapy
DOTS	Directly observed therapy, short course
DST	Drug-susceptibility testing
EPTB	Extrapulmonary tuberculosis
HIV	Human immunodeficiency virus
hsp65	Partial heat shock protein 65
IGRA	Interferon gamma release assay
IPT	Isoniazid preventative treatment
IU/L	International units per liter
LMIC	Low to middle-income country
LTBI	Latent Tuberculosis Infection
LTFU	Lost to follow-up
MAC	*Mycobacterium avium* complex
MDR	Multidrug-resistant
MGIT	Mycobacteria growth indicator tube
MIC	Minimal inhibitory concentration
MTC	*Mycobacterium tuberculosis* complex
ND	Not determined
NST	Nationale Stichting Tuberculose bestrijding Suriname
NTM	Non-tuberculous mycobacteria
NTM-PD	Non-tuberculous mycobacterial pulmonary disease
NTP	National Tuberculosis Program

Table 2. Abbreviations (O-Z).

OR	Odds ratio
PAS	Para-aminosalicylic acid
PCR	Polymerase chain reaction
PLHIV	People living with HIV
PPD	Purified protein derivative
PTB	Pulmonary tuberculosis
R	Resistant
RBT	Rifabutin
RGM	Rapid-growing mycobacteria
RIVM	Rijksinstituut voor Volksgezondheid en Milieu
RR	Rifampicin-resistant
RR/MDR-TB	Rifampicin-resistant, multidrug-resistant tuberculosis
RR-TB	Rifampicin resistant tuberculosis
S	Susceptible
SD	Standard deviation
SE	Standard error
SES	Socioeconomic status
SGM	Slow-growing mycobacteria
SNP	Single nucleotide polymorphism
TB	Tuberculosis
TST	Tuberculin skin test
Tyr/Y	Tyrosine
WGS	Whole genome sequencing
WHO	World Health Organization
XL	Extra-large
XS	Extra-small
ZN	Ziehl-Neelsen

1
Introduction



M. Tuberculosis strains in humans and animals.
Source: Adapted from Bos K.I. et al., 2014. DOI: 10.1038/nature13591

Worldwide, tuberculosis (TB), an ancient airborne infectious disease present in humans, was the cause of 1.5 million deaths in 2018 [1]. Moreover, from 2015 to 2030, some 28 million people could die from TB if no action is taken. TB also places an enormous economic burden on humankind, at a cost of 616 billion US dollars globally between 2000 and 2015 and a projected expenditure of nearly one trillion US dollars from 2015 to 2030 [2]. One fourth of the global population is considered to have latent TB infection (LTBI) and in 2018 some 10 million cases of TB were reported to the World Health Organization (WHO). Most cases were in South-East Asia (India, Pakistan, and Bangladesh), Africa (Nigeria and South Africa), and the Western Pacific (China, Indonesia, and the Philippines), whereas the Eastern Mediterranean, the Americas, and Europe contributed fewer TB cases [3] (see also, Figure 1). To end the TB pandemic, the WHO has launched the END TB Strategy, meant to end the global tuberculosis epidemic by 2035 by means of implementing and endorsing national TB control efforts.

Figure 1. WHO Estimated TB incidence in 2018.
Source: Adapted from WHO, Global Tuberculosis Report 2019.

A synopsis of Mycobacteria

Mycobacteria are a group of bacteria that differ in their capability to cause disease in humans and animals. They have different reservoirs and *in vitro* growth features. Because of these characteristics, mycobacteria can be divided into four major groups: *Mycobacterium leprae*, *Mycobacterium ulcerans*, non-tuberculous or atypical mycobacteria, and *Mycobacterium tuberculosis* complex (MTC) (see also, Figure 2). These organisms are aerobic, rod-shaped, gram-positive bacteria that are 0.3 to 0.5 µm in diameter and with a variable length.

They are acid fast—and thus resistant to decolorization by acids during the Ziehl-Neelsen or Auramine staining procedures—and their cell walls contain mycolic acid which renders them resistant to cell lysis. Other bacteria with comparable traits are *Nocardia*, *Rhodococcus* and *Corynebacterium* [4], which can be mistaken for mycobacteria in the Ziehl-Neelsen stain test.

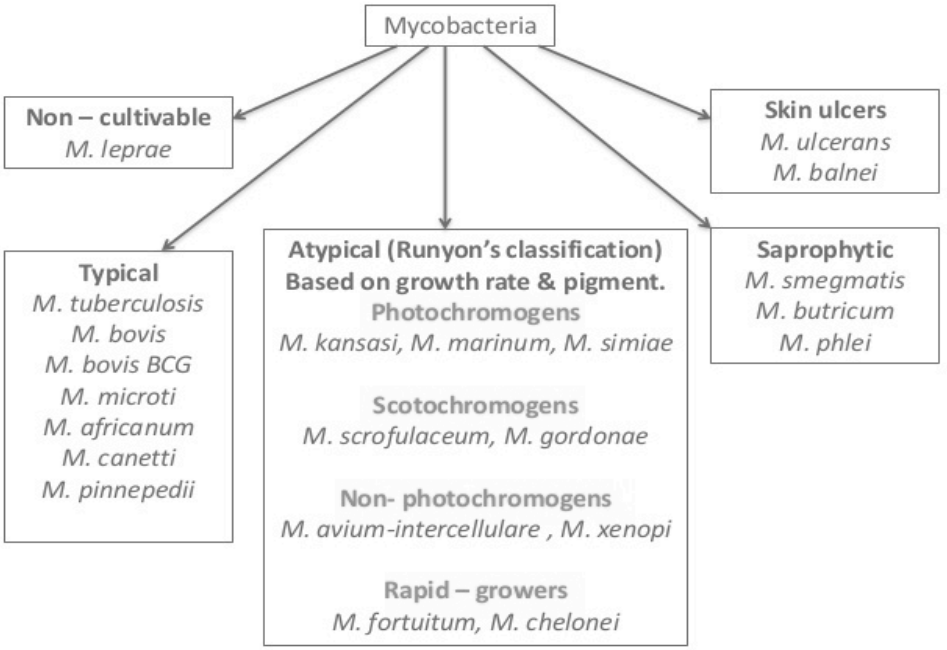


Figure 2. Classification of mycobacteria.
Source: EXAMS AND ME: Photochromogens.

Mycobacterium leprae is the cause of leprosy and affects many tissues, such as mucosa, bones, lymph nodes, and the respiratory tract, but mainly affects the peripheral nerves of the skin, nose, eye, and muscle.

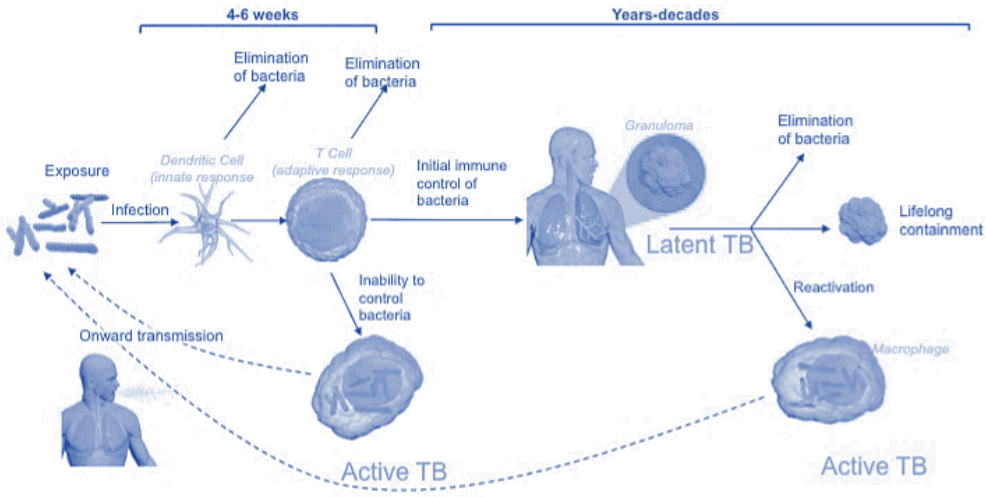
Mycobacterium ulcerans is an aquatic environmental pathogen that causes destruction of soft tissue, resulting in ulcers.

Non-tuberculous mycobacteria (NTM), also known as mycobacteria other than tuberculosis (MOTT) or atypical mycobacteria (with over 150 species identified), can be found ubiquitously in soil, groundwater, and drinking water. Depending on their growth rate, NTM are classified as rapid-growing mycobacteria (RGM; replication in fewer than 7 days) and slow-growing mycobacteria (SGM). Although NTM are less pathogenic, they are increasingly recognized as a cause of illness in humans, especially in immunocompromised patients or those who suffered from previous pulmonary diseases.

Globally, *M. avium* complex (MAC), which comprises the species *M. avium* and *M. intracellulare*, is the most common cause of non-tuberculous mycobacterial pulmonary disease (NTM-PD) [5]. *M. kansasii*, *M. malmoense*, and *M. xenopi* also cause pulmonary infections.

NTM infections are difficult to diagnose. Diagnosis depends on clinical, radiological, and microbiological results. Treatment is lengthy—consisting of multiple antibiotics, which are frequently poorly tolerated by patients infected with NTM—and is advocated when the same pathogen is detected in 2 separate sputum samples from the patient. The treatment regimen depends on the isolated NTM species, drug susceptibility, and severity of disease [6].

***Mycobacterium tuberculosis* complex (MTC)** comprises the following species: *M. tuberculosis*, *M. bovis* (subspecies *bovis* and *caprae*), *M. africanum*, *M. canettii*, *M. microti*, and *M. pinnipedii* [7]. *M. tuberculosis*, discovered in 1882 by Robert Koch, is the main cause of TB in humans. Transmission of pathogens occurs through the inhalation of infectious droplets, which arise from the coughs or sneezes from patients with open pulmonary TB [8]. Risk of infection increases with overcrowding and through poor cough hygiene. *M. bovis* can be contracted from close contact with infected cattle or consumption of unpasteurized dairy products. Mycobacteria infect the macrophages, and in most cases the immune system of the host encapsulates the bacilli without causing symptoms or disease. This dormant state of infection is designated as LTBI (latent tuberculosis infection) and can persist for years but may progress to active disease when the host immune system is compromised [8] (see also, Figure 3). Although every organ can be affected, most patients present with pulmonary tuberculosis (PTB), while 15 to 25% of patients present with extrapulmonary tuberculosis (EPTB) [9]



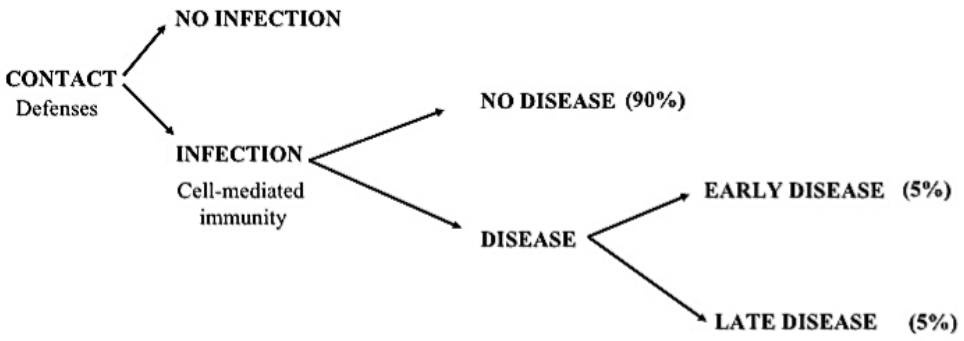


Figure 3. Natural history of tuberculosis.
Source (above): Adapted from Infection Landscapes: Tuberculosis.
Source (below): TB transmission.

A brief history of tuberculosis disease

The genus *Mycobacterium* is thought to have originated more than 150 million years ago, as is assumed by the distribution of *M. ulcerans*, which requires a specific habitat. This global distribution pattern could only have been possible by virtue of the Gondwanaland continental landmass during the Jurassic period [10].

Some 3 million years back, an early progenitor of *M. tuberculosis* infected early hominids in East Africa, the ancestral home of the tubercle bacilli and humans [11]. Some 1.7 million years ago, early people began to move out of Africa to other parts of the world, obviously taking along their diseases (Figure 4).

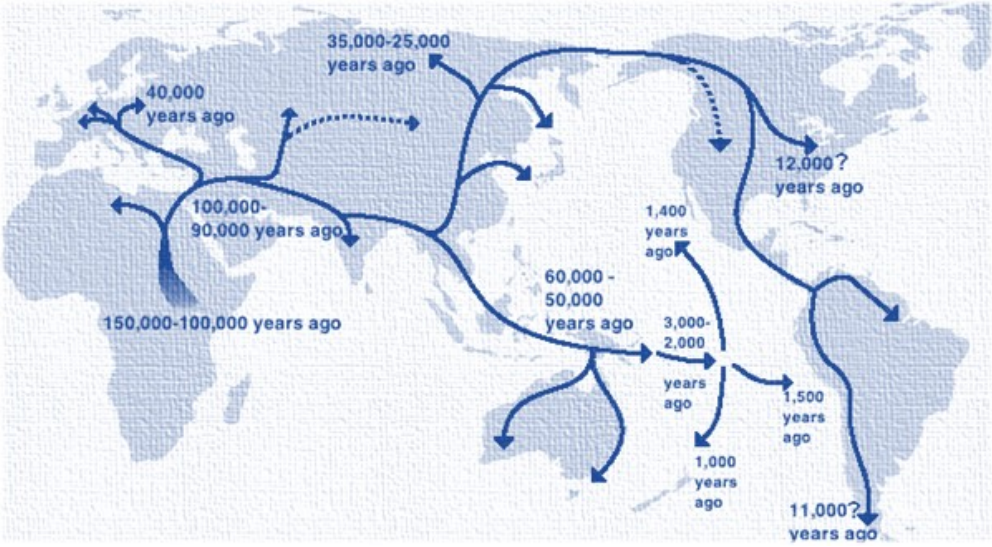


Figure 4. Migration of people from Africa.
Source: Adapted from wikimedia.org.

About 20,000 to 15,000 years ago, the modern strain of *M. tuberculosis* evolved from a common African ancestor [12]. The most ancient evidence of tuberculosis is dated 500,000 years old and was found in western Turkey as leptomeningeal tuberculosis in a Homo erectus frontal bone, while the oldest evidence of tuberculosis in humans is dated 9000 years old and was found in the eastern Mediterranean [13]. Although archeological evidence of tuberculous disease is lacking in East Africa and there are no written reports on Egyptian medical papyri, illustrations of Egyptian mummies from 5000 years ago showed skeletal deformities resembling Pott's disease and, in 2010, the presence of *M. tuberculosis* DNA in Egyptian mummies was demonstrated by Donoghue et al. [14].

The first written reports of TB date back 3300 years ago from India, found in the Rig Veda written in 1500 BCE, where the disease is named "yaksma."

In the Atharvaveda, the first description of scrofula is given and in the Yajurveda patients with TB are advised to move to higher altitudes, away from the village, probably implicating the infectious nature of TB. In the Sushruta Samahita of 600 BC, the recommended treatment of TB was cow milk, meat, and rest [13]. Descriptions of the disease are also found in different old civilizations: the Babylonians reported a chronic lung disease, the Chinese medical work Huang Ti Nei-Ching described a "wasting disease," and in classical Greece it was described as "a grievous consumption which took the soul from the body and caused a person to lie in sickness, a long time wasting away" [13].

Hippocrates, who lived from 460 to 370 BCE in ancient Greece, described "phtisis" (wasting) as a fatal disease, especially in young adults, and Isocrates considered phtisis to be an infectious disease. In 174 CE, Galen described symptoms of TB to be: fever, sweating, cough, and blood-stained sputum. In the Middle Ages, scrofula was designated as cervical lymph node TB, which could be treated by "touch of the monarch," and, in 1735, tuberculosis was designated a notifiable disease in Lucca, Italy.

In 1793, Matthew Baille introduced the term "tubercles" for caseous necrotic phtisis abscesses, and, in 1834, Johan Lucan Schonlein coined the name "tuberculosis" (TB), giving the disease its present name. In the 18th and 19th century, TB was epidemic in Europe and related to poverty, malnutrition, and overcrowding [13], [15], [16].

On March 24, 1882, the German physicist Robert Koch presented his postulates demonstrating the infectious etiology of TB. These postulates dictate that the bacteria must be present in every case of the disease and that the isolated bacteria of the sick host must be grown in pure culture, and when a healthy susceptible host is inoculated with the pure culture, the specific disease must be reproduced. In 1890, Koch made public that he had isolated a substance from the tubercle bacilli, which he named tuberculin. This substance could render pathogenic bacteria found in the body harmless, without disadvantage to the body. When Koch injected himself with tuberculin and developed high fever, this made him conclude that tuberculin could be used as a diagnostic tool for tuberculosis infection, leading Danish veterinarians to use tuberculin on cattle.

Between 1907 and 1908, Clemens Freiherr von Pirquet and Charles Mantoux perfected the tuberculin test. This test is performed by injecting a small amount of tuberculin (purified protein derived from *Mycobacterium tuberculosis*) into the forearm and measuring the ensuing wheal 48 to 72 hours after the injection [17]. In 1909, von Pirquet set a cut-off point of 5 mm for the tuberculin reaction in children who did not manifest TB and noted that a positive reaction suggested the presence of LTBI.

Calmette and Guerin developed a vaccine against TB with attenuated *M. bovis*, which, in 1921, was administered to an infant whose mother died of TB, shortly after giving birth. The infant did not contract TB and survived. BCG (Bacillus Calmette-Guerin) vaccine was established. In 1934, Seibert developed a stable and consistent tuberculin, which was named purified protein derivative (PPD), which is still in use today [18].

In 1952, Palmer and Bates presented a study in which TB patients injected with PPD showed a mean and mode reaction of 15 mm. In 1955 the WHO confirmed the results of Palmer and Bates in a study conducted among school children of various populations. This study also showed that in countries with a high TB prevalence (e.g., Ethiopia and the Philippines), healthy school children had similar reactions as TB patients and were hence designated as having LTBI. But in some populations, the children had smaller reactions, giving way to the thought of cross reactivity with environmental mycobacteria, which was later confirmed by Edwards and Palmer in their study with guinea pigs [19].

After World War II, TB steeped into Europe and Asia, and in 1948 UNICEF started a TB control program for children with tuberculin testing and BCG vaccination, which was adopted by many countries. With the discovery of anti-TB drugs from 1943 onwards, the disease could be treated well. Since the 1980's, with the emergence of HIV/AIDS, which impairs the human immune system, tuberculosis has made a major comeback. According to the WHO (2015), people living with HIV are 16 to 27 times as likely of developing TB as people without an HIV infection.

In 1995, the WHO launched the directly observed therapy, short course (DOTS) program to ensure tuberculostatics intake by patients, and, in 2014, the End TB Strategy was formulated with following targets: to reduce TB deaths by 95%, to cut new cases of TB by 90% between 2015 and 2035, and to ensure that no family is burdened with catastrophic expenses due to TB.

In 1995, the WHO declared the 24th of March to be the "World Tuberculosis Day."

A summary of the diagnosis and treatment of tuberculosis

In Western literature, the infectious nature of TB was probably first suggested in 1790 by Marten. In 1865, Villemin demonstrated TB's infectious character. He had inoculated a rabbit with purulent fluid originating from a cavitary lesion of a patient who had died of TB. The rabbit seemed well, but an autopsy, three months after inoculation, showed that the animal had extensive TB. In 1882, Koch isolated TB bacilli. During World War I, military recruits were screened for TB using chest X-rays, followed, thereafter, by the general population of Europe for three decades.

From 1948 onwards, the tuberculin skin test (TST), also known as the Mantoux test, was used to screen for TB. From 1974 onwards, the WHO promoted sputum microscopy in symptomatic individuals and those at risk for TB [15].

The laboratory methods used to diagnose TB include microscopy using Ziehl-Neelsen (Figure 5) or Auramine staining techniques, nucleic acid amplification test like the GenXpert and Hain test, and bacterial cultures in different media. Drug susceptibility testing is either done classically, in culture media, or with molecular test methods such as whole genome sequencing (WGS) [8], [20].

Fresh air, milk, and sea voyages as successful treatment for TB were mentioned in 174 CE by Galen. In the Middle Ages, treatment of scrofula (cervical lymphnode TB), also known as the "King's Evil," was performed through the "royal touch," and, from 1735 onwards, patients with TB were treated with isolation in specific treatment places such as Lucca in Italy. In 1859, Hermann Brehmer opened what was probably the first sanatorium (Figure 6), located in Görbersdorf Germany with a regimen of rest, a rich diet, and tailored exercise.

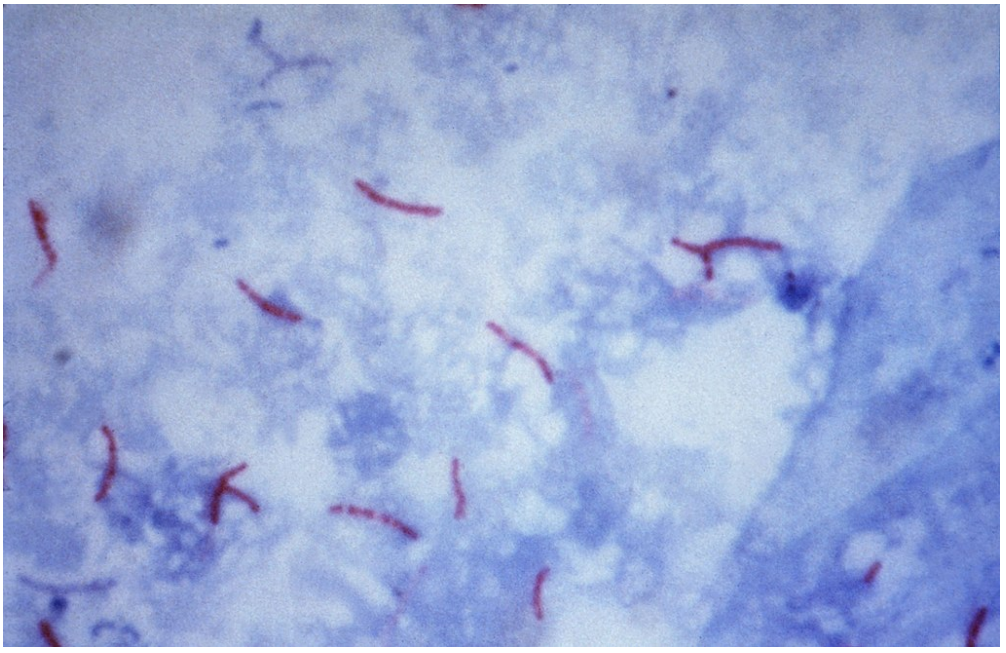


Figure 5. *Mycobacterium tuberculosis* in Ziehl-Neelsen stain.
Source: CDC-PHIL, ID#: 5789.

