Tampere University

PIRRE EMILIA RÄISÄNEN

Tuberculosis among Persons Born Abroad, 1995-2017

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ACADEMIC DISSERTATION
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Dedicated
to my mother, father, and brothers,
to Jukka, Aston and Alissa

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ABSTRACT

Tuberculosis (TB) is an infectious disease that is transmitted through air. An evidence-based approach based on knowledge of local epidemiology is essential to intercept tuberculosis transmission. Previous, as well as modern evidence recommends that efficient public health interventions can make a difference in tuberculosis epidemiology. Tuberculosis remains a public health concern, even though effective and economical treatment is known. People from high tuberculosis incidence countries have a high risk of contracting tuberculosis. As a result of people being very mobile, migration may affect the epidemiology of TB, particularly in low TB incidence (TI) countries. Migrants are a heterogeneous group, such as students, labor migrants or family members, refugees, or asylum seekers. The surrounding conditions and circumstances of migration often increase the risks to the social, physical, and mental well-being of migrants.

This study provides an insight into the effect of migration on the epidemiology of TB in Finland. Using a nationwide, population-based approach with register data commencing in the year 1995, the national trends on the epidemiology of TB can be characterized. The transition may be described in terms of an epidemiological situation, where most reported cases have been reactivation of LTB in older Finnish adults to TB cases in young migrants.

The study objectives were to describe the characteristics of national trends in the epidemiology of TB in Finland, to describe the TB screening cascade and to evaluate the extent of clustering and TB transmission between foreign- and Finnish-born populations.

The data were collected from the National Infectious Disease Register (NIDR) and from reception centers' national health record system (HRS). In addition, a questionnaire focused on enhanced surveillance of TB was sent to physicians with the aim of eliciting comprehensive knowledge of immigrant and second-generation TB cases. NIDR included all TB cases from 1995 and laboratory information is linked to NIDR. Laboratory information consists of *M. tuberculosis* isolations including characterization using spoligotyping and mycobacterial interspersed repetitive unit variable number tandem repeat (MIRU-VNTR) methods. HRS data were used to assess TB in asylum seekers and screening of TB.

This nationwide, population-based study showed that during the 23-year study period the epidemiology of TB has experienced a transition in Finland. The major reason is not migration but rather the decrease of TB cases in the Finnish-born population. The incidence among foreign-born populations has decreased in other low TI countries as well as in Finland. During the years 1995-2017, a total of 9314 TB cases were reported to NIDR. Of those cases, 7605 (81.7%) were Finnish-born and 1614 (17.3%) were foreign-born. In 95 (1%) of the cases the origin was not available. The median age was 66 years (range 0-105), 56.6% were male, 0.8% had contracted multidrug resistant tuberculosis and 68.6% had pulmonary TB of which 47.7% were sputum smear positive.

Since refugees and asylum seekers are screened in Finland on arrival, they are easy to reach. Other migrants may be difficult to reach because they do not come to the country via a single-entry point and they might relocate directly for work, to join a family member or to study. While evaluating the screening for active TB in asylum seekers in Finland during their large influx in 2015-2016, half of the TB cases among asylum seekers were found in the primary screening, and over 40% of these cases did not have TB symptoms at the time of screening. TB yield among individuals screened was 0.19% (95% CI, 0.14-0.25%) and number needed to screen was 522.

During 2014-2017, *M. tuberculosis* isolates were characterized by spoligotyping and MIRU-VNTR. Altogether 76 isolates belonged to the 14 mixed clusters: 39 (51.3%) were from Finnish-born cases, 36 (47.4%) from foreign-born, and one of unknown origin. Foreign-born cases originated from Europe (9 cases), Asia (13 cases) and Africa (14 cases, 6/14 from Somalia).

In conclusion, the epidemiology of TB has experienced a transition in Finland from 1995 to 2017. As TB becomes even less common in the Finnish-born population over time, increasing TB cases in the foreign-born population will probably change the epidemiology in the future as has occurred in other northern European countries. Half of the TB cases among asylum seekers were first suspected in screening; over 40% were asymptomatic. The screening guidelines are adequate for Finland. Although a large proportion of TB cases are found in people born abroad, the population born abroad has no significant effect on the TB epidemic among populations born in Finland. Migration from high TI countries does not form a significant threat to Finnish public health.

TIIVISTELMÄ

Tuberkuloosi on tartuntatauti, joka tarttuu ilman välityksellä ihmisestä toiseen. Historialliset ja nykyaikaiset tutkimukset viittaavat siihen, että tehokkailla kansanterveystoimenpiteillä voidaan pysäyttää tuberkuloosin leviäminen, mutta paikallisen epidemiologian tunteminen on avainasemassa. Tuberkuloosi on edelleen kansanterveysongelma, vaikka tehokas ja taloudellinen hoito tunnetaan. Korkean tuberkuloosin ilmaantuvuuden maista tulevilla ihmisillä on korkea riski sairastua tuberkuloosiin, ja koska ihmiset matkustavat paljon, muuttoliike voi vaikuttaa tuberkuloosin epidemiologiaan, etenkin maissa, joissa tuberkuloosin esiintyvyys on pieni, kuten Suomessa. Maahanmuuttajat ovat heterogeeninen ryhmä, johon lukeutuvat niin opiskelijat, työn perässä muuttavat kuin perheenyhdistämisen kautta tulleet maahanmuuttajat sekä pakolaiset ja turvapaikanhakijat. Muuttoliikkeeseen liittyvät olosuhteet lisäävät usein maahanmuuttajien fyysiseen, henkiseen ja sosiaaliseen hyvinvointiin liittyviä riskejä.

Tämä tutkimus antaa käsityksen maahanmuuton vaikutuksista tuberkuloosin epidemiologiaan Suomessa. Tuberkuloosin epidemiologiaa voidaan kuvailla käyttämällä valtakunnallista, väestöpohjaista rekisteritietoa vuodesta 1995 alkaen. Historiallisesti Suomessa tavatut tuberkuloositapaukset olivat latentin tuberkuloosin uudelleenaktivoitumista vanhemmalla suomalaisella sukupolvella, mutta tänä päivänä tuberkuloosin epidemiologinen tilanne on kääntynyt niin, että yhä enemmän tuberkuloosia tavataan nuorissa maahanmuuttajissa.

Tämän tutkimuksen tavoitteena oli kuvata tuberkuloosin epidemiologia, seulontatavat ja -toteutus sekä arvioida klusteroitumisen ja tuberkuloosin leviämisen laajuutta maahanmuuttajien ja Suomessa syntyneiden populaatioiden välillä Suomessa.

Tiedot kerättiin kansallisesta tartuntatautirekisteristä (TTR) ja vastaanottokeskusten kansallisesta terveysjärjestelmästä (HRS). Lisäksi aineistona käytettiin lääkäreille lähetettyä kyselyä koskien tuberkuloosin tehostettua seurantaa, saadaksemme kattavampaa tietoa maahanmuuttajien ja toisen sukupolven tuberkuloositapauksista. TTR sisältää kaikki tuberkuloositapaukset vuodesta 1995, mukaan lukien laboratoriotiedot, jotka on linkitetty TTR:iin. Laboratoriotiedot koostuvat *M. tuberculosis* -kannoista, mukaan lukien tuberkuloosikantojen

spoligotyypitys ja MIRU-VNTR-tiedot. HRS tietoja käytettiin turvapaikanhakijoiden tuberkuloositapausten määrittämiseen sekä seulonnan tulosten arviointiin.

Tämä valtakunnallinen väestöpohjainen tutkimus osoitti, että 23 vuoden tutkimusjaksolla tuberkuloosin epidemiologia on kokenut Suomessa muutoksen. Tuberkuloositapausten väheneminen Suomessa syntyneessä väestössä on suurin syy muutokselle, ei niinkään maahanmuutto. Ulkomailla syntyneiden tuberkuloosi-ilmaantuvuus on vähentynyt Suomessa. Sama ilmiö on havaittu myös muissa matalan ilmaantuvuuden maissa.

Muita maahanmuuttajia, kuin pakolaisia ja turvapaikanhakijoita voi olla vaikea tavoittaa seulontaa varten Suomeen saapuessaan, koska he eivät tule maahan tiettyä reittiä pitkin, vaan he saattavat muuttaa työn perässä, perheenjäsenen luokse tai opiskelemaan. Kun arvioitiin tuberkuloosin seulonnan toimivuutta turvapaikanhakijoilla Suomessa pakolaisvirran aikana vuosina 2015–2016, puolet turvapaikanhakijoiden tuberkuloositapauksista löydettiin seulonnassa ja yli 40 % näistä oli oireettomia. Kaikista seulotuista 0,19 % (95 % CI, 0.14-0.25 %) todettiin tuberkuloosi ja yhden tuberkuloositapauksen löytymiseen suoritettiin 522 seulontaa.

Vuosina 2014–2017 *M. tuberculosis*-kannoille tehtiin spoligotyypitys ja MIRU-VNTR. Kaiken kaikkiaan 14 klusteria sisälsi niin maahanmuuttajien kuin suomalaissyntyisten kantoja yhteensä 76 kappaletta, joista 39 (51.3 %) oli suomalaisten kantoja, 36 (47.4 %) ulkomailla syntyneiden kantoja ja yksi tuntemattomasta alkuperästä. Ulkomailla syntyneet tapaukset olivat peräisin Euroopasta (9 tapausta), Aasiasta (13 tapausta) ja Afrikasta (14 tapausta, 6/14 Somaliasta).

Yhteenvetona voidaan todeta, että tuberkuloosin epidemiologiassa on tapahtunut muutos Suomessa vuodesta 1995 vuoteen 2017. Koska tuberkuloosista tulee ajan myötä yhä harvinaisempaa suomalaissyntyisessä väestössä, ulkomailla syntyneen väestön tuberkuloosin lisääntyminen todennäköisesti muuttaa epidemiologiaa tulevaisuudessa entisestään, mikä on jo tapahtunut muissa Pohjois-Euroopan maissa. Puolet turvapaikanhakijoiden tuberkuloositapauksista todettiin seulonnassa; yli 40 % heistä oli oireettomia. Ja vaikka suuri osa tuberkuloositapauksista diagnosoidaan maahanmuuttajilla, sillä ei ole merkittävää vaikutusta tuberkuloosiepidemiologiaan suomalaissyntyisessä väestössä. Tuberkuloosin korkean ilmaantuvuuden maista tulevat maahanmuuttajat eivät muodosta merkittävää uhkaa Suomen kansanterveydelle.

CONTENTS

List of Figures

List of Tables

ABBREVIATIONS

BCG	Bacillus Calmette-Guérin
CAS	Central Asian Strain
CI	Confidence Interval
CXR	Chest X-Ray
DNA	Deoxyribonucleic Acid
EAI	East African-Indian
ECDC	European Centre for Disease Prevention and Control
EEA	European Economic Area
EPTB	Extrapulmonary Tuberculosis
EU	European Union
FSU	Former Soviet Union
HIV	Human Immunodeficiency Virus
HRS	Reception centers' National Health Record System
IGRA	Interferon Gamma Release Assay
LAM	Latin American and Mediterranean
LTB	Latent Tuberculosis
M. tuberculosis	*Mycobacterium tuberculosis*
MDR-TB	Multidrug-Resistant Tuberculosis
MIRU-VNTR	Mycobacterial Interspersed Repetitive Unit Variable Number Tandem Repeat
NID	Unique National Identifier
NIDR	National Infectious Disease Register
NNS	Number Needed to Screen
PTB	Pulmonary Tuberculosis
RR-TB	Rifampicin-Resistant Tuberculosis
SIT	Spoligo International Type
SNP	Single Nucleotide Polymorphism
SPSS	Statistical Package for the Social Sciences
TB	Tuberculosis
THL	Finnish Institute for Health and Welfare

TI	Tuberculosis incidence or notification rate: number of new tuberculosis cases/100,000 population/year
USA	United States of America
WGS	Whole Genome Sequencing
wgSNP	Whole Genome Single Nucleotide Polymorphism
WHO	World Health Organization
XDR-TB	Extensively Drug-resistant Tuberculosis
95% CI	95% Confidence Incidence

ORIGINAL PUBLICATIONS

I Räisänen PE, Soini H, Vasankari T, Smit PW, Nuorti JP, Ollgren J, Ruutu P, Lyytikäinen O. Tuberculosis in immigrants in Finland, 1995-2013. Epidemiol Infect. 2016 Jan;144(2):425-33.

II Räisänen PE, Soini H, Turtiainen P, Vasankari T, Ruutu P, Nuorti JP, Lyytikäinen O. Enhanced surveillance for tuberculosis among foreign-born persons, Finland, 2014-2016. BMC Public Health. 2018 May 9;18(1):y.

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1 INTRODUCTION

Tuberculosis (TB) is an infectious disease that is transmitted through air (Churchyard et al., 2017). Close contacts of pulmonary TB (PTB) cases are most vulnerable to infection and, if infected, to develop the disease, especially within the first year after exposure (Fox et al., 2013). An evidence-based approach based on knowledge of local epidemiology is essential to intercept TB transmission. Previous and modern evidence recommends that efficient public health interventions can make a difference in TB epidemiology. (Dowdy et al., 2017.) TB still remains a public health concern, even though effective and economical treatment is known (World Health Organization, 2018a).

The most affected areas are South-East Asia, Africa, and Western Pacific regions. The burden of disease in the world varies from TI<5 to TI>500, with the global average being around 130. The countries with the lowest burden of disease are found in Western and Northern Europe and North America. (World Health Organization, 2018a.)

Migrants from high incidence TB countries, defined as TI > 50 (ECDC, 2015b), are at increased risk of TB for the rest of their lives after migration because of an increased risk of reactivation of latent TB (LTB) (Aldridge et al., 2016; Lillebaek et al., 2002; McPherson et al., 2008; Vos et al., 2004). Some migrants may also be vulnerable to TB because of risk factors associated with migration, such as environmental factors within the origin country and epidemiological characteristics of the transit route. In particular refugees and people affected by human trafficking are potentially exposed to poor and dangerous travel conditions, overcrowded housing, and poor access to healthcare on the emigration route. (Castelli & Sulis, 2017; Langholz Kristensen et al., 2019.) After arrival in the host country, potential barriers, such as language, lack of knowledge of the healthcare system and patient rights can present challenges in accessing the healthcare system (Castelli & Sulis, 2017; de Vries et al., 2017).

The foreign-born population constitutes an increasing and notable number and proportion of all TB cases in low TI countries (ECDC/WHO Regional Office for Europe, 2018; Lonnroth et al., 2015). More than one fourth of reported TB cases in 2017 in the European Union/European Economic Area (EU/EEA) were

reported in the foreign-born population (ECDC/WHO Regional Office for Europe, 2018). This proportion has been increasing constantly; in 2007, 13.6% of TB cases were reported in migrant populations whereas in 2017, the proportion was 33.1% (ECDC/WHO Regional Office for Europe, 2018; ECDC/WHO Regional Office for Europe, 2019). In nearly half of the EU/EEA countries most TB cases occur among foreign-born individuals (ECDC/WHO Regional Office for Europe, 2018).

Between 2007 and 2012, the EU/EEA countries received on average 1.5 million migrants from outside the EU/EEA. In 2015-2016 the figure rose to approximately 2.6 million asylum seekers. As a result, the foreign-born population constitutes approximately 12% of the population in the EU/EEA. (Eurostat, 2019; International Organization for Migration, 2019.) A considerable proportion of these migrants were born in countries with a high burden of TB (Greenaway et al., 2018). It is seen in EU/EEA countries that TB case notifications in migrant populations are increasing and the TB rates in native populations are decreasing, including Finland (Greenaway et al., 2018).

In Finland, TB has almost been defeated as a result of a century long fight against TB (Tala-Heikkila, 2003). Now, like other Nordic countries, Finland belongs to low TI countries (i.e. TI<10) (ECDC/WHO Regional Office for Europe, 2019). TB in children and adolescents (under the age of 15) has almost disappeared, but in the population above the age of 70 the incidence is almost eight times higher than for those under the age of 70 (The Finnish Institute for Health and Welfare, 2018). In addition to the elderly population, migrants, especially migrants from high TI areas, constitute another risk group for TB. Overall, in low TI countries TB mainly affects vulnerable populations, such as migrants, prison inmates or people co-infected with human immunodeficiency virus (HIV). (ECDC/WHO Regional Office for Europe, 2018; Tala-Heikkila, 2003.)

2 REVIEW OF THE LITERATURE

2.1 Tuberculosis disease

TB is an infectious disease caused by a mycobacterium belonging to the *Mycobacterium tuberculosis* complex. This complex includes five closely related mycobacterium species: *Mycobacterium tuberculosis (M. tuberculosis), Mycobacterium bovis, Mycobacterium africanum, Mycobacterium microti* and *Mycobacterium canettii.* The main bacterium infecting human beings is *M. tuberculosis.* The bacterium can resist the immune system and adapt to difficult conditions in various tissues due to its complicated genetic diversity. (Lawn & Zumla, 2011.) A most important feature of *M. tuberculosis* is the impervious cell wall structure, which is a barrier to drugs and gives a strong virulence to the bacterium (Delogu et al., 2013).

TB most commonly affects the lungs as the bacteria grow most successfully in tissues with high oxygen content (Lawn & Zumla, 2011). When the bacteria have infected the lungs, the disease is called PTB. In the lungs the bacteria multiply and cause inflammation. The doubling time of *M. tuberculosis* is 12–24 hours (Delogu et al., 2013). From the lungs bacteria can spread to other parts of the body through the blood or lymphatic system. TB is called extrapulmonary TB (EPTB) when the bacteria have infected other parts of the body than the lungs. For example, lymph nodes, bones, urinary tract or genitals, brain, skin, or it may develop as a generalized infection. If the bacteria have affected the lungs and some other part of the body at the same time, it is classified as PTB. (Filha, 2019; World Health Organization, 2018a.)

Symptoms of TB are similar to many other diseases and therefore it is not easy to diagnose. PTB symptoms may be similar to the common cold: a cough for at least 3 weeks, the coughing up of sputum or blood, fever, night sweats, loss of appetite and/or weight loss. EPTB symptoms usually appear around the affected organ as a lump, swelling or pain. Symptoms usually appear slowly and are not distinct at first. Some might not have any symptoms. (Filha, 2019.)