In 1696, Giorgio Baglivi described improvement in a TB patient who developed a pneumothorax after a sword wound. In the late 19th and early 20th century, cavitary pulmonary TB was treated through surgical pulmonary collapse procedures, an artificial pneumothorax, which resulted in pulmonary cavity closure and conversion to negative sputum [13], [15]. Surgical resection of pulmonary lobes is still performed in persistent TB and drug resistant TB.

Chemotherapy for the treatment of tuberculosis started after discovery of para-aminosalicylic acid (PAS) in 1943, followed by streptomycin in 1944, thiosemicarbazone in 1945, isoniazid in 1952, pyrazinamide in 1954, rifamycin in 1957, ethambutol in 1960, and rifampicin in 1972.

For over 30 years, the standard treatment for tuberculosis has been a 6-month regimen, which comprises two months of isoniazid/rifampicin/ethambutol and pyrazinamide followed by four months of isoniazid and rifampicin. Due to drug resistance, treatment schemes have been prolonged or updated with second-line drugs such as: ethionamide, fluoroquinolones, aminoglycosides, and the recently approved delamanid (2006), bedaquiline (2005), and linezolid (1998) [21], [22].

Figure 6. Heilenstalt sanatorium in Görbersdorf, opened by Hermann Brehmer.
Source: Adapted from Agarwal et al., 2017 [13].

A resume of tuberculosis in the Americas and Suriname

Humans, probably from Central Asia, reached the Americas by crossing the Bering Strait land bridge from Siberia to Alaska in two waves of migration. The first migration occurred 25,000 to 20,000 years ago, while the second migration occurred 12,000 to 11,000 years ago. Between 20,000 and 12,000 years ago, the land bridge was covered with glacial ice and 10,000 years ago, the Bering Strait became submerged.

The early immigrants had no permanent residence and were nomadic hunters-gatherers. The earliest settlements date back 12,500 years ago, being Mont Verde in Central Chili and the Clovis in New Mexico USA, some 11,500 years ago.

The earliest evidence of a TB epidemic in the Americas comes from Peruvian mummies, dating back to 900 CE, long before "the European discovery" of the Americas and the Caribbean [19], [23]. Those early TB strains are different from the modern TB strains found in the Americas, which are closely related to the European strains. Kirsten Bos et al. addressed this discrepancy in 2014, revealing that seals and sea lions were the cause of TB transmission to the human population of South America in the pre-Columbian era. This transmission of tuberculosis from pinnipeds to humans probably occurred between 700 CE and 1000 CE [24]. As tuberculosis epidemics lasted for 300 to 400 years before herd immunity developed, it is clear that the indigenous population of the Americas was very susceptible to tuberculosis when this microorganism was reintroduced to the New World by European colonists [19].

Suriname is a low to middle-income country (LMIC) located in northeastern South America, bordering the Atlantic Ocean. For centuries, Suriname has been a Dutch colony and achieved independence in 1975. Because of its colonial past, Suriname has a unique multi-ethnic population with Indigenous people being the native population. Due to colonization, slavery, and immigration, the population also comprises Europeans, Maroons, Creoles, Chinese, Hindustanis, Javanese, mixed people, and some minor nationality groups.

Inevitably, TB occurs in Suriname. In 1828, many plantation slaves had TB, and, in 1883, TB was endemic among young goldminers. From 1913 to 1918, the first TB consultation bureau was active in Paramaribo, under government supervision. In this period 400 people were examined, of which 24 were diagnosed with TB. Back in 1920, one hundred patients died of TB in Paramaribo, which formed 8.5% of the total mortality of Paramaribo. From 1924 onwards, admittance of TB patients was possible in the former military hospital (nowadays known as the "barakken" of 's Lands Hospitaal) (Figure 7).

In 1927, the “Dienst ter bestrijding van Volks- en Besmettelijke Ziekten,” the predecessor of the current “Bureau voor Openbare Gezondheidszorg” (BOG), was established. In 1931, TB mortality was 6.5% for Paramaribo as opposed to 4.8% for the other districts, indicating that Paramaribo had most of the TB cases.

Figure 7. Tuberculosis wing of the former military hospital in Paramaribo.
Source: Adapted from Stichting Surinaams Museum.

Between the 1940’s and 50’s, the mortality of TB declined due to the prescription of tuberculostatics, a combination of streptomycin and para-amino salicylic acid, to which isoniazid was added in the 1950’s. In the 1970’s, treatment consisted of rifampicin, isoniazid and ethambutol for 9 months. The current standard treatment is a 6-month regimen with isoniazid, rifampicin, ethambutol, and pyrazinamide. On the public health front, BCG vaccinations were performed in Suriname from 1949 to 1975 (F.M.G. Brandts), and a mass BCG vaccination campaign was executed from November 1955 to September 1956, when some 95,042 patients underwent a TST, of whom 55,521 had a negative TST result and were subsequently BCG vaccinated.

Analyses performed by Bleiker and van Erpecum between 1962 and 1965 revealed nonspecific tuberculin sensitivity to be very high.

From 1965 to 1974, some 145,000 persons, mainly school children, underwent mass tuberculin testing followed by chest X-ray exams in positive tested persons. Only 18 cases of tuberculosis were detected, five being smear positive. Because of this low yield (and subsequently unfavorable cost-benefit ratio), the tuberculin testing program was abandoned in 1974 (van Geuns/van Erpecum).

In 1979, van Weissenbruch also reported nonspecific tuberculin sensitivity to occur frequently among school children and young adults at the pediatric clinic of the Academic Hospital of Paramaribo. Population screening for TB, with (mobile) chest X-ray examinations, was started in 1958. The last mass screening was conducted between1966 and 1971, when this program was terminated due to the low yield of patients diagnosed with TB. Instead, TB contact tracing was recommended and has been performed since.

After the proclamation of a separate Ministry of Health in 1949, a “consultatie bureau voor longziekten” was installed that same year, and the first pulmonologist in Suriname, F. Phenning, started his residency. In January 1953, the “Long Paviljoen,” located at the Picorniestraat (figure 8), was put into service, and, in 1954, the “Consultatie Buro voor Longziekten” (CBL) moved to its current location at the Rode Kruislaan [25]. The Central Laboratory of the Buro of Public Health (BOG) was established in 1961, and, in 1962, the notification of TB disease was enforced by law, based on legislation of 1953. In 1963, a private partnership, the “Nationale Stichting Tuberculose bestrijding Suriname” (NST) was launched to assist the government with TB issues. To raise funds, special post stamps were issued and the “maandag cent actie” was reactivated on behalf of the NST.

Since the 1990s, Suriname has been hit by “Double Trouble” (HIV/TB coinfection). To address this situation, collaborative programs were implemented: anti-retroviral therapy was introduced in 2004, and the National Tuberculosis Program (NTP) was formed. All patients diagnosed with TB should be reported to the NTP, where patients are registered, TB medication is provided free of charge through a DOTS (directly observed therapy, short course) program, and TB contact tracing is performed. Also, for all patients who tested positive for TB, mandatory HIV testing was implemented. In 2011, the first Surinamese TB guidelines were released, based on the Caribbean guidelines and WHO recommendations. In 2012, the GenXpert test was introduced, which led to higher accuracy TB diagnosis and the detection of rifampicin resistant TB. Recently this resistance proofed to be low level mono resistance to rifampicin, which could be treated with high dose of rifampicin, a regimen which has been applied for some time now [26], [27], [28], [29].

The purpose and outline of this thesis

The End TB Strategy program launched in 2015 by the WHO strives to decrease TB transmissions by 90% and decrease TB deaths by 95% by the year 2035. Although a national TB program has been in place in Suriname since 2011, there has been no decrease in TB incidence, which has varied around 30 (from 25 to 38) per 100,000 population between 2015 and 2019 [30]. To better understand the TB situation in Suriname, we conducted several studies. Data from the NTP and the sole pulmonary medicine clinic of Suriname, located at the Academic Hospital of Paramaribo, was analyzed. In this thesis we describe a) the TB epidemiology of multi-ethnic Suriname and ethnicity-related risk factors of TB; b) the abundant prevalence of NTM in Suriname; c) the TB diagnostic procedures and their improvement and impact on TB classification; and d) the determination of drug-resistant TB and its treatment outcome.

Insights gained with our studies could give way to changes in our TB program with the goal to eliminate TB in Suriname.

Chapter two describes the level of TB incidence among the various ethnic groups of Suriname, and what the probable driving factors of TB in these groups are.

Chapter three describes the presence of NTM in sputum of patients treated for TB, prior to the introduction in 2012 of the GenXpert test in Suriname, which could have resulted in overdiagnosis of TB.

In chapter four the results, classification, and follow-up of the tuberculin skin test (TST) policy in Suriname are evaluated. The TST is used in the detection of LTBI, which serves as a pool for TB reactivation.

In chapter five, rifampicin resistant tuberculosis (RR-TB) in Suriname is addressed. Patients from Suriname with RR-TB, detected by the GenXpert test, and who had been treated with first-line tuberculostatics (isoniazid, rifampicin, ethambutol and pyrazinamide) also had good treatment outcome, comparable to that of patients treated for rifampicin sensitive tuberculosis.

Figure 8. Longpaviljoen/Sanatorium Academisch Ziekenhuis Paramaribo, 2021.
Source: Gopie F.A.

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2

Ethnic disparities in tuberculosis incidence and related factors among indigenous and other communities in ethnically diverse Suriname

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Abstract

Background

In Suriname, a country home to many ethnic groups, a high incidence of tuberculosis (TB) has been found among Indigenous Trio Amerindians. However, whether wider ethnic disparities in TB incidence and its associated risk factors (e.g., diabetes mellitus and HIV) exist in Suriname, is not known. We sought to investigate disparities in TB incidence and its risk factors on ethnicity in Suriname, as this could give way to targeted TB intervention programs.

Methods

Anonymized patient data from 2011 to 2015 was extracted from the National TB Registry and analyzed. Differences in the five-year incidence rates of TB for the six largest ethnic groups—Creole, Hindustani, Indigenous, Javanese, Maroon, and Mixed—were assessed using a chi-square goodness-of-fit test, and TB patient differences regarding ethnicity were evaluated for selected factors using a multinomial logistic regression with Creole patients as reference.

Results

662 Patients were eligible for analyses with the following ethnic makeup: Creole (36.4%), Hindustani (15.6%), Indigenous (8.6%), Javanese (10.6%), Maroon (15.1%), and Mixed ethnicity (13.7%). Differences in five-year incidence rates for TB were significant, $\chi 2(5, N = 662) = 244.42$, $p < .001$, and the highest TB rates were found for Indigenous (280 per 100,000) and Creole people (271 per 100,000). HIV coinfection was a TB risk factor for Creoles (38.2% of these patients were HIV positive). Several variables (i.e., those for drug use) had high levels of incomplete or missing data.

Conclusions

Our study has demonstrated that ethnic disparities in tuberculosis incidence exist in Suriname and that they are associated with specific, known risk factors such as HIV (especially for Creole people). For Indigenous people, risk factors may include diminished access to health care facilities and low socioeconomic status. However, direct data on these factors was unavailable. These findings call for targeted national intervention programs—with special attention given to the vulnerabilities of susceptible ethnic groups—and improved data collection.

1. Introduction

Tuberculosis (TB) is the leading cause of death from a single infectious agent. In 2018, some 10 million people fell ill with active TB and an estimated 1.5 million TB-related deaths occurred. The burden of TB, however, is an unequal one. TB is associated with poverty, overcrowding, and malnutrition [1]. This disease may also vary by ethnicity. For example, globally, Indigenous peoples are generally burdened with TB at a disproportionate rate [2]. This inequality has implications for Suriname, a highly diverse country.

Suriname is a lower middle-income country bordering northern Brazil that had a population of 541,638 in 2012 [3] and a TB incidence rate of about 38 cases per 100,000 in 2018 [4]. All cases of TB in Suriname should be reported to the National Tuberculosis Program (NTP), a government workforce that is responsible for registering TB patients and their treatment outcome nationwide, the availability of the tuberculin skin test, the free provision of TB medication through the Directly Observed Therapy program, and TB contact tracing. Screening prisoners for TB is also part of the NTP's activities. In 2011, the NTP released the first Surinamese TB guidelines, which were recently updated according to WHO recommendations. Persons suspected of having TB are evaluated, classified, and treated with first-line tuberculostatic drugs according to WHO guidelines [5].

Suriname's multicultural society harbors numerous ethnic groups, in part due to its colonial past [6]; the six largest groups are: a) Creoles (including Afro-Surinamers; 16.4%), descendants of African slaves that may also have European and other ancestors; b) Hindustanis (27.4%), descendants of contract laborers from what was then British India; c) Indigenous Amerindians (3.7%), a group comprising multiple tribes (e.g., the Trio, Wayana, and Akurio); d) Javanese (13.7%), descendants of contract laborers predominantly from Java, Indonesia (then the Dutch East Indies); e) Maroons (21.7%), descendants of escaped African slaves that mostly settled Suriname's interior; and f) individuals of Mixed ethnicity (13.4%). Many Indigenous and Maroon people continue to live in tribal communities spanning Suriname's remote, densely forested interior and continue to maintain their cultural beliefs and traditions. Almost 90% of Suriname's inhabitants live in the more accessible coastal area. The remaining population lives in the interior, which is mainly accessible by air and river transportation. Suriname's capital, Paramaribo, is also located near the coast and is home to 45% of the population [3], [7].

Regarding TB, the Indigenous population in Suriname deserves special consideration. In neighboring Brazil, higher rates of TB among Indigenous peoples were associated with poverty, limited living space, and limited healthcare access [8]. Globally, Indigenous Amazonian groups are among the worst affected populations [2].

Suriname is home to Indigenous communities that share similarities with their Brazilian counterparts and therefore compose a potentially vulnerable group regarding TB. An investigation by van Crevel *et al.* assessing TB cases between 1995 and 2000 among Trio Indians living in Kwamalasamutu—a village remotely situated in Suriname's tropical rainforest interior near the southern border with Brazil—revealed a higher incidence and familial clustering of TB. These observations were attributed to lifestyle, a possible genetic predisposition for TB, and limited access to healthcare among the Trio Indians [9], who live in relative isolation [10]. Tollefson *et al.* estimated that the prevalence of TB among this community was seven times higher than Suriname's national comparison rate [2].

In the past two decades TB rates have been on the rise in Suriname [11]. This increase has probably been fueled by HIV, with most HIV positive patients being of Creole and Maroon descent [12]. This led to collaborative programs to address the dual health threat. People living with HIV (PLHIV) and presenting with prolonged cough and or weight loss are referred to the NTP for free of charge tuberculin skin testing and sputum examination. Considering this observation, the high incidence of TB in Suriname's Indigenous communities, and the significantly higher prevalence of diabetes mellitus (DM; a TB risk factor) among Hindustanis [13], we investigated differences between ethnic groups on TB incidence and risk factors in Suriname, as this could contribute to a better understanding of the state of TB in Suriname and give way to targeted TB intervention programs.

2. Methods

We conducted a retrospective cohort study of National TB Registry records from January 1st, 2011 to December 31st, 2015. To that end, relevant information on ethnicity, age, sex, HIV status, DM status, substance abuse, alcohol consumption, smoking, TB presentation (pulmonary or extra pulmonary TB), case type, and outcome was extracted from the NTP register.

Genotyping of TB strains is not available in Suriname. As a result, it is not possible to determine whether patients referred for retreatment of TB have been infected with another TB strain or if their previous TB infection has flared up. Therefore, only the first entry of a patient in the NTP register during the study period was considered for analysis. Consequently, of patients with multiple entries in the NTP registry during the assessed timeframe (due to, for example, relapse or resumption of treatment after loss to follow-up), only the first entry was included in analyses.

2.1. Ethics

This study was conducted with the approval of the Ministry of Health (letter #VG 010-15). Only retrospective data was considered, and the dataset used for analyses was anonymized.

2.2. Tuberculosis testing algorithm and patient work-up

Patients suspected of having TB (i.e., presenting with prolonged cough, fever, night sweats, and weight loss) can have their sputum collected locally at their residence. The sputum is thereafter sent to Paramaribo for further diagnostic evaluation, be it at the Academic Hospital or the Central Laboratory of the Bureau of Public Health. If acid-fast bacilli are detected in the sputum or clinical suspicion of TB arises, patients are referred by their physician or local health official (or nursing aide in Suriname's interior) to the capital, Paramaribo, for further evaluation and treatment by a pulmonologist, infectious disease specialist or pediatrician.

Most patients are referred to pulmonologists, who practice in the sole national pulmonary medicine clinic at the Academic Hospital in Paramaribo. Evaluation of patients suspected of TB includes a detailed anamnesis and chest X-ray examination, with emphasis on upper lobe consolidation, miliary consolidation, cavitary lesions, confluencing patchy infiltrates, enlarged mediastinal lymph nodes, and/or pleural effusion. Additional diagnostic testing consists of sputum examinations for acid-fast bacilli (AFB) in Ziehl-Neelsen or Auramine staining and, from May 2012 onwards, Xpert MTB/RIF (Cepheid, Sunnyvale, CA, USA) tests on a patient's first sputum sample. In young children unable to cough on demand, empty stomach aspirate is obtained thrice and examined. Occasionally a tuberculin skin test is performed, with a result of 10 mm or more considered positive for those in the general population and 5 mm or more considered positive for PLHIV or children under 5 years of age. Tuberculous meningitis is assumed on clinical presentation and the ruling out of other central nervous system infections based on the chemical, cellular, and bacteriological composition of cerebrospinal fluid [5]. Patients are assigned a diagnosis of pulmonary TB mainly based on the sputum test results or on clinical presentation.

Children up to 15 years of age are treated by pediatricians and most adult patients are admitted by pulmonologists (at the sanatorium of the Academic Hospital Paramaribo) or occasionally treated by an internal medicine specialist. After discharge patients are given an outpatient appointment with their medical specialist, and daily visits by DOT-supporters are conducted (e.g., to maintain medication supplies and adherence).

2.3. Study variables

The study variables were extracted from the NTP records, the main variable being self-reported ethnicity. The categories of ethnicity that were assessed—regarding individuals of Creole, Hindustani, Indigenous, Javanese, Maroon, and Mixed ethnicity—all corresponded to ethnic or racial categories used in the 2012 census [7], [14]. Due to the paucity of patients from other ethnic or racial groups, individuals not belonging to one of these six categories were omitted from analysis.

Other variables investigated as factors were: age (measured in years), sex (female, male), HIV status (negative, positive, unknown), DM status (no, yes; fasting blood glucose [FBG] level ≥ 6.5 mmol/l—when TB patients with DM were admitted, their FBG level was measured twice a week), substance abuse (no, yes), alcohol consumption (no, yes), and smoking (no, yes).

2.4. Statistics

Information—on age, sex, HIV status, DM status, substance abuse, alcohol consumption, and smoking—was compiled and tabulated for each of the six assessed ethnic groups. Except for age, which was used as a continuous variable, all other variables were categorical. For analyses that included HIV status as a variable, patients with an unknown HIV status were excluded (listwise deletion). TB manifestation was excluded from analysis due to the difficulty in correctly diagnosing extrapulmonary TB in Suriname [15].

Independent univariate analyses were performed to gauge the association between each of the remaining variables and ethnicity. For age, a continuous variable, this was a one-way ANOVA. For the categorical variables, sex and HIV status, chi-square tests were used.

For each ethnic group, the five-year incidence rate for TB was calculated by dividing the number of unique patients of an assessed ethnicity entered in the NTP registry during the study period by the number of individuals of that ethnicity living in Suriname according to the 2012 census. These incidence rates, based on the patient population's ethnic makeup, were then compared to the expected five-year incidence rates based on the demographic breakdown of the 2012 census using a chi-square goodness-of-fit test. Incidence rates were reported per 100,000 population. A similar analysis, limited to HIV negative patients, was also performed.

A multinomial logistic regression was used to evaluate selected factors against the six assessed ethnic groups. Age, sex, and HIV status were used as predictors. Cases involving Creole patients were used as a benchmark because, compared to the other ethnic groups, they contributed the largest number of eligible TB patients (n = 241).

Statistical analyses were performed using SPSS version 20.0 (computer software; IBM Corp., 2011). For significance testing, all alpha levels were set at 0.05.

3. Results

Between 2011 and 2015, a combined total of 716 new and retreatment TB cases were reported to the NTP. Table 1 shows the number of TB cases by ethnicity per year. At presentation, a diagnosis of TB was assumed in 61% of cases based on the presence of acid-fast bacilli.

In the remaining 39%, a TB diagnosis was assumed on basis of clinical presentation. From May 2012 onwards, an average of 64% of all TB diagnoses were confirmed through GeneXpert tests—approximately 72% of pulmonary TB and 12% of extrapulmonary TB cases were confirmed by PCR test. Culture was done in 502 cases with growth of bacilli detected in 368 cases (73%). We performed our analysis on unique patients in the NTP database. Consequently, one case with incomplete data was excluded, leaving 715 cases (adult, n = 683; pediatric, n = 32). Further excluded from analysis were (a) 15 cases concerning patients of Chinese, European, or Brazilian descent (due to the small number of cases concerning these groups) and (b) 38 subsequent repeat cases of patients that were recorded twice or thrice in the NTP register during the study period (due to their resumption of treatment after being lost to follow-up). Analyses were performed using the remaining 662 cases, which corresponded to 662 unique patients (Table 2), of whom 569 were classified as pulmonary TB and 93 as extra pulmonary TB.