TB is one of the oldest diseases and has accompanied mankind during its evolution (Magda, 2015). The TB bacillus was first identified by the German scientist Robert Koch on March 24, 1882 (Koch, 1891). The antituberculosis

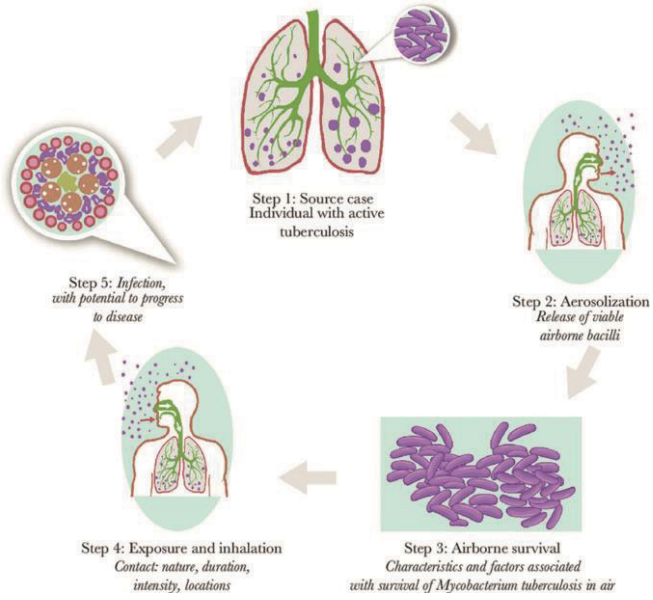
vaccine Bacillus Calmette-Guérin (BCG) was invented by Albert Calmette and Camille Guérin in 1921 and it is still the only vaccine (several different products are available) in use today, even if it prevents only severe forms of TB (Luca & Mihaescu, 2013).

2.1.1 Transmission

Robert Koch said in his Nobel Lecture in 1905 that "tuberculosis has been called plainly, and quite justly, a disease of accommodation" (Koch, 1905). The longer a person spends time in a closed space with an infectious person, the higher is the risk of becoming infected. (Kozińska & Augustynowicz-Kopeć, 2016.)

TB spreads from person to person through the air, when a person with PTB coughs, sneezes, sings, or spits and the bacteria are inhaled by another person. Persons with smear-positive PTB are highly infectious. (Filha, 2019; World Health Organization, 2018a.) A simple chain of transmission is proposed in which 1) an infectious person 2) exhales bacteria that 3) survive in the air and 4) are inhaled by a person 5) who becomes infected and 1) who develops TB (figure 1) (The Aurum Institute, 2019). Transmission can be reduced with proper treatment initiated as early as possible, already in the latent phase or in the early stage of active disease (World Health Organization, 2018a).

Figure 1. A simple chain of TB transmission (The Aurum Institute, 2019)



Exposure to the bacteria does not always lead to infection, as the body's immune system most often kills the bacteria before active replication of the bacteria starts (Delogu et al., 2013). It has been estimated that one-fourth of the global population are infected (LTB) and of that proportion, only one-tenth develop the disease (Lawn & Zumla, 2011; World Health Organization, 2019). The risk of developing active disease is higher within two years of the exposure (Lawn & Zumla, 2011). Unvaccinated children under the age of five have an increased risk of developing the disease after exposure. Half of the children under the age of one and one-fourth of the children under the age of five develop the disease after getting infected. (Filha, 2019.)

In low TI countries, TB transmission mainly occurs within households (Barrera et al., 2015; Churchyard et al., 2017; Fox et al., 2013). Within households, it is estimated that the risk of becoming infected is approximately 50% (Fox et al., 2013). Studies suggest that the risk of transmission from migrant populations to host populations is generally low. (Aldridge et al., 2016; Sandgren et al., 2014.) In high TI countries, TB transmission is more likely to happen in other environments than home (Andrew et al., 2014; Corbett et al., 2007; Telisinghe et al., 2014; Yates et al., 2016).

A previous study conducted in Finland in 2013 showed that only 10% of clusters included both foreign- and Finnish-born cases (Smit et al., 2013). It has been suggested that clustered isolates implicate chains of recent transmission which are epidemiologically linked (Murray & Nardell, 2002). It has also been shown that simultaneous reactivation of LTB among older Finns is the most likely cause for clustering in Finland (Smit et al., 2014).

A systematic review of TB transmission in the EU/EEA suggests that foreign-born cases are more often not part of a cluster compared to native born cases (Sandgren et al., 2014). Unique isolates have been assumed to represent the reactivation of LTB (Murray & Nardell, 2002). One third of the clusters in the review were mixed including both foreign- and native-born cases. Transmission of *M. tuberculosis* from foreign populations to native populations takes place as often as vice versa, although different studies have provided variable results in this respect. In the EU/EEA countries the median proportions of clusters including isolates from both native- and foreign-born cases is estimated to be 32% (Sandgren et al., 2014).

2.1.2 Latent tuberculosis

The condition when a person has been infected and has the TB bacteria in his/her body, but with non-multiplication of the bacteria, is called latent TB (LTB). The body's immune system keeps control of the bacteria and the person does not have any symptoms nor cannot transmit the disease. (Getahun et el., 2015.) In LTB the bacteria remain inactive in the lungs even for decades or a lifetime and when the body's immune system weakens the bacteria may reactivate and cause the disease (ECDC, 2018a).

Reactivation of LTB accounts for the majority of new TB cases, especially in low TI countries (Getahun et al., 2015; Shea et al., 2014). The likelihood of the progression of LTB to becoming an active disease is related to numerous factors, such as the number of bacteria in the body, the age of the person, their immune system, and environmental factors, such as migration and poor living conditions. (Getahun et al., 2015.) Effective drugs are available for the treatment of LTB and, when treatment has been correctly instituted, it can prevent the transformation of infection to active TB (disease) (World Health Organization, 2018b). When LTB develops to TB, the bacteria become active and multiply in the body. A person may develop symptoms like cough, fever, night sweats, weight loss, lump etc. and can transmit the disease, if it is the pulmonary form. (World Health Organization, 2018a.)

A tuberculin skin test or interferon gamma release assays (IGRA) can be used for testing LTB (World Health Organization, 2018b). Current tests are defective when measuring the global prevalence of LTB but it has been estimated that approximately 1.7 billion people have LTB (World Health Organization, 2019). They have a 10% lifelong risk of falling ill with TB. However, the probability of developing TB disease is much higher among people with risk factors, such as malnutrition, diabetes, smoking and alcohol/drug abuse, and people infected with HIV. (World Health Organization, 2018a.) Other clinical risk groups, such as patients receiving dialysis, patients who are prepared for organ or hematological transplantation or patients initiating biological drugs especially those with severe autoimmune disease who are on anti-tumor necrosis factor treatment, have the highest likelihood of developing active TB disease and should be prioritized for systematic testing and treatment of LTB (World Health Organization, 2018b).

2.1.3 Diagnostics and treatment

In differential diagnostics, the symptoms of TB are similar to many other illnesses, and therefore diagnosing TB may be difficult. A chest X-ray (CXR) is the first line diagnostic method for active PTB. If radiological lung abnormalities are observed, sputum TB smear and culture are performed. Sputum smear microscopy is the fastest and cheapest test to make a preliminary TB diagnosis. The result of a sputum smear cannot differentiate *M. tuberculosis* from other mycobacteria, and it is less sensitive than culture. If the smear is positive, gene probe tests can be used for rapid differentiation between mycobacterial strains causing TB versus other mycobacteria. Even if smear is negative, TB cannot be ruled out before the sputum culture is negative. The sputum culture is more sensitive than the sputum smear, but it takes at least 2 to 3 weeks, usually up to 5 to 8 weeks, to get the results. Bronchoscopy, biopsy, urine culture or special imaging (computerized tomography, magnetic resonance imaging) can be used, depending on the suspected location of the TB. (Liippo, 2010; Migliori et al., 2018.) Also for small children, a gastric aspiration can be performed (Filha, 2019).

Even active, drug-susceptible TB disease can be treated and cured. TB treatment consists of a standard 6-month course of antimicrobial drugs that are provided every day to the patient by a healthcare worker. All patients who have not been previously treated (including those with HIV co-infection), receive an internationally accepted first-line treatment regimen. The patient is treated for two months with isoniazid, rifampicin, pyrazinamide, and ethambutol. The continuation phase consists of 4 months of isoniazid and rifampicin. (Migliori et al., 2018.)

Most TB cases can be cured when medicines are provided and taken properly. Often directly observed treatment is used, where the patient takes the drugs under supervision. (Migliori et al., 2018.) Drugs for TB were developed 70 years ago and are still used for the treatment of TB. Resistance, causing multidrug-resistance TB (MDR-TB) or extensively drug-resistant TB (XDR-TB), is increasing, making treatments less effective. (Hum, 2013.)

Over recent years, new TB drugs have been developed and old drugs have been recognized and approved for the use in treatment of MDR-TB; bedaquiline, delamanid, linezolid, rifapentine and terizidone (Ignatius & Dooley, 2019). Bedaquiline is in use for MDR-TB treatment in Finland, as recommended by the WHO (World Health Organization, 2017).

2.1.4 Drug-resistance

When a TB disease is caused by bacteria which are resistant to the two most powerful first-line drugs isoniazid and rifampicin, the form of the disease is called MDR-TB. If the bacteria are resistant only to rifampicin it is called rifampicin-resistant TB (RR-TB). MDR-TB can be cured by using second-line drugs. However, second-line treatment lasts up to 2 years and the medications are expensive and toxic and the available drug repertoire is limited. (Hum, 2013.) In 2017, 4.1% of new and 19% of previously treated TB cases in the world are estimated to have RR-/MDR-TB; 558 000 people (range, 483,000–639,000) had RR-TB, and of these, 82% had MDR-TB. Almost 50 % of the world's RR-/MDR-TB cases were found from India (24%), China (13%) and the Russian Federation (10%). (World Health Organization, 2018a.)

When a TB disease is caused by bacteria which are resistant to second-line drugs as well, the form of the disease is called XDR-TB and it is a more serious form of MDR-TB, often leaving patients without any further treatment options (Hum, 2013). Among cases of MDR-TB in 2017, 8.5% (95% CI; 6.2–11%) were estimated to have XDR-TB globally (World Health Organization, 2018a).

2.2 Genotyping of *Mycobacterium tuberculosis* isolates

The molecular epidemiology basically aims to find out if naturally occurring strains differ in epidemiology (Mathema et al., 2006). Genotyping consists of laboratory methods used to analyze the genetic material (e.g., DNA) of *M. tuberculosis*. When genotyping results are combined with epidemiological data, results can identify TB patients included in the same chain of a recent transmission. On the other hand, genotyping helps to differentiate those whose TB is a result of reactivation of LTB from those who have recently contracted TB. Thus, genotyping is a tool that significantly augments the ordinary contact tracing. (Amlerova et al., 2018; Magda, 2015.) Also, the cost of the ideal typing system should be as low as possible to be able to be used where needed. (Schurch & van Soolingen, 2012.)

When two or more *M. tuberculosis* isolates have the same results from genotyping methods (i.e., same spoligotype and MIRU-VNTR patterns), they are identified as a genotype cluster. Cases who belong to the same genotype cluster most probably have the same strain due to a recent transmission. Despite that, results from genotyping are only one piece of evidence used to determine transmission patterns

and epidemiological information also needs to be used. (Centers for Disease Control and Prevention, 2018.)

Over recent years, there has been an increasing acknowledgment of the diversity that exists among *M. tuberculosis* isolates (Reed et al., 2009). Isolates are further classified into lineages which display a high degree of geographic restriction (figure 2). The major lineages are: Haarlem, Latin America and Mediterranean (LAM), T-lineage, X-lineage, S-lineage, East African-Indian (EAI), Manu lineage, Central Asian (CAS) and Beijing. (Amlerova et al., 2018; Magda, 2015; Reed et al., 2009.)

Figure 2. World distribution of *M. tuberculosis* lineages by regions (Magda, 2015)

2.2.1 Spoligotyping

Kamerbeek et al. (Kamerbeek et al., 1997) developed a genotyping method in 1997, called spacer oligonucleotide typing or spoligotyping. Spoligotyping identifies the *M. tuberculosis* genotype if one or more repeats of the same nucleotide sequences are found (Centers for Disease Control and Prevention, 2018). Spoligotyping also differentiates between *M. bovis* and *M. tuberculosis*. (Amlerova et al., 2018; Kamerbeek et al., 1997; Magda, 2015.) This well repeatable method gives results in a standardized 15-digit code that can be easily analyzed and communicated between laboratories and TB programs, as an international database SITVIT2 (Pasteur

Institute of Guadeloupe) gathers spoligo-international types (SITs) in one database (Couvin et al., 2019).

2.2.2 Mycobacterial interspersed repetitive unit variable number tandem repeat

Mycobacterial interspersed repetitive unit variable number tandem repeat (MIRU-VNTR) differentiates the *M. tuberculosis* strains by the difference in the number of copies of tandem repeats at specific regions, or loci, of the genome (Centers for Disease Control and Prevention, 2018). MIRU-VNTR is fast and cheap and easy to use. The results provided by it are expressed as standardized numerical codes. Therefore, the results of different laboratories can be reliably compared. A combined use of MIRU-VNTR and spoligotyping may be useful, to get more precise results of strain differentiation. (Amlerova et al., 2018; Demay et al., 2012; Magda, 2015.)

2.2.3 Whole Genome Sequencing

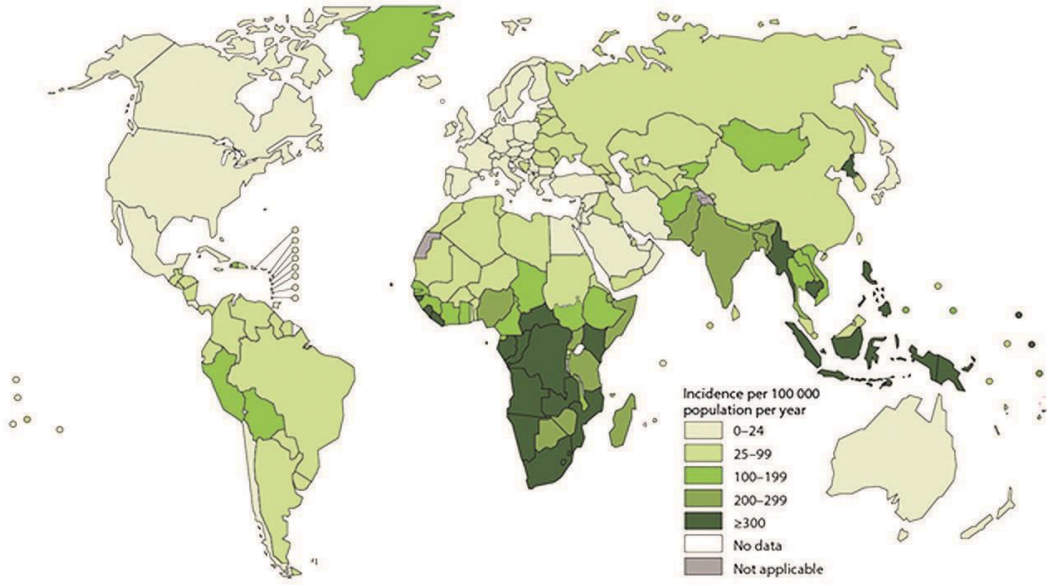
Whole genome sequencing (WGS) basically searches all variations in a bacterial genome and has the highest power for strain differentiation. WGS data are used to perform a whole-genome single nucleotide polymorphism analysis (or wgSNP analysis). A single nucleotide polymorphism (or SNP) is a mutation at a single position in the DNA sequence. wgSNP analysis uses WGS data to identify SNPs which are helpful for studying the genetic relationship between isolates. (Comin et al., 2020; Talarico et al., 2018). WGS gives more accurate information on transmission chains and clusters than spoligotyping or MIRU-VNTR. (Amlerova et al., 2018; Magda, 2015; Talarico et al., 2018.) WGS allows sequencing the genomes of multiple strains simultaneously, saving time, simplifying the analysis and providing considerably more information compared to spoligotyping and MIRU-VNTR methods (Nikolayevskyy et al., 2016).

2.3 Global epidemiology of tuberculosis

TB is one of the top ten diseases contributing to burden of deaths worldwide and the most affected areas are South-East Asia, Africa, and Western Pacific regions

(figure 3). The countries with the lowest burden of disease are found from Western and Northern Europe, North America. Australia and New Zealand are also low TI countries. It is estimated that in 2018, 10 million people (95% uncertainty interval 9.0–11.1 million) fell ill with TB and 1.45 million lost their lives. (World Health Organization, 2019.) Approximately 54 million people were successfully treated from 2000 to 2017 (World Health Organization, 2018a). In most low TI countries, like Sweden and Norway, nearly all of the diagnosed TB cases are among those foreign-born. Migrants from high TI countries are overrepresented. (Lonnroth et al., 2017.) In many countries, MDR-TB is more common among the foreign-born than among the native-born (Dhavan et al., 2017). In low TI countries most drug-susceptible and drug-resistant TB cases, who are foreign-born, have contracted the infection outside the host country (Lonnroth et al., 2017; Pareek et al., 2016).

Figure 3. Estimated TI by WHO, 2017 (World Health Organization, 2018c)



European Centre for Disease Prevention and Control (ECDC) estimated that in 2017, approximately 290,000 new and previously treated TB cases (range 251,000–333,000) occurred in the European region (Table 1). The average TI in the region was 30.7 (27.3–36.3), which represents about 3% of the total burden of TB in the world. TB cases of foreign origin represent 7.9% in the European region and 33.1% in EU/EEA countries. (ECDC/WHO Regional Office for Europe, 2019.)

Table 1. Characteristics of TB cases in selected countries by foreign-born cases, 2017 by ECDC (ECDC/WHO Regional Office for Europe, 2019)

Country	Number of cases	TI	Foreign-born cases, %	PTB, %	MDR-TB, %
Sweden	520	5.2	90.0	62.3	2.6
Norway	261	5.0	88.5	60.5	4.2
The Netherlands	787	4.6	74.5	58.1	1.4
Germany	5 486	6.6	69.6	70.9	3.0
Denmark	275	4.8	66.9	79.3	0.9
Finland	237	4.3	40.1	71.3	2.6
Estonia	175	13.3	13.1	96.0	25.4
Latvia	552	28.3	7.4	94.6	10.6
Russia	114 187	79.3	2.2	91.8	42.4[a]
Lithuania	1 387	48.7	1.1	92.6	21.7

TI, TB incidence or notification rate: number of new TB cases/100,000 population/year
[a] Data available only on pulmonary TB (PTB) cases

The WHO End TB Strategy, adopted by the World Health Assembly in May 2014, is a strategy to end the TB epidemic by cutting down TB deaths, incidence, and downshifting costs. It aims to reduce TB deaths by 95%, to cut new cases by 90% between 2015 and 2030, and to ensure that no-one is burdened with extensive costs due to TB. The objective of 90% decline in TI means that the global incidence should be <100 cases per million population by 2035 – similar to the current level in low TI countries today. With an increasingly mobile world population, prevention measures and improved TB care must be emphasized in both high and low TI countries. (World Health Organization, 2018a.)

2.4 History of tuberculosis in Finland

In Finland, TB mortality was extremely high before the end of the First World War as the deathrate from PTB was 250-300 per 100,000 population. Then, from 1948 to 1949 a large nation-wide BCG vaccination campaign was implemented, new drugs were developed at the beginning of the 1950s and hygiene and nutrition improved. These factors may explain that by 1953 the deathrate had dropped to 56 and 27 per 100,000 in males and females, respectively. (WHO Tuberculosis, 1955.)