Table 1. TB cases by ethnicity between 2011-2015.

Group/Year	2011	2012	2013	2014	2015
Creole	59	52	45	60	46
Hindustani	17	30	16	20	22
Maroon	19	17	22	27	20
Mixed	14	9	28	24	20
Javanese	9	15	18	12	21
Indigenous	11	11	10	12	14
Chinese	0	0	2	2	6
European	2	1	0	1	0
Brazilian	1	0	0	0	0
No data	0	0	0	0	1
Total	132	135	141	158	150

All patients belonged to one of the six assessed ethnic groups: a) 241 (36.4%) were Creole; b) 103 (15.6%) were Hindustani; c) 57 (8.6%) were Indigenous; d) 70 (10.6%) were Javanese; e) 100 (15.1%) were Maroon; and f) 91 (13.7%) were of Mixed ethnicity. 175 patients (26.4%) were HIV positive, of whom 138 had a known CD4 count, with the average count being 174/mm^3 and most patients (92.8%) having a count below the 500/mm^3 threshold. Also, of the 175 HIV/TB patients, 109 were on ART—86 of these patients had a known CD4 count, with the average count being 154/mm^3 and almost all patients (97.7%) having a count below the 500/mm^3 threshold. NTP records also show that: a) 67 patients (10.1%) had a positive DM status; b) 191 (28.9%) used drugs (i.e., substance abuse); c) 149 (22.5%) consumed alcohol; and d) 159 (24%) smoked cigarettes. Because data on these last four variables were often missing or inconclusive, we omitted them from quantitative analysis (Table 2).

Table 2 Breakdown by ethnicity of variables recorded for TB patients.

Variable[1]	Category	Creole		Hindustani		Indigenous		Javanese		Maroon		Mixed		Total	
Age†, $p < .001$	Years (SD)	44	(13.6)	44.1	(15.5)	38	(18.5)	49.9	(16.2)	33.8	(16.5)	37.5	(17.6)	41.7	(16.3)
Sex	Male	175	(72.6)	86	(83.5)	37	(64.9)	49	(70)	65	(65)	58	(63.7)	470	(71)
$p = .021$‡	Female	66	(27.4)	17	(16.5)	20	(35.1)	21	(30)	35	(35)	33	(36.3)	192	(29)
HIV	Negative	142	(58.9)	73	(70.9)	49	(86)	68	(97.1)	73	(73)	60	(65.9)	465	(70.2)
$p < .001$‡	Positive	92	(38.2)	24	(23.3)	7	(12.3)	1	(1.4)	24	(24)	27	(29.7)	175	(26.4)
	No data*	7	(2.9)	6	(5.8)	1	(1.8)	1	(1.4)	3	(3)	4	(4.4)	22	(3.3)
Diabetes	Positive	11	(4.6)	13	(12.6)	12	(21.1)	19	(27.1)	5	(5)	7	(7.7)	67	(10.1)
	No data	230	(95.4)	90	(87.4)	45	(78.9)	51	(72.9)	95	(95)	84	(92.3)	595	(89.9)
Substance abuse	Yes	77	(32)	29	(28.2)	12	(21.1)	14	(20)	32	(32)	27	(29.7)	191	(28.9)
	No data	164	(68)	74	(71.8)	45	(78.9)	56	(80)	68	(68)	64	(70.3)	471	(71.1)
Alcohol consumption	Yes	46	(19.1)	24	(23.3)	19	(33.3)	9	(12.9)	24	(24)	27	(29.7)	149	(22.5)
	No data	195	(80.9)	79	(76.7)	38	(66.7)	61	(87.1)	76	(76)	64	(70.3)	513	(77.5)
Smoking	Yes	59	(24.5)	25	(24.3)	14	(24.6)	15	(21.4)	19	(19)	27	(29.7)	159	(24)
	No data	182	(75.5)	78	(75.7)	43	(75.4)	55	(78.6)	81	(81)	64	(70.3)	503	(76)

Notes. Values within brackets give the percentage breakdown of categories within a variable for an ethnic group.
† One-way ANOVA, *p*-value
‡ Chi-square test, *p*-value
* Category excluded from Chi-square analysis

The number of TB patients per ethnic group and the five-year incidence for TB by ethnicity are shown in Table 3. The lowest incidence rate was observed among Hindustani people (69 per 100,000). The highest incidence rates were found among Indigenous (280 per 100,000) and Creole people (271 per 100,000). A chi-square goodness-of-fit test was used to compare the patient population's ethnic makeup to that of Suriname's population. The observed distribution of TB patients did not match the expected distribution, $\chi^2(5, N = 662) = 244.42$, $p < .001$ (Table 3). Regarding the HIV negative cohort, the five-year incidence for TB was also highest in Indigenous and Creole people and lowest in Hindustani people (Table 4). Post hoc testing revealed that Creole and Indigenous patients had a significantly higher TB incidence than all other groups in both the general (Table 3) and HIV negative cohort (Table 4). No broad differences were apparent between HIV positive and HIV negative patients regarding age and sex (Table 5).

Regarding univariate analyses performed to explore the respective relationships between ethnicity and age, sex, and HIV status, several significant results were found (Table 2). To determine a statistically significant difference between ethnic groups on age, a one-way ANOVA was conducted. There was a significant effect of ethnicity on age for the six groups $F(5, 656) = 12.35$, $p < .001$. Chi-square tests of independence were performed to examine the relation between ethnicity and sex and HIV status, respectively. Significant relationships were found between ethnicity and sex (χ^2 [5, N = 662] = 13.23, $p = .021$) and ethnicity and HIV status (χ^2 [5, N = 640] = 47.64, $p < .001$; unknown cases [n = 22] excluded). In comparing ethnic groups, a multinomial logistic regression was performed to model the relationship between selected variables and ethnicity. Age, sex, and HIV status were used as predictors in this analysis. Addition of the predictors to a model containing only the intercept significantly improved model fit, χ^2 (15, N = 640) = 124.3, $p < .001$, with the proportion of variance explained being: $R^2 = 0.18$ (Cox & Snell)/$R^2 = 0.18$ (Nagelkerke). Additionally, predictors that were found to be significant using likelihood ratio tests were age ($p < .001$) and HIV status ($p < .001$).

Table 3 Nationwide five-year incidence of TB by ethnic group from 2011 through 2015.

Ethnic group[1234]	Pop. Reference, # (%)[123]	TB cases, # (%)	TB cases, 95% CI (low, high)	5-year TB inc.[5], 95% CI (low, high)
Creole[ABCD]	88856 (17)	241 (36.4)	(31.5, 41.3)	271 (235, 308)
Hindustani[AEF]	148433 (28.5)	103 (15.6)	(11.9, 19.3)	69 (53, 86)
Indigenous[EGHI]	20344 (3.9)	57 (8.6)	(5.7, 11.5)	280 (187, 374)
Javanese[BG]	73975 (14.2)	70 (10.6)	(7.4, 13.7)	95 (66, 123)
Maroon[CH]	117567 (22.5)	100 (15.1)	(11.4, 18.8)	85 (64, 106)
Mixed[DFI]	72340 (13.9)	91 (13.7)	(10.2, 17.3)	126 (94, 158)
Total	521515 (100)	662 (100)	---	127

Notes.
[1]A chi-square goodness-of-fit test was used to compare the patient population's ethnic composition to that of Suriname's total population— χ^2 (5, N = 662) = 244.42, $p < .001$.
[2]Data applies to the population of Suriname and figures are based on the 2012 census. According to this census, Suriname had a total population of 541,638 (this figure includes 20123 individuals belonging to groups that were not included in this analysis).
[3]Total number of individuals of a given ethnic group according to the 2012 census. In this analysis the Creole ethnic group (N = 84,933, 15.7%) and Afro-Surinamese ethnic group (N = 3923, 0.7%) have been combined.
[4]A total of 15 post hoc pairwise comparisons were performed between ethnic groups. Bonferroni corrections were applied. Pairs of uppercase letters behind the group names in superscript represent group comparisons that revealed statistically significant differences.
[5]Per 100,000 population.
TB = Tuberculosis
Pop. = Population
inc. = incidence

Table 4 Approximate nationwide five-year incidence of TB for HIV negative persons by ethnic group from 2011 through 2015.

Ethnic group[1234]	Pop. Reference, # (%)[123]	TB cases, # (%)	TB cases, 95% CI (low, high)	5-year TB inc.[5], 95% CI (low, high)
Creole[ABCD]	~88100 (17)	142 (30.5)	(24.9, 36.2)	161 (132, 191)
Hindustani[AEFG]	~147100 (28.5)	73 (15.7)	(11.3, 20.1)	50 (36, 64)
Indigenous[EHIJ]	~20200 (3.9)	49 (10.5)	(6.8, 14.3)	243 (156, 329)
Javanese[BFH]	~73300 (14.2)	68 (14.6)	(10.3, 18.9)	93 (65, 120)
Maroon[CI]	~116500 (22.5)	73 (15.7)	(11.3, 20.1)	63 (45, 80)
Mixed[DGJ]	~71700 (13.9)	60 (12.9)	(8.8, 17)	84 (57, 110)
Total	~516900 (100)	465 (100)	---	90

Notes.
[1]A chi-square goodness-of-fit test was used to compare the patient population's ethnic composition to that of Suriname's estimated HIV negative population—χ^2 (5, N = 465) = 138.89, p < .001.
[2]Data applies to population of Suriname and figures are based on the 2012 census. According to this census, Suriname had a total population of 541,638 (this figure includes 20123 individuals belonging to groups that were not included in this analysis). This analysis is limited to the population of Suriname living without HIV. Population figures were estimated by subtracting the number of PLHIV per ethnic group. This is based on an HIV figure of 0.9% [AA 11Y] (this method does not, however, account for difference in HIV prevalence between ethnic groups).
[3]Total number of individuals of a given ethnic group according to the 2012 census. In this analysis the Creole ethnic group (N = 84,933, 15.7%) and Afro-Surinamese ethnic group (N = 3923, 0.7%) have been combined.
[4]A total of 15 post hoc pairwise comparisons were performed between ethnic groups. Bonferroni corrections were applied. Pairs of uppercase letters behind the group names in superscript represent group comparisons that revealed statistically significant differences.
[5]Per 100,000 population.
TB = Tuberculosis
Pop. = Population
inc. = incidence

Table 5 Breakdown by ethnicity of variables recorded for TB patients by HIV status.

Variable[1]	HIV status	Category	Creole		Hindustani		Indigenous		Javanese		Maroon		Mixed		Total	
Age	Negative	Years (SD)	44	(14.9)	45.1	(16.7)	37.2	(19)	50.3	(16.5)	33	(17.1)	35.5	(18.2)	41.6	(17.6)
	Positive	Years (SD)	45	(10.2)	41	(10)	46.4	(14.8)	---	---	39.1	(9.4)	43.7	(11.5)	43.6	(10.6)
Sex	Negative	Male	107	(75.4)	57	(78.1)	33	(67.3)	47	(69.1)	46	(63)	39	(65)	329	(70.8)
		Female	35	(24.6)	16	(21.9)	16	(32.7)	21	(30.9)	27	(37)	21	(35)	136	(29.2)
	Positive	Male	62	(67.4)	23	(95.8)	3	(42.9)	1	(100)	17	(70.8)	17	(63)	123	(70.3)
		Female	30	(32.6)	1	(4.2)	4	(57.1)	0	(0)	7	(29.2)	10	(37)	52	(29.7)

Notes.
Values within brackets give the percentage breakdown of categories within a variable for an ethnic group.
[1]Age information suppressed for small groups.

Multiple significant parameter estimates were found (Table 6). Regarding age, Indigenous patients were significantly younger than Creole patients ($p = .03$, aOR = 0.979, 95% CI 0.96 – 0.98), as were Maroon ($p < .001$, aOR = 0.959, 95% CI 0.943 – 0.976) and Mixed patients ($p = .002$, aOR = 0.974, 95% CI 0.957 – 0.991). Conversely, Javanese patients were significantly older than Creole patients ($p < .008$, aOR = 1.024, 95% CI 1.006 – 1.042).

HIV was also a significant predictor. Compared to Creole patients, Hindustani patients were less likely to be HIV positive ($p = .015$, aOR = 0.515, 95% CI 0.302 – 0.877), as were Indigenous ($p = .001$, aOR = 0.232, 95% CI 0.1 – 0.537) and Javanese patients ($p < .001$, aOR = 0.023, 95% CI 0.003 – 0.17).

4. Discussion

The distribution of five-year incidence rates for TB (2011–2015) by ethnicity differed significantly from the demographic breakdown of ethnicity in Suriname's population. The highest incidence rates were found among Indigenous and Creole people; both groups were overrepresented among TB patients. Indigenous and Creole people respectively made up 3.9% and 17% of the assessed population of Suriname but made up 8.6% and 36.4% of the assessed TB patients (Table 3). When only HIV negative patients were considered, Indigenous and Creole people still had the highest TB incidence rates. When adjusted for HIV coinfection, the very high TB incidence in Indigenous people, compared to other ethnicities becomes even more apparent, demonstrating that other risk factors are very likely implied; Table 4). Indigenous people, exhibit the highest level of material poverty in Suriname [16]. As such poor socioeconomic status (SES), which is related to increased TB levels [17], [18], [19], possibly constitutes a risk factor for this group regarding TB. Another factor to be considered is that many Indigenous people live in remote locations with fewer medical resources. Only 20.1% of Indigenous people live in Paramaribo, while the remainder inhabit rural districts and Suriname's interior [20]. Medical Mission, a non-governmental organization, provides much of the primary healthcare in the interior but secondary care is mostly concentrated in Paramaribo [10], [21].

Table 6 Evaluation of differences between TB patients grouped by ethnicity compared to creole TB patients using multinomial statistical regression.

Variable: category (reference)[†‡]	B	SE	Sig.	aOR	95% CI	
Hindustani						
Intercept	-0.968	0.43	.024*			
Age, continuous	-0.004	0.008	.646	0.996	0.98	1.012
Sex: female (male)	0.599	0.31	.053	1.82	0.991	3.341
HIV: pos. (neg.)	-0.664	0.272	.015*	0.515	0.302	0.877
Indigenous						
Intercept	-0.014	0.438	.975			
Age, continuous	-0.021	0.01	.03*	0.979	0.96	0.998
Sex: female (male)	-0.247	0.329	.453	0.781	0.41	1.489
HIV: pos. (neg.)	-1.46	0.428	.001*	0.232	0.1	0.537
Javanese						
Intercept	-1.619	0.475	.001*			
Age, continuous	0.023	0.009	.008*	1.024	1.006	1.042
Sex: female (male)	-0.317	0.319	.321	0.729	0.39	1.362
HIV: pos. (neg.)	-3.765	1.017	.001*	0.023	0.003	0.17
Maroon						
Intercept	0.987	0.365	.007*			
Age, continuous	-0.042	0.009	.001*	0.959	0.943	0.976
Sex: female (male)	-0.069	0.272	.799	0.933	0.548	1.59
HIV: pos. (neg.)	-0.505	0.279	.07	0.603	0.349	1.043
Mixed						
Intercept	0.357	0.388	.357			
Age, continuous	-0.027	0.009	.002*	0.974	0.957	0.991
Sex: female (male)	-0.203	0.276	.461	0.816	0.475	1.401
HIV: pos. (neg.)	-0.287	0.272	.292	0.751	0.44	1.28

Notes.
[1]Patients (n = 22) of whom the HIV status was not known were not included in this analysis.
Sig. = significance
*significant at $p < .05$
aOR = adjusted odds ratio

Creoles had the second highest TB incidence and have the highest HIV prevalence in Suriname [22]. HIV is a known risk factor for the progression of latent TB infection to active TB disease [23], [24]. This may contribute to the elevated TB incidence rate among Creole people. The demographic makeup of Paramaribo, Suriname's capital city, may also play a role. Increased community spreading of TB in Paramaribo is a possibility as most TB patients reside there [25]. Paramaribo is also the most densely populated Surinamese district by far [3], and increased population density may contribute to higher TB levels [18], [26]. Therefore, because most Creoles (72.4%) reside in Paramaribo [20], this group may have a higher exposure to TB.

Hindustanis had the lowest incidence of TB during our study period. This observation may be explained by this group being less exposed to TB due to their tendency to reside in more rural areas. In fact, only 37.2% of the Hindustani population lives in Paramaribo [20], where most TB transmission occurs [25]. Javanese patients had a low rate of HIV coinfection. This group is also likely to reside outside the capital; only 32% of the Javanese population lives in Paramaribo [20]. Moreover, those Hindustani and Javanese people that do live in Paramaribo are underrepresented in resorts/jurisdictions [20] that are more characterized by poor living conditions [27], a known TB risk factor [18], [19].

Indigenous, Maroon, and patients of Mixed ethnicity presented with TB at a younger age compared to Creole patients. In the general population there is an age gap between Maroons and Creoles with the former being younger on average than the latter and historically possessing a higher birthrate [3], [28]. A difference in age is relevant and may explain the lower TB rates among Maroons compared to Creoles due to reactivation of latent TB infections in older people [29]. However, material poverty among Maroons is high [16]. Also, while Maroon people are less likely to reside in Paramaribo (32.7%) than Creoles (72.4%) and even Hindustanis (37.2%) [20], those that do live in Paramaribo mostly inhabit resorts/jurisdictions [20] that are more characterized by poor living conditions [27], a known TB risk factor [18], [19].

4.1. Limitations

Our study has several limitations that may have influenced findings. Underreporting of TB cases to the NTP and overdiagnosis of TB in the pre-Xpert MTB/RIF period—during which patients with non-tuberculous *Mycobacterium* infection may have been misclassified as having TB [30]—could have affected the total number of TB patients.

Also, although over three quarters of patients provided an address in the capital, Paramaribo [25], the city is home to only 45% of Suriname's population [3]. This discrepancy could be the result of patients being referred or temporarily migrating from rural or interior areas of Suriname to Paramaribo due to lack of local diagnostic and treatment capacity. Underreporting is especially relevant regarding Indigenous people. Despite possessing the highest TB rate found by this study, Indigenous individuals are also more likely to live far removed from the health system. The TB incidence for this group may thus be an underestimate.

Large differences in material poverty exist between ethnic groups in Suriname, with high levels of material poverty observed among Indigenous and Maroon patients [16]. Poverty is an important determinant of TB [19], thus underscoring the importance of patient information pertaining to SES. However, SES data was unavailable in this study.

Data on several factors (e.g., DM status and alcohol consumption) was incomplete and was omitted from analysis. Gaining a better understanding of these factors is important. For example, globally, differences exist between Indigenous and non-Indigenous populations regarding TB risk factors such as DM [31], and elevated DM rates among Indigenous patients in Suriname [13] may help explain their increased vulnerability to TB.

4.2. Conclusions

In sum, our retrospective results indicate that Indigenous and Creole individuals had the highest TB incidence in Suriname between 2011 and 2015. HIV, which has an adult (15–49 year) prevalence of 0.9% [12], is an important TB risk factor that does not affect all ethnicities equally. However, data regarding other risk factors (e.g., SES) was limited. We recommend that for better control of TB in Suriname, special attention should be given to the vulnerabilities of different ethnic groups (i.e., frequent monitoring of Indigenous villages in remote areas of Suriname) and to improve access and adherence to antiretroviral therapy for of HIV positive patients. We also recommend that the NTP refine data collection on DM, substance abuse, smoking, and alcohol consumption to make the national TB registry much more complete.

CRediT authorship contribution statement

F.A. Gopie: Conceptualization, Data curation, Investigation, Writing - original draft. **A. Hassankhan:** Writing - review & editing. **S. Ottevanger:** Data curation, Formal analysis, Writing - review & editing. **I. Krishnadath:** Formal analysis, Writing - review & editing. **W. de Lange:** Writing - review & editing. **C.W.R. Zijlmans:** Conceptualization, Supervision, Writing - review & editing. **S. Vreden:** Conceptualization, Supervision, Writing - review & editing.

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Declaration of Competing Interest

The main author is a treating physician within the NTP program. Authors further declare no conflict of interest.

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3

Non-tuberculous mycobacteria in sputum cultures in Suriname

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Abstract

Background

Non-tuberculous mycobacteria (NTM) are now widely recognized as a potential cause of pulmonary disease and are sometimes detected in cultures of patients suspected of having tuberculosis. Before 2012 (the year in which the GeneXpert MTB/RIF test was introduced in Suriname), patients were treated for tuberculosis based on clinical evaluation and positive Ziehl-Neelsen sputum. Culture results mostly became available after patients had completed their tuberculosis treatment, and NTM growth was detected frequently among them. Because the NTM-NET collaborative study had no data on Suriname, we evaluated and highlighted the presence of NTM there.

Methods

We performed a retrospective analysis of culture identification results of patients treated for TB in 2010 and 2011 (prior to the GeneXpert era in Suriname).

Results

379 isolates were analyzed, of which 161 (42%) yielded growth of NTM. The most frequently cultured NTM were *M. fortuitum* and *M. gordonae.*

Conclusions

We describe the presence of NTM in Surinamese patients (over-)treated for tuberculosis. In TB suspects, the potential of NTM as causative agents needs to be considered, as these require a different diagnostic and management approach.

1. Introduction

Suriname is a South American lower middle-income country with a population that comprised approximately 542,000 inhabitants in 2012 [1]. Tuberculosis (TB) is a notifiable disease in Suriname, and all patients treated for TB are registered with the National Tuberculosis Program (NTP), which maintains the national TB register. In 2015, Suriname had a TB incidence of 115 to 152 cases [2], which translates to an incidence rate of about 21 to 28 cases per 100,000 population. Until 2012, when the GeneXpert MTB/RIF (Cepheid, Sunnyvale, CA, USA) test was introduced in TB diagnostics in Suriname, diagnosis of TB was made based on WHO criteria of a patient presenting with cough, weight loss, night sweats, chest x-ray abnormalities, and acid-fast bacilli (AFB) presence in sputum [3]. The sputum of suspected pulmonary TB patients was sent to the Central Laboratory of the Bureau of Public Health for smear microscopy, culture, and identification, which was based on bacterial growth patterns.