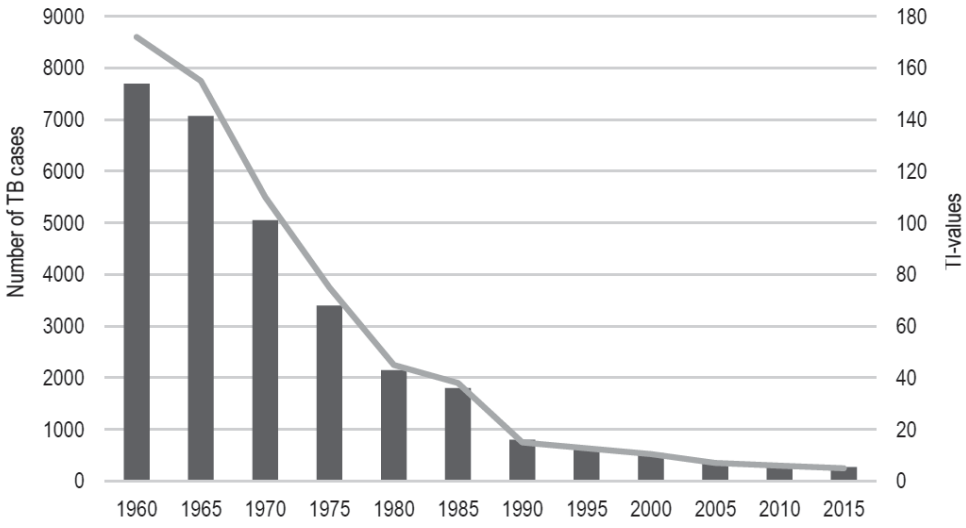
From the 1960s the TI has been in use to determine the burden of the disease (figure 4). The rapid decline of TI from 1960 to 1995 is one of the fastest in Europe.

In 1960 more than 7500 cases were diagnosed, the TI being 172. In 1970, approximately 5,000 cases were diagnosed, and the TI had dropped to 100 and in 1980 approximately 2,200 cases were diagnosed, and the TI had dropped to 45. (Tala-Heikkila, 2003.) A major milestone was reached in 2001 when Finland obtained the low TI country status (TI<10) with TI of 9.7. (Kela et al., 2001.)

From 1941 to 2006 all children in Finland were vaccinated for TB. In 2001, the new-born vaccination program was evaluated, and it was concluded that a selective BCG vaccination strategy would be a safe and cost-effective approach in preventing tuberculosis in Finland (Tala-Heikkilä et al., 2001). In 2006 the vaccination program was revised because of side-effects due to a change of a vaccine product in 2002. Also, TI had dropped dramatically in Finland. The new vaccination policy includes only children born to parents from high TI countries and others at an elevated risk of contracting TB. (The Finnish Institute for Health and Welfare, 2019b.)

Finland is classified as a low TI country (World Health Organization, 2018a). Increasing migration from high TI countries constitutes a growing risk for the low TI in Finland. The recent transition from an epidemiological situation where most reported cases have been reactivations of LTB in older Finnish adults to TB cases in young migrants has implications for national control, screening, diagnosis, and treatment strategies for TB.

Figure 4. Number of TB cases (columns) and TI-values (curve) 1960-2015 in Finland



2.5 Global trends in migration

Migration is a global phenomenon that has multidimensional impacts on individuals and societies. Migration patterns are increasingly complex and diverse, and are specific to location, time, and population. (International Organization for Migration, 2018.) Migration varies from voluntary to forced migration (Table 2) (McMichael et al., 2012).

Table 2. Terminology for migration and different groups of foreign-born persons used in this study by the International Organization for Migration and the United Nations

Term	Definition
Immigration	A process by which non-nationals move into a country for the purpose of settlement (International Organization for Migration, 2011)
Immigrant	A person undertaking immigration (International Organization for Migration, 2011)
Migrant	Persons, and family members, moving to better their material or social conditions and improve the prospect for themselves or their family (International Organization for Migration, 2011) In this study the term 'migrant' includes international migrants, international students, labor migrants, family reunion, asylum seekers, refugees and other persons whose country of birth or the most recent nationality is other than their country of living.
International migrants	Persons, and family members, moving to another country to better their material or social conditions and improve the prospect for themselves or their family (International Organization for Migration, 2011)
Internal migrants	Persons, and family members, moving within a country to better their material or social conditions and improve the prospect for themselves or their family (International Organization for Migration, 2011)
Labor migrant	A person who migrates for the purpose of seeking employment or who has been granted residency through employment purpose (International Organization for Migration, 2011)
Asylum-seeker	A person who seeks safety from persecution or serious harm in a country other than his or her own and awaits a decision on the application for refugee status under relevant international and national instruments (International Organization for Migration, 2011) Asylum seekers are determined as 'migrants'.
Refugee	A person who, owing to a well-founded fear of persecution for reasons of race, religion, nationality, membership of a particular social group or political opinions, is outside the country of his nationality and is unable or, owing to such fear, is unwilling to avail himself of the protection of that country (United Nations, 1951)

Migrants represented 3.4% (258 million) of the world population in 2017 and most of them lived in Asia (80 million) and Europe (78 million). Globally, almost 75% of migrants were 20 to 64 years old. (United Nations, 2017a.) Almost 70% of all international migrants were labor migrants (International Organization for Migration, 2018).

In 2017, 68.5 million individuals were forcibly displaced, including internal migrants, and 10% (26 million) of the global migrant population were international migrants (UNHCR, 2017; United Nations, 2017b). Most of the refugees in 2017 were from Syria, Afghanistan, or South Sudan. Turkey, Pakistan and Uganda were the top receiving countries (UNHCR, 2017).

Most international migrants move between countries of the same region, as in the case of Europe where 67% of migrants (41 million) are born in other European countries. In Europe, 10.5% of the total population were migrants in 2017, of whom 52% were women. (United Nations, 2017a.)

In the autumn of 2015, Europe faced a large migrant influx as 1.2 million first time asylum seekers were registered, mainly from Middle Eastern countries and the Horn of Africa (ECDC, 2015a; WHO Regional Office Europe, 2016).

2.5.1 Migration and tuberculosis

Migration can have an effect on the epidemiology of TB in low TI countries (Lonnroth et al., 2017; MacPherson & Gushulak, 2006; Pareek et al., 2016). Migrants may have an increased risk of TB, reactivation of LTB or poor treatment outcomes, as well as drug resistance of the bacteria causing their infection. Risk factors, such as poor living and working conditions, socio-economic status and poor access to services may increase the risk. (Dhavan et al., 2017; Pareek et al., 2016.) Furthermore, people have different health status, beliefs and cultural values affecting their access to health care and health-seeking behaviors (Gushulak & MacPherson, 2006).

Migrants are a heterogeneous group, such as students, labor migrants and seasonal cross-border workers. Also, refugees and asylum seekers are very heterogeneous groups. Whatever the characterization, all migrants leave their home country and transit to a new host country and might have lost their support systems, both emotional and structural. All migrants are dealing with new customs and legislation in new social, cultural, and economic environments. All this causes stress that affects the immune system. (Bhugra, 2004.)

The conditions and circumstances involved in migration often increase the risks of poor physical, mental and social well-being of migrants (Figure 5) (Dhavan et al., 2017; Kontunen et al., 2014; Zimmerman et al., 2011). While various social determinants can affect health, certain subgroups may be more vulnerable than others due to age, sex, origin, and the character of migration. The health status, and

the availability and accessibility of health services before and during migration, including the experience of any epidemics, disasters, or conflicts, affect the overall health and risk of TB. (Van Hear et al., 2009.) There are three components for the TB burden observed in foreign-born individuals:

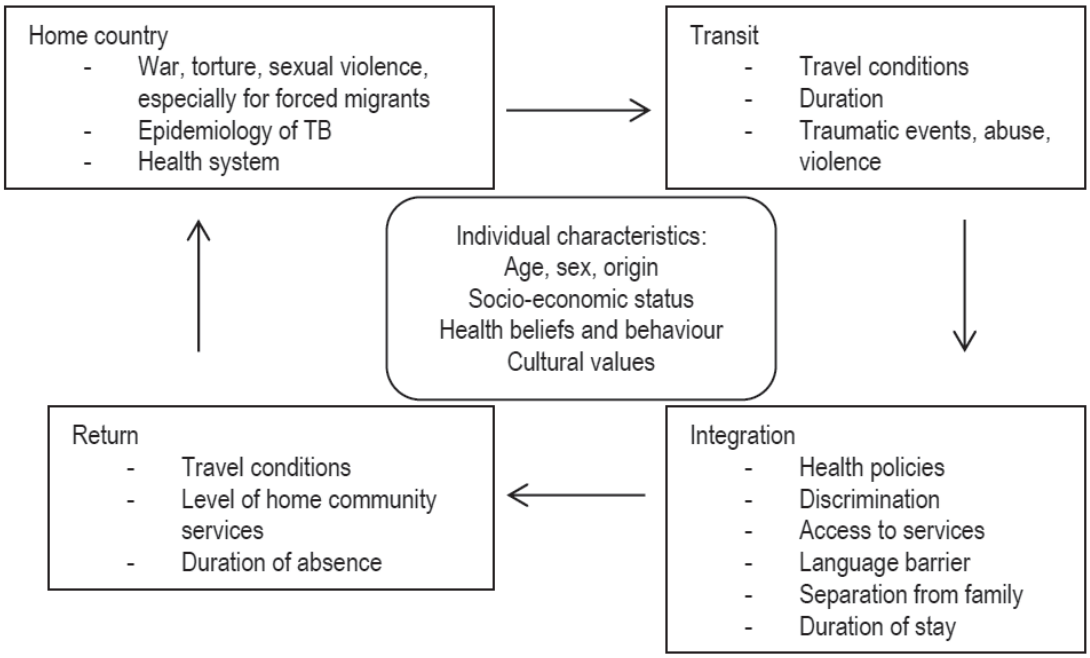
1) Migrants have active TB on arrival or

2) Migrants have LTB which reactivates post-arrival or

3) Migrants acquire TB, after arrival, through local transmission or during a visit to the country of origin (Pareek et al., 2016).

Modern migration patterns, with visits to the country of origin, also increase the risk of transmission, infection and may interrupt the treatment (Abubakar et al., 2011; Weinberg et al., 2016). In the new host country, individual's personal characteristics, social and community impact, living and working conditions, and general socio-economic, cultural, language and environmental factors may contribute to the risk of contracting TB. (Dhavan et al., 2017; Menzies, 2000; Vos et al., 2004.)

Figure 5. Migration cycle and vulnerability to TB



2.5.2 Migration in Finland

EU nationals or nationals who have a Finland residency permit, and have lived or have the intention to live in Finland for a minimum of one year can be registered in the population information system with a municipality of residence and unique national identifier (NID) (Finlex, 1994; Finlex, 2019).

Refugees are considered permanent residents at the time of arrival to Finland and are entitled to municipality of residence and NID (Digital and Population Data Services Agency, 2019). While asylum seekers and other migrants, who do not have a residency permit to Finland, are waiting for a decision on the residency permit application, they are not considered permanent residents in Finland and are not registered in the population information system. Once a residency permit is received, they are registered in the population information system and assigned a municipality of residence and NID. The Finnish Immigration Service is responsible for the processing of asylum applications and organization of services, including healthcare services, for asylum seekers. The Finnish Immigration Service also maintains a register for asylum applications. (Finlex, 2019.)

In Finland, as in many other European countries (Olaru et al., 2018; Rechel et al., 2013) the most commonly used determinant of migrant origin is the country of birth, and if the data are not available, the most recent nationality is used.

From 1995 to 2017 the international migrant population in Finland has increased from 2.1% (106,303) to 5.8% (321,494). In 1995, the largest migrant populations originated from Sweden (n=26 617), the Former Soviet Union or Russia (n=24,810), Estonia (n=6,698) and Somalia (n=3 229). In 2017, the largest immigrant populations originated from the Former Soviet Union or Russia (n=70 923), Estonia (n=46 022), Iraq (n=16 306) and Somalia (n=11 437). The gender distribution has stayed stable at approximately 50%. In 1995, 73% and in 2017, 85% of migrants were between 15 and 64 years old. (Statistics Finland, 2019b.)

Yearly an average of 5,000 asylum applications are received in Finland. About half of the asylum seekers are between 18-34 years of age and nearly 90% are male. Of those who seek asylum, approximately half are granted a residence permit. On average 60,000 residence permits are issued yearly, including asylum seekers and other migrants. (Finnish Immigration Service, 2018.) In 2015, Finland received the third largest number of applications in Europe (European Migration Network, Finnish Immigration Service, 2016; European Migration Network, Finnish Immigration Service, 2017); 615 applications per 100,000 inhabitants, compared with 1,727 in Sweden, 653 in Norway and 537 in Germany (Finnish Immigration

Service, 2017). The majority of these asylum seekers were born in Iraq, Afghanistan, Somalia and Syria, and about 25% were children (Finnish Immigration Service, 2018). The nearly tenfold increase in asylum seekers coming to Finland compared to previous years was among the highest in Europe (European Migration Network, Finnish Immigration Service, 2016; European Migration Network, Finnish Immigration Service, 2017). During the large influx of asylum seekers in 2015-2016, Finland faced a new challenge when the screening of TB needed to be executed in a short period of time (Tiittala et al., 2018a).

2.6 Tuberculosis control in Finland

In Finland TB control focuses on risk groups i.e. older people, migrants, substance abusers and drug-resistant TB cases and their close contacts. The high prevalence of TB in Finland's neighboring countries (Russia and the Baltics), increasing travelling to high TI countries, as well as migration, challenge the control of TB in Finland. The Tuberculosis Control Program 2013 (Ministry of Social Affairs and Health, 2013) sets the following objectives to control TB in Finland:

- identification of diseased persons as early as possible
- efficient and successful treatment in 80% of those with infectious PTB
- efficient prevention of new infections
- reducing the risk of contracting the disease
- improved knowledge and skills of health care staff

Compared to previous TB control programs, the 2013 program aims to increase the role of primary and occupational health care in TB control and increase the preparedness related to the additional challenges posed by migration

- to improve the efficiency of treatment in all patient groups
- to prevent infections developing into a disease
- to strengthen the early detection of the disease and infections
- to increase training and research (Ministry of Social Affairs and Health, 2013)

2.6.1 Tuberculosis screening

Finland, as well as several other European countries, has adopted WHO screening protocols for early detection of active TB for asylum seekers and refugees (Table 3) (World Health Organization, 2013). The aim of TB screening is to find infectious cases at an early stage, which protects the population and subject's own health and interrupts the transmission chains.

Table 3. Recommendations on risk groups to be screened by WHO (World Health Organization, 2013)

The following risk groups should always be screened for active TB, in all settings:	1. Close contacts of people with TB 2. People living with HIV 3. Workers in silica exposed workplaces
The following risk groups may be prioritized for screening based on local TB epidemiology, health systems capacity, resource availability, and feasibility of reaching the risk groups:	4. People in prisons and other penitentiary institutions, and prison staff 5. People with untreated fibrotic CXR lesion 6. People in high TB burden settings (estimated TI>100 in the general population) who are seeking care or who are in care and belong to selected risk groups, and health care workers. 7. Geographically defined sub-populations with extremely high levels of undetected TB (>1% prevalence), and other sub-populations with very poor health care access.

In Finland, asylum seekers and refugees coming from countries where the estimated TI is >50 are screened. The current TB screening policy for refugees and asylum seekers in Finland has been in effect since 2009 (Ministry of Social Affairs and Health, 2014). When large numbers of asylum seekers arrived in Finland in 2015–2016, the policy was modified to also include individuals arriving from conflict areas (such as Iraq and Syria) or refugee camps. The policy concerning other migrants, such as students and labor migrants, has been in effect since 2014 and was modified in 2016 (TI threshold was increased to >150 to increase cost-effectiveness). (Soini et al., 2017.) Despite recent recommendations by the ECDC, Finland does not currently routine screen migrants for LTB (ECDC, 2018b).

Published studies provide limited comparable information about evaluation of screening in EU/EEA countries. Many low TI countries in the EU/EEA screen migrants for active TB at or soon after arrival. (Bozorgmehr et al., 2017; Greenaway et al., 2018; Kunst et al., 2017.) The screening guidelines for active TB in migrants are lacking at the EU/EEA level and therefore the migrant groups targeted for screening and the location of screening are different for each country (Greenaway et al., 2018). Belgium, Germany, Greece, Norway, Switzerland and Sweden screen

all asylum seekers and refugees; the Netherlands and Spain screen migrants arriving from high TI areas; Italy does not conduct systematic TB screenings for asylum seekers, and the United Kingdom systematically screens only those who enter the country with a visa. LTB is routinely screened in Sweden, the Netherlands and Norway in migrants arriving from high TI countries (Kunst et al., 2017). Also, the timing and site of screening varies: pre-entry/pre-migration screening, port of arrival screening at the harbor or airport at arrival, reception/holding/transit center screening shortly after arrival in the country, and community post-arrival screening. In some countries TB screening is voluntary and other countries have a compulsory screening strategy. (Bozorgmehr et al., 2017; Greenaway et al., 2018; Kunst et al., 2017.)

TB screening among migrants has been extensively studied in EU/ETA countries (Bozorgmehr et al., 2017; Greenaway et al., 2018; Kunst et al., 2017), but only a few studies have previously been published of voluntary TB screening among asylum seekers at reception centers (Arrazola de Onate et al., 2016; Vanino et al., 2017).

2.6.2 Contact tracing

Contact tracing is used to interrupt the transmission chain (The Finnish Institute for Health and Welfare, 2019a). Contact tracing has been a standard practice for decades in low TI countries (Fox et al., 2013) and it is performed by a nurse when a new infectious PTB case is diagnosed. (The Finnish Institute for Health and Welfare, 2019a.) Contact tracing contains a systematic evaluation of the contacts of an infectious TB patient (Fox et al., 2013; The Finnish Institute for Health and Welfare, 2019a) and may include clinical assessment, CXR, and microbiological evaluation of sputum or an IGRA test to detect LTB in close contacts of an infectious case (Hwang et al., 2011). Contact tracing is a key component of TB prevention, especially in high-risk populations: children and people living with HIV (Andrews et al., 2014; Fox et al., 2013). Contact tracing may help to identify cases earlier, to possibly decrease disease severity and to reduce transmission. WHO recommends that all contacts of infectious TB patients should be followed up and screened for TB. (ECDC/WHO Regional Office for Europe, 2018.)

In Finland, contact tracing is legislated by the Communicable Diseases Act 1227/2016 (Finlex, 2016) and conducted according to the guideline for TB contact tracing in Finland issued by The Finnish Institute for Health and Welfare (THL)

(The Finnish Institution for Health and Welfare, 2019). The goals of contact tracing in Finland are to identify contacts exposed to a person with TB, especially PTB and require treatment, and to find the person who is the primary source of transmission and to provide them information about TB. (The Finnish Institution for Health and Welfare, 2019.)

3 AIMS OF THE STUDY

The overall aim of this study is to evaluate the effects of migration on tuberculosis epidemiology in Finland during 1995-2017

The specific aims are:

1. to characterize national trends among foreign- and Finnish-born populations in the epidemiology of tuberculosis in Finland (I, II, IV)

2. to describe the screening practices for tuberculosis among asylum seekers (II, III)

3. to evaluate the extent of clustering and tuberculosis transmission between foreign- and Finnish-born populations (I, IV)

4 MATERIALS AND METHODS

4.1 The national infectious disease register

The Finnish Institute for Health and Welfare (THL) operates in Finland as an expert agency for infectious disease prevention and control. THL maintains a statutory national infectious disease register (NIDR), to which also TB cases are notified. Register information is used in the prevention and control of infectious diseases, and in research. Approximately 90,000 cases of infectious diseases are entered in the NIDR per year. The data have been gathered since 1995 and in 2017 reporting was changed from paper forms to an electronic platform. (The Finnish Institute for Health and Welfare, 2017.)

Physicians notify clinically suspected and confirmed TB cases; reporting is mandatory. Each physician's notification on the NIDR includes: NID if available, the name, date of birth and gender. In addition, the notification of the physician includes country of birth, nationality, place of residence and treatment, dates of symptom onset and diagnosis, diagnostic method, clinical presentation (PTB/EPTB), and additional information on the contact tracing (free text). If the patient has NID, the NIDR data are completed with information from the population information system. This information includes details of the patient's municipality of residence, country of birth, nationality, and possible death. (The Finnish Institute for Health and Welfare, 2017.)

In addition, from 1995 to 2006, the case definition for TB surveillance included all cases confirmed by culture, sputum smear, nucleic acid amplification or histology (The Finnish Institute for Health and Welfare, 2017). With the adoption of the standard European Union case definition for TB in 2007 (EUR-Lex, 2003), a new reporting category was added to NIDR: 'physician's decision to initiate full TB treatment on the basis of clinical suspicion of TB in the absence of laboratory confirmation'. (The Finnish Institute for Health and Welfare, 2017.)

4.1.1 Laboratory notification and methods (I, IV)

Clinical microbiology laboratories notify new *M. tuberculosis* isolations directly to the NIDR, maintained by THL, and submit isolates to the Mycobacterial Reference Laboratory at THL for drug susceptibility testing and genotyping. A laboratory's notification includes identification information and details about place of treatment, sampling date, examination finding, microbe detection method, sample type and the name of the reporting laboratory. (The Finnish Institute for Health and Welfare, 2017.) All isolates are mandatorily submitted to the national isolate collection of NIDR at THL.

4.1.1.1 Study I

M. tuberculosis isolates from culture-positive TB cases reported during 2008–2013 were characterized by spoligotyping according to standard methods at the THL Mycobacterial Reference Laboratory (Kamerbeek et al., 1997). The resulting spoligotype patterns were compared to the data in the international SITVITWEB database (Demay et al., 2012). An isolate was assigned a SIT and a lineage if the same spoligotype was found in the database. Only isolates from foreign-born cases were analyzed.

4.1.1.2 Study IV

Culture-positive *M. tuberculosis* isolates are routinely sent to the THL Mycobacterial Reference Laboratory for drug susceptibility testing and genotyping by spoligotyping and MIRU-VNTR according to standard protocols at the THL Mycobacterial Reference Laboratory (Kamerbeek et al., 1997; Supply et al., 2006). The resulting spoligotype patterns were compared to the data in the international SITVITWEB 2 database (Couvin et al., 2019). An isolate was assigned a SIT and a lineage if the same spoligotype was found in the database. The MIRU-VNTR results were analyzed by the MIRU-VNTR plus database (Weniger et al., 2010) using the Bionumerics 6.6 software (Applied Maths, Sint-Martens-Latem, Belgium). When two or more *M. tuberculosis* isolates matched by genotyping methods (i.e., identical spoligotype and MIRU-VNTR patterns), they were considered a genotype cluster. Clusters which included Finnish- and foreign-born cases were evaluated by using the additional information obtained by contact tracing: type of social contacts, such

as schoolmates, friends, relatives, and family members. The genotypes of the mixed clusters were compared with a local genotyping database obtained from *M. tuberculosis* strains isolated in Finland to determine whether the clusters had been detected in Finland earlier.

4.2 Enhanced surveillance questionnaire (II)

A web-based questionnaire was sent to medical doctors responsible for communicable disease control in regional hospital districts, where foreign-born or pediatric TB cases were diagnosed from 1.1.2014 to 31.12.2016 and reported to the NIDR. Questionnaire included questions regarding country of birth, date of arrival to Finland, travel route to Finland, whether the person has lived in a refugee camp before arriving in Finland, whether the person has stayed in a reception center in Finland, participation in TB screening, date of first symptoms (e.g. cough, night sweats, weight loss, swelling or a lump), and possible contact tracing results. For pediatric cases, the parents' country of birth was reported.

4.3 Reception centers' national health record system (III)

In publication III reception centers' national health record system (HRS) was used as a data source. The following HRS data were collected on asylum seekers: name, date of birth, gender, nationality, date of interview and health check-up, date, and findings of CXR, TB - related symptoms, date of symptom onset and further examinations performed.

All healthcare professionals, including nurses in reception centers, are obliged by law to document all patient records. HRS was introduced to reception centers in 2014, but during the large influx in 2015, HRS was not fully implemented in all the operating reception centers leading to incomplete records and potential underreporting of screenings. Until 2016, some of the health records were still made manually. HRS is used for health records of all asylum seekers who live in reception centers or in private apartments but are obliged to use reception centers services. HRS is maintained by the Finnish Immigration Service. (Tiittala et al., 2018b.)

The information about asylum seeking status is not notified in the NIDR data. Therefore, NIDR data of foreign-born TB cases, notified during 2015-2016, were linked with the HRS data by name, date of birth and origin to find out whether the

TB cases were asylum seekers who had arrived in Finland during 2015-2016 and had undergone TB screening. Linkage could not be made by using NID as asylum seekers are assigned it only after receiving a residency permit.

4.4 Tuberculosis screening in Finland (III)

TB screening in Finland is legislated by the Communicable Diseases Act 1227/2016 (Finlex, 2016) and the policy for screening asylum seekers and refugees is set by the Ministry of Social Affairs (Ministry of Social Affairs and Health, 2009).

Information about healthcare services to which asylum seekers are entitled is given in a health information session and/or in an interview at the reception center, including information about the Finnish healthcare system, infectious diseases, dental problems and mental healthcare (Skogberg et al., 2019). Asylum seekers are asked to fill in a symptom-based health questionnaire on their own health, which is used to plan the health check-up and the need for infectious disease screening. A nurse implements the health check-up for adults and a physician for children, pregnant women and disabled persons (Tiittala et al., 2018a).

Voluntary TB screening consists of two phases. First, in the basic health check-up a nurse interviews the asylum seeker about their TB risk factors, such as symptoms (including EPTB symptoms), past residency in a refugee camp or conflict area, or previous history of TB. In the second phase of TB screening, CXR should be performed within two weeks of arrival. It is offered to asylum seekers who have risk factors of TB and/or are coming from high TI countries (TI>50).

In 2015-2016, asylum seekers' CXR were performed at two nationally contracted private healthcare providers.

TB screening is also offered to other migrants (labor, family reunification, study) who come from countries with a very high TI (TI≥150), and who plan to stay in Finland for 3 months or longer. Despite the guideline for other migrants' screening protocol by THL (Soini et al., 2017), the implementation varies widely in Finland.

4.5 Population data

The number of persons living in Finland by year and country of birth was obtained from the population information system (Statistics Finland population database)

which contains data on all persons residing legally in Finland (Statistics Finland, 2019a).

Aggregated data on all asylum seekers and residence permits by age group, gender, country of origin, time of application and the reason for applying residency were obtained from the Finnish Immigration Service (Finnish Immigration Service, 2018)

4.6 Definitions

A Finnish-born is defined as a person born in Finland or, if the country of birth is not known, the most recent nationality is Finnish. A foreign-born person/migrant was defined as a person born outside of Finland or, if the country of birth was not known, the most recent nationality was not Finnish. A pediatric case/child was defined as a person under 18 years old at the time of diagnosis. A second-generation migrant was defined as a person under 18 years old, born in Finland and having at least one foreign-born parent.

4.7 Data analysis and statistics

Statistical significance for categorical variables were analyzed with the $\chi 2$ test or Fisher's exact test. Continuous variables were analyzed using the Mann–Whitney U test. Cross-tabulation was used to analyze characteristics. IBM SPSS v. 22.0 (publication I) and 25.0 (publications III and IV) (SPSS Inc., USA) or Statistical Analysis System Software, version 9 (publication III) (SAS Institute, Inc., Cary, North Carolina) and Microsoft Excel (Microsoft Corp., USA) were used to analyze the data.

Incidence was calculated by the annual number of cases divided by the population at the end of the year and is expressed as cases per 100 000 population per year. The population at risk was calculated by persons living in Finland each year. The rate was calculated by the number of cases divided by the population at risk. Screening yield was defined as the percentage of TB cases identified among screened asylum seekers and was further stratified by country of origin. Number needed to screen (NNS) was calculated as number of persons screened divided by the number of TB cases found in screening. The overall clustering rate was calculated by the number of clustered cases divided by the number of culture-

positive isolates. The confidence intervals (CI) were calculated according to Wald (Fagerland, Lydersen, & Laake, 2015).

Statistics Finland data were used as denominators to calculate age- and gender-specific TIs (Statistics Finland, 2019a). A Poisson regression model was used to assess the significance of the log-linear trend in annual incidence rates. Aggregated data of all asylum seekers by age group and country of origin were obtained from the Finnish immigration service (Finnish Immigration Service, 2018). The number of CXRs performed for asylum seekers was obtained from the previous study by Tiittala et al. (Tiittala et al., 2018a.)

4.8 Ethical considerations

The study was performed according to research ethical principles outlined in "the ethical principles of research with human participants and ethical review in the human sciences in Finland" by the Finnish National Board on Research Integrity (The Finnish National Board on Research Integrity, 2019). Information and data collected from different registers were handled confidentially as required by the Data Protection Act (Finlex, 2018). The results were analyzed in coded form, so that no individual could be identified without the code key. The code key that identifies the individual's identity was stored in a locker at THL and the information is not provided to persons outside the research group. The interpretation of research results emphasizes their use in prevention and early detection, in the interest of both the individual and the community. When reporting the results of the studies, attention was drawn to the fact that no individual is identifiable from the results; final research results were reported at group level and reporting ensured that the results of the research cannot be interpreted as discriminatory. The researcher has undergone Ministry of the Interior training on the basics of information security. In addition, the researcher has taken a mandatory university level education in research ethics and proper data management. No contact was made between the researcher and individuals in the group included in the study.

Ethics approval was not applicable in studies I, II and IV as data in these studies were analyzed within the epidemiological research purposes authorized by the Finnish Communicable Diseases Act 1227/ 2016, 42 §. Therefore, ethical approval was deemed unnecessary.

The study III was approved by the Ethics Committee of the Hospital District of Southwest Finland (§326, 9.8.2018) and by the Finnish Immigration Service (permission number MIG-1815473, 3.9.2018).

5 RESULTS

5.1 The epidemiology of tuberculosis in Finland between 1995 and 2017 (I, II, IV)

Spanning the years 1995-2017, a total of 9314 TB cases were reported to NIDR (Table 4). Of them, 7605 (81.7%) were Finnish-born and 1614 (17.3%) were foreign-born, for 95 (1%) of the cases the origin was not available. The median age was 66 years (range <1-105), 56.6% were male, 0.8% had MDR-TB and 68.6% had PTB, of which 47.7% were sputum smear positive (Table 5).

Among Finnish-born cases, the median age was 70 years (range 0-105), 57.5% were male, 0.3% had MDR-TB, and 69.9% had PTB, of which 47.1% were sputum smear positive. The TI among Finnish-born cases ranged from 12.1 in 1995 to 2.3 in 2016, being 2.7 in 2017. (Table 4).

Among foreign-born cases, the median age was 29 years (range 1-93), 52.3% were male, 3.1% had MDR-TB, 62.8% had PTB, of which 44.0% were sputum smear positive. (Table 5) The TI ranged from 46.4 in 1998 to its lowest level 27.1 in 2017. Overall, foreign-born cases were born in 92 different countries; most cases were born in Somalia (28.5%), the former Soviet Union (FSU)/Russia (6.6%) and Vietnam (6.1%). (Table 6).

Nearly 90% of the foreign-born cases were born in high TI countries (TI>50 cases). For most of the countries the TI in Finland was similar or lower than in most of the countries of origin (Table 6). Exceptions were persons born in Somalia and Ethiopia, among whom the TI in Finland was higher compared to the reported TI in their country of origin. The proportion of male cases born in the Philippines and Thailand was only 19% and 11%, respectively. MDR-TB was more common among cases born in Estonia and FSU/Russia compared to other countries of birth.

MDR-TB is increasing among foreign-born TB cases. During 1995–2004, 11 foreign-born MDR-TB cases were diagnosed (range by year 0–4), during 2005–2013, 18 foreign-born MDR-TB cases were diagnosed (range by year 0–5) and during 2014-2017, 21 foreign-born MDR-TB cases were diagnosed (range by year 5-6).

Table 4. Incidence of TB cases in the whole, Finnish-born, and foreign-born populations in Finland, 1995-2017

Year	All cases			Finnish-born cases			Foreign-born cases		
	Population in Finland [a]	Number of cases [b]	TI (95%CI)	Finnish-born population in Finland (%) [a]	Number of cases (%)	TI (95%CI)	Foreign-born population in Finland (%) [a]	Number of cases (%)	TI (95%CI)
1995	5116826	654	12.8 (11.8-13.8)	5 010 523 (97.9)	608 (93.0)	12.1 (11.2-13.1)	106303 (2.1)	38 (5.8)	35.7 (26.0-49.1)
1996	5132320	632	12.3 (11.4-13.3)	5 021 189 (97.8)	584 (92.4)	11.6 (10.7-12.6)	111131 (2.2)	41 (6.5)	36.9 (27.2-50.1)
1997	5147349	557	10.8 (10.0-11.8)	5 029 279 (97.7)	508 (91.2)	10.1 (9.3-11.0)	118070 (2.3)	46 (8.3)	39.0 (29.2-52.0)
1998	5159646	610	11.8 (10.9-12.8)	5 034 596 (97.6)	549 (90.0)	10.9 (10.0-11.9)	125050 (2.4)	58 (9.5)	46.4 (35.9-60.0)
1999	5171302	598	11.6 (10.7-12.5)	5 040 182 (97.5)	541 (90.5)	10.7 (9.9-11.7)	131120 (2.5)	47 (7.9)	35.8 (26.9-47.7)
2000	5181115	545	10.5 (9.7-11.4)	5 044 912 (97.4)	497 (91.2)	9.9 (9.0-10.8)	136203 (2.6)	47 (8.6)	34.5 (25.9-45.9)
2001	5194901	503	9.7 (8.9-10.6)	5 049 766 (97.2)	434 (86.3)	8.6 (7.8-9.4)	145135 (2.8)	66 (13.1)	45.5 (35.7-57.9)
2002	5206295	477	9.2 (8.4-10.0)	5 054 238 (97.1)	428 (89.7)	8.5 (7.7-9.3)	152057 (2.9)	49 (10.3)	32.2 (24.4-42.6)
2003	5219732	415	8.0 (7.2-8.8)	5 060 865 (97.0)	363 (87.5)	7.2 (6.5-7.9)	158867 (3.0)	51 (12.3)	32.1 (24.4-42.2)
2004	5236611	335	6.4 (5.7-7.1)	5 070 250 (96.8)	290 (86.6)	5.7 (5.1-6.4)	166361 (3.2)	42 (12.5)	25.2 (18.7-34.2)
2005	5255580	373	7.1 (6.4-7.9)	5 078 968 (96.6)	319 (85.5)	6.3 (5.6-7.0)	176612 (3.4)	54 (14.5)	30.6 (23.4-39.9)
2006	5276955	295	5.6 (5.0-6.3)	5 089 045 (96.4)	239 (81.0)	4.7 (4.1-5.3)	187910 (3.6)	53 (18.0)	28.2 (21.5-36.9)
2007	5300484	350	6.6 (5.9-7.3)	5 097 956 (96.2)	276 (78.9)	5.4 (4.8-6.1)	202528 (3.8)	74 (21.1)	36.5 (29.1-45.9)
2008	5326314	343	6.4 (5.8-7.2)	5 107 688 (95.9)	288 (84.0)	5.6 (5.0-6.3)	218626 (4.1)	54 (15.7)	24.7 (18.9-32.2)
2009	5351427	416	7.8 (7.1-8.6)	5 118 244 (95.6)	285 (68.5)	5.6 (5.0-6.3)	233183 (4.4)	125 (30.0)	53.6 (45.0-63.9)
2010	5375276	323	6.0 (5.4-6.7)	5 127 141 (95.4)	213 (65.9)	4.2 (3.6-4.8)	248135 (4.6)	106 (32.8)	42.7 (35.3-51.7)
2011	5401267	326	6.0 (5.4-6.7)	5 135 119 (95.1)	240 (73.6)	4.7 (4.1-5.3)	266148 (4.9)	80 (24.5)	30.1 (24.1-37.4)
2012	5426674	276	5.1 (4.5-5.7)	5 141 203 (94.7)	182 (65.9)	3.5 (3.1-4.1)	285471 (5.3)	81 (29.3)	28.4 (22.8-35.3)
2013	5451270	271	5.0 (4.4-5.6)	5 146 991 (94.4)	182 (67.2)	3.5 (3.1-4.1)	304279 (5.6)	87 (32.1)	28.6 (23.2-35.3)
2014	5471753	264	4.8 (4.3-5.4)	5 149 776 (94.1)	172 (65.2)	3.3 (2.9-3.9)	321977 (5.9)	88 (33.3)	27.3 (22.2-33.7)
2015	5487308	272	5.0 (4.4-5.6)	5 150 146 (93.9)	151 (55.5)	2.9 (2.5-3.4)	337162 (6.1)	115 (41.9)	34.1 (28.4-40.9)
2016	5503297	233	4.2 (3.7-4.8)	5 145 756 (93.5)	117 (50.2)	2.3 (1.9-2.7)	357541 (6.5)	111 (47.6)	31.0 (25.8-37.4)
2017	5513130	246	4.5 (3.9-5.1)	5 140 328 (93.2)	139 (56.5)	2.7 (2.3-3.2)	372802 (6.8)	101 (41.1)	27.0 (22.3-32.9)
Total		9314			7606 (81.7)			1614 (17.3)	

CI, Confidence Interval; TI, Tuberculosis incidence: number of new tuberculosis cases/100,000 population/year

[a] Population Information system (Statistics Finland, 2019a)

[b] Includes 95 cases without country of birth or nationality

The TI in Finland ranged from 12.8 in 1995 to 4.2 in 2016, being 4.5 in 2017. The number of TB cases decreased by 62.4% during this period (Table 4). TB cases in the Finnish-born population decreased by 77.1% from 1995 to 2017. During the same period, the number of TB cases in the foreign-born population increased by 165.8% and the number of foreign-born persons living in Finland increased by 250.7% (Table 4).