While assessing the incidence of TB in Suriname, we noted the presence of non-tuberculous mycobacteria (NTM) in Surinamese patients who were treated for TB. Up till now, there has been no published data on NTM isolation in Suriname. In the NTM-NET collaborative study, which presents an overview of the geographic distribution of cultured and identified NTM species, no data was obtained from Suriname [4]. Nowadays, NTM are increasingly recognized as important opportunistic pathogens of humans which can cause TB-like pulmonary disease [5]. To address the presence of NTM in Suriname, we conducted a retrospective analysis of sputum culture results from patients treated for suspected pulmonary TB in 2010 and 2011.

2. Methods

Sputum culture results and identification results—from patients with a prolonged cough, a positive tuberculin skin test (TST), and those treated for suspected TB in 2010 and 2011—were extracted from the Central Laboratory database. The sputum evaluation process at the Central Laboratory consisted of direct microcopy using Ziehl-Neelsen staining and culture on Lowenstein Jensen media. Presumptive identification of *M. tuberculosis* was done locally based on the bacterial colony morphology. The cultured isolates and lysates were sent via CAREC (Caribbean Epidemiology Center, Trinidad) to the University of Massachusetts, USA, to identify the isolate by DNA sequencing of the partial *hsp65* gene.

3. Results

In 2010 and 2011, a total number of 9004 samples consisting of sputum and other bodily fluids were sent to the Central Laboratory for evaluation; 668 (7.4%) of the 9004 samples yielded growth in culture. Of these samples, 379 were sent abroad for identification.

These samples included sputum (358 samples), tracheal fluid (10 samples), gastric lavage (seven samples), pus (two samples [lymph node aspirates]) and one urine sample. The origin of one sample was not known. Forty-eight individuals had multiple positive cultures sent for identification. Identification results of cultured mycobacteria are shown in Table 1. In 191 (50%) of the 379 isolates, *M. tuberculosis* complex (MTB) was cultured, while in 161(42%) of the isolates, growth was detected of 180 NTM from 47 different NTM species. M. *fortuitum* (48 cultures), *M. gordonae* (31 cultures), *M. abscessus* (nine cultures), and *M. senegalense* (eight cultures) were the most cultured NTM. Twenty-seven (8%) isolates were bacteria like *Nocardia* and *Rothia* species or possessed DNA that was unsuitable for analysis. The gastric aspirates showed growth of MTB in three samples, growth of NTM in three samples, and one sample could not be classified. The urine sample yielded growth of *M. flavescens*. Pus samples and the unclassified sample showed growth of MTB. Samples of eight patients yielded growth of both an NTM and MTB.

Mycobacterium avium complex (MAC) species were cultured in nine sputum samples from seven patients (of which two were HIV positive). *M. abscessus* was cultured in nine sputa from eight patients. One patient, whose HIV status was unknown, had two sputum samples sent in with a time interval of two months.

Both sputum samples yielded growth of *M. abscessus*. Sputum of one patient, whose HIV status was also unknown, yielded growth of *M. kansasii.* The identified NTM are listed in Table 1, which shows 47 different NTM species cultured in sputa from 148 patients treated for suspected TB.

4. Discussion

To our knowledge, this is the first study describing the isolation of NTM from clinical samples of Surinamese patients suspected of having (pulmonary) TB. Our study data revealed the presence of NTM in Suriname. These positive cultures may have been presumed to be MTB, while awaiting the identification results from the supranational reference laboratories. This wait for identification results may have led to overtreatment. With the introduction of the GeneXpert MTB/RIF assay in 2012, the possibility of overdiagnosis and overtreatment has diminished, but consequently, cases of NTM disease are likely to be missed.

Between 2010 and 2011, some 47 species of NTM were cultured from lysates of TB suspects (Table 1), with *M. fortuitum* (27%) and *M. gordonae* (17%) being the most frequently cultured NTM, which is similar to the NTM species distribution seen in neighboring French Guyana [6]. Both *M. fortuitum* and *M. gordonae* can cause pulmonary disease but their isolation most frequently represents temporary colonization of the airways [4], [7], [8].

These mycobacteria could be present in water [9], [10]. Analysis of quality control data of the Central Laboratory showed no NTM contamination of laboratory equipment or water (data not shown).

Nevertheless, we also identified several potential pathogens, namely *M. abscessus* (nine cultures), MAC (nine cultures), and *M. kansasii* (one culture)—the latter two species are associated with HIV. In 2011, the estimated HIV prevalence in the adult population (15–49 years) of Suriname was estimated to be between 0.7% and 1.5% [11]. In 2016, the patient with two sputum cultures of *M. abscessus* was treated for GeneXpert proven rifampicin-sensitive pulmonary TB. His HIV status turned out to be positive with a viral load of 330,000 copies per ml. Possibly, the *M. abscessus* pulmonary infection in 2012 was an opportunistic infection of an already immunocompromised host.

With this retrospective study we have demonstrated the presence of NTM in patients suspected of having TB in Suriname and possible overdiagnosis and overtreatment of TB prior to the GeneXpert MTB/RIF era. Our study has some limitations, however.

Not all sputum culture results from the Central Laboratory could be matched to patients treated for TB according to the NTP registry, probably due to registration disparities between the databases of the NTP and the Central Laboratory. Due to this mismatch, we could not reliably identify cases of overtreatment.

To address this mismatch, we recommend the set-up of one central database which includes the clinical and laboratory data of patients.

A key limitation of the current study is that we do not have access to clinical data to investigate the clinical significance of NTM isolation in the affected patients. Another limitation is that not all positive cultures were sent to the supranational reference labs; this may bias the NTM species distribution we observed in this study. Our dated culture results constitute another limitation. As far as we know NTM culture results are not available from 2012 onwards, so the contemporary presence of NTM could not be evaluated.

In summary, NTM were isolated frequently from clinical samples of TB suspects in Suriname. The *M. fortuitum* complex species were most frequently isolated, while the most notorious NTM pathogens, MAC, and *M. abscessus*, were less frequently cultured. The clinical significance of NTM isolation in patients from Suriname warrants follow up and separate investigation to determine the impact on a patient's health status.

Table 1 NTM detected in 161 lysates from 148 Surinamese patients in 2010 and 2011.

Group	Species (n)
M. avium complex	*M. avium* (4) *M. intracellulare* (2) *M. chimaera* (2) *M. timonense* (1)
Other slow growers	*M. gordonae* (31) *M. terrae* (5) *M. kumamotonense* (3) *M. asiaticum* (1) *M. arupense* (1) *M. hibernae* (1) *M. sherrisii* (1) *M. saskatchewanense* (1) *M. shimoidei* (1) *M. kansasii* (1) *M. gastri* (1)
M. fortuitum group	*M. fortuitum* (48) *M. senegalense* (8) *M. conceptionense* (3) *M. houstonense* (1)
M. chelonae-abscessus group	*M. abscessus* (9) *M. chelonae* (2) *M. bolletii* (2)
Other rapid growers	*M. phocaicum* (4) *M. lacticola* (4) *M. engbaekii* (3) *M. novocastrense* (3) *M. mucogenicum* (3) *M. austroafricanum* (1) *M. flavescens* (1) *M. boenickei* (1) *M. aichiense* (1) *M. obuense* (1) *M. brumae* (1) *M. hassiacum* (1)
Uncharacterized NTM species	*M. senuense* (6) *M. vanbaalenii* (2) *M. chlorophenolicum* (1) *M. sp. 2000-301223* (8) *M. sp. Asan 3* (2) *M. sp. GN10803* (1) *M. sp. 2000-301020* (1) *M. sp.Bejaia* (1) *M. sp. JLS* (1) *M. sp. JDM601* (1) *M. sp. 6PY1* (1) *M. sp. M05* (1) *M. sp. IEC35* (1)

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Source: Gopie F.A.

4

Indications, interpretation and clinical consequences of tuberculin skin tests in resource limited settings

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Abstract

Objective

To evaluate the policy of TST testing in Suriname. As there is no gold standard to diagnose latent tuberculosis infection (LTBI), the tuberculin skin test (TST) is used to diagnose LTBI. However, internationally, the cut-off values of the TST are not uniform and depend on local tuberculosis (TB) epidemiology and guidelines for test initiation. In Suriname, where currently several indications exist for TSTs, cut-off values are set at 5 mm or 10 mm, depending on the age and/or medical history of the patient. LTBI classification is performed by pulmonologists primarily based on the American Thoracic Society targeted TB testing guidelines.

Method

Retrospective analysis of outpatient TST data between 2011 and 2019 from Suriname's sole pulmonary medicine clinic.

Result

1373 patients were evaluated. 590 patients were from the screening group of whom 253 had a positive TST result, 46 of whom were classified as LTBI. In the contact tracing group of 649 patients, 616 had a positive TST, 352 of whom were classified as LTBI. In the medical condition group of 134 patients, 96 had a positive TST, 38 of whom were classified as LTBI. Eventually, positive TST results were found for 965 tested patients: 436 patients were classified as LTBI and 529 non-LTBI patients were not prescribed chemoprophylaxis. None of the non-LTBI TST-positive patients were diagnosed with active TB, including 174 patients with a TST result of 15 mm or greater and in need of IPT, but not prescribed by judgement of the pulmonologist or because of loss to follow-up.

Conclusion

the overrepresentation of positive TST results in Suriname is attributable to stringent cut-off values, especially among patients who do not disclose TB risk factors. In our opinion the TST cut-off value for such patients in Suriname and other similar settings could be set at 15 mm. We also promote that for all patients with a TST result of 15 mm or greater, offering IPT should be considered (after excluding active TB).

Keywords: tuberculin skin test, cut-off values, guidelines, revision.

Sponsorship: none.

Introduction

Infection of humans by tuberculosis (TB) bacilli can either result in no disease symptoms and spontaneous healing, active disease (with pulmonary TB being the most common and infective form), or latent TB infection (LTBI). The latter, non-infective form [1], [2], is the major source of new active TB cases [3], [4], [5], [6]. In 2014, some 1.7 billion people were estimated to have LTBI, equivalent to 23% of the world population [4]. LTBI is defined by WHO as "a state of persistent immune response to stimulation by *Mycobacterium tuberculosis* antigens with no evidence of clinically manifest active TB." The lifetime risk of LTBI reactivation in healthy individuals ranges from 5% to 15% but may increase depending on concomitant risk factors and comorbidity, eventually resulting in the potential development of active TB. As such, people living with HIV (PLHIV) have about a 100-fold increased risk of developing active TB [7].

As there is no gold standard to diagnose LTBI [3], [5], [7], TB contact screening, Interferon Gamma Release Assays (IGRAs), and tuberculin skin tests (TSTs) are used in clinical practice to evaluate LTBI. The IGRA has a better predictive ability but is expensive compared to the TST, which in turn has the disadvantage of requiring multiple visits to the test facility [8]. According to criteria of the American Thoracic Society (ATS), skin indurations of 5 mm or 10 mm are classified as a positive TST result depending on the patient's age, HIV status, TB exposure, chest X-ray findings, comorbidities, injection drug use, and occupation. A TST result of 15 mm or greater is considered positive in persons with no risk factors for TB [9], [10], [11].

Suriname, a low- and middle-income country in the South American tropics, can be considered a low TB incidence country (defined as a TB incidence rate of less than 100 per 100,000) [7], with an estimated TB incidence of 24 per 100,000 in 2000, 46 per 100,000 in 2010, and 29 per 100,000 in 2019 [12]. In 2012, the National Tuberculosis Program (NTP) launched the first national TB guidelines on behalf of the Ministry of Health. Per these guidelines, the cut-off values for TSTs were set at 5 mm for PLHIV and children under 5 years of age and 10 mm for all other persons [13].

For decades, Bacillus Calmette-Guerin (BCG) vaccinations have not been administered in Suriname. As it turns out, the BCG vaccination program carried out from 1955 to 1956 among 56,000 of Suriname's inhabitants was the last mass vaccination program. Nonspecific tuberculin sensitivity in Suriname seems to be frequent, as reported by Bleiker and van Erpecum from 1962 to 1965 and by van Weissenbruch in 1979.

Between 1966 and 1971, screening for TB using chest X-ray among 60,301 people resulted in signs of TB for only 60 people. Also, from 1965 to 1974, a tuberculin survey among 156,000 people revealed only 88 positive cases [14]. The population of Suriname was 379,607 in 1970 [15].

Non-tuberculous mycobacteria (NTM) are commonly present in Suriname [16]. Between 2007 and 2011, growth of NTM was detected in sputum cultures from patients suspected of TB, varying from 30.1% in 2009 to 47.7% in 2007, with a yearly average of 39.2%. *M. tuberculosis* growth during this time was noted in 50.6% of the sputum cultures of patients treated for TB (data from the national tuberculosis laboratory of the Central Laboratory, Bureau of Public Health).

The WHO encourages countries to develop and implement national TB guidelines at their own discretion [7]. As such, all patients with TB in Suriname should be registered with the NTP, a government workforce that is responsible for TB contact tracing and public health measures regarding TB. Since IGRAs are not available in Suriname, the TST is used to identify LTBI. Other than for TB contact tracing, in Suriname the TST is sometimes required for a work permit or for admission to a nursing home. In addition, countries like the USA and Belgium require a negative TST result or LTBI treatment from Surinamese nationals for the purposes of emigration or study.

Having utilized the TST cut-off values of 5 mm and 10 mm for many years, we had the impression of over designation of positive TST results, as a consequence of the NTP guidelines. As such we were curious to evaluate how the TST results, of TB contact tracing patients, screening patients, and patients with a medical condition other than TB, were dealt with in clinical practice and if adjustments needed to be made to the TST policy of Suriname. Our investigative parameters were a) the reason a TST was performed; b) the numerical value and designation of the TST; and c) the policy pursued by the treating physician and eventually the pulmonologist.

Method

TST testing algorithm and patient workup

Indication: to evaluate tuberculosis exposure, the TST can be ordered by any physician practicing in Suriname, which is performed by the NTP with purified protein derivative (PPD RT23/SSI Copenhagen Denmark) (Figure 1). NTP personnel measure the skin induration in mm and designate the TST result as negative or positive, according to the NTP guidelines. Tested persons with a positive TST result are advised to consult a medical specialist for additional evaluation, namely a pulmonologist for adults and a pediatrician for children.

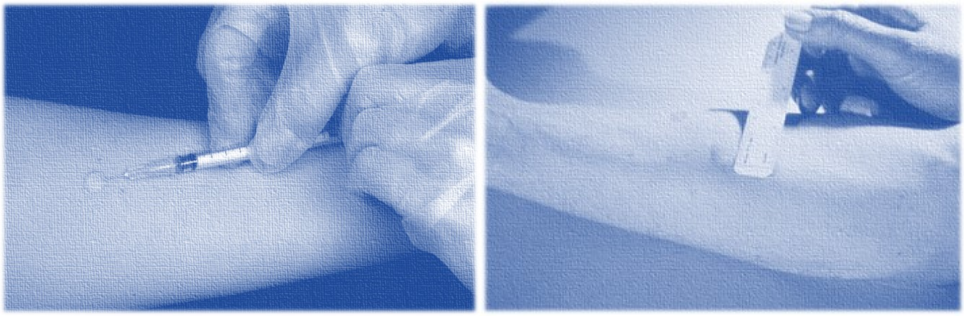

Figure 1. Placement and measurement of the Tuberculin Skin Test.
Source: Adapted from Centers for Disease Control and Prevention, Public Health Image Library, ID#: 6806 (left), 3752 (right).

Interpretation: for the classification of a positive TST test result a detailed anamnesis is taken at the pulmonology clinic and a chest X-ray is performed, which is evaluated for pulmonary lesions like consolidation, broadened hila, granulomas and miliary TB [17]. Subsequently the pulmonologist categorizes the TST as done in case of a) screening (for a work permit, admittance to a nursing home, study abroad, or emigration); b) TB contact tracing; or c) an additional test to rule out LTBI in patients with medical conditions like chronic cough, weight loss, fatigue, hemoptysis, and ocular disease. Patients referred for TB contact tracing and medical conditions also have their sputum examined for acid fast bacilli (AFB) with Ziehl-Neelsen (ZN) staining and, from 2012 onwards, with the Xpert MTB/RIF (Cepheid Sunnyvale). After this work up it is decided by the pulmonologist, having ruled out active TB and considering the anamnesis and chest X-ray result, if a patient with a positive TST result is at risk for developing TB and as such needs to be classified as LTBI.

Clinical consequence: no follow-up is conducted by the pulmonologist if a person has a negative TST result and is without an anamnesis or signs of TB. In the TB contact tracing group and the medical condition group, patients classified as LTBI [9] by the pulmonologist are offered isoniazid preventative treatment (IPT), whereas patients with a positive TST but not classified as LTBI are

assigned to a "wait and see, no IPT" policy for 2 years—as this is the most likely time for TB reactivation to occur [5]—except in the presence of comorbidities such as diabetes mellitus (DM), HIV, cancer, and chronic renal failure. No follow-up or "wait and see, no IPT" policy is applied to screening group patients who have a positive TST result (as designated by the NTP) but who were not classified as LTBI by the pulmonologist.

Patients classified as LTBI are offered 6 months of IPT and are monitored by pulmonologist for adverse reactions, liver function tests—aspartate aminotransferase (AST) and alanine transaminase (ALT)—and treatment adherence. IPT is completed after 6 months of isoniazid intake, during which the patient should have no signs of active TB. If an LTBI patient declines IPT or does not complete IPT, follow-up evaluations are offered for a period of 2 years [5].

Study Protocol

We compiled outpatient data and conducted a study regarding the TST results of patients—who had a TST done at the NTP between January 1st, 2011 and December 31st, 2019 and were referred to Suriname's sole pulmonary medicine clinic at the Academic Hospital Paramaribo (children were mostly referred to the pediatrician). Follow-up data of these patients were collected until December 31st, 2020. Excluded from analysis were patients who had been treated for TB or presented with active TB and persons who had no numerical value for their TST result. The extracted data were anonymized and categorized into three TST indication groups (i.e., the screening, TB contact tracing, and medical condition groups), and included: sex, age, TST indication and TST result, co-morbidities known to be risk factors for TB [7], and the interventions undertaken by the pulmonologist.

Statistics

Statistical analyses included the calculation of follow-up durations using the mid-year date of the year in which the TST was performed (the exact dates on which TSTs were carried out were unavailable) and the end date of the study period. Differences between TST groups—which are based on the reason for the test: screening, TB contact tracing, and medical condition—on selected variables were analyzed with chi-square tests for categorical variables. Statistical analyses were performed using SPSS version 20.0 (computer software; IBM Corp., 2011). For significance testing, all alpha levels were set at .05.

Ethics

Our study was performed with anonymized patient data from our own clinic and was approved by the Ministry of Health.

Results

During the study period, 1384 patients with a TST result were referred. Excluded from analysis were 11 patients who had no numerical TST result. Data from 1373 patients were analyzed. Mean age at the time of referral was 37.3 years; the average follow-up time for all positive patients was 4.3 years. Our study cohort included 96 children, of whom 11 were under the age of 5 years; 85 were between 5 and 15 years.

Based on the NTP cut-off values, 408 patients (29.7%) had a negative TST result (including 24 patients from the TB contact tracing group with a TST result between 5 mm and under 10 mm; see Table 1 and Figure 2). 965 patients (70.3%; including a 4-year-old girl with a TST result of 8 mm) had a positive TST result (of 10 mm or greater unless otherwise noted), including 9 patients who developed skin blisters of up to 55 mm after PPD injection. In none of the patients with a positive TST result was active TB diagnosed by the pulmonologist. Finally, 436 patients (45.2%) with a positive TST result were classified as LTBI by the pulmonologist. IPT was prescribed to 325 (74.5%) of the LTBI patients, of whom 284 (87.4%) completed treatment. The remaining 529 patients (54.8%) with a positive TST result, of whom 91 were lost to follow up after the first visit to the pulmonologist, were not classified as LTBI by the pulmonologist, although 174 (32.9%) had a TST result that was 15 mm or greater. In the latter group, 142 patients were not prescribed IPT by judgement of the pulmonologist, while the other 32 patients with a TST result of 15 mm or greater did not return to the pulmonologist after their first consultation.

The reason a TST was performed, the numerical value of the TST, and the classification of the TST result by the pulmonologist are shown in Figure 2. In the screening group of 590 patients (43% of the study cohort), a total of 46 patients (7.8%) were classified as LTBI, but 64 patients (out of 93 with a TST result of 15 mm or greater) were not classified as LTBI and were assigned to a wait-and-see policy. Also, in the screening group, 159 patients had a TST result between 10 mm and under 15 mm, of whom 17 (10.7%) were classified as LTBI. In the TB contact tracing group of 649 patients (47.3% of the study cohort), 352 patients (54.2%) were designated as LTBI. Even in the TB contact tracing group, 93 patients (out of 276 with a TST result of 15 mm or greater) were not classified as LTBI and were assigned to the wait-and-see policy. In the medical condition group of 134 patients (9.8% of the study cohort), 38 patients (28.4%) were classified as LTBI (see Table 2).

Table 1. Patient classification with selected details.