The proportion of reported foreign-born TB cases increased from 5.8% in 1995 to 41.1% in 2017 while the proportion of all foreign-born in the Finnish population increased from 2.1% in 1995 to 6.8% in 2017 (Table 4).

Over the period 1995–2017, foreign-born TB cases were significantly younger, more often female, had EPTB and MDR-TB more often than Finnish-born cases (Table 5). Finnish-born cases had more often smear positive PTB than foreign-born TB cases ($p<0.01$, for all the comparisons).

Table 5. Characteristics of all, Finnish-born, and foreign-born TB cases in Finland, 1995-2017

	All [a] (n=9314)	Finnish-born (n=7606)	Foreign-born (n=1614)	*P*-value [b]
Median age, years (range)	66 (0-105)	70 (0-105)	29 (1-94)	<0.01
Age group, years, n (%)				
0-14	124 (1.3)	47 (0.6)	74 (4.6)	
15-29	984 (10.6)	200 (2.6)	747 (46.3)	
30-44	1083 (11.6)	550 (7.2)	515 (31.9)	
45-59	1630 (17.5)	1479 (19.4)	160 (9.9)	
60-74	2507 (26.9)	2435 (32.0)	67 (4.2)	
75-	2946 (31.6)	2894 (38.1)	51 (3.2)	
Male cases, n (%)	5269 (56.6)	4373 (57.5)	844 (52.3)	<0.01
PTB, n (%)	6391 (68.6)	5318 (69.9)	1014 (62.8)	<0.01
Smear positive, n (%)	3046 (47.7)	2506 (47.1)	446 (44.0)	<0.01
MDR-TB, n (%)	75 (0.8)	22 (0.3)	50 (3.1)	<0.01

PTB, Pulmonary tuberculosis; MDR-TB, Multidrug-resistant tuberculosis
[a] Includes 95 cases without country of birth or nationality
[b] Between Finnish-born and foreign-born

Table 6. Characteristics and TI in migrants from the most frequent countries of birth in Finland, 1995-2017

Country of birth [a]	TI (CI 95 %) by WHO in 2017	Number of cases (%)	Median age, years (range)	Male cases, % ([b])	Population at risk (person years)	TI	MDR-TB, %	PTB, %
Somalia	266 (172–380)[c]	460 (28.5)	25 (5-76)	51 (53)	149 652	307	3.3	46.3
Ethiopia	164 (115–221)[c]	48 (3.0)	27 (7-70)	71 (57)	27 673	173	0	68.8
Afghanistan	189 (122–270)[c]	65 (4.0)	25 (5-87)	54 (56)	47 344	137	3.1	80.0
Philippines	554 (311–866)[c]	42 (2.6)	29 (7-59)	19 (27)	38 668	109	4.8	47.6
Vietnam	129 (106–155)[c]	98 (6.1)	31 (14-79)	47 (46)	94 728	103	0	72.4
Thailand	156 (119–199)[c]	86 (5.3)	36 (1-64)	11 (22)	113 276	76	1.2	51.2
Iraq	42 (37–48)[c]	43 (2.7)	31 (3-74)	67 (61)	138 471	31	2.3	79.1
Estonia	15 (13–17)[c]	46 (2.8)	42 (18-91)	69 (48)	472 567	10	13.0	87.0
FSU/Russia	60 (39–85)[c]	106 (6.6)	47 (16-93)	40 (38)	1 110 621	10	12.3	82.1
Unknown	-	114 (7.1)	28 (1-94)	61 (49)	126 718	90	6.1	70.2
Other	-	507 (31.4)	30 (1-90)	62 (57)	2 577 966	20	0.6	67.1
Total		1615	29 (1-94)	52 (50)	4 897 684	33	3.1	62.8

TI: Tuberculosis incidence or notification rate: number of new tuberculosis cases/100,000 population/year; WHO, World Health Organization; MDR, Multidrug-resistant tuberculosis PTB, Pulmonary tuberculosis; FSU, Former Soviet Union

[a] By TI (high to low)

[b] Proportion of males of the population from specific country in Finland (Statistics Finland, 2019a)

[c] World Health Organization, 2018

5.2 Tuberculosis screening (II, III)

5.2.1 Enhanced surveillance, 2014–2016 (II)

During the study period from 2014 to 2016, 771 TB cases were diagnosed in Finland: 314 (41%) were foreign-born and 48 (6%) were pediatric cases (foreign-born or born in Finland).

A web-based questionnaire was answered for 203 (65%) of 314 foreign-born TB cases (Table 7). According to the questionnaire, TB was detected in screening completed at arrival in 42 (21%) cases, 18 (9%) cases were found at contact tracing of another TB patient, and 143 (70%) cases sought care due to symptoms or were found by chance (e.g. CXR taken due to an accident). The time between arrival in Finland and the date of diagnosis of TB was less than three months in 48 (24%) cases, between three months to two years in 55 (27%) cases, and more than two years in 84 (42%) cases, the time of disease onset was not available for 16 (8%) cases.

Of the cases questionnaire data available, 30 (15%) cases had been in a refugee camp prior to arrival in Finland and 35 (17%) had stayed in a reception center in Finland. Of the 203 foreign-born TB cases, no symptoms compatible with TB were reported in 50 (25%) cases. Thirteen (26%) of the asymptomatic cases were detected in screening performed at or soon after arrival, 10 (20%) due to being investigated because of an accident or death, and 12 (24%) due to contact tracing. In 15 cases this information was not available. Of the foreign-born TB cases without symptoms, 42 (84%) had PTB, 9 (18%) had stayed in a refugee camp on the way to Finland and 14 (28%) had lived in a reception center in Finland. The proportion of PTB was higher among asymptomatic cases (84%) than among symptomatic cases (54%).

Table 7. Results of the enhanced surveillance questionnaire, Finland, 2014-2016

	Foreign-born case (n=203)[1]
Stayed in a refugee camp abroad n (%)	30 (15)
Stayed in a reception center in Finland n (%)	35 (17)
TB found in screening n (%)	42 (21)
TB diagnosed within two years after arrival to Finland n (%)	103 (51)
Symptoms of TB n (%)	153 (75)
PTB n (%)	140 (69)

[1] questionnaire data available

5.2.2 Screening of asylum seekers, 2015-2016 (III)

Between 1.1.2015 and 31.12.2016, a total of 38,134 asylum seekers applied for asylum to Finland (Table 8); 80% were men and more than half were aged between 18-34. More than 80% of these asylum seekers were from Iraq, Afghanistan, Somalia, or Syria.

Within the same timeline, 386 abnormal screening results were recorded in the HRS; 210 (54%) were examined further, and 39 (19%) of them were lost to follow-up. Altogether 105 asylum seekers were identified in the NIDR who were diagnosed with TB in 2015-2016; 9 asylum seekers had arrived in Finland before 2015 and therefore were excluded from the analysis. A total of 96 asylum seekers, who had arrived in Finland during 2015-2016, received a diagnosis of TB during 2015-2016, and of them 48 (50%) were diagnosed based on screening. In 40 (42%) cases TB suspicion arose because symptoms appeared after screening, for 5 (5%) cases the reason of TB suspicion was unknown, 2 (2%) were found before screening and 1 (1%) in contact tracing.

Of the 48 TB cases diagnosed based on screening, 83% were male and the median age was 25 years (range, 3-62) (Table 8). The most common countries of origin were Somalia (40%), Afghanistan (27%) and Iraq (12.5%). PTB was diagnosed in 44 (91.7%) cases; 27 (61.4%) were culture-confirmed, 27 (56%) had symptoms, and 7 (14.6%) were sputum smear positive. EPTB was diagnosed in 4 (8.3%) cases and all were found in basic health check-up. The date of CXR was available for 41 cases; the mean time from CXR screening to the time of diagnosis was 35 days (95%CI, 15.9-54.3).

Overall, 77 (80%) of the asylum seekers diagnosed with TB had attended the health information session and/or basic health check-up; the attendance was not documented in 19 (20%) cases. Screening CXR was performed in 94 of the 96 (98%) cases; 44 (47%) cases had abnormal findings, 32 (34%) had normal findings, and for 18 (19%) cases detailed CXR results were not documented.

TB yield among individuals screened was 0.19% (95%CI, 0.14-0.25%) and NNS 522 (Table 8). If assumed that all asylum seekers from the same country of origin were screened, TB yield ranged from 0 to 0.83% by country of origin, being highest for Somalia. Accordingly, screening prevalence rate among asylum seekers was 191/100 000 and ranged from 0 to 828 cases/100,000 by country of origin.

Table 8. Characteristics of asylum seekers, TB cases among asylum seekers, TB cases diagnosed based on screening and yield of TB cases diagnosed based on screening in Finland, 2015-2016

		All asylum seekers; n (%),	All TB cases among asylum seekers; n (%),	TB cases diagnosed based on screening; n (%)	Yield of TB cases diagnosed based on screening; (%)
		n=38,134	n=96	n=48	0.19
Men[a]		30 122 (79)	71 (74)	40 (83)	
Age group[b]	0–13	5 669 (15)	3 (3)	1 (2)	
	14–17	3 740 (10)	13 (13.5)	9 (19)	
	18–34	22 397 (59)	65 (68)	27 (56)	
	35–64	6 024 (16)	13 (13.5)	11 (23)	
	65 or above	114 (0.3)	2 (2)	0	
Origin[c]	Iraq	21 731 (57)	11 (11)	6 (12.5)	0.028[d]
	Afghanistan	5 968 (16)	17 (18)	13 (27)	0.22[d]
	Somalia	2 413 (6)	49 (51)	20 (42)	0.83[d]
	Syria	1 479 (4)	2 (2)	0	0[d]
	Other	6 493 (17)	17 (18)	9 (19)	NA
PTB			71 (74)	44 (91.7)	
MDR-TB			8 (8.3)	4 (8.3)	

[a] For 53 (0.1%) asylum seekers, information on sex was missing.
[b] For all asylum seekers, age at the time of immigration; for TB cases age at the time of diagnosis. Of all the asylum seekers, 190 (0,5%) had unknown age
[c] Origin is based on country of birth, and if not available, on nationality. Of all the asylum seekers, 50 (0,1%) had unknown origin.
[d] stratified by country of birth

5.3 Tuberculosis in children (II)

Between 2014 and 2016, 48 pediatric TB cases were identified from the NIDR: 36 (75%) were foreign-born and 12 (25%) were born in Finland. We received 27 (56%) replies for the enhanced surveillance web-based questionnaire, and in 5 cases both parents were born in Finland. These cases were excluded from the analysis.

Of the remaining 22 pediatric TB cases with questionnaire data available, 17 (77%) were foreign-born and 5 (23%) were born in Finland, classified as second-generation migrants. All their parents were born in high TI countries, except two of the fathers who were born in Finland. Six (27%) children were born in Afghanistan,

3 (14%) in Somalia and one (5%) in Bahrain, Ethiopia, Malawi, Myanmar, the Philippines, South Africa, Thailand, and Vietnam.

19 children (86%) had PTB and 2 (11%) had MDR-TB. All Finnish-born pediatric cases (5) had PTB and were identified during contact tracing of another TB patient. Of the foreign-born pediatric TB cases, 7 (41%) were identified in screening performed on arrival, 6 (35%) cases sought care due to symptoms or were found by chance (e.g. CXR taken for another reason) and 4 (24%) cases were found during contact tracing of another TB patient. The time between arrival to Finland and the date of diagnosis of TB was less than three months in 9 (53%) cases, three months to two years in 4 (24%) cases, and more than two years in 4 (24%) cases. Eight children (47%) had stayed in a reception center in Finland, and 5 (29%) had stayed in a refugee camp prior to arrival in Finland.

When comparing the results between adults and children, seeking care due to symptoms was more common among foreign-born adults than children ($p < 0.01$) (Table 9). TB detected less than three months after arrival, asymptomatic disease, and staying at a reception center were more common among children than adults ($p < 0.01$).

Table 9. Characteristics of adult and pediatric foreign-born TB cases in Finland, 2014-2016

	Adult n (%) (n=186) [a]	Pediatric n (%) (n=17) [a]	*p*-value
PTB	125 (67)	14 (82)	0.198
MDR	7 (6)	2 (14)	0.099
Method TB detected			
Screening performed at arrival	35 (19)	7 (41)	0.029
During contact tracing of another TB patient	14 (8)	4 (24)	0.026
Sought care for symptoms or by chance	137 (74)	6 (35)	<0.01
Time from arrival to Finland to diagnosis of TB			
< 3 months	39 (21)	9 (53)	<0.01
3-23 months	51 (27)	4 (24)	0.73
≥ 24 months	80 (43)	4 (24)	0.119
Unknown	16 (9)	0 (0)	0.254
Person had resided in			
reception center in Finland	27 (15)	8 (47)	<0.01
Refugee camp abroad	25 (13)	5 (29)	0.076
No TB-related symptoms	40 (22)	10 (59)	<0.01

[a] questionnaire data available

5.4 Transmission patterns and clustering (I, IV)

5.4.1 Study I

During 2008–2013, 433 isolates from culture-positive foreign-born cases were characterized by spoligotyping: the isolates belonged to 10 different lineages. The EAI and T family were the most common clades in foreign-born cases in Finland, 78 (18%) and 75 (17%) isolates, respectively. Both lineages were common among isolates from cases born in Somalia. Altogether, nine different lineages were identified in TB cases born in Somalia. Beijing lineage was the third most common lineage among isolates from foreign-born cases, representing 14% of the isolates. Most of these cases were born in the former Soviet Union/Russia, Estonia, Vietnam, or Thailand.

5.4.2 Study IV

During 2014-2017, 795 isolates from culture-positive cases were characterized by spoligotyping and MIRU-VNTR. Overall clustering rate was 31.2% (248/795). A total of 80 different clusters were identified (range 2-13 isolates); 42 (52.5%) clusters included only isolates from Finnish-born cases, 24 (30%) only isolates from foreign-born cases and 14 (17.5%) clusters were mixed clusters. Altogether 9.6% (76/795) cases were part of mixed clusters. Of the culture-positive cases, 25% isolates of the Finnish-born cases were clustered and 24.1% isolates of the foreign-born cases.

Altogether 76 isolates belonged to the 14 mixed clusters: 39 (51.3%) were from Finnish-born cases, 36 (47.4%) from foreign-born, and one of unknown origin. Foreign-born cases originated from Europe (9 cases), Asia (13 cases) and Africa (14 cases, 6/14 from Somalia) (Table 10). Most of the isolates, 53 (70%) were from male cases and the median age of the cases was 42 years (range, 13-86). Five cases (6.6%) were under the age of 18. Out of the 76 isolates, 69 (91%) were from PTB cases, and 38 (55%) of these were smear positive. Based on the date of symptom onset or diagnosis in our data, in 7 (50%) clusters the case with the first date was foreign-born and in 7 (50%) Finnish-born. In 13 of the clusters the first case in our data was a PTB case and in one cluster both cases were EPTB cases. However, these cases cannot be considered as the primary or index cases of the clusters because most of the detected genotypes are common in Finland and for some clusters as for SIT149+594-15, the primary case is well known (Smit, Pieter W. et al., 2015) and is

not included in this study period. Out of the 14 clusters, the genotype of 10 clusters containing 67 (88%) cases had been detected also before the year 2014 in Finland, some during several years. The largest mixed cluster consisted of 13 cases, 12 of which were Finnish-born and had a genotype that is very common in Finland. The highest proportion of foreign-born cases (83%) were found in a Beijing-genotype cluster consisting of eight isolates. The four mixed clusters that had not been detected in Finland previously contained two or three isolates and all the cases of three of these clusters were diagnosed within one year, but the cases were, however, detected in several locations.

Based on the epidemiological background information, in two clusters the epidemiological link was definite (same school or household/friendship) between Finnish- and foreign-born cases. In both clusters, the foreign-born case was the first case diagnosed in our data. In four clusters, the links were less clear: one cluster included cases from the same city and in three clusters most of the cases were living in the same city. In the rest 8 clusters cases were detected in several different regions in Finland.

Based on the spoligotyping results, 7 different lineages were detected among the mixed clusters. Beijing, LAM and T lineages were the most common, including 5, 3 and 3 clusters, respectively. Altogether 81.6% isolates belonged to these most common lineages.

Table 10. Characteristics of TB transmission patterns in clusters including both Finnish-born and foreign-born cases in Finland, 2014-2017

Spoligotype + MIRU-VNTR	No of cases	Male, n	Age range, years	Pulmonary /Smear positive	Foreign-born, %	Foreign area of birth	Diagnosis time frame	District	Epidemiological background information	Lineages/Notes
SIT53 + 1112-15[a]	13	8	24-86	10/5	7.7	Europe: 1	2014-2017	Several regions	Unknown	T1 lineage, the most common in Finland
SIT1 + 94-32[a]	8	5	18-63	8/5	62.5	South-Asia: 2 North-Asia: 3	2014-2017	Several regions	Unknown	Beijing lineage, very common in Finland
SIT149 + 594-15[a]	8	7	17-63	8/4	75	East Africa: 5 South-East Asia: 1	2014-2017	Several regions	5 cases from the same city	T3-ETH lineage, common in Finland
SIT42 + 1119-52[a]	8	5	30-69	8/6	25	Europe: 2	2014-2015	Several regions	5 cases from the same city	LAM9 lineage, very common in Finland
SIT1 + 100-32[a]	7	5	34-78	6/3	71.4	Europe: 3 North Asia: 2 Unknown: 1	2014-2017	Regional	6 cases from the same city	Beijing lineage, very common in Finland MDR cluster (one case is not MDR)
SIT1 + 342-32[a]	7	4	16-83	7/3	57.1	East Africa: 2 South-East Asia: 2	2015	Several regions	5 cases from the same school	Beijing lineage, very common in Finland
SIT381 + 18194-32[a]	7	5	13-34	7/3	42.9	East Africa: 3	2015-2017	Local	household and friendship	CAS1-Delhi lineage, not common in Finland
SIT50 + 172-69[a]	4	4	19-36	3/2	75	Southwest Asia: 1 West Africa: 2	2015-2017	Several regions	Unknown	Harlem3 lineage, very common in Finland
SIT254 + 9118-52	3	3	37-46	3/2	66.7	Europe: 2	2014	Several regions	Unknown	LAM-RUS lineage, not common in Finland
SIT2028 + 1481-66[a]	3	2	15-61	3/3	33.3	Europe: 1	2014-2015	Local	3 cases from the same city	Unknown lineage

Table 10. Characteristics of TB transmission patterns in clusters including both Finnish-born and foreign-born cases in Finland, 2014-2017

Spoligotype + MIRU-VNTR	No of cases	Male, n	Age range, years	Pulmonary /Smear positive	Foreign-born, %	Foreign area of birth	Diagnosis time frame	District	Epidemiological background information	Lineages/Notes
SIT1 + 3882-32	2	0	28-43	2/1	50	South-East Asia: 1	2014-2016	Several regions	Unknown	Beijing lineage, very common in Finland
SIT42 + 5014-218	2	2	31-71	2/0	50	East Africa: 1	2015	Several regions	Unknown	LAM9 lineage, very common in Finland
SIT1 + 3894-32[a]	2	1	39-51	2/1	50	South-East Asia: 1	2016	Several regions	Unknown	Beijing lineage, very common in Finland
SIT928 + 18673-15	2	2	19-57	0/0	50	East Africa: 1	2016	Several regions	Unknown	T lineage, common in Finland
Total	76 (2-13)	53 (70%)	13-86	69/38	47.4		2014-2017			

[a] The cluster detected in Finland before the year 2014

6 DISCUSSION

6.1 The effects of migration on the epidemiology of tuberculosis in Finland

In low TI countries, TB control has earlier been focused on the early identification and treatment of active TB and contact tracing (Pareek et al., 2016). The effects of migration on TB epidemiology in low TI countries are well-recognized and there has been a shift towards enhancing TB control by screening migrants for TB (Lonnroth et al., 2013; Lonnroth et al., 2017; Pareek et al., 2016). The incidence among foreign-born populations has decreased in Finland as well as in other low TI countries (Lonnroth et al., 2017). Finland has focused on two methods: at-arrival screening and contact tracing together with raising awareness on TB among foreign-born populations and healthcare professionals. However, in the recent Cochrane systematic review, there were no studies found where the proof of effectiveness of contact tracing would have been conducted in a randomized trial study setting (Braganza Menezes et al., 2019).

This nationwide, population-based study showed that during the 23-year study period the epidemiology of TB has experienced a transition in Finland. The major reason is not migration but the decrease of TB cases in Finnish-born population.

The number of TB cases in foreign-born population tripled in Finland, as the migrant population from high TI countries increased. The proportion of migrants of all TB cases increased more than 7-fold due to both the increase of migrants and the decrease of Finnish-born cases. TI among foreign-born persons decreased over the study period, as the number of TB cases among them did not increase relatively as much as the number of them living in Finland. Patient characteristics in foreign-born TB cases were different from Finnish-born TB cases. Migration from high TI countries thus does not form a significant threat to Finnish public health.

In Finland, most TB cases are still reported in the Finnish-born population. Despite the increase in the number of foreign-born people living in Finland, Finland has not reached the epidemiological situation found in other low TI countries, such as Sweden, Norway, Denmark and The Netherlands (Brudey et al., 2004; Dahle, U. R., Sandven, Heldal, & Caugant, 2001; Dahle, Ulf R., Eldholm, Winje, Mannsåker,

& Heldal, 2007; Kamper-Jorgensen et al., 2012; Svensson et al., 2011; van Deutekom et al., 1997), where TB cases in the foreign-born population dominate the epidemiology of TB. However, the proportion of foreign-born TB cases among all TB cases in Finland is higher than the proportion in Europe or in EU/EEA (ECDC/WHO Regional Office for Europe, 2019). The number of Finnish-born cases will probably continue decreasing when less LTB cases exist.

There are currently less foreign-born persons in Finland than in the other Nordic countries. However, in the future, when more foreign-born people move to Finland, TB in the foreign-born population group is likely to change the epidemiological picture to be similar to that in other Nordic countries. Almost 90% of cases who are born abroad in Finland were born in countries with TI over 50 (e.g. Somalia, Russia, Vietnam, and Thailand). Similar proportions have been reported from Sweden (Svensson et al., 2011), Norway (Dahle, U. R. et al., 2001) and The Netherlands (Valcheva, Mokrousov, Narvskaya, Rastogi, & Markova, 2008), where the majority of cases with a foreign background are from Asia or Africa, mainly from Somalia. This result is in line with a strategy that focuses on screening migrants from countries with a high TI, in order to diagnose and treat PTB as early as possible to reduce further transmission of *M. tuberculosis*.

Surveillance data do not often include the reason for migration, and typically only focus on the epidemiology of TB in foreign-born compared with native-born (Poulain, 2008). This complicates TB surveillance and control, as there is a difference in risks contracting TB between migrant groups. (Khan et al., 2016; Ködmön, Zucs, & van der Werf, Marieke J., 2016; Pareek et al., 2016.)

In Finland, asylum seekers have a higher risk of contracting TB compared to other migrants. Nearly half of the TB cases among foreign-born are notified in asylum seekers. A systematic review and meta-analysis (Arshad, Bavan, Gajari, Paget, & Baussano, 2010) found that refugees and asylum seekers were four times more likely to be diagnosed with active PTB than other migrants. Asylum seekers and refugees have often been forced to flee their home countries. They may have had to spend time in overcrowded refugee camps and/or travel in poor conditions without proper health care before and during a flight to the host country. (Van Hear et al., 2009.)

Migration itself might influence the TB epidemiology (Lonnroth et al., 2017; MacPherson & Gushulak, 2006; Pareek et al., 2016). A great deal of global migration is voluntary and planned (Lonnroth et al., 2017). Migration to Finland is mostly due to labor, study, or family reunification. Asylum seekers and refugees are only a small part of all migrants moving to Finland. (Finnish Immigration Service, 2018; Statistics

Finland, 2019a.) Currently, the overall TI of foreign-born population in Finland is less than the high TI threshold (TI>50) and is declining. However, there is a wide range of TI among persons with different origin, and TI among persons born in Somalia, Ethiopia, Afghanistan, Philippines, Vietnam, and Thailand is above the high TI threshold.

According to publication II, only 20% of the TB cases among migrants had stayed in a reception center in Finland (classified then as asylum seekers or refugees). Most often foreign-born cases had come to Finland to work or study or for family reunification. The difference in the proportion of asylum seekers among foreign-born TB cases in publications II and III might be due to the fact that, during the large influx of asylum seekers, Finland received seven times more asylum applications than in previous years (Finnish Immigration Service, 2018). Also, in publication II the response rate was only 65% and most probably the questionnaire was not returned on cases who were asylum seekers due to difficulties gathering the information on the cases. In publication III the estimated proportion of asylum seekers among foreign-born cases might be an overestimate compared to a stable situation due to increase in asylum seekers entering Finland.

More than half of the cases born abroad had been diagnosed within two years of entry. However, cases that had lived in Finland for more than ten years were also observed. It is not known whether these persons have been infected with *M. tuberculosis* when visiting their home country, whether they have been infected in Finland or whether their LTB was activated. Our previous study using molecular genotyping methods shows that TB was most often a result of the activation of LTB rather than transmission of infection between people born abroad and Finland (Smit, P. W. et al., 2013). In addition, people coming from countries with a high TI always have a higher risk of developing TB. Similar cases have been reported in Sweden, where 23% of all cases of TB with a foreign background have resided in Sweden for more than 10 years. (Nkulu, Hurtig, Ahlm, & Krantz, 2010).

The relationship between TI in the country of origin and the risk of developing TB after migration is difficult to determine. This is due to the different ways in which Finland and the country of the case monitor TB, different healthcare systems and different population characteristics in different countries. However, the rates in Finland were overall lower than in the country of origin. For example, the rate of TB reported in Russia is six times higher than that reported in Finland for FSU/Russian births. However, Russia's migrant population is relatively well off in Finland and in Russia TB disease mainly occurs in prisoners, homeless people and drug addicts (Sarang, Platt, Vyshemirskaya, & Rhodes, 2016). Only among the immigrants from

Somalia and Ethiopia, the probability of a TB diagnosis was higher in Finland than in the country of their birth. This could be due to the fact that in Somalia and Ethiopia TB is a more common disease than the official TI figures indicate (World Health Organization, 2019), many people unknowingly have LTB and TB is not just a disease of a particular population or group. In addition, most Somalis and Ethiopians come to Finland either as asylum seekers or as refugees and they are screened for TB as soon as they arrive in the country and their TB is diagnosed without a delay.

The proportion of male cases among cases born in Thailand and the Philippines was considerably lower compared to other birth countries. However, the proportion of males living in Finland from these birth countries was also considerably lower compared to other birth countries. Females from Asia are a growing labor migrant population all over the world (International Labor Organization, 1996). This reflects the gender distribution of persons from Thailand and the Philippines living in Finland and, therefore, the gender distribution among TB cases from Thailand and the Philippines becomes biased.

Of the 22 pediatric TB cases diagnosed in Finland, three out of four were diagnosed in children born abroad, one in eight diagnosed was a second-generation immigrant and one of the eight children diagnosed was of Finnish origin. The population of second-generation immigrants is much smaller than that of Finnish descent. In addition, the response rate of the questionnaires used to explore pediatric tuberculosis was small. For these reasons, we can only assume that the TI among second-generation immigrants is much higher than among children of Finnish descent. The same results have been reported from Berlin as well (Marx et al., 2015).

MDR-TB is one of the greatest threats to the fight against TB worldwide. MDR-TB in low TI countries is more prevalent among the foreign-born than among the native-born (Dhavan et al., 2017; Ködmön et al., 2016), as is the case in Finland. MDR-TB cases are increasing among migrants in Finland and this increase may be due to an increase in MDR-TB in high TI countries, such as Somalia and Russia (World Health Organization, 2018a). Cases born in the FSU/Russia or Estonia have higher proportions of MDR-TB compared to cases from other countries of birth. This reflects the TB epidemiology in Russia and Estonia, where MDR-TB is more prevalent than in other birth countries of migrants in Finland (World Health Organization, 2019).

6.2 Tuberculosis screening

Active TB screening among migrants from high TI countries is a key component of TB elimination strategies in low TI countries. To ensure early detection of TB and prevent transmission, screening of migrants from high TI countries is essential. In addition, increased awareness among patients and physicians of the typical symptoms of TB improves the detection of TB in the early stages of the disease. A comparative analysis revealed that different countries have different practices and recommendations concerning screening of TB among migrants. (Kunst et al., 2017.)

In Finland, CXR is combined with a large-scale interview about a person's symptoms. Recommendations and policies for screening migrants in low TI countries vary widely and may affect observed TB rates(Douglas et al., 2017).

Refugees and asylum seekers are under surveillance in Finland upon arrival, so they are easily accessible and screened. Screening is regularly done in reception centers and screening coverage is moderate (Tiittala et al., 2018a). Data concerning screening are gathered into HRS. When evaluating the screening for active TB in asylum seekers in Finland during their large influx in 2015-2016, half of the TB cases among asylum seekers were found in the primary screening, and over 40% of these cases did not have TB symptoms at the time of screening. A 40-fold difference in TB prevalence was observed between asylum seekers from different countries. The prevalence of Iraqis was low. On the other hand, half of all TB cases were found among Somalis, although only 6% of asylum seekers were of Somali origin.

Other European countries also screened asylum seekers at reception centers during 2015-2016. We found that the yield in Finland was higher than the average yield elsewhere in Europe (0.19% vs. 0.12%) (Kunst et al., 2017). However, the screening prevalence rate of TB (191/100,000) and NNS (522) in Finland differed significantly from the corresponding figures in Italy and Germany (Bozorgmehr et al., 2017; Vanino et al., 2017). In Italy, post-entry screening TI among asylum seekers was 535 and NNS 187. This TI was among the highest rates in Europe. In Italy, most asylum seekers (82%) came from African countries where TI is really high, thus increasing screening yield. In Germany, where participation in screening is mandatory, the prevalence was 347/100,000 and NNS 288. The reasons for variation can be explained by differences in countries of origin and migration routes (Bozorgmehr et al., 2017; Vanino et al., 2017).

A quarter of TB cases among foreign-born people is diagnosed within three months of arriving in Finland, and about half of the cases is diagnosed within two years of arrival. The results of the meta-analyzes showed that the proportion of

migrants with active TB is relatively low at the time of migration (0.35 %) (Arshad et al., 2010; Klinkenberg, Manissero, Semenza, & Verver, 2009; Pareek et al., 2016). The time between CXR screening and TB diagnosis ranged from 1 to 376 days (median, 18 days), consistent with the results of a systematic review and meta-analysis. (Getnet, Demissie, Assefa, Mengistie, & Worku, 2017). In a previous Finnish study (Tiittala et al., 2018a), the median time between arrival and CXR of an asylum seeker was 74 days for adults and 43 days for children. Combining our result (18 days) with previously reported results, the median time between arrival in Finland and TB diagnosis was about two to three months. In addition, it is not known whether the diagnostic delay is due to delays in the health care system or whether the patient has not searched for help early enough. Also, the patient may have sought help earlier, but the possibility of TB has not been considered by the practitioners.

Other migrants are also under surveillance if they are from very high TI countries (TI>150) but their screening takes place in different locations depending on the reason of migration; for labor migrants in occupational health care, for students in student health care, for family reunification/marriage and adopted children in health-care centers. This challenges the reporting and control of other migrants' screening program and data sharing. Because routine screening of all migrants is not realistic, public health efforts target situations where TB transmission is likely to occur or would have serious consequences for those affected, such as schools, daycares, and hospitals. (Finlex, 2016.)

Other migrants can be difficult to reach because they do not enter the country through a single-entry point but rather, they may move to work, join a family member or study. A Canadian study (Thomas & Gushulak, 1995) suggested that TB screening of all migrants is not an easy task. However, preventive screening significantly reduces TB morbidity and prevents close contact infections (Thomas & Gushulak, 1995). Since migrants can develop a disease years after immigration and are often moving between places at a fast pace, it is important to raise awareness of TB and its symptoms in addition to comprehensive screening. (Heuvelings et al., 2017; Seedat et al., 2018; Thomas & Gushulak, 1995).

In order to integrate screening policies in Europe, it is necessary first to agree on the standard information needed to adequately evaluate migrant screening programs. A long-term goal to start making routine reports in a European database needs a standardized protocol to collect variables, share data and build better systems at national and international levels. (Kunst et al., 2017.)

Publication II shows that 25% of foreign-born cases had reported no symptoms and that TB was still present in a CXR taken for screening or contact tracing

purposes. Therefore, transmission of TB was prevented as it was detected before symptoms occurred. The proportion of PTB was higher among cases who did not have any symptoms than among symptomatic cases. First, EPTB can cause pain and/or abscess in the affected part of the body at an early stage and, for this reason, the person consults a doctor. Second, PTB does not always cause significant symptoms at an early stage, especially in previously healthy youth. Third, foreign-born people do not always want to report their TB symptoms for fear of stigma or deportation. Large proportions (60%) of pediatric patients did not report any symptoms. Children do not always have typical symptoms and it might be difficult for young children to tell their symptoms. Due to the fact that children were mainly staying in reception centers where screening practices were regularly implemented, their TB was detected earlier than the TB of adults.

Our results support the new guidelines of The Finnish Ministry of Health in which all migrants arriving from very high TI countries and who are planning to stay in Finland for more than 3 months should be screened for active TB on arrival with both CXR and health check-up (Soini et al., 2017). According to previous guidelines, only refugees and asylum seekers were screened (Ministry of Social Affairs and Health, 2014).

TB prevention policies worldwide focus on rapid diagnosis and treatment of people with active TB. In addition, in low TI countries this is supplemented by the contact tracing of smear-positive PTB cases with the overall aim to halt transmission. However, this method of TB control does not identify persons with LTB or the possibility of activation – such as seen in migrants. Studies on a dynamic transmission model concluded that focusing control measures on both persons with active TB and persons with LTB will improve TB control. (Cohen, Lipsitch, Walensky, & Murray, 2006; Dye & Williams, 2008; Pareek et al., 2016; Ziv, Daley, & Blower, 2001.) A systematic review and meta-analysis concluded that effective cross-border TB control strategies should also include preventive treatment of LTB and post-migration follow-up (Chan et al., 2017). WHO guidelines recommend to screen all migrants from high TI countries. This recommendation emphasizes the importance of intercepting LTB of developing to active TB. (Pareek et al., 2016; World Health Organization, 2018b.)

Although screening of LTB may considerably improve TB screening, its implementation on immigrants can be difficult (Pareek et al., 2016). Furthermore, health and economic analyzes have shown that the fight against TB in low TI countries would benefit to some extent from targeted LTB screening and treatment of migrants from countries with high TB burden. However, Finland does not

currently routine screen for LTB among migrants. (ECDC, 2018b.) Based on this study, Finland would benefit on the LTB screening policy for migrants from very high TI countries. According to the results, most often TB in migrants is a reactivation of LTB contracted in the country of origin. Issues and barriers in implementation must be recognized in order to ensure the effectiveness of the program.

6.3 The extent of clustering and transmission between foreign- and Finnish-born populations

In order to stop the transmission of TB, it is essential to use an evidence-based approach based on knowledge of local epidemiology. Previous and modern evidence recommends that efficient public health interventions can make a difference in TB epidemiology. (Dowdy et al., 2017.) In recent years, the diversity of *M. tuberculosis* isolates has been increasingly recognized. Molecular epidemiology can help routine TB control activities (Mathema, Kurepina, Bifani, & Kreiswirth, 2006; Reed et al., 2009; Sandgren et al., 2014). Molecular epidemiological investigations have estimated the extent of recent transmission or reactivation and the transmission dynamics within specific populations are understood better. (Mathema et al., 2006; Reed et al., 2009; Sandgren et al., 2014.) Close contacts of PTB cases are vulnerable to become infected and, if infected, to develop the disease, particularly within the first year after exposure (Fox et al., 2013). The effect of TB transmission from foreign-born to the native-born population has been difficult to measure (Dahle, Ulf R. et al., 2007).

Our data over the years 2014-2017 show that over 50% of the clusters included isolates from Finnish-born patients only, and 30% from foreign-born cases only. Furthermore, more than half of the foreign-born clusters included cases only from one country. This finding is in line with other studies conducted in low TI countries that suggest an increased risk of transmission in migrant households and migrant communities, but not between the host and the immigrant population. (Aldridge et al., 2016; Sandgren et al., 2014).

When evaluating the extent of transmission among foreign-born and Finnish-born population, less than 20% of all clusters included both Finnish-born and foreign-born cases which is less than the median 32% in the EU/EEA countries (Sandgren et al., 2014). In a previous study conducted in Finland between 2008-2011, only 10% of clusters included isolates from both Finnish-born and foreign-born

cases (Smit et al., 2013). The increase of mixed clusters might be due to an increase in the number of foreign-born people living in Finland and to the fact that Finnish-born and foreign-born are interacting more with each other (Lonnroth et al., 2017).