Classification	n	%
Total	1373	100%
TST negative	408	29.7%
TST positive	965	70.3%
No LTBI	529	54.8%
TST under 15 mm	355	67.1%
TST ≥ 15 mm	174	32.9%
LTBI	436	45.2%
No IPT administered, LTFU	114	26.1%
IPT administered†	322	73.9%
Completed IPT	284	88.2%
Discontinued by patient	5	1.6%
Discontinued due to side effects	33	10.2%
AST and/or ALT over 200 IU/L	26	78.8%
Nausea and pruritis	7	21.2%

Notes.
† While IPT was prescribed to 325 patients, three patients did not wish to start treatment.
TST, tuberculin skin test
LTBI, latent tuberculosis infection
IPT, isoniazid preventive therapy
LTFU, loss to follow-up
AST, aspartate transaminase
ALT, alanine aminotransferase
IU/L, international units per liter

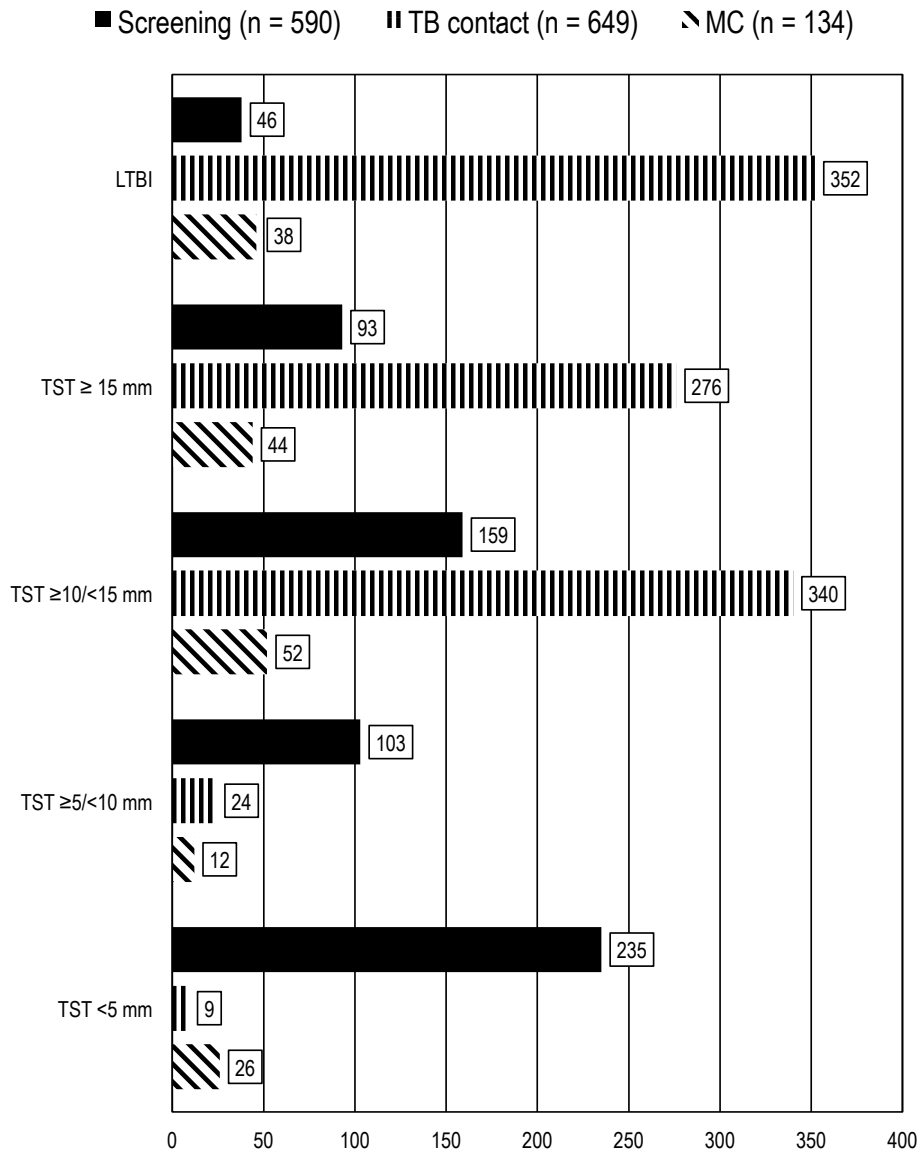

Figure 2. Numerical TST values, reason for TST, and classification by pulmonologist.

Notes.
TST, tuberculin skin test
LTBI, latent tuberculosis infection

Table 2. Patient classification and the reason for TST.

Classification	n	%
Total	**1373**	**100%**
Screening group†	**590**	**43%**
TST negative	337	57.1%
TST, positive: No LTBI	207	35.1%
TST under 15 mm	*143*	*69.1%*
TST ≥ 15 mm	*64*	*30.9%*
TST, positive: LTBI	46	7.8%
IPT completed	*31*	*67.4%*
Other (LTFU, IPT discontinued, etc.)	*15*	*32.6%*
Contact tracing group†	**649**	**47.3%**
TST negative	33	5.1%
TST, positive: No LTBI	264	40.7%
TST under 15 mm	*171*	*64.8%*
TST ≥ 15 mm	*93*	*35.2%*
TST, positive: LTBI	352	54.2%
IPT completed	*228*	*64.8%*
Other (LTFU, IPT discontinued, etc.)	*124*	*35.2%*
Medical condition group†	**134**	**9.8%**
TST negative	38	28.4%
TST, positive: No LTBI	58	43.3%
TST under 15 mm	*41*	*70.7%*
TST ≥ 15 mm	*17*	*29.3%*
TST, positive: LTBI	38	28.4%
IPT completed	*25*	*65.8%*
Other (LTFU, IPT discontinued, etc.)	*11*	*28.9%*

Notes.
† A chi-square test of independence was used to compare the proportion LTBI to that of non-LTBI cases within each TST group—χ^2 (2, N = 965) = 308.3, $p < .001$.
TST, tuberculin skin test
LTBI, latent tuberculosis infection
IPT, isoniazid preventive therapy
LTFU, loss to follow-up
AST, aspartate transaminase
ALT, alanine aminotransferase
IU/L, international units per liter

During follow-up, three patients with a TST result between 10 and 14 mm developed active pulmonary TB between 3 to 7 years after their first visit to the pulmonologist. Two patients were from the TB contact tracing group and had been classified as LTBI and were prescribed IPT, which was rejected by one patient and discontinued by the other patient due to elevated liver enzymes, ALT and AST (over two times the upper limit on two consecutive occasions that were at least 1 week apart). The third patient was from the medical condition group and had been treated for non-TB pneumonia in 2015 and presented with pulmonary TB in 2018. After presenting with active TB disease, these three patients were successfully treated with first line tuberculostatics [18]. Regarding progression to TB, three TB cases correspond to an incidence rate of 0.7 per 1000 person-years among those with a positive TST result.

Regarding risk factors for TB, HIV was reported in 10 patients (0.7%) with 6 patients being on antiretroviral therapy (ART), of which 5 could be prescribed IPT; 55 patients (4%) with a positive TST result had DM, 25 were classified as LTBI, 17 completed IPT; 8 female patients had cancer (0.6%), 6 cases of breast cancer and two cases of ovary cancer of whom two were prescribed IPT; and 6 patients (0.4%) had chronic renal failure, of whom two were prescribed IPT.

In our database, we came across three foreign patients with a TST result of 15 mm who had been BCG vaccinated in their home country. An additional 14 patients were noted with NTM in their sputum, with their TST result ranging from 0 mm to 21 mm.

Our cohort also had 11 children under the age of 5, of whom 6 (55%) had a negative TST result and thus no follow-up. Of the remaining 5 children with a positive TST result, four had no follow-up or were lost to follow-up, including one child (9%) classified as LTBI. One child with a positive TST result was assigned to a wait-and-see policy and completed 2 years of observation without displaying signs of active TB.

Discussion

In our study cohort, 4 out of 10 patients had a TST done for screening purposes, of whom less than 8 out of 100 were ultimately classified as LTBI. Regarding the patients with a positive TST result, more than half were not classified as LTBI according to the ATS guidelines.

While the ATS recommends a TST cut-off value of 5 mm for recent contacts of TB case patients (9), and 24 patients in our cohort did meet this criterion, their TST results between 5 mm and under 10 mm were designated TST negative and not classified as LTBI by pulmonologists because their anamnesis yielded no indication of overt exposure to TB and because of the abundant prevalence of NTM [16] in tropical Suriname. None of these patients developed active TB during the following 1 to 9 years (until the end of 2020), but latent TB infection is still possible [5].

On the other hand, these positive TST results may have been the result of cross-reactions with NTM [19]. Incorrect administration of PPD or TST reading errors could also play a role, but this seems less likely. A positive TST result due to BCG vaccinations may be ruled out because mass BCG vaccinations in Suriname were suspended in 1956.

In our opinion, the high proportion of positive TST results combined with the relative paucity of progression to active TB cases during follow-up—especially among those in which, based on clinical judgment, it was decided not to prescribe IPT—is due to the arbitrarily opted cut-off value of 10 mm for the TST. In all three indication groups, there were patients with a TST result of over 15 mm that were not designated as LTBI but were submitted to the wait-and-see policy. The reason for this approach could not be clarified. However, none of these patients developed active TB. The three patients with a positive TST result who did progress to active TB, years after initial presentation, could be cases of reinfection and not necessarily reactivation [20]. Still a more comprehensive policy in the approach of these patients is warranted and therefore included in the general approach that we propose below.

The TST remains a valuable tool in the diagnosis of LTBI, especially in resource-limited settings and in the absence of advanced diagnostic means. We observed that there are still indications for performing TSTs in Suriname that are not supported by ATS or other guidelines. The requirement of a TST before being allowed to emigrate to another country is not subject to our decision making, and therefore cannot be abandoned, but the cut-off value for the designation of a positive result should be raised to 15 mm in people with no TB risk factors. Given the low TB incidence, requesting a TST for elderly home admissions or work permits is not indicated and should in our view be abandoned. In such cases anamnesis, physical examination, and chest X-rays should suffice to rule out infectious tuberculosis.

The cut-off value of 5 mm for people with HIV should be maintained and followed by an examination of sputum using the GeneXpert test. If this test is negative, initiation or continuation of ART should be advised. This advice is based on our finding that most HIV infected TB patients in Suriname have low CD4 counts and/or are not using ART [21].

The cut-off value of 5 mm should also be used and designated positive for those in recent contact with TB patients. For patients with medical conditions the cut-off value should be related to TB exposure and illness being a risk factor for TB, as advocated by the ATS [9].

All patients with a TST result of over 15 mm should be considered infected, but before the diagnosis of LTBI is considered and IPT is offered, it is important to verify that such a patient does not have active TB.

If IPT is contra-indicated, rejected, or terminated due to side effects, patients should be followed by the pulmonologist and properly instructed to report symptoms that could indicate active TB.

Regarding children, the very low number of children under 5 years of age with a positive TST result in our cohort is probably because children are preferentially referred to the pediatrician and does not allow for any conclusions or suggestions about alterations to the algorithm applied to this age group.

In view of our results, we recommend the TST cut-off value to be set at 15 mm for people with no risk factors for TB, based on the following data: Suriname is a low TB incidence country, with an abundant prevalence of NTM and historical nonspecific tuberculin reactivity, where progression to active TB—in persons with a TST test designated positive by the current NTP guidelines—is very low.

The strength of our study is the sample size of the population that could be evaluated during a prolonged testing period. We assume that our study cohort is representative for the tested population in Suriname since people with a positive TST result are almost exclusively referred to the pulmonologist. A limitation of this study is that while our outpatient clinic is the only pulmonary medicine clinic in Suriname, we may have missed patients with a positive TST result who did not visit our clinic after referral by the NTP, particularly people living in remote areas of the country with limited access to health care. Another limitation of our study concerns patient follow-up. Over half of patients with a positive TST result, including one in four patients classified as LTBI, were lost to follow-up or had no follow-up appointment with the pulmonologist. We may have missed people developing active TB who moved abroad and people who have died of TB without being diagnosed as such.

In conclusion, considering the incidence of TB and NTM in Suriname, our study emphasizes that TST results should be interpreted depending on the reason the TST was requested—in line with TB risk assessments and in conjunction with the incidence of TB and NTM—as advocated by the ATS. Diagnosis of LTBI should be made considering the TST in relation to regional TB incidence, patient exposure to TB and chest X-ray abnormalities compatible with undiagnosed TB. Adherence to this policy may lead to healthcare cost reductions and could result in less anxiety and less inconvenience for patients. In our opinion the TST remains a valuable tool in the diagnosis of LTBI, especially in resource-limited settings and in the absence of advanced diagnostic means. As such, our results probably may be of value to communities with a comparable TB incidence.

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Author contributions

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5

Should treatment of low-level rifampicin mono-resistant tuberculosis be different?

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Abstract

Background

Rifampicin resistant tuberculosis (RR-TB) was frequently detected in Suriname after the introduction of Xpert MTB/RIF in 2012. Subsequent phenotypic drug-susceptibility testing (DST) was not conclusive at that moment, while RR-TB patients treated with first-line tuberculostatics had good treatment outcome. In our study, we analyzed this interesting observation.

Methods

We collected demographic and clinical characteristics and treatment outcome of TB patients from May 2012-December 2018 and performed a univariate and multivariate analysis to assess possible associations with resistance to rifampicin. Secondly, we conducted whole genome sequencing on all available *Mycobacterium tuberculosis* isolates that had a rifampicin resistance in the Xpert MTB/RIF test and performed phenotypic DST on selected isolates.

Findings

RR-TB was detected in 59 (9.6%) patients confirmed by Xpert. These patients were treated with rifampicin-containing regimens in most (88%) of the cases. In all 32 samples examined, a D435Y mutation in the *rpoB* gene was identified; only one isolate revealed an additional isoniazid mutation. Phenotypic DST indicated low-level rifampicin resistance. In multivariate analysis, the Creole ethnicity was a factor associated with rifampicin resistance (aOR 3.5; 95%CI 1.9–6.4). The treatment success rate for patients with RR-TB (78.0%) was comparable to the treatment outcome in non-RR-TB patients 77.8%.

Interpretation

This study confirms a low-level rifampicin mono-resistance in TB patients of Suriname. These patients could benefit from a first-line regimen with high dose rifampicin (or rifabutin), rather than from the lengthy treatment regimens for rifampicin-resistant and multi-drug resistant TB, a concept of stratified medicine also advocated for the treatment of TB.

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Keywords: Drug resistance; Treatment Outcome; Xpert MTB/RIF; Drug-susceptibility testing; Tuberculosis

1. Introduction

Globally, an estimated 10 million people developed tuberculosis (TB) in 2018; half a million of them had rifampicin-resistant (RR) TB [1], of which 78% had also confirmed resistance to isoniazid (INH) and were hence classified as multidrug-resistant (MDR) TB.

The last decade brought large improvements in the diagnosis and treatment of RR/MDR-TB [2]. For instance, rifampicin resistance can now be diagnosed with rapid molecular tests and new effective second-line drugs as bedaquiline and linezolid, are now included in injection-free treatment regimens recommended by the World Health Organization (WHO) [3]. The new diagnostic tests and drugs have become available to low and middle-income countries at special pricing schemes e.g. through support of the Global Fund to fight AIDS, TB and Malaria. Despite these advances, globally only 51% of patients with confirmed TB were tested for rifampicin resistance in 2018. Moreover, only 33% of all estimated RR/MDR-TB patients were enrolled in treatment, with a treatment success rate of 56% [1].

Suriname is a country with a multi-ethnic population of 575,991 in 2018 (https://data.worldbank.org/country/Suriname) consisting of Hindustani (27%), Maroon (22%), Creole (16%), Javanese (14%), mixed (13%) or people with other ethnic background (8%) (https://statistics-suriname.org/nl/censusstatistieken-2012–2/). The TB notification rate was 30 per 100,000 population in 2018; WHO estimated the TB incidence at 38 per 100,000 [1]. Before 2012, drug susceptibility testing (DST) was not routinely available in Suriname. Samples were sent abroad, and only two MDR-TB patients were diagnosed from 2005 till 2011. In May 2012, the Xpert® MTB/RIF test (Cepheid, Sunnyvale, CA, USA) was introduced in Suriname. The unexpected high proportion of rifampicin-resistant Xpert results has puzzled national and international TB experts for several years. Phenotypic drug susceptibility testing (DST) performed by one international laboratory in 2012 showed susceptibility to rifampicin, while re-analysis by the supranational reference laboratory several years later showed rifampicin resistance in these strains [4]. In 2018, 12.4% of confirmed cases in Suriname had RR-TB, which is the highest proportion in the WHO Region of the Americas [1].

This study aims to identify characteristics of the RR-TB patients in Suriname, understand the resistance pattern found, search for similar strains in the Netherlands, a country with strong historical ties to Suriname, and identify possible implications for treatment recommendations.

2. Methods

2.1. Patients

In Suriname, TB patients are mandatory reported to the National Tuberculosis Program (NTP), which maintains an electronic national TB register. In our study, we included TB patients who were notified between May 2012 and December 2018. Patients were treated according to National Treatment Guidelines, which had been based on the 2010 Caribbean TB guidelines [5], with a standard regimen of isoniazid, rifampicin, ethambutol and pyrazinamide. Streptomycin and/or ciprofloxacin were added to the regimen in some patients who had previous TB treatment or RR-TB. Patients treated with a regimen without rifampicin were treated for 12–18 months. Patients, including those with RR-TB, were not actively followed up after treatment completion.

The following data were obtained from the register: sex, age, ethnicity, site of disease, smear results, Xpert results, drug-resistance, case type (new or previously treated), current TB treatment regimen, co-morbidities (HIV, diabetes mellitus), illicit drug use (marihuana or hard drugs) and treatment outcome. Treatment outcomes (including RR-TB) were based on the definitions and reporting framework for drug-sensitive TB [6], e.g., failure was defined if the sputum was microscopically or culture positive after 5 months treatment and cure if the smear was microscopically negative after 6 months treatment. A positive smear was graded as previously described [7].

We compared demographic and clinical characteristics of Xpert-confirmed rifampicin-sensitive and rifampicin-resistant TB patients. Data were analyzed with SPSS version 24 (SPSS, Inc., Chicago, IL, USA), including a univariate analysis to estimate the Odds Ratio (OR) and 95% Confidence Intervals (95%CI) and a multivariate regression analysis including those variables that attained a P value < 0.25 in the univariate analysis.

2.2. Mycobacterium tuberculosis isolates Suriname

In Suriname, samples of all TB patients are sent to the Central Laboratory, which accommodates the national TB reference laboratory, and performs culture (Löwenstein Jensen) and strain identification (SD BIOLINE TB Ag MPT64). Cultured *M. tuberculosis* isolates are stored at minus 80° Celsius.

In 2018, 32 stored Xpert rifampicin-resistant *Mycobacterium tuberculosis* isolates were re-cultured and sent to the National Tuberculosis Reference Laboratory of the National Institute for Public Health and the Environment (RIVM) in the Netherlands for further analysis. These isolates were from patients diagnosed in 2012 (n = 4), 2013 (n = 4), 2014 (n = 10), 2015 (n = 8), 2017 (n = 3) and 2018 (the first three RR-TB patients in that year).

Rifampicin-resistant *M. tuberculosis* isolates from 2016 were not available for analysis. At the RIVM, whole genome sequencing (WGS) was applied to detect mutations associated with resistance and to determine the genetic distance between the isolates, as a proxy for epidemiological links between cases. Additionally, reverse line blot assays (GenoType MTBDR*plus*® Hain Lifesciences, Nehren, Germany) and phenotypic DST were performed on selected isolates.

2.3. Similar isolates in the Netherlands

We searched the Dutch TB laboratory database at the RIVM for isolates with the same mutation found in Suriname and obtained data from the Dutch National TB Register of patients infected with *M. tuberculosis* isolates with this mutation. Isolates that were possibly identical with the strain found in Suriname were subjected to WGS.

2.4. Ethical consideration

Ethical approval for this study was obtained from the Human Scientific Research Ethic Committee of the Ministry of Health of Suriname. The Dutch National TB Registration Committee approved the use of the data from the Netherlands for this study.

3. Results

3.1. Patients

Between May 2012 and December 2018, a total of 978 TB patients were notified to the NTP in Suriname. The male–female ratio was 2.5 (696 male patients; 71%) with a median age of 42 years (interquartile range [IQR] 29–53). Patients' ethnicity was mostly Creole (32%), followed by Maroon (16%), Hindustani (15%) or mixed ethnicity (16%). Eighty-six percent (n = 838) of the patients had pulmonary TB; 599 had a smear positive sputum with microscopy (71% of pulmonary TB patients). Xpert was positive in 64% (n = 623) of the patients; whilst negative or not done in the remaining 36% (n = 355) of patients. Rifampicin resistance was determined in 59 (9.5%) of Xpert-positive patients (Table 1). Nine percent of patients (n = 91) were previously treated for TB. HIV status was known in 939 patients (96%) and HIV co-infection was present in 23% (n = 218) of tested patients. Diabetes mellitus was prevalent in 13% of the patients (n = 123) and illicit drug use was reported in 24% (n = 239) of the patients.

Table 1. Total number of tuberculosis (TB) and Xpert MTB/RIF rifampicin-resistant TB patients in Suriname, May 2012 - December 2018.

Year	Number of TB patients	Number of patients with confirmed diagnosis by Xpert MTB/RIF	Number of rifampicin-resistant TB (by Xpert MTB/RIF)	Proportion Xpert MTB/RIF-positive patients with rifampicin resistant TB
May-Dec. 2012*	98	74	8	10.8
2013	141	91	8	8.8
2014	158	112	10	8.9
2015	150	78	8	10.3
2016	116	80	4	5.0
2017	136	83	8	9.6
2018	179	105	13	12.4
Total	978	623	59	9.5

Notes.
Abbreviations: TB = tuberculosis
*The total number of tuberculosis patients in the year 2012 (January-December) was 135

In univariate analysis, RR-TB patients were significantly more often in the age group 45–60 years (reference 15–24 years), had the Creole ethnicity, were previously treated for TB, had HIV co-infection and had documented illicit drug use, compared to patients with rifampicin-sensitive TB. Pulmonary RR-TB patients had more frequently microscopy-positive sputum smears (97%; 56/58) than pulmonary rifampicin-sensitive-TB patients (88%; 480/548) ($p = 0.07$). In multivariate analysis, patients with RR-TB were significantly more often of Creole ethnicity (aOR 3.5) (Table 2). HIV and illicit drug use were confounding factors related to Creole ethnicity: 32% (64/198) of all Xpert-positive Creole TB patients were HIV co-infected and 42% (84/198) had documented illicit drug use versus respectively 12% and 23% of patients with other ethnicities.