Systematic reviews have reported that foreign-born TB cases belong to clusters less often than native born cases (Fok, Numata, Schulzer, & FitzGerald, 2008; Sandgren et al., 2014). Clustered isolates have been said to represent epidemiologically linked chains of recent transmission, whereas unique isolates have been taken to represent the reactivation of LTB (Murray & Nardell, 2002). No difference was found in proportions of clustered isolates among Finnish-born and foreign-born populations in Finland as 25% of the Finnish-born cases and 24.1% of the foreign-born cases were part of a cluster. The proportion in Finland of the clustered isolates from foreign-born cases is similar to Spain, where 22– 28% of the isolates from foreign-born TB cases were part of a cluster (Borrell et al., 2010; Inigo et al., 2013). Other European countries have reported higher proportions; 30% in Norway (Dahle et al., 2003), 35% in France (Gutierrez et al., 1998), 46% in Italy (Franzetti et al., 2010) and 56% in Sweden (Kan et al., 2008). It is possible that some of the foreign-born TB cases are infected in the host country. However, it cannot be ruled out that LTB caused by the same *M. tuberculosis* strain acquired in the country of origin activates simultaneously in several immigrants causing a formation of a cluster. (Pareek et al., 2016.) It has been shown that more than half of the foreign-born TB cases are diagnosed within two years after arrival to Finland (II), which supports the concept that TB in foreign-born cases also in Finland is more often caused by a reactivation of TB obtained in their country of birth (Smit et al., 2013). It can be concluded, that most often foreign-born population's TB is a result of LTB activation taking place after migration from high TI countries.

Only 6 out of 14 mixed clusters had a definite or possible epidemiological link between cases. Most often the link was related to the place of residence. However, most of the cases in the same cluster were diagnosed in several regions in Finland. It is known that migrants are very mobile and also therefore clusters may have spread around the country (Blumberg et al., 2010). Only two clusters had a definite link, one cluster was transmitted in a school and another between friends and family.

The full size of the clusters is not captured since TB transmission chains are building up slowly, TB has a long exposure and incubation time and delays in diagnosis can be substantial. Therefore, we cannot assume that the first case diagnosed would be the index case of a cluster. In this study, most of the mixed clusters had a genotype that had been seen in Finland earlier. The proportion of Finnish- and foreign-born cases varied within the mixed clusters. The largest mixed

cluster consisted of 13 cases, 12 of which were Finnish-born and had a *M. tuberculosis* genotype that is very common in Finland and is known to cause local, knowingly unrelated, outbreaks in various locations. Thus, the infection of the foreign-born patient in this cluster has probably been acquired from a Finnish-born case, although this genotype is also common elsewhere. The greatest proportion of foreign-born patients were found in the Beijing-genotype clusters and in widely spread (MDR-TB) clusters SIT1+100-32 and SIT1+94-32 (Engström et al., 2019). Approximately half of the cases of the mixed clusters were Finnish-born and half foreign-born. Thus, we can assume that both Finnish-born and foreign-born cases contribute to the same extent to TB transmission in mixed clusters and that the cross-transmission between foreign- and native-born populations is bidirectional in Finland, as reported also in a systematic review in the EU/EEA countries (Sandgren et al., 2014). To verify this assumption, WGS combined with thorough analysis of contact tracing data should be performed (Comin et al., 2020).

Within the years 2008-2013, the most common spoligotype lineages of TB strains in foreign-born population in Finland were found to be the EAI clade and T family clade, which are also common in Sweden (Svensson et al., 2011). When comparing the lineages of foreign-born cases with the lineages found in their country of birth, in most cases the same clades were common in both Finland and in the country of birth. EAI lineage is frequent in South East Asia, India, and Western Africa (Brudey et al., 2006). A total of 10 different clades were identified in foreign-born cases in Finland in general, and nine of the clades were found in cases born in Somalia, supporting the evidence that a wide variety of *M. tuberculosis* isolates circulate in Somalia (Abubakar et al., 2011). A detailed analysis of molecular epidemiology of TB in Finland previously found that T and Haarlem strains were the most common in Finnish-born isolates (Smit, P. W. et al., 2014).

6.4 Strengths and limitations of the study

This thesis is the first comprehensive analysis of the epidemiology of TB among different population groups in Finland. The present study evaluated the effects of migration on TB epidemiology in Finland, examined the prevention, early diagnosis, screening, and transmission of TB among Finnish- and foreign-born population in Finland, and evaluated the guidelines applied in this field. The study lays the ground for further research and policy development in TB control among migrants in Finland.

The strength of our analysis is rooted in the 24-year study period when evaluating the effects of migration on the epidemiology and characterizing the national trends in the epidemiology of TB. Finland has been moving away from an epidemiological situation in which the majority of reported cases have been reactivation of LTB in older Finnish adults to the situation where most cases are of young people with a foreign background. This study provides insight into the epidemiology of TB in a nationwide, population-based approach.

The sensitivity of TB control improved in 2007 when the case definition of TB was changed. The change is likely to have had a corresponding impact on the number of foreign-born and Finnish-born cases. In addition, the change may have improved the sensitivity of detecting PTB more than the sensitivity of detecting EPTB. Moreover, during the study period, different national screening guidelines have been in place and they have affected the target groups and practices for TB screening. The first two guidelines, published in 1993 and 2009 concentrated on screening of infectious diseases in general among refugees and asylum seekers (Nohynek et al., 1993; The National Institute for Health and Welfare, 2009). In 2014 additional guidelines were published for screening of TB among other migrant groups (Ministry for Social Affairs and Health, 2014). In 2017 guidelines for among asylum seekers were updated as well as the country list specifying the target groups (Soini et al., 2017). Furthermore, the new National Tuberculosis Control Program was published in 2020. The updated program clarifies the roles of different actors controlling TB in Finland and collects the currently available national guidelines for easier access. (The Finnish Institution for Health and Welfare, 2020.)

We defined foreign-born as a person born outside Finland. If information on the country of birth was missing, the foreign-born was defined as a person whose most recent nationality was not Finnish. This definition was based on the administrative classification available and was chosen because a person can only have one country of birth. However, it is possible that a Finn born abroad would be defined as foreign-born, but this was rare. Further, besides publication II, by this definition second generation immigrants are defined as Finnish-born. The country of birth or ethnicity of the parents of the case have sometimes been used (Abubakar et al., 2011; Kamper-Jorgensen et al., 2012; Svensson et al., 2011) and would probably be more accurate in defining the foreign-born/Finnish-born status, as it would cover second-generation immigrants. However, this information was not available in our surveillance data.

The major limitation of our publication II was the low response rate. The questionnaire was sent to the doctor responsible for infectious diseases, not directly

to the doctor who was responsible for the patient. Patient data may not have been stored consistently or the requested data may have been missing. This is particularly common for asylum seekers and undocumented persons, who often move within and between countries, and their health information does not always follow. In addition, asylum seekers do not receive the Finnish NID needed to link health data.

During the time of the large influx of asylum seekers in 2015, HRS was not fully implemented in all the operating reception centers leading to incomplete records and potential underreporting of screening results. Until 2016, some of the health records were still made manually, which makes their exploitation in research difficult. Overall, for only 80% of the asylum seeker TB cases there was documentation on the health information session and/or basic health check-up information. Those 20%, whose attendance was not documented, could have attended the session but it had not been documented. Also, it is not mandatory for asylum seekers to attend the sessions, but highly recommended. Furthermore, all CXR results were not systematically documented. Systematic use of the HRS should be strengthened in order to increase the reliability of register information for monitoring, surveillance, and research.

The spelling of asylum seekers' names and dates of birth might have varied in different databases, causing difficulties in linkage of HRS and NIDR. All this reflects that the numerator in calculating the yield from screening might be larger. This can possibly be attributed to human error occurring at several points of the documentation and some of the TB cases found in screening might not have been documented in the HRS. Also, the denominator might have been greater as we did not have individual level data on conducted screenings. Furthermore, it is possible that TB was not always detected in CXR during screening; nearly 20% of abnormal screening results were lost to follow-up.

While asylum seekers and other migrants, who do not hold a residency permit for Finland, are waiting for a decision on the residency permit application, they are not considered permanent residents in Finland and are not registered in the population information system (Finlex, 2019). Furthermore, undocumented migrants are a group, who do not have needed documents for residency and are not entitled to public healthcare services in Finland. However, as TB is classified into generally hazardous communicable diseases, undocumented migrants are entitled to urgent and essential care of TB. It has been estimated that approximately thousand undocumented migrants are living in Finland. (The Finnish Institution for Health and Welfare, 2020.) For those reasons, the TI is an overestimate as these migrants

who do not have a residency permit for Finland are not counted as part of the Finnish population.

Using only spoligotyping and MIRU-VNTR genotyping methods to characterize transmission patterns gives an estimation of transmission between foreign- and Finnish-born cases. WGS could have defined the clusters more accurately than the methods used in this study. WGS method with higher discriminatory power probably would have detected less clustered cases (Smith et al., 2015; Jajou et al., 2018) or possibly could have identified more clusters by splitting clusters smaller (Roetzer et al., 2013). Our research may also underestimate recent transmission due to limited observation time. The size of the clusters will not be captured, as the chains of transmission of TB are growing slowly and delays in diagnosis can be considerable.

7 CONCLUSIONS

Based on observations from this study, the following conclusions may be drawn:

1. The epidemiology of TB has experienced a transition in Finland from 1995 to 2017. As TB becomes even more common in the foreign-born population over time, increasing cases of TB in the foreign-born population are likely to change epidemiology in the future, as has happened in other Nordic countries.

2. Nearly 90% of the foreign-born TB cases in Finland were born in high TB incidence countries (TI>50).

3. Case characteristics in foreign-born TB cases were different from native TB cases; foreign-born TB cases were significantly younger, more often female, had EPTB and MDR-TB more often than Finnish-born cases. Finnish-born cases had more often smear positive PTB than foreign-born TB cases.

4. The yield of TB screening of asylum seekers was average compared to studies from other European countries that have carried out systematic TB screening. Half of the TB cases among asylum seekers were first suspected in screening; more than 40% did not report any symptoms. The TB yield varied widely between asylum seekers from different geographical locations.

5. Transmission between the foreign-born population and native-born population does not have a significant influence on the TB epidemiology among Finnish-born population. Furthermore, cross-transmission was suggested to be bidirectional in Finland.

6. The proportion of mixed clusters was less than the average in the EU/EEA and no difference was found among the proportion of clustered isolates within Finnish-born and foreign-born cases in Finland.

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9 PUBLICATIONS

PUBLICATION I

Tuberculosis in immigrants in Finland, 1995–2013

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Tuberculosis in immigrants in Finland, 1995–2013

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SUMMARY

Increasing immigration from high tuberculosis (TB) incidence countries is a challenge for surveillance and control in Finland. Here, we describe the epidemiology of TB in immigrants by using national surveillance data. During 1995–2013, 7030 (84.7%) native and 1199 (14.4%) immigrant cases were identified. The proportion of immigrant cases increased from 5.8% in 1995 to 32.1% in 2013, consistent with increasing immigrant population (2.1–5.6%) and decreasing incidence of TB in the native population (from 12.1 to 3.5/100 000). TB cases in immigrants were significantly younger, more often female, and had extrapulmonary TB more often than native cases ($P < 0.01$ for all comparisons); multidrug resistance was also more common in immigrants than natives ($P < 0.01$). Immigrant cases were born in 82 different countries; most commonly in Somalia and the former Soviet Union/Russia. During 2008–2013, 433 Mycobacterium tuberculosis isolates from immigrants were submitted for spoligotyping; 10 different clades were identified.

Clades were similar to those found in the case's country of birth. Screening immigrants from high-incidence countries and raising awareness of common characteristics and symptoms of TB is important to ensure early diagnosis and to prevent transmission.

Key words: Epidemiology, immigrants, molecular epidemiology, Mycobacterium tuberculosis, spoligotyping, tuberculosis (TB).

INTRODUCTION

According to the World Health Organization (WHO), tuberculosis (TB) remains one of the most important infectious diseases, with an estimated 8.6 million incident TB cases and about 1.3 million deaths reported globally in 2013 [1]. Finland is classified as a low TB incidence country (<10/100 000 population) [2]. However, increasing immigration from high TB incidence countries constitutes a growing risk group for TB. The recent transition from an epidemiological situation where most reported cases have been reactivation of latent TB infection in older Finnish adults to highly infectious pulmonary TB cases in young immigrants has implications for national screening, diagnosis and treatment strategies for TB [3]. We evaluated national trends in the epidemiology of TB cases in immigrants during 1995–2013 and characterized Mycobacterium tuberculosis isolates by genotyping and antimicrobial susceptibility patterns during 2008–2013 by using population-based surveillance data.

METHODS

National surveillance of TB in Finland

Clinical microbiology laboratories notify new M. tuberculosis isolations directly to the National Infectious Disease Register (NIDR) and submit isolates to the Mycobacterial Reference Laboratory at National Institute for Health and Welfare (THL) for drug susceptibility testing and genotyping. In addition, physicians notify clinically suspected or confirmed TB cases; reporting is mandatory. From 1995 to 2006, the case definition for TB surveillance included all culture or sputum smear-positive cases or histologically confirmed cases. However, with the adoption of the standard European Union case definition for TB in 2007 [4] a new reporting category was added to NIDR: 'physician's decision to initiate full TB treatment on the basis of clinical suspicion of TB despite lack of laboratory confirmation'. Data collected with each notification include age, gender, country of birth, nationality, place of residence, date of diagnosis, and clinical syndrome of TB (pulmonary/extrapulmonary).

Laboratory methods

M. tuberculosis isolates from culture-positive TB cases reported during 2008–2013 were characterized by spoligotyping according to standard methods at the THL Mycobacterial Reference Laboratory [5]. The resulting spoligotype patterns were compared to the data in the international SITVITWEB database [6]. An iso- late was assigned a shared type (SIT) if the same spoligotype was found in the database. Genotypic clades were obtained from the SITVITWEB database.

Definitions

Pulmonary and extrapulmonary TB were defined according to WHO guidelines [1]. In this study, a native was defined as a person born in Finland or, if the country of birth was not known, the most recent nationality was Finnish. An immigrant was defined as a person whose country of birth was not Finland or, when the country of birth was not known, the most re- cent nationality was other than Finnish.

Population data

The number of persons immigrating to Finland by year and country and the size of different immigrant populations in Finland was obtained from the Statistics Finland population database (National Population Information System) which contains data on all persons residing legally in Finland (http://www.stat.fi/index_en.html).

Statistical analysis

Statistics Finland data were used as denominators to calculate age- and gender-specific TB incidence rates. Statistical significance for categorical variables were analysed with the $\chi 2$ test or Fisher's exact test. Continuous variables were analysed using the Mann–Whitney U test. A Poisson regression model was used to assess the significances of the log-linear trend in annual incidence rates. IBM SPSS v. 22.0 (SPSS Inc., USA) and Microsoft Excel (Microsoft Corp., USA) were used to analyse the data.

RESULTS

From 1995 to 2013, a total of 8299 TB cases were reported to NIDR. Of these cases, 7030 were defined as native [6978 (84.1%) on the basis of country of birth and 52 (0.6%) on the basis of most recent nationality]; 1199 (14.4%) of reported cases were defined as immigrants, 1085 (90.5%) on the basis of country of birth and 114 (9.5%) on the basis of most recent nationality (Table 1). Overall, 74 (0.9%) had no information on country of birth or nationality.

The annual incidence of TB in Finland decreased from 12.8/100 000 population in 1995 to 5.0/100 000 in 2013. The number of TB cases decreased by 58.6% during this period (Table 1). TB cases in the native population decreased by 70.0% from 1995 to 2013. The Poisson regression model showed a decreasing log-linear trend in the TB rate both overall ($P < 0.001$) and for natives ($P < 0.001$), with mean annual rate decreases of 5.2% and 6.7%, respectively. During the same period, the number of TB cases in immigrants increased by 128.9%. However, as the number of immigrant population increased, the trend in TB rate was not significant ($P = 0.344$). The overall incidence of TB in immigrants ranged be- tween 24.7 and 53.6/100 000 by year.

Table 1. Incidence of tuberculosis cases in all, native and immigrant populations in Finland, 1995–2013

	All cases			Native cases			Immigrant cases		
Year	Population in Finland*	No. of cases†	Incidence‡ (95% CI)	Native population in Finland (%)*	No. of cases (%)	Incidence‡ (95% CI)	Immigrant population in Finland (%)*	No. of cases (%)	Incidence‡ (95% CI)
1995	5 116 826	654	12.8 (11.8–13.8)	5 010 523 (97.9)	608 (93.0)	12.1 (11.2–13.1)	106 303 (2.1)	38 (5.8)	35.7 (26.0–49.1)
1996	5 132 320	632	12.3 (11.4–13.3)	5 021 189 (97.8)	584 (92.4)	11.6 (10.7–12.6)	111 131 (2.2)	41 (6.5)	36.9 (27.2–50.1)
1997	5 147 349	557	10.8 (10.0–11.8)	5 029 279 (97.7)	508 (91.2)	10.1 (9.3–11.0)	118 070 (2.3)	46 (8.3)	39.0 (29.2–52.0)
1998	5 159 646	610	11.8 (10.9–12.8)	5 034 596 (97.6)	549 (90.0)	10.9 (10.0–11.9)	125 050 (2.4)	58 (9.5)	46.4 (35.9–60.0)
1999	5 171 302	598	11.6 (10.7–12.5)	5 040 182 (97.5)	541 (90.5)	10.7 (9.9–11.7)	131 120 (2.5)	47 (7.9)	35.8 (26.9–47.7)
2000	5 181 115	545	10.5 (9.7–11.4)	5 044 912 (97.4)	49 (91.2)	9.9 (9.0–10.8)	136 203 (2.6)	47 (8.6)	34.5 (25.9–45.9)
2001	5 194 901	503	9.7 (8.9–10.6)	5 049 766 (97.2)	434 (86.3)	8.6 (7.8–9.4)	145 135 (2.8)	66 (13.1)	45.5 (35.7–57.9)
2002	5 206 295	477	9.2 (8.4–10.0)	5 054 238 (97.1)	428 (89.7)	8.5 (7.7–9.3)	152 057 (2.9)	49 (10.3)	32.2 (24.4–42.6)
2003	5 219 732	415	8.0 (7.2–8.8)	5 060 865 (97.0)	363 (87.5)	7.2 (6.5–7.9)	158 867 (3.0)	51 (12.3)	32.1 (24.4–42.2)
2004	5 236 611	335	6.4 (5.7–7.1)	5 070 250 (96.8)	290 (86.6)	5.7 (5.1–6.4)	166 361 (3.2)	42 (12.5)	25.2 (18.7–34.2)
2005	5 255 580	373	7.1 (6.4–7.9)	5 078 968 (96.6)	319 (85.5)	6.3 (5.6–7.0)	176 612 (3.4)	54 (14.5)	30.6 (23.4–39.9)
2006	5 276 955	295	5.6 (5.0–6.3)	5 089 045 (96.4)	239 (81.0)	4.7 (4.1–5.3)	187 910 (3.6)	53 (18.0)	28.2 (21.5–36.9)
2007	5 300 484	350	6.6 (5.9–7.3)	5 097 956 (96.2)	276 (78.9)	5.4 (4.8–6.1)	202 528 (3.8)	74 (21.1)	36.5 (29.1–45.9)
2008	5 326 314	343	6.4 (5.8–7.2)	5 107 688 (95.9)	288 (84.0)	5.6 (5.0–6.3)	218 626 (4.1)	54 (15.7)	24.7 (18.9–32.2)
2009	5 351 427	416	7.8 (7.1–8.6)	5 118 244 (95.6)	285 (68.5)	5.6 (5.0–6.3)	233 183 (4.4)	125 (30.0)	53.6 (45.0–63.9)
2010	5 375 276	323	6.0 (5.4–6.7)	5 127 141 (95.4)	213 (65.9)	4.2 (3.6–4.8)	248 135 (4.6)	106 (32.8)	42.7 (35.3–51.7)
2011	5 401 267	326	6.0 (5.4–6.7)	5 135 119 (95.1)	240 (73.6)	4.7 (4.1–5.3)	266 148 (4.9)	80 (24.5)	30.1 (24.1–37.4)
2012	5 426 674	276	5.1 (4.5–5.7)	5 141 203 (94.7)	182 (65.9)	3.5 (3.1–4.1)	285 471 (5.3)	81 (29.3)	28.4 (22.8–35.3)
2013	5 451 270	271	5.0 (4.4–5.6)	5 146 991 (94.4)	182 (67.2)	3.5 (3.1–4.1)	304 279 (5.6)	87 (32.1)	28.6 (23.2–35.3)
Total		8299			7026 (84.7)			1199 (14.4)	

CI, Confidence interval.
* Statistics Finland (www.stat.fi).
† Includes 74 cases without country of birth or nationality.
‡ Cases per 100 000 population.