Treatment outcome was successful (cured/completed) in 74.6% of all TB patients, in 77.8% of patients with Xpert rifampicin-sensitive TB and in 78.0% of patients with Xpert diagnosed RR-TB (Table 3). Second-line drugs (ciprofloxacin (n = 15), streptomycin (n = 2), or both ciprofloxacin and streptomycin (n = 20)) were added to the standard first-line treatment regimen in 37 patients; 21 of these patients had rifampicin-sensitive TB (4% of all rifampicin-sensitive TB patients) and 16 had RR-TB (27% of all RR-TB patients). Fifty-two (88%) RR-TB patients were treated with rifampicin-containing first-line regimens (11 out 52 were also treated ciprofloxacin and/or streptomycin), five (8%) patients were treated with the first-line drug regimen without rifampicin, but to which was added ciprofloxacin and/or streptomycin, and two (3%) patients did not start treatment.

In total, 12 RR-TB patients were previously treated for TB (one person was treated for TB two times and another person three times) (Table 4). Three of these patients restarted treatment after discontinuing the treatment in the first episode (two had RR-TB in the first episode, the other one had a diagnosis before 2012) and nine completed treatment in the first episode (two diagnosed with RR-TB before, one with rifampicin-sensitive TB, five had a TB diagnosis before 2012 with an unknown resistance pattern, and in one patient DST was not done in the previous episode).

Table 2. Demographic and clinical factors of tuberculosis patients with positive Xpert MTB/RIF results in Suriname, May 2012 -December 2018.

Characteristics	Patients with rifampicin sensitive TB (n = 564)		Patients with rifampicin-resistant TB (n = 59)		Unadjusted odds ratio		Adjusted odds ratio	
	N	%	N	%	OR	CI	OR	CI
Male sex	420	74.5	48	81.4	1.5	0.8-3.0	0.9	0.4-2.0
Age group								
0-14 years	12	2.1	2	3.4	4.0	0.7-23.0	5.9	1.0-35.3
15-29 years	121	21.5	5	8.5	1		1	
30-44 years	167	29.6	16	27.1	2.3	0.8-6.5	1.4	0.5-4.2
45-59 years	187	33.2	32	54.2	4.1	1.6-10.9	2.4	0.9-6.8
60 years and above	77	13.7	4	6.8	1.3	0.3-4.8	1.0	0.3-4.1
Ethnicity*								
Creole	161	28.5	37	62.7	1		3.5	1.9-6.4
Other than Creole ethnicity	*(403)*	*(71.5)*	*(22)*	*(37.3)*	*(4.2)*	*(2.4-7.4)*	1	
Maroon	87	15.4	5	8.5	0.3	0.1-0.7		
Mixed	98	17.4	5	8.5	0.2	0.1-0.6		
Hindustani	85	15.1	7	11.9	0.4	0.2-0.8		
Javanese	64	11.3	4	6.8	0.3	0.1-0.8		
Amerindian	58	10.3	1	1.7	0.1	0.0-0.6		
Other/Unknown	11	2.0	0	0.0	0.0			
Pulmonary TB	548	97.2	58	98.3	1.7	0.2-13.0		
Previous TB treatment	46	8.2	12	20.3	2.9	1.4-5.8	2.0	1.0-4.3
HIV positive	95	16.8	20	33.9	2.5	1.4-4.5	0.8	0.4-1.5
Diabetes mellitus	98	17.4	7	11.9	0.6	0.3-1.5		
Illicit drug use	155	27.5	27	45.8	2.2	1.3-3.8	0.7	0.4-1.2

Notes.
Abbreviations: CI = 95% confidence interval; HIV = human immunodeficiency virus; OR = odds ratio; TB = tuberculosis
* Creole: descendant of African slaves that may also have European and other ancestors; Maroon: descendant of escaped African slaves; Hindustani: descendant of contract laborers from what was then British India; Javanese: descendant of contract laborers predominantly from Java, Indonesia [30].

Table 3. Treatment results of tuberculosis patients in Suriname, May 2012 - December 2018.

	All TB patients		TB patients with positive Xpert MTB/RIF with negative test for rifampicin resistance		TB patients with positive Xpert MTB/RIF with positive test for rifampicin resistance	
	N	%	N	%	N	%
Successful (cured/completed)	730	74.6	439`	77.8	47	79.7
Treatment failed	2	0.2	2	0.4	0	0.0
Died	136	13.9	59	10.5	4	6.8
Lost to follow-up	68	7.0	42	7.4	6	10.2
Treatment stopped (medical reason)	21	2.1	5	0.9	1	1.7
Not evaluated*	21	2.1	17	3.0	1	1.7
Total	978		564		59	

Notes.
Abbreviations: TB = tuberculosis
*Not evaluated: patients transferred out and patients whose treatment outcome was unknown.

Table 4. Patients with rifampicin-resistant tuberculosis in Suriname who were previous treated for tuberculosis, May 2012 - December 2018.

	Previous episode(s)			Last episode (RR-TB)	
Number	Year(s)	DST	Treatment result	Year	Treatment result
1	2009	Unknown		2012	Cured
2	2009	Unknown	Cured	2012	Cured
3	2012	RR	LTFU	2013	LTFU
4	2009	Unknown	Cured	2013	Cured
5	2012	RR	LTFU	2013	LTFU
6	2000	Unknown	LTFU	2014	Cured
7	2013	RR	Cured	2014	Cured
8	2013	RR	Cured	2015	Cured
9	2008	Unknown	LTFU	2017	Died
	2015	ND	Cured		
10	2013	Sensitive	Cured	2017	LTFU
11	2014	ND	Completed	2017	LTFU
	2015	ND	LTFU		
	2016	ND	Cured		
12	2010	Unknown	Cured	2018	Cured

Notes.
DST = drug susceptibility test; LTFU = lost to follow-up; ND = not determined; RR = rifampicin resistance; TB = tuberculosis.

Table 5. Patients with Mycobacterium tuberculosis isolates with a D435Y mutation in the Netherlands, 2003-2018.

Number	Year	Country/region of birth	Drug-susceptibility test results			
			INH	RIF (MIC)	RIF (MGIT; 1 mg/l)	RBT
1.	2003	Eastern-Europe	R	R (>5 mg/L)	ND	S
2.	2003	Netherlands	R	R (2 mg/L)	ND	S
3.	2003	European Union	R	R (2 mg/L)	ND	S
4.	2005[1]	Suriname	S	R (2 mg/L)	ND	ND
5.	2006	Netherlands	R	S (0.5 mg/L)	ND	S
6.	2010[1]	Suriname	S	ND	S	ND
7.	2011	European Union	R	R (2 mg/L)	R	S
8.	2011	Africa	R	R (2 mg/L)	ND	S
9.	2012	Africa	R	R (2 mg/L)	ND	R
10.	2012[1]	Suriname	S	ND	S	ND
11.	2013	Asia	R	ND	R[2]	R[2]
12.	2014[1]	Suriname	S	R (2 mg/L)	ND	S
13.	2016	Eastern-Europe	R	ND	S	S
14.	2016	Africa	R	S (0.5 mg/L)	S	S
15.	2017[1]	Suriname	S	R (5 mg/L)	S	S

Notes.
Abbreviations: INH = isoniazid; MGIT = Mycobacteria Growth Indicator Tube; MIC = minimal inhibitory concentration (by Middlebrook 7H10 agar proportion method); ND = not determined; R = resistant; RBT = rifabutin; RIF = rifampicin; S = susceptible.
[1]Patients 4, 6, 10, 12 and 15 had clustering *M. tuberculosis* isolates in Whole Genome Sequencing (≤12 single nucleotide polymorphism difference).
[2]The *M. tuberculosis* isolate had two mutations in the *rpoB* gene (i.e., D435Y and S450L).

3.2. Whole genome sequencing (WGS) and additional laboratory tests

WGS revealed a D435Y mutation in the *rpoB* gene in all 32 rifampicin-resistant *M. tuberculosis* isolates. One isolate had an additional resistance mutation in the *inhA* gene S94A, but not in the more common *inhA* promoter gene region, and by definition labelled as MDR. None of the remaining 31 isolates had additional first-line drug resistance-associated mutations in the *katG*, *inhA*, *fabG1*, *ahpC*, *embA*, *embB*, *pncA*, or *rpsA* genes. The 32 isolates were all linked together by WGS in one genetic cluster with ≤ 12 single nucleotide polymorphisms (SNPs) difference to each other.

The GenoType MTBDR*plus* analysis of 14 isolates (from 2015 to 2018) showed loss of hybridization of wild type probes 3 and 4, and no hybridization of the known and most frequently reacting mutation probes. Phenotypic DST, done by the Middlebrook 7H10 agar proportion method [8], indicated a MIC (minimal inhibitory concentration) for rifampicin of 1–5 mg/L, known as low level resistance (cut-off is 1 mg/L) and showed susceptibility to rifabutin for the three isolates tested (all patients diagnosed in 2018). These three isolates were also tested in the MGIT and were found susceptible to rifampicin.

3.3. D435Y isolates and patients in the Netherlands

The Dutch national TB laboratory database contained 15 *M. tuberculosis* isolates with the same D435Y mutation found in Suriname (Table 5). The isolates were from patients born in Europe (n = 6), Suriname (n = 5), Africa (n = 3) and Asia (n = 1). The isolates from the 10 non-Suriname-born patients were resistant to isoniazid and 8 out of 10 susceptible to rifabutin; patients were treated accordingly (Table 5). The isolates from the 5 Suriname-born patients were all susceptible to isoniazid, rifampicin-susceptible in two cases (both tested by MGIT-DST) and low-level rifampicin-resistant in three cases (one patient with recurrent TB was counted twice; all these isolates were tested by Middlebrook 7H10). The two patients with rifampicin-sensitive TB completed standard first-line treatment, including standard dose rifampicin. One RR-TB patient was treated for 6 months with a first-line regimen, containing rifabutin instead of rifampicin, to which the strain was susceptible. The patient diagnosed twice with RR-TB first completed 12 months treatment with isoniazid, ethambutol, moxifloxacin, and 2 months pyrazinamide, but developed RR-TB again after ten years. This second time, he was treated for 6 months with the first-line drug regimen, with rifabutin, to which the strain was susceptible, replacing rifampicin. Genotypically, all five *M. tuberculosis* isolates of the Suriname-born patients in the Netherlands clustered in the WGS with those of the 32 patients diagnosed in Suriname.

4. Discussion

Our study shows that rifampicin-resistant TB in Suriname is caused by a *M. tuberculosis* isolate with a D435Y mutation in the *rpoB* gene, known to be associated with a low-level resistance for rifampicin [9], [10], [11], [12]. Only one patient had also an uncommon mutation coding for isoniazid resistance and hence had MDR-TB; all other RR-TB patients had rifampicin mono-resistant isolates. RR-TB patients were mainly treated with rifampicin-containing regimens. Treatment outcome was similar in patients with rifampicin-sensitive and RR-TB, with a successful treatment completion rate of 78% in both groups. Patients were not actively followed up after treatment completion and only identified with recurrent TB if they presented with symptoms and were diagnosed. Patients with isolates harboring the D435Y mutation were also identified in the Netherlands, but only the patients born in Suriname had an infection with a rifampicin mono-resistant strain. These patients had been treated either as rifampicin-sensitive TB, or with first-line regimens including rifabutin.

Rifampicin resistance in *M. tuberculosis* is mostly caused by an undisputed mutation in the *rpoB* gene, most commonly the S450L mutation. The D435Y mutation described in our study is a mutation with disputed drug-resistance and characterised by a substitution of the amino acid asparagine (Asp/D) by tyrosine (Tyr/Y) in codon 516 [13]. In the previous classification with *E. coli* codon numbering, this mutation was known as D516Y or GAC516TAC and renamed with the H37Rv numbering to D435Y. Studies investigating the accuracy of current laboratory tests to identify resistance in D435Y mutation isolates concluded that low level rifampicin resistance is often missed in the single point concentration MGIT-DST, while it is identified by MIC methods like Middlebrook 7H10 and Löwenstein-Jensen and by molecular test such as Xpert and MTBDR*plus* [9], [10], [11], [14]. Other studies concluded that the rifampicin resistance is often borderline or low level [12], [15], [16], [17], [18], [19]. Almost all studies concluded that isolates with a D435Y mutation are susceptible to rifabutin [10], [15], [16], [17], [20].

The Suriname NTP had difficulties in the interpretation of the rifampicin resistance detected by the Xpert test. In 2012, six Xpert rifampicin-resistant *M. tuberculosis* isolates were transported to an international laboratory, where MGIT-DST and 7H10 Middlebrook MIC method revealed susceptibility to rifampicin in all isolates. In 2016, the supranational reference laboratory of Massachusetts re-analysed these isolates using an agar proportion method and found rifampicin resistance in four of the six isolates. Furthermore, it performed PCR-mediated direct DNA sequencing of the *rpoB* gene on these six isolates and on 10 lysates of Xpert rifampicin-resistant *M. tuberculosis* isolates from 2014, revealing the D435Y mutation in 14 of the 16 samples [4].

WHO's treatment advise on rifampicin mono-resistant TB has changed over time. In the first guidelines on drug-resistant TB, a 12–18 months regimen with isoniazid, ethambutol and a fluoroquinolone, and pyrazinamide for at least two months, was recommended [21]. These guidelines also advised a retreatment regimen with first-line drugs and streptomycin ("Category 2 regimen") for patients with relapse or return after loss to follow-up. In 2011, WHO published an update stating that the detection of rifampicin resistance by Xpert test usually suffices to prescribe second-line TB regimen [22], but also cautioned for situations in which the Xpert test has a low predictive value and advised that results need to be confirmed by phenotypic DST or line probe assay. The update also noted that a potential harm from placing all rifampicin-resistant patients on an MDR-TB regimen, was the exclusion of isoniazid from their treatment, thus depriving them of a safe and useful bactericidal drug [22]. A systematic review in 2016 identified only three studies reporting treatment outcomes for patients with RR-TB, preventing a *meta*-analysis [23]. Since 2016, WHO guidelines on drug-resistant TB recommend similar treatment regimens for patients with RR-TB and MDR-TB [3], [24]. The guideline for treatment of TB and RR/MDR-TB in Suriname was updated following these latest recommendations of the WHO and does not include ciprofloxacin and streptomycin anymore because of limited evidence of their effectiveness and sterilizing activity.

The clinical relevance of disputed mutations with low-level rifampicin resistance has been an issue of debate. One study indicated that disputed mutations had the same poor clinical prognosis as the most frequent undisputed mutations [25]. Williamson *et al.* suggested to conduct a multi-center retrospective study to correlate the different types of *rpoB* mutations with clinical outcomes [18]. They stated that the retrospective nature of such a study would actually become a methodological strength, as it would allow data on treatment outcome to be obtained, and thus allow the clinical relevance of mutations to be assessed [18]. We consider our observational study to be such a study that contains, to our knowledge, the largest set of patients infected with *M. tuberculosis* strains carrying the D435Y mutation. Our observation of good treatment results of patients with this peculiar type of low-level rifampicin resistance and susceptibility for isoniazid, suggests that treatment regimens with isoniazid and rifampicin can still be effective. The relatively high number of RR-TB cases with previous TB treatment is a concern and suggests that a sterilizing effect was not achieved. However, one-quarter of these patients did not complete the previous treatment which obviously contributed to relapse, while reinfection is also possible in an environment with ongoing transmission.

Several authors have proposed alternative treatment options for patients infected with a low-level rifampicin resistance, e.g. a higher dose of rifampicin or replacing rifampicin by rifabutin [10], [16], [18], [20], [26]. The currently recommended dose of rifampicin has been challenged over the last years [27], [28]. Dosage studies indicate that 35 mg/kg rifampicin instead of 10 mg/kg is well tolerated and more effective than the standard dose [29], [30]. These authors recommend high dose rifampicin for patients with TB meningitis, co-infection with HIV, diabetes mellitus and serious ill TB patients, since plasma concentrations of rifampicin are often too low. Our hypothesis is that patients with low-level rifampicin mono-resistant TB could benefit more from a first-line regimen, including isoniazid and high dose rifampicin (or rifabutin), rather than from a lengthy regimen for RR/MDR-TB treatment or the standard TB treatment. We have developed a study to treat these patients accordingly in Suriname and a protocol has been developed and cleared by the Human Scientific Research Ethic Committee, and includes informed consent of the patient for treatment with high-dose rifampicin (30 mg/kg); timely WGS testing of all RR-isolates; measuring of rifampicin blood levels; close supervision of treatment, including monitoring of side effects; case discussion in a Concilium; and a minimal follow-up of one year after treatment.

Our study also revealed several other issues, some beyond the scope of this study. All examined isolates of RR-TB patients, both found in Suriname and the Netherlands, belonged by WGS genetically to one large molecular transatlantic cluster. Transmission of the rifampicin-resistant strain is likely to be ongoing in Suriname, and possibly also in the Netherlands. Second, the observed TB/HIV co-infection rate (23%) is one of the highest in the WHO Region of the Americas [1]. More TB/HIV collaborative efforts are needed to control TB and move towards TB elimination in Suriname. RR-TB was more often detected in Creole people, which is also the ethnic group with a very high TB incidence, HIV co-infection rates and illicit drug use. Our data show a high TB case fatality of 14%, which has been associated with higher age and HIV co-infection [31].

Our study had several strengths and limitations. We made use of a detailed electronic database and advanced molecular tests were applied on a subset of rifampicin-resistant *M. tuberculosis* isolates, although not all rifampicin-resistant isolates were available for additional typing. The 100% concordance of rifampicin resistance found by Xpert in Suriname and by WGS done in the Netherlands, confirmed that these patients actually had RR-TB. The major limitation of our study is that RR-TB patients were not actively followed up for recurrent TB after treatment completion. We will address this issue in the planned prospective study. Our analysis did not include rifampicin-susceptible isolates. Recently, we analyzed another 118 lysates, including 18 rifampicin-resistant strains of patients diagnosed in 2018–2020.

All rifampicin-resistant isolates had the D435Y mutation; none of the other strains carried mutations in the *katG* or *inhA* genes or had other first-line drug resistance-associated mutations.

The findings of our study provide clarity to the rifampicin resistance situation in Suriname and possible implications for tailored treatment regimens. Our study shows that an epidemic of RR-TB was driven by a mutation of which the clinical significance is disputed. All but one strains examined revealed low-level rifampicin resistance and isoniazid susceptibility. Treatment results with rifampicin-containing regimens were unexpectedly good. Further research is needed to study alternative treatment options for these patients, such as regimens with high dose rifampicin for these specific group of patients, with systematic follow-up after treatment completion. We state that one size does not fit all for the treatment of RR/MDR-TB, i.e. some people need XL (extra-large) and others XS (extra-small) treatment regimens, depending on the causative strain. Technological advances make it increasingly possible to tailor treatment to the patient and their bacteria. Furthermore, collaborative networks of professionals and countries with different resources can work together to provide the necessary scientific evidence for effective XL or XS RR/MDR-TB treatment regimens. In the end, we want to provide each patient the right treatment, not too much and not too little, a concept of stratified medicine also advocated for the treatment of TB [32].

Ethical statement

Ethical approval for this study was obtained from the Human Scientific Research Ethic Committee of the Ministry of Health of Suriname. The Dutch National TB Registration Committee approved the use of the data from the Netherlands for this study.

CRediT authorship contribution statement

F.A. Gopie: Conceptualization, Methodology, Writing - original draft. **E. Commiesie:** Conceptualization, Methodology, Writing - original draft. **S. Baldi:** Data curation, Writing - review & editing. **M. Kamst:** Data curation, Writing - review & editing. **D. Kaur:** Writing - review & editing. **W.C.M. de Lange:** Writing - review & editing. **P.S. Pinas:** Writing - review & editing. **D. Stijnberg:** Data curation, Writing - review & editing. **M. Wongsokarijo:** Data curation, Writing - review & editing. **C.W.R. Zijlmans:** Writing - review & editing. **R. de Zwaan:** Writing - review & editing. **D. van Soolingen:** Writing - review & editing. **S.G.S. Vreden:** Supervision, Writing - review & editing. **G. de Vries:** Conceptualization, Formal analysis, Methodology, Supervision, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Niagara Falls International Rainbow bridge [Canada-US], 2018.
Source: Gopie F.A.

6
Discussion

Tuberculosis (TB) affected an estimated 10 million people in 2019, with a global mortality of 1.2 million, and an additional 208,000 deceased patients who were co-infected with HIV [1]. Between 2000 and 2015, some 33 million people have died due to TB according to WHO estimates. The global financial loss in that same period was about 616 billion US$, and if no action is taken another 28 million deaths due to TB could occur between 2015 and 2030, as well as a global financial loss of 984 billion US$ [2]. To address this unfavorable outlook, the WHO has launched the End TB Strategy 2035, which should result in reduction of TB deaths by 95% and cut new cases of TB by 90% between 2015 and 2035 and ensure that no family is confronted with catastrophic expenses owing to TB [3].

TB is a well-treatable disease, with crucial treatment aspects being a) availability of appropriate tuberculostatic drugs; b) treatment adherence of patients; and c) drug susceptibility testing. Knowledge of the patient's HIV status and other medical conditions as diabetes mellitus (DM) and renal insufficiency is important for treatment success, as well as the socioeconomic status and other risk factors for TB such as drug abuse, which have a negative effect on treatment outcome [4], [5], [6]. Another population to reckon with are Indigenous people. As shown by Cormier et al. in their systematic review, Indigenous populations are vulnerable to TB [6].

TB contact tracing and the treatment of latent tuberculosis infection (LTBI)—a reservoir of TB, which can progress to active TB when the patient is immunocompromised—are important means toward TB control and eradication. But diagnosing LTBI can be challenging as there is no gold standard to this diagnosis [7]. This problematic situation is illustrated by the WHO's recent adjustment of the global estimate of the number of people living with LTBI. The estimate was decreased from one-third to one-fourth of the global population having LTBI [8], [9]. An applicable algorithm to diagnose LTBI, is the one advocated by the American Thoracic Society (ATS) and the Centers for Disease Control and Prevention [10].

Traditionally, the diagnosis of TB is assumed on basis of the anamnesis, clinical findings, chest X-ray, and (sputum) microscopy and afterwards confirmed by the growth of *Mycobacterium tuberculosis* in culture samples [11]. The most-used culture medium is Lowenstein-Jensen solid media, with the disadvantage of the time required for bacillary growth, which can be up to 6 weeks for paucibacillary TB. Drug susceptibility testing (DST) is also mostly performed on Lowenstein-Jensen solid media and could take up to 8 weeks before results are available. In the 1980's, liquid medium for the isolation of mycobacteria and DST was introduced, including the MGIT (mycobacterial growth incubator tube) system, which significantly decreases TB detection times.

Additionally, the last two decades have brought enormous improvement in TB diagnostics and DST, such as fluorescence microscopy, nucleic acid amplification tests, and line probe assays, which can detect TB as well as drug resistance [12].

Drug resistant TB has become a matter of great concern and is a public health threat. Resistance to tuberculostatic drugs can be a primary resistance, in a patient never treated for TB, due to infection with a drug resistant TB strain. More frequently the case is one of acquired resistance during treatment for TB because of inappropriate use of medication and poor compliance by patients or inadequate treatment regimens prescribed by physicians. Other means of acquired drugs resistance are irregular drug supplies and poor drug quality with low bioavailability [13]. In 1943 to 1944, para-aminosalicylic acid and Streptomycin were the first drugs introduced for the treatment of TB. In the following years, many drugs (isoniazid in 1952 and rifampicin in 1972) have been introduced for the treatment of TB, with rifampicin being the cornerstone in the WHO recommended first-line TB treatment regimen consisting of isoniazid, rifampicin, ethambutol, and pyrazinamide. Anno 2019, worldwide, about 3.3% of new TB cases and 17.7% of previously treated TB cases were diagnosed with drug resistant TB, and, in total, an estimated half million patients worldwide had rifampicin resistant TB, with 78% of them being multidrug resistant TB cases [1]. The development of new drugs against TB has been slow and it is only recently that new drugs to treat drug resistant TB, such as linezolid, bedaquiline, and delamanid [14], [15], have been approved by the WHO.

The Bacillus Calmette-Guerin (BCG) vaccine against TB, has shown to be less effective in adults to prevent pulmonary TB and hence ineffective in preventing TB spread [16]. To contain the spread of (drug resistant) TB and to reach the goals of the WHO End TB Strategy by 2035, the development of new TB vaccines has become a priority for the WHO.

In Suriname, the National Tuberculosis Program is the guardian of the national TB registry and is, among other things, also responsible for TB contact tracing, directly observed therapy (DOT), providing incentives to TB patients and supply tuberculostatic drugs free of charge to these patients. Treatment of TB patients in Suriname is mostly done by the pulmonologist and sometimes by the internal medicine specialist, while children are treated for TB by the pediatrician.

Although TB was determined in just 139 patients in 2019 (incidence of 23.9 per 100.000 population), in the past two decades the number of TB patients has shown a gradual increase, from 90 patients in 2000 to 170 patients in 2018. In 2019 HIV co-infection was detected in 27% of TB patients. Additionally, of the TB patients, 25% reported drug abuse, 30% reported alcohol abuse and 20% were inmates or had been in prison before.

Treatment had been successful in 87% of TB patients in 2018, with mortality being 8.4% and 33% of the deceased patients being co-infected with HIV [17]. A study by Stijnberg et al. on TB patients from Suriname has found that HIV co-infection and older age in men is associated with a higher mortality rate [18].

Our research has uncovered aspects of TB in Suriname that could be utilized to optimize our endeavor to eliminate TB.

Almost all patients diagnosed with TB are natives from Suriname and most patients reported an address in Paramaribo, where transmission of TB occurs the most. Most TB case notifications were from Latour [17], a neighborhood of Paramaribo with a higher degree of poor living conditions [19]. Although people from Brazil, Venezuela, China, and Haiti have immigrated to Suriname in the last 2 decades, foreigners are rarely diagnosed with TB despite all these countries having a much higher incidence of TB compared to Suriname. These immigrants rarely make use of the Surinamese health care system.

Indigenous people and Creoles had the highest notification rate of TB, with risk factors being access to care and low socioeconomic status in Indigenous people and HIV co-infection in Creoles. Creole ethnicity is also associated with rifampicin resistance in Suriname. From 2012 onwards, after the introduction of the GenXpert test, it has become possible to detect rifampicin resistant TB. As further evaluation back then was not possible, the rifampicin resistant samples were kept refrigerated at the Central Laboratory. From 2018 onwards, with assistance of the Rijksinstituut voor Volksgezondheid en Milieu (RIVM) it became possible to evaluate the detected rifampicin resistance. All cases of drug resistant TB turned out to be low level mono resistance to rifampicin, due to the D435Y mutation in the *rpoB* gene [17], [20]. Only one patient also had resistance against isoniazid and hence multi drug resistant TB. Of the 59 rifampicin resistant cases, 47 were new cases, implying ongoing transmission of the same primary rifampicin resistant TB strain. In any case, the introduction of the GenXpert test in 2012 has increased the diagnostic accuracy of TB and shortened the time to diagnose drug resistant TB.

Our study results about the tuberculin skin test (TST) imply that the 10 mm cut-off value for the TST [21] in people not at risk of contracting TB is too stringent, resulting in an excess of positively designated TST results along with the accompanying inconveniences for patients and added costs for the health care system. Another finding to reckon with, is the detection of non-tuberculous mycobacteria (NTM) in the sputum of Surinamese patients treated for TB [22]. The historical nonspecific tuberculin sensitivity in the Surinamese population, reported by Bleiker and van Erpecum from 1962 to 1965 and van Weissenbruch in 1979, should also be considered. As is known, NTM can provoke a false positive TST [23].

As such, the targeted tuberculin testing algorithm of the ATS is a convenient way to evaluate LTBI, which reckons with TB risk factors and infection pressure.

These observations merit changes to the programmatic approach of TB in Suriname. In our endeavor to control and eradicate TB in Suriname certain recommendations could be made.

Most TB patients live in Paramaribo. In the context of active case finding, the identification of possible TB hotspots in Paramaribo and regular surveillance of these hotspots can be performed. Most of the 40.000 Brazilians living in Suriname are goldminers working in the interior of Suriname; a health survey among goldminers could identify people infected with TB. Regular monitoring, especially for infectious diseases, of this everchanging migrant population of goldminers is advisable to provide treatment for diseases and to protect the local native population from infectious diseases.

The uneven distribution of TB among the different ethnicities in Suriname urges the consideration of ethnically correlated risk factors when developing TB intervention programs. Recommendations could be the discouragement of (excessive) alcohol consumption, strict regulation of DM, advocacy of safe sex, and improvement of socioeconomic status for vulnerable groups.

The good treatment results observed in patients with low level rifampicin mono resistance, due to the D435Y mutation in the *rpoB* gene, gives way to personalized medicine or stratified treatment of these patients [24], [25], [26]. First-line tuberculostatic drugs; isoniazid, ethambutol, pyrazinamide, and rifampicin in a dose of 30 mg/kg (to a maximum of 1800 mg) instead of 10 mg/kg, can be prescribed for these patients [27], [28], [29]. The advantage of this regimen is the avoidance of second-line TB treatment, which is expensive, less effective, lengthy and hence can lead to diminished patient compliance. But still, we need to have some stock of WHO recommended second-line tuberculostatic regimens, in case of treatment failure with high dose rifampicin.

Our study results suggest that rifampicin resistant TB in Suriname is likely to be caused by the spread of the same resistant TB strain. This observation suggests a common source of spread, which should be investigated by a dedicated NTP team through thorough case reviews of RR-TB patients, with the focus being on contacts, family relations, leisure activity and professional activities.

Some 20 to 30% of Surinamese TB patients report alcohol use and drug abuse [17], which are risk factors impeding with treatment adherence [30], [31]. The provision of addiction care by the Bureau Alcohol and Drugs (BAD) in our TB treatment program, and the appointment of counselors for drug addicts could result in improved treatment adherence.

When evaluating people for LTBI, the algorithm advocated by the ATS should be used, where the cut-off value of the TST for people not at risk of contracting TB is set at 15 mm. This change of policy will guard patients from inconvenience and can be cost saving. As such the preserved funds can be used to guarantee the availability of the Xpert MTB/RIF test as a diagnostic means, which has increased the diagnostic accuracy of TB and sped up the detection of rifampicin resistant TB. Although resistance to isoniazid in recent years was detected only once, it is advisable to opt for molecular tests which can also detect isoniazid resistance.

In the era before the availability of the GenXpert test in Suriname, all patients with a positive sputum Ziehl-Neelsen (ZN) result and anamnesis compatible with TB disease were treated for TB. In 2012, the Central Laboratory was able to send sputum samples, from 2010 and 2011, abroad for identification. The sputum samples had been stored for months in the refrigerator and the most viable deemed samples, based on their growth pattern (a probable source of bias), were selected for identification. Fortunately, sequential sputum samples of 48 patients could also be identified, a procedure needed to determine TB treatment success. Apart from MTB, growth of NTM was frequently detected in these sputum samples, with growth of two or more NTM in 15 sputum samples. Surprisingly, the most common cultured NTM in HIV infected patients was *M. chordonae* (three samples) followed by *M. avium* complex (two sputum samples). Because NTM species are increasingly identified as a cause of disease in humans, which have a different treatment regimen [32], we recommend that measures be taken to restore the detection and identification of NTM. As such the partial heat-shock protein 65 (hsp65) gene can be used [33]. The hsp65 gene is present in all mycobacteria and due to its variability in the gene sequence, it can be used to identify slow and rapid growing mycobacteria.

Thus, to eliminate TB in Suriname by 2035, our National TB Program should design and implement intervention programs which address the identified TB factors in Suriname, with the focus being on the accurate diagnosis and adequate treatment of TB, the improvement of patient compliance, and the prevention of TB transmission.

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7 Summary

In this thesis we describe the epidemiology of tuberculosis in multi-ethnic Suriname, as well as progress in diagnosis and treatment trends of tuberculosis (TB) in Suriname.

Chapter one gives a general overview of the history of global and regional perspectives of TB.

Chapter two describes the incidence of TB in the different ethnic groups of Suriname and what the probable driving factors of TB in these groups are. The highest TB incidence was noted in Indigenous and Creole people, with the drivers of TB being HIV co-infection in Creole people and probably low access to care and low socioeconomic status in Indigenous people.

Chapter three describes the presence of non-tuberculous mycobacteria (NTM) in the sputum of patients treated for TB prior to the introduction in 2012 of the GenXpert test in Suriname. The most identified NTM were *M. fortuitum* and *M. gordonae*, both present in water. The GenXpert test has increased the accuracy of TB diagnoses and also revealed the presence of rifampicin resistant tuberculosis (RR-TB) in Suriname.

In chapter four, the results, classification and follow-up of the tuberculin skin test (TST) policy in Suriname is evaluated. As there is no gold standard to detect latent tuberculosis infection (LTBI), means such as the TST are used to diagnose LTBI. About one fourth of the global population is estimated to have LTBI, which is a reservoir for active TB. Hence detection and treatment of LTBI is important in the End TB Strategy. In Suriname the TST, also known as the Mantoux test, is used to identify patients with LTBI, with the cut-off values for a positive TST result set at 5 and 10 mm, according to the National Tuberculosis Program guidelines. In our opinion, the cut-off value of 10 mm for people not at risk of TB, is too stringent and results in the overestimation of positive TST results. Based on our evaluation, we advocate a TST cut-off value of 15 mm for people not at risk for tuberculosis, as recommended by the American Thoracic Society (ATS).

In chapter five, RR-TB in Suriname is addressed. Patients from Suriname with RR-TB, detected by the GenXpert test, and who had been treated with first-line tuberculostatics (isoniazide, rifampicin, ethambutol, and pyrazinamide) had a good treatment outcome, comparable to that of patients treated for rifampicin sensitive TB. Molecular analysis revealed this interesting observation to be low-level mono resistance to rifampicin, due to the D435Y mutation in the *rpoB* gene. Being of Creole ethnicity was a risk factor for developing rifampicin resistance.

Letter by van Deun & Decroo and response by Gopie et al.

In a recent addition of the Journal of Clinical Tuberculosis and Other Mycobacterial Diseases, a letter was published by van Deun & Decroo in which some concerns were expressed about our approach. For the purposes of transparency, we have, after obtaining permission from the editor, decided to include the entire letter below, followed by our response.

Letter by van Deun & Decroo

Dear editor,

Gopie and colleagues speculate that triple-dose rifampicin in the World Health Organization (WHO) 6-month Category 1 regimen (Cat1) will cure rifampicin-resistant TB (RR-TB) in Suriname [1]. All RR-TB isolates tested belonged to a single clone with the "disputed" 435Tyr low-level *rpoB* mutation, susceptible to isoniazid and other drugs. Regardless of baseline rifampicin susceptibility 78% of all patients registered were treated successfully and about 1% experienced treatment failure after standard first-line (normal-dose) treatment, with in some patients little effective modifications. Although passive relapse follow-up was recognized as the main study limitation, the possible extent of its impact was overlooked.

Among 59 Surinam NTP RR-TB registrations, 20% (12/59, with 9/12 relapses) were retreatments, significantly higher than 8% (46/564, $P<0.01$) among those with rifampicin-susceptible TB. The effectiveness of first-line treatment for RR-TB with 435Tyr mono-resistance was thus clearly inadequate. Without post-treatment monitoring, the reportedly high success rate is not a reliable measure of relapse-free cure. Indeed, repeated relapse after standard first-line treatment is typical for "disputed" low-level RR-TB [2]. RR-TB transmission uninterrupted by first-line treatment is also suggested by the Surinam RR-TB prevalence, highest of the WHO Americas region. Despite correct 435Tyr resistance diagnosis by Xpert MTB/RIF since its roll-out in 2012, the proportion with RR rose further to 12% in 2018 [1].

In our opinion, this report is an example of the under-estimated threat posed by a good number of *rpoB* mutations with disputed significance for relevant rifampicin resistance. They are often missed in phenotypic, growth-based DST (pDST). Partial inhibition by the drug on top of (strongly) reduced fitness does retard growth in presence of rifampicin to such an extent that resistance has no chance to be identified, particularly with rapid automated methods such as MGIT [3]. Also genotypic methods can miss resistance, particularly in case of heteroresistance, when both mutant and wildtype DNA are present. Due to the presence of wildtype DNA Xpert probes do not drop out but are delayed [4], whereby the resistance cut-off will rarely be reached. In our collection, heteroresistance is found more frequent for these disputed *rpoB* mutations.

Disputed mutations also pose a problem for line probe assay (LPA) interpretation. On LPA all disputed show an absent or weak wildtype band, even harder to detect with heteroresistance.

RR-TB repeatedly misdiagnosed and/or undertreated with (mainly) first-line drugs results in repeated recurrences and periods of transmission, which explains their epidemiological importance. We have reported a large series of outcomes with unmodified rifampicin-throughout WHO regimens, with about 75% failure or relapse, very similar to rates for non-disputed mutations [2]. During repeated rifampicin-based treatment resistance will at some point amplify, while compensatory mutations may restore fitness. A first Surinam strain already showed a low-level *inhA* isoniazid resistance mutation, undetectable by LPA. Outbreaks with disputed 430Pro, 445Asn, 452Pro and 491Phe have been reported. First Tugela Ferry, with 100% mortality the birth of the term "XDR", caused by a 435Tyr MDR besides a 452Pro MDR [5]. The transmission chain showed that the 452Pro strain first attained high-level RR by acquiring a very rare 435Gly mutation, before amplifying to XDR. In Eswatini a 491Phe MDR strain, always missed by MGIT and undetectable by Xpert or LPA, became the driver of the RR-TB endemic after acquiring a compensatory *rpoC* mutation, and its clones with rv0678 bedaquiline resistance mutations are now appearing [6].

The authors claim that second-line TB treatment is not justified for isoniazid-susceptible 435Tyr-TB, based on their "largest" set of outcomes for such patients. This statement is misleading, because it concerns only one strain, atypically rifampicin mono-resistant, as shown by their own collection in the Netherlands [1], and our own. Though more than welcome, the results of their planned trial on the efficacy of triple-dose rifampicin first-line treatment may not be valid for the large majority of 435Tyr-TB. Besides, considering the 4-13 RR-TB cases detected annually in Surinam, it is questionable whether the study will be sufficiently powered to identify a difference for the main outcomes of interest: bacteriological failure, relapse and acquired resistance with additional mutations conferring resistance to rifampicin or other main drugs.

The authors encourage treatment tailored to the mutation identified and co-resistance rather than standard second-line treatment for all RR-TB. They also point out the benefit of maintaining isoniazid in the treatment regimen for the treatment of their strains, but this is a feature of for instance the shorter RR-TB regimen as well [7]. Tailored treatment may very well be beneficial to individual patients in some settings. However, when the necessary expertise and resources for testing are not available or accessible to the large majority of RR-TB patients, trying to make it work forcedly through referrals for state-of-the-art testing is bound to fail. Even with a standardised approach, implementation challenges are so common that a good regimen for RR-TB has to be sturdy, not only just enough.

While in the original TB chemotherapy trials the effectiveness of the isoniazid/rifampicin/pyrazinamide combination could not be improved by adding ethambutol or streptomycin [8], for mass programmatic treatment one companion drugs was always added to the intensive phase, together with directly supervised intake meant to protect the core drug. The first African country documented to reach 5% RR prevalence among new patients was Ivory Coast, that went for isoniazid/rifampicin/pyrazinamide without companion nor supervised intake [9].

The newly published WHO report on isoniazid and rifampicin resistance recommends standard second-line treatment for all RR-TB, irrespective of the mutation, besides halving the rifampicin critical concentration for MGIT and agar proportion, the least sensitive pDST methods [10]. The term "disputed" was abandoned.

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Reply by Gopie et al.

Dear Editor,

We thank Decroo and Van Deun for their interest in our article describing the treatment results of 59 patients with low-level rifampicin-resistant (RR) tuberculosis (TB) in Suriname. We appreciate their concerns regarding possible induction of multidrug-resistant (MDR) and extensively resistant (XDR)-TB, if rifampicin mono-resistant TB is not treated according to the recent WHO guidelines.

In our cohort all low-level rifampicin resistant *Mycobacterium tuberculosis* isolates (n=32) examined showed the D435Y mutation, which is characterized by a substitution of the amino acid asparagine (Asp/D) by tyrosine (Tyr/Y) in *rpoB* codon 516. Patients were mostly treated with a standard first-line TB drug regimen, due to discrepant results between the genotypic and phenotypic drug-susceptibility testing (DST); these mutations were for a long time indicated as 'disputed', due to unknown level of resistance and clinical relevance.

The authors mentioned that our reference to Williamson *et al.* [1], who suggested to conduct a multi-centre retrospective study to correlate the different types of *rpoB* mutations with clinical outcome and our statement that our observational study is such a study that contains the largest set of patients infected by *M. tuberculosis* strains carrying the D435Y mutation, is "misleading". Clearly, it was not our intention to "claim" that our study was a multi-centre study and indeed our study did not include a variety of *rpo*B mutations. However, our study reported on the treatment results of a large data set of patients infected by a *M. tuberculosis* strain carrying the D435Y mutation. Subsequently, our suggestions for alternative treatment options only concern patients infected by this specific strain; our results are not generalizable to the treatment of patients with other disputed mutations. Nonetheless, our observation is valid for this frequently encountered type of cases and adds important information to the questions raised by Williamson *et al*.

We also share the concerns of Decroo and Van Deun regarding the possible higher relapse rates after treatment of RR-TB patients. In our study, we did show in univariate analysis that RR-TB patients had been significantly more often treated previously and had illicit drug use, than patients with drug-sensitive TB, but the correlation was (just) not significant in multivariate analysis (aOR 2.0; CI: 1.0-4.3). We provided additional details, such as DST and treatment result in the previous treatment episode (Table 4 in our article) for the 12 RR-TB patients who were previously treated. Decroo and Van Deun also assumed that all of these patients had RR-TB in the previous episode and stated that the treatment for RR-TB with D435Y mono-resistance was clearly inadequate.

This is however unknown, because the DST results of the previous episode was only available in 5 patients (1 drug-susceptible and 4 rifampicin-resistant isolates) and unknown in 7 patients (6 diagnosed before 2012; the Xpert MTB/RIF testing was only introduced in Suriname in 2012). Two of the 4 (50%) RR-TB patients with a confirmed RR-TB relapse discontinued their treatment in the first episode, which most likely caused the recurrence of the disease.

We do agree with Decroo and Van Deun that our observational study shows how rifampicin resistance, if caused by disputed mutations, can be over- and under-estimated. The Xpert MTB/RIF in fact indicates rifampicin resistance in the classical sense, with no distinction between low- and high-level resistance. In phenotypic DST in the MGIT strains with such disputed mutations can score either rifampicin susceptible or resistant [2]. In reversed line blot assays such isolates will yield the disappearance of wildtype bands, while resistance bands will not show up. Only if the true nature of disputed mutations is revealed, like in whole genome sequencing, they are no longer 'disputed', but invariably associated with a certain (low) level of rifampicin resistance [2]. But also in extended MIC testing with multiple concentrations the low-level rifampicin resistance will be adequately visualized. These laboratory tests to reveal the exact nature of resistance mutations are generally not present in low and middle income settings. Within the Suriname-Netherlands collaboration all rifampicin-resistant *M. tuberculosis* isolates are heat-killed and sent to the Netherlands for WGS analysis, as soon as the culture becomes positive.

We fully agree with the authors that post-treatment monitoring is necessary to measure the efficacy of treatment adequately. Therefore, systematic follow-up of RR and multidrug-resistant (MDR)-TB at 3-, 6- and 12-months post-treatment has now been incorporated in the programmatic management of all RR/MDR-TB patients in Suriname.

Isoniazid and rifampicin are the two most potent drugs in the treatment for TB. The WHO shorter (9-12 months) all-oral bedaquilin-containing regimen for the treatment of RR/MDR-TB includes high dose isoniazid, irrespective of isoniazid drug-susceptibility testing [3]. Molecular testing nowadays makes it increasingly possible to rapidly diagnose or exclude isoniazid resistance and differentiate between rifampicin mono-resistant and MDR-TB. This makes it possible to critically value the use of isoniazid in (RR-)TB treatment regimens. All tested RR-TB patients in our study, except one (in 2014), had rifampicin mono-resistant TB, and thus would benefit from isoniazid, even in standard dose. As argued in our paper, it may be worthwhile also to consider the use of triple-dose rifampicin in patients with borderline rifampicin mono-resistance. The currently used dose of rifampicin, 10 mg/kg, is in fact too low in the adequate treatment of TB. Higher doses of rifampicin up to 35 mg/kg are safe and well tolerated, and achieve much higher exposure in plasma [4].

Our observational study was never set up as a clinical trial and not powered to identify significant differences in the main outcomes, but should be considered as a 'study under operational conditions' closely monitoring effects and programmatic impact on RR-TB in Suriname. We like to affirm that the latest WHO treatment recommendations have been included in the TB treatment guidelines in Suriname. All RR-TB patients are discussed in a TB concilium, and if required treatment will be based on bedaquilin-containing WHO-recommended regimens.

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Samenvatting

Tuberculose is een eeuwen oude infectie ziekte die voornamelijk wordt gezien onder omstandigheden van overcrowding, armoede en slechte hygiëne. Daarnaast zijn er risico factoren die het optreden van tuberculose bevorderen zoals HIV, diabetes mellitus, nierinsufficiëntie, alcohol gebruik, kanker, weerstand verlagende middelen en gevangenschap. Het overgrote deel van de patiënten presenteert zich met longtuberculose en ongeveer 20% met tuberculose in andere organen zoals de wervelkolom, lymfeklieren en hersenvliezen. De besmetting vindt aerogeen plaats via droplets, opgehoest door patiënten met open longtuberculose. Deze patiënten kunnen zich presenteren met langdurig hoesten, soms met opgeven van bloed, alsook koorts, vermagering en nachtzweten. In 2019 werd wereldwijd bij 10 miljoen mensen tuberculose vastgesteld en eiste deze ziekte 1.4 miljoen doden, waarvan 208.000 besmet waren met HIV.

Traditioneel werd longtuberculose gediagnosticeerd aan de hand van de anamnese, thoraxfoto, sputum microscopie (waarin ZN positieve bacillen gezien dienen te worden) en bevestigd door groei van mycobacterium tuberculose complex in de sputumkweek. Behalve tuberculose zijn er andere bacteriën die bij microscopisch onderzoek ook ZN positief kleuren, zoals *Nocardia*, *Rhodococcus*, *Corynebacterium* en de non tuberculeuze mycobacteriën. Vanwege de natuurlijke trage groei van de tuberculose bacil, waarvoor speciaal kweekmedium nodig is, duurt het enkele weken voordat bevestigd kan worden dat er sprake is van mycobacterium tuberculose en wat de drugsgevoeligheid is van de gekweekte tuberculose stam. Ondertussen wordt de patiënt behandeld voor vermeende normaal gevoelige tuberculose.

Gedurende het afgelopen decennium is er internationaal grote vooruitgang geboekt in de diagnostiek van tuberculose door onder andere moleculaire technieken, die naast tuberculose DNA ook resistentie voor tuberculostatica kunnen aantonen. Door deze verfijnde diagnostiek en resistentie bepaling kan de diagnose tuberculose in enkele uren bevestigd worden en kan op grond van het resistentie patroon het behandelschema bijgesteld worden. Tuberculose is een goed behandelbare ziekte waarvan patiënten kunnen genezen en waarbij van eminent belang zijn beschikbaarheid van tuberculostatica, therapietrouw van de patiënt en mede behandeling van relevante co-morbiditeit als bijvoorbeeld HIV/AIDS. Therapie ontrouw van de patiënt resulteert in onvolledige behandeling met eventueel relapse (terugkeer van ziekte) en tuberculostatica resistentie. Wereldwijd werd in 2018 bij een half miljoen mensen drug resistente tuberculose vastgesteld. Drug resistentie is een toenemend probleem, waarbij patiënten met 2de lijns tuberculostatica behandeld dienen te worden.

Deze middelen zijn duurder, minder effectief, vaak toxisch en de behandelduur is veel langer dan de gangbare 6 maanden therapie (met de eerste lijn middelen: isoniazide, rifampicine, ethambutol en pyrazinamide),

bij normaal gevoelige tuberculose. Daarenboven is in de afgelopen jaren maar aan een beperkt aantal nieuwe medicamenten, waaronder bedaquilline, delamanid, linezolid en moxifloxacin, registratie verleend als 2de lijns tuberculostaticum en zijn deze medicamenten niet eenvoudig verkrijgbaar.

Geschat wordt dat een kwart van de wereldbevolking latente tuberculose heeft. Bij deze vorm van tuberculose is de persoon besmet, maar toont geen ziekteverschijnselen en is aldus een reservoir voor nieuwe tuberculose patiënten. In geval de weerstand van zo een persoon met latente tuberculose vermindert, bijvoorbeeld ten gevolge van HIV infectie, kan de latente vorm van tuberculose zich ontwikkelen tot manifeste tuberculose. In het kader van de End TB Strategy van de WHO, is het van belang latente tuberculose te diagnosticeren en behandelen, echter is er geen gouden standaard om deze diagnose te stellen. Afhankelijk van de infrastructuur en financiële mogelijkheden van een land, wordt er gebruik gemaakt van IGRA testen of de tuberculine huidtest om latente tuberculose op het spoor te komen. De IGRA test is specifieker voor het vaststellen van de diagnose latente tuberculose, maar de tuberculine huidtest is goedkoper en eenvoudiger uit te voeren. De indicatie en interpretatie van de tuberculine huidtest dient secuur te gebeuren, preferentieel conform de richtlijnen van de American Thoracic Society, om latente tuberculose over-classificatie en daarmee ongemak voor de patiënt, overbehandeling en meer zorgkosten te voorkomen.

In mijn dissertatie beschrijven we aspecten van tuberculose in ons multi-etnisch en multicultureel Suriname, waar wij in harmonie en vrede met elkaar leven. Besproken worden in deze thesis de epidemiologie, vooruitgang in diagnostiek en de behandeltrend van tuberculose in Suriname.

In hoofdstuk één wordt een historisch overzicht van mondiale tuberculose gepresenteerd naast regionale aspecten van tuberculose en in hoofdstuk twee worden de incidentie en risicofactoren van tuberculose bij de verschillende bevolkingsgroepen in Suriname beschreven. Het blijkt dat tuberculose vaker voorkomt bij Inheemsen die ver van het modern zorgsysteem wonen en een lage SES (socio-economische status) hebben en bij Creoolse mensen die HIV infectie als risicofactor hebben, waarbij de hogere incidentie blijft bestaan, ook als er gecorrigeerd wordt voor co-infectie met HIV.

In hoofdstuk drie wordt de aanwezigheid van non-tuberculeuze mycobacteriën (NTM) aangetoond in het sputum van patiënten die voor longtuberculose behandeld werden, vóór de introductie van de GenXpert test in 2012. Deze test maakt het mogelijk om onderscheid te maken tussen 'echte' tuberculose en NTM. Bovendien kan met deze test ook worden vastgesteld of de aangetoonde tubercel bacteriën resistent zijn tegen rifampicine, één van de belangrijkste middelen uit de cocktail waar tuberculose mee wordt behandeld.

Dit impliceert dat patiënten mogelijk onterecht geclassificeerd en behandeld werden als tuberculose patiënt. De GenXpert test heeft ook mogelijk gemaakt dat vroegtijdig rifampicine resistente tuberculose kon worden vastgesteld, welke in hoofdstuk vijf wordt beschreven. Opvallend was dat zowel patiënten met rifampicine gevoelige als rifampicine resistente tuberculose goede behandeluitkomsten hadden. Analyse toont dat er in Suriname sprake is van een milde vorm van rifampicine resistente tuberculose, welke behandeld zou kunnen worden door de dosis van rifampicine te verhogen.

In hoofdstuk vier wordt de interp retatie van de tuberculine huidtest oftewel de Mantoux huidtest onder de loep genomen. Onzes inziens is de in Suriname gehanteerde afkapwaarde van 10 mm te scherp voor de groep mensen die geen risicofactoren voor tuberculose hebben, en zou de afkapwaarde voor de Mantoux test voor deze groep 15 mm moeten zijn.

Resumen

Tuberculosis en Suriname

Tendencias en epidemiología, diagnóstico y tratamiento

La tuberculosis es una enfermedad infecciosa de la antigüedad que se presenta principalmente en condiciones de hacinamiento, pobreza y falta de higiene. Además, existen factores de riesgo que pueden estimular la aparición de tuberculosis como el VIH, la diabetes mellitus, la insuficiencia renal, el consumo de alcohol, el cáncer, los fármacos para reducir la resistencia y el encarcelamiento. La gran mayoría de los pacientes se presentan con tuberculosis pulmonar y alrededor del 20% con tuberculosis en otros órganos como la columna vertebral, los ganglios linfáticos y las meninges cerbrales. La infección se produce de forma aerogénica a través de microgotas de aerosol que son producidas por pacientes con tuberculosis pulmona activa. Estos pacientes pueden presentarse con tos prolongada, a veces con expectaración con sangre, así como fiebre, pérdida de peso y sudores nocturnos. En 2019, 10 millones de personas en todo el mundo fueron diagnosticadas con tuberculosis y la enfermedad causó 1,4 millones de muertes, de las cuales 208.000 estaban infectadas con el VIH.

Tradicionalmente, la tuberculosis pulmonar ha sido diagnosticada por antecedentes, rayos X de thórax, microscopía de esputo (en la que deben verse bacilos ZN positivos) y confirmada por el crecimiento del complejo de mycobacterium tuberculosis en el cultivo de esputo. Además de la tuberculosis, hay otras bacterias que también tiñen ZN positiva en el examen microscópico, como Nocardia, Rhodococcus, Corynebacterium y las micobacterias no tuberculosas. Debido al lento crecimiento natural del bacilo de la tuberculosis, que requiere un medio de cultivo especial, se necesitan varias semanas para confirmar la presencia de Mycobacterium tuberculosis y la sensibilidad a los medicamentos de la cepa de tuberculosis cultivada. Mientras tanto, el paciente está siendo tratado por sospecha de tuberculosis normalmente sensible. Durante la última década, se ha avanzado mucho a nivel internacional en el diagnóstico de la tuberculosis mediante técnicas moleculares, que pueden demostrar resistencia a fármacos tuberculostáticos además del ADN de la tuberculosis.

Gracias a este diagnóstico sofisticado y la determinación de la resistencia, el diagnóstico de tuberculosis se puede confirmar en unas pocas horas y el programa de tratamiento se puede ajustar según el patrón de resistencia. La tuberculosis es una enfermedad fácilmente tratable de la que los pacientes se pueden curar y en la que tienen una importancia eminente la disponibilidad de tuberculostáticos, el cumplimiento del paciente y el tratamiento de las comorbilidades relevantes como el VIH / SIDA.

El tratamiento incomplete da como resultado una posible recaída (recurrencia de la enfermedad) y resistencia a la tuberculosis. En todo el mundo, a medio millón de personas se les diagnosticó tuberculosis farmacorresistente en 2018. La resistencia a los medicamentos es un problema creciente, que requiere que los pacientes sean tratados con medicamentos tuberculostáticos de la segunda línea. Estos medicamentos son más caros, menos eficaces, a menudo tóxicos y la duración del tratamiento es mucho más larga que los 6 meses habituales de terapia (con los agentes de primera línea: isoniazida, rifampicina, etambutol y pirazinamida), para la tuberculosis normalmente sensible. Además, solo un número limitado de medicamentos nuevos, incluidos bedaquillin, delamanid, linezolid y moxifloxacin, se han registrado como agentes tuberculostáticos de la segunda línea en los últimos años y estos no son fácilmente disponibles.

Se estima que una cuarta parte de la población mundial tiene tuberculosis latente. Con esta forma de tuberculosis, la persona está infectada, pero no muestra síntomas de la enfermedad y, por lo tanto, es un reservorio para nuevos pacientes con tuberculosis. En caso de que se reduzca la resistencia de una persona con tuberculosis latente, por ejemplo debido a la infección por VIH, la forma latente de tuberculosis puede convertirse en tuberculosis activa. Como parte de la Estrategia End TB de la OMS, es importante diagnosticar y tratar la tuberculosis latente, pero no existe un regla de oro para hacer este diagnóstico. Dependiendo de la capacidad financiera de un país, las pruebas IGRA o la prueba cutánea de tuberculina se utilizan para detectar la tuberculosis latente. La prueba IGRA es más específica para el diagnóstico de tuberculosis latente, pero la prueba cutánea de tuberculina es más barata y más fácil de realizar. La indicación e interpretación de la prueba cutánea de la tuberculina debe realizarse con precisión, preferiblemente de acuerdo con las directrices de la American Thoracic Society, para evitar la sobreclasificación de la tuberculosis latente y, por tanto, el malestar del paciente, el sobretratamiento y el aumento de los costes sanitarios.

En mi disertación describimos aspectos de la tuberculosis en nuestro Suriname multiétnico y multicultural, donde vivimos en armonía y paz. Esta tesis analiza la epidemiología, los avances en el diagnóstico y el tratamiento de la tuberculosis en Suriname. En el capítulo uno se presenta la história de la tuberculosis mundial además de los aspectos regionales de la tuberculosis y en el capítulo dos se describen la incidencia y los factores de riesgo de la tuberculosis en los diferentes grupos de la población de Suriname. Parece que la tuberculosis se presenta con mayor frecuencia en los pueblos indígenas que viven lejos del sistema de salud moderno y tienen un nivel socioeconómico bajo y en los criollos que tienen la infección por el VIH como factor de riesgo.

En el capítulo tres, se demuestra la presencia de micobacterias no tuberculosas (NTM) en el esputo de pacientes tratados por tuberculosis pulmonar, antes de la introducción de la prueba GenXpert en 2012. Esto implica que los pacientes pueden haber sido clasificados y tratados incorrectamente como pacientes con tuberculosis. La prueba GenXpert también permitió la detección precoz de la tuberculosis resistente a la rifampicina, que se describe en el capítulo cinco. Fue notable que los pacientes con tuberculosis sensible a la rifampicina como resistente a la rifampicina obtuvieran buenos resultados del tratamiento. El análisis muestra una forma leve de tuberculosis resistente a la rifampicina, que podría tratarse aumentando la dosis de rifampicina. En el capítulo cuatro se hablan sobre la interpretación de la prueba cutánea de tuberculina o prueba cutánea de Mantoux. En nuestra opinión, el valor de 10 mm utilizado en Surinam es demasiado estricto para el grupo de personas que no tienen factores de riesgo de tuberculosis, y el umbral la prueba de Mantoux para este grupo debería ser de 15 mm.

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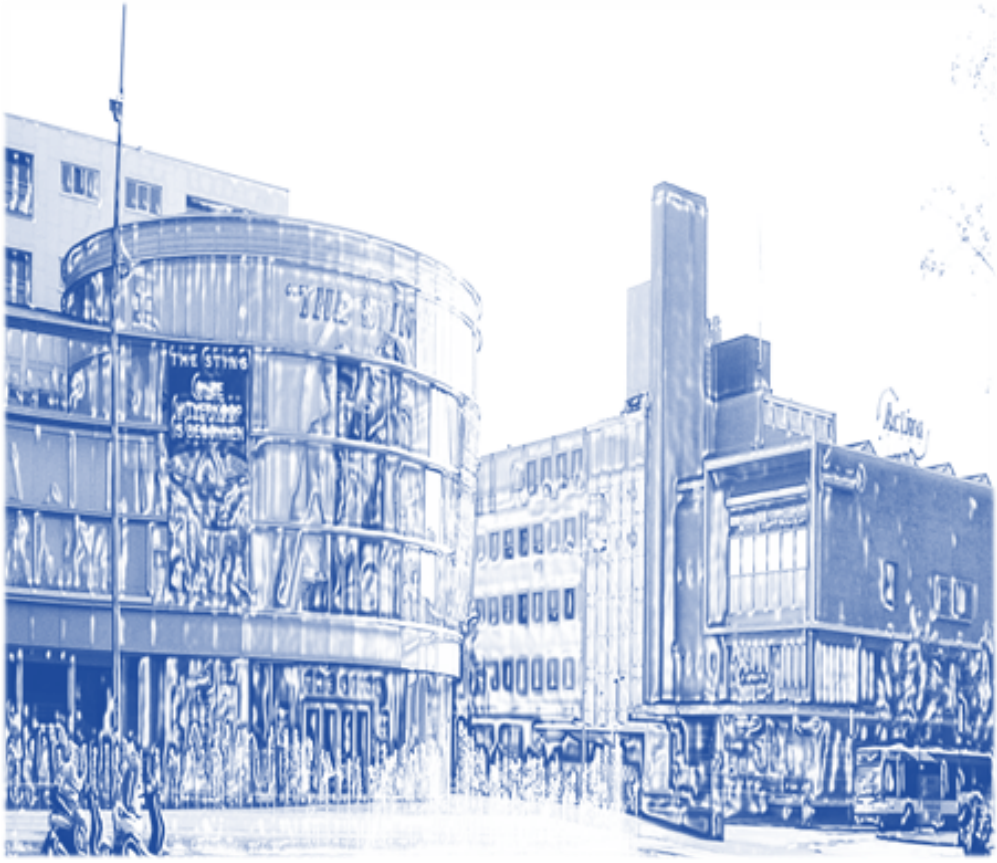

City center, Enschede, The Netherlands.
Source: Gopie F.A.

Dankwoord

U bladert door het promotieboekje van Anoep, het eindpunt van een traject.

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Dr. Wilco Zijlmans,

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zijn kritische begeleiding heeft een opvatting ondersteund door data doen sublimeren in manuscripten.

Dr. Jaap Klein, ons voorgegaan op 10 oktober 2020, mijn opleider longziekten in Enschede.

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waardoor je vaak alleen moest laveren,
maar je hebt het fantastisch gedaan,
ondanks je drukke baan.

Statue of Mother Suriname embracing her multi-ethnic offspring
Source: Gopie F.A.

About the author

Fitzgerald Anoep Gopie, was born September 21st, 1969, in Paramaribo, Suriname. He finished his medical education in 1998 and did the obligatory government apprenticeship the following year. From 1999 till 2001 he worked at the emergency department of the Academic Hospital Paramaribo. In 2001 he started the preliminary pulmonologist training after nomination by the residing pulmonologist Percy Herkul. From 2003 till 2007 he continued and completed his pulmonary medicine training at Medisch Spectrum Twente in Enschede Netherlands, supervised by Jaap Klein, Paul van der Valk and Hugo Schouwink.

Since December 2007 he holds a position as pulmonologist at the Academic Hospital of Paramaribo Suriname and is part time lecturer pulmonary medicine at the Faculty of Medicine,Anton de Kom University of Suriname.

Fitzgerald is married to Gaitrie Dataram and they have 2 children, Nicole and Gerard.

Miami shoreline.
Source: Gopie F.A.

List of publications

1. Gopie F.A., Hassankhan A., Ottevanger S., Krishnadath I., de Lange W., Zijlmans C.W.R., Vreden S. Ethnic disparities in tuberculosis incidence and related factors among indigenous and other communities in ethnically diverse Suriname. Journal of Clinical Tuberculosis and Other Mycobacterial Diseases. 2021 Mar 10;23:100227. DOI: 10.1016/j.jctube.2021.100227 PMID: 33851035 PMCID: PMC8022245

2. Gopie F.A., Hassankhan A., Zijlmans W., de Lange W.C.M., Vreden S.G.S., van Ingen J. Non-tuberculous mycobacteria in sputum cultures in Suriname. International Journal of Tuberculosis and Lung Disease. 2020 Oct 1;24(10):1106–1108. DOI: 10.5588/ijtld.20.0249 PMID: 33126947

3. Gopie F.A., Hassankhan A., Zijlmans C.W.R., Vreden S.G.S. Indications, interpretation and clinical consequences of tuberculin skin tests in resource limited settings. Journal of Tuberculosis Research. 2021 Aug 16;9:172–183. DOI: 10.4236/jtr.2021.93016

4. Gopie F.A., Commiesie E., Baldi S., Kamst M., Kaur D., de Lange W.C.M., Pinas P.S., Stijnberg D., Wongsokarijo M., Zijlmans C.W.R., de Zwaan R., van Soolingen D., Vreden S.G.S., de Vries G. Should treatment of low-level rifampicin mono-resistant tuberculosis be different? Journal of Clinical Tuberculosis and Other Mycobacterial Diseases. 2021 Jan 29;23:100222. DOI: 10.1016/j.jctube.2021.100222 PMID: 33598570 PMCID: PMC7869001

5. Gopie F.A., Commiesie E., de Lange W.C.M., van Soolingen D., Vreden S.G.S., de Vries G. Should treatment of low-level mono-resistant tuberculosis be different? Journal of Clinical Tuberculosis and Other Mycobacterial Diseases. 2021 Apr 30;23:100241. DOI: 10.1016/j.jctube.2021.100241 PMID: 34095547 PMCID: PMC81674

As a consequence of her colonial history, Suriname has a multi-ethnic and racially diverse population, a veritable playground for humanistic science. These circumstances have been the trigger to investigate the presence of tuberculosis among the ethnic groups of Suriname.

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