The proportion of reported TB cases who were immigrants increased from 5.8% in 1995 to 32.1% in 2013 while the proportion of all immigrants in the Finnish population increased from 2.1% in 1995 to 5.6% in 2013. Over the period 1995–2013, TB cases in immigrants were significantly younger, more often female and had extrapulmonary TB more often than native cases (Table 2). Multidrug resistance was more common in immigrants than natives ($P < 0.01$). The median age of TB cases in immigrants remained stable at about 30 years (range 27–34 years). Minimum age was 1 year (range 1–16 years) and maximum age 93 years (range 70–93 years). Overall, 78.4% of the immigrant cases were aged 15–44 years.

Table 2: Characteristics of immigrant and native tuberculosis cases in Finland, 1995-2013.

	Native (n = 7026)	Immigrant (n = 1199)	p-value
Median age (min-max)	70 (0-105)	30 (1-93)	<0.01
Age groups, n (%)			
0-14	34 (0.5)	55 (5)	
15-29	183 (3)	544 (45)	
30-44	522 (7)	396 (33)	
45-59	1417 (20)	111 (9)	
60-74	2268 (32)	53 (4)	
75-	2602 (37)	40 (3)	
Male cases, n (%)	4027 (57)	609 (51)	<0.01
Pulmonary tuberculosis, n (%)	4870 (69)	726 (61)	<0.01
Smear positive, n (%)	2356 (48)	339 (47)	0.397
Multidrug resistance, n (%)	17 (0.2)	29 (2)	<0.01

The 1085 immigrant TB cases for whom data on the country of birth was available were born in 82 different countries (Table 3). The most common countries of origin were Somalia, the former Soviet Union/Russia and Vietnam. Of the 1085 immigrant TB cases, 947 (87.3%) were born in high-incidence countries (>50 cases/100 000 population) and 138 (12.7%) in middle- or low-incidence countries (<50 cases/100 000). Of the 947 cases born in high-incidence countries, 708 (74.8%) were born in very high-incidence countries (>150 cases/100 000).

Table 1: Incidence of tuberculosis cases among immigrants by country of birth in Finland, 1995-2013.

Country of birth*	Incidence of tuberculosis **	Number of cases (%)	Population at risk (person years)***	Rate per 100000/year (CI 95 %)	No. of multidrug resistant cases	No. of pulmonary cases
Somalia	286	354 (33)	10 6489	332 (299-368)	8	152
Ethiopia	247	36 (3)	19 408	185 (133-256)	0	26
Democratic Republic of the Congo	327	18 (2)	11433	157 (99-249)	0	14
Afghanistan	189	36 (3)	26935	134 (97-186)	0	25
Vietnam	147	76 (7)	66661	114 (91-143)	0	54
Philippines	265	24 (2)	23580	102 (68-152)	1	6
Thailand	119	60 (6)	73593	82 (64-106)	1	29
India	176	35 (3)	43912	80 (57-111)	0	11
Former Socialist Federal Republic of Yugoslavia	-	31 (3)	94236	33 (23-47)	0	28
Iraq	45	26 (2)	87 668	30 (20-44)	0	19
Estonia	23	30 (3)	293 753	10 (7-14)	3	26
Former Soviet Union/Russia	91	83 (8)	834 489	10 (8-12)	8	68
Unknown	-	114 (10)	94 014	121 (101-145)	7	80
Other	-	276 (23)	1 732 031	16 (14-18)	1	188

CI, Confidence interval
*By rate (high to low)
**Cases per 100 000 population (WHO, 2013 [1])
*** Statistics Finland (www.stat.fi)

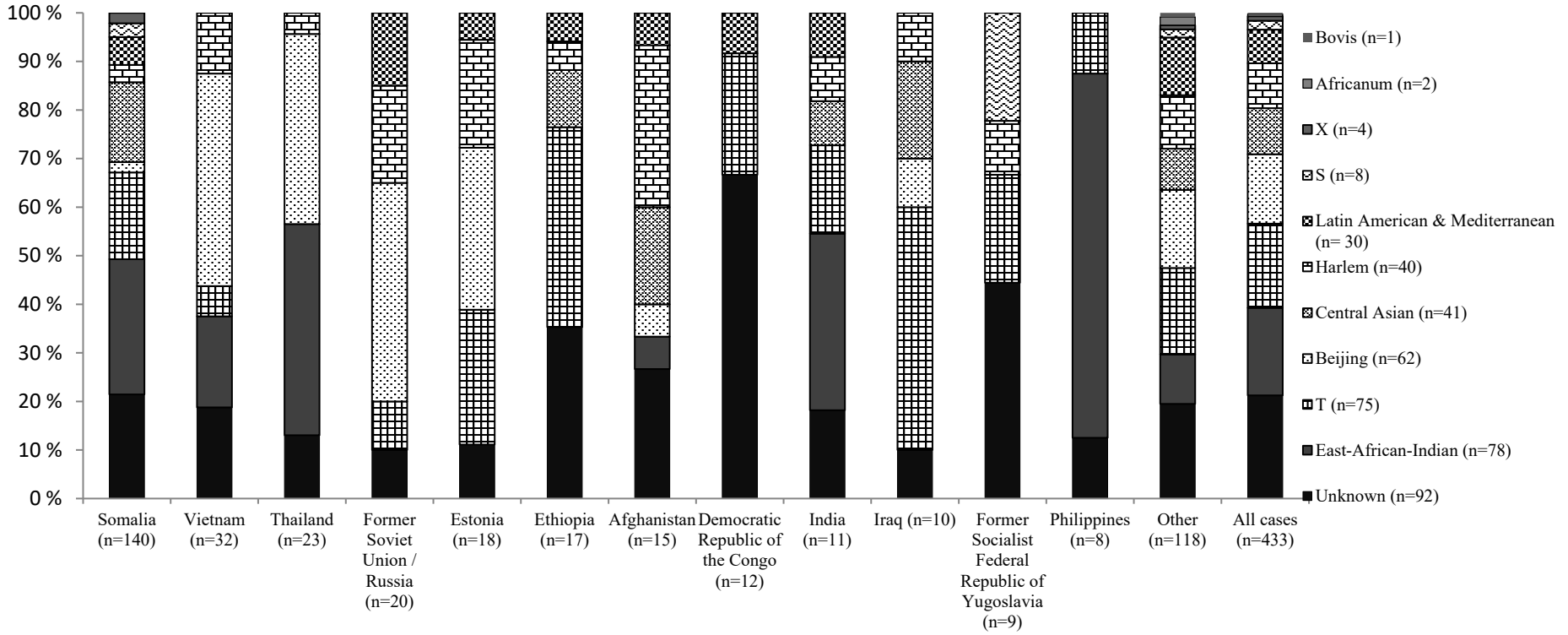
Of the 1199 immigrant cases, 726 (60.6%) had pulmonary TB and 473 (39.4%) extrapulmonary TB. Of all pulmonary cases 410 (56.5%) were male, 339 (46.7%) were sputum smear positive (range 9–30 cases per year). Of the sputum smear-positive cases, 60 were born in Somalia, 40 in the former Soviet Union/Russia, 26 in Vietnam and 16 in the former Socialist Federal Republic of Yugoslavia. The country of birth was unknown in 44 sputum smear-positive cases.

In 29 (2.4%) immigrant cases the M. tuberculosis isolate was resistant to at least isoniazid and rifampicin (MDR-TB) (Table 3). Of the 29 TB cases caused by a MDR-TB strain, eight were born in the former Soviet Union/Russia, eight in Somalia, three in Estonia and one each in The Netherlands, Pakistan, The Philippines, Lithuania and Thailand. The country of birth was unknown for five MDR-TB cases. During 1995–2004 and 2005–2013, there were 11 (range by year 0–4) and 18 (range by year 0–5) MDR-TB immigrant cases, respectively.

Genotyping

During 2008–2013, 533 cases of TB were reported in immigrants born in 57 countries. Of those, 433 (81.2%) M. tuberculosis isolates were submitted for genotyping. On the basis of the spoligotyping results, the isolates belonged in 10 different clades. The distribution of spoligotype clades in isolates obtained from immigrants is shown in Figure 1. The East-African- Indian (EAI) and T family were the most common clades in immigrants in Finland, 78 (18%) and 75 (17%) cases, respectively. Of TB cases born in Somalia both of these clades were common as there were 39 (28%) cases belonging to the EAI clade and 25 (18%) belonging to the T family. Altogether, nine different clades were identified in TB cases born in Somalia. There were 62 (14%) cases belonging to Beijing clade. Most of these cases were born in the former Soviet Union/Russian, Estonia, Vietnam or Thailand.

Figure 1: Distribution of spoligotype clades by country of birth in Finland, 2008-2013.



DISCUSSION

Our nationwide, population-based study showed that during the 19-year study period the number of TB cases in immigrants tripled as the immigrant population from high-incidence countries grew. The proportion of all TB cases who were immigrants increased more than fivefold reflecting both increased immigration and the decrease in the number of native TB cases in Finland. Reported TB cases were born in over 80 different countries, nearly 90% were born in high TB incidence countries and more than a third were born in Somalia. Patient characteristics in immigrant TB cases were different from native TB cases.

In other low-incidence countries such as Sweden, Norway, Denmark and The Netherlands [7–13], TB cases in the immigrant population dominate the epidemiology of TB. In these countries, the proportion of immigrant cases varies between 50% and 85% of all cases. In Finland, the majority of TB cases are still reported in the native population and represent re- activation of an infection acquired decades ago when TB transmission was common. The number of native cases will probably decrease as the population of older adults with latent TB contracted decades ago decreases. Finland currently has fewer immigrants than other Nordic countries. However, as more foreign-born persons move to Finland, TB cases in the immigrant population are likely to change the epidemiological picture to become similar to other Nordic countries in the future.

Nearly 90% of the immigrant TB cases in Finland were born in countries where the incidence of TB is 550/100 000 population (e.g. Somalia, Russia, Vietnam and Thailand). Similar proportions have been reported from Sweden [8], Norway [9] and The Netherlands [14], where most immigrant cases are from Asia or Africa, mostly from Somalia. This finding supports the strategy of focusing screening efforts on immigrants from high-incidence countries to ensure timely detection and treatment of pulmonary TB cases and interrupting the transmission. However, we did not have information on the immigrant cases' time of arrival in Finland and whether their TB was diagnosed immediately after arrival through screening or by clinical symptoms years after arrival. Our results are in line with the new Finnish Ministry of Health guidelines in which all immigrants arriving from high-incidence countries who intend to stay in Finland for more than 3 months should be screened for active TB on arrival with chest X-ray and health check-up. In previous guidelines, only refugees and asylum seekers were screened [15].

A recent systematic review and meta-analysis [16] found that refugees were four times more likely to be diagnosed with active pulmonary TB than other immigrants. Refugees usually have left their country of origin against their will and might have stayed in overcrowded camps before moving to the host country. Immigrants who are not refugees may be difficult to reach because they do not come to the country via a single entry point, as they might relocate for work, to join a family member or to study. As refugees are under surveillance at arrival, they are easy to reach and screen but other immigrants are not comprehensively covered by any surveillance system in Finland even if they are from high-incidence TB countries. A Canadian study suggested that screening of all immigrants is not an easy task [17]. However, proactive screening, significantly reduces morbidity, prevents secondary infection of contacts, and is cost-effective. As immigrants might develop a disease years after re-locating and may often be mobile, raising awareness about TB and its symptoms is important in

addition to comprehensive screening [17].

When comparing the incidence rates in the cases' country of birth with the respective group's incidence rate in Finland, we found that Somalis had a higher risk of being diagnosed with TB in Finland than in Somalia. For most of the countries the reported rate was similar or somewhat smaller in Finland compared to the country of origin. Exceptions were persons born in the Philippines, Estonia and the former Soviet Union/Russia in whom the TB rate in Finland was considerably lower compared to the reported rate in their country of origin. Comparing the TB incidence rates reported in the cases' country of birth, and their likelihood of being diagnosed with TB after im- migration to Finland, is difficult because of differences in surveillance and healthcare systems and population characteristics. As expected, observed rates were generally lower in Finland than in the country of birth. For example, the reported TB rate in Russia is nine times higher than the reported rate in Finland in persons born in the Soviet Union/Russia. This reflects the characteristics of the Russian immigrant population in Finland and the disease epidemiology in Russia where TB transmission occurs mainly in prisoners, homeless people and drug addicts. It was only in the Somali population that the likelihood of being diagnosed with TB in Finland appeared higher than reported from their country of birth. This could be due to the fact that in Somalia TB is very common, many people have latent TB infection and TB is not restricted to any specific population or group in Somalia. Moreover, as most Somalis who come to Finland are asylum seekers they are screened immediately after arrival in Finland, allowing for an early detection of TB.

In our study the male/female sex ratio in immigrant TB cases was equal, even though several international surveys have shown that TB occurs more often in males than in females [13, 18]. These analyses, however, have generally included only pulmonary TB cases. Our study shows a similar trend as inter- national surveys in which males have more pulmonary TB and females extrapulmonary TB.

MDR-TB is increasing in immigrant TB cases in Finland. In a previous study of MDR-TB in Finland by Vasankari et al. [19] 14 immigrant MDR-TB cases were notified during 1994–2005. Towards the end of our study period the number of MDR-TB cases increased, as 18 MDR-TB immigrant cases out of the total 29 cases were detected during the last 9 years of the study (2005–2013). The increase in MDR-TB cases in Finland may be associated with the increase in MDR-TB in countries with high incidence of TB such as Somalia and Russia [1].

The most common spoligotype clades of TB strains in immigrants in Finland were found to be the EAI clade and T family clade, which are also common in Sweden [8]. When comparing the clades in TB cases' country of birth, we observed that in most cases the EAI and T clades were common also in the country of birth. A total of 10 different clades were identified in immigrant patients in Finland in general, and nine of the clades were found in cases born in Somalia, suggesting that a wide variety of M. tuberculosis isolates circulate in that country. A detailed analysis of molecular epidemiology of TB in Finland [20, 21] recently found that T and Haarlem strains were the most common in Finnish isolates. By combining spoligotyping and MIRU-VNTR, only 10 out of 100 clusters were found to contain both Finnish and foreign-born cases. In addition, clustering was less common in immigrants than natives, suggesting that TB in immigrants is more often caused by a re- activation of TB obtained in their country of birth, than recent transmission of TB in Finland.

There are several limitations in our study. First, the sensitivity of TB surveillance increased in the middle of our study period as the case definition for TB was changed in 2007. This change is likely to affect the number of immigrant and native cases similarly. Furthermore, the change may have affected the sensitivity for detecting pulmonary TB more than extrapulmonary TB. However, pulmonary TB was not more common in immigrants. Second, we defined an immigrant as a person born outside Finland. If data on the country of birth was missing, and immigrant was defined as a person whose recent nationality was not Finnish. This definition was based on the available administrative classification and chosen because a person can only have one country of birth. However, it is possible that a Finn who was born abroad would therefore be defined as an immigrant, but this was rare. Further, second-generation immigrants are defined as natives by this definition. Beside nationality, the parents' country of birth or ethnic background has sometimes been used [8, 11, 22] and would probably be more accurate in defining the immigrant/native status, as it would cover second-generation immigrants. However, this in- formation was not available in our surveillance data. Third, we did not have information on the immigrant cases' time of arrival in Finland and whether their TB was diagnosed immediately after arrival through screening or by clinical symptoms years after arrival. We also did not have information avail- able about the coverage and timeliness of the screening of refugees and asylum seekers in Finland. Moreover, we did not have data available on the visa status of the immigrants to determine whether the immigrants came to Finland as refugees or with a working visa. Fourth, the study period of genotyping data was shorter compared to the epidemiology data as genotyping information has only been available since 2008. A strength of our analysis is the ability to link the NIDR data to a laboratory database and analyse isolates by spoligotyping and characterize them to obtain a national view of our genotypes. Only spoligotyping data was used in this study, in order to obtain a general picture of the population structure of M. tuberculosis isolates. Previous studies have shown that a better resolution of M. tuberculosis isolates is obtained by combination of spoligotyping and MIRU-VNTR typing data [7, 14, 20]. A more detailed comparison of the immigrant and native M. tuberculosis isolates will pro- vide specific information about transmission of TB in Finland.

As TB becomes less common in native Finns over time, increasing TB cases in the immigrant population will probably change the epidemiology in the future as has occurred in other northern European countries. Screening of immigrants from high-incidence countries and raising awareness of typical TB signs and symptoms, both in patients and clinicians, is important to ensure early diagnosis and to prevent transmission of TB in Finland.

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DECLARATION OF INTEREST

None.

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PUBLICATION II

Enhanced surveillance for tuberculosis among foreign-born persons, Finland, 2014–2016

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RESEARCH ARTICLE Open Access

Enhanced surveillance for tuberculosis among foreign-born persons, Finland, 2014–2016

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Abstract

Background: Tuberculosis (TB) in foreign-born residents is increasing in many European countries including Finland. We conducted enhanced TB surveillance to collect supplementary information on TB cases among recent immigrants and their children to provide data for revising TB control policies in Finland to take into account the decrease in native cases and increase in foreign-born cases.

Methods: TB cases were identified from the National Infectious Diseases Register. Data on foreign-born (if not available, most recent nationality other than Finnish) TB cases notified during 2014–2016 (country of birth, date of arrival to Finland, participation in TB screening, date of first symptoms, and details of possible contact tracing) were requested from physicians responsible for regional communicable disease control through a web-based questionnaire.

Results: Questionnaires were returned for 203 (65%) of 314 foreign-born TB cases; 36 (18%) were paediatric cases TB was detected in arrival screening in 42 (21%) and during contact tracing of another TB case in 18 (9%); 143 (70%) cases sought care for symptoms or were identified by chance (e.g. chest x-ray because of an accident). Of cases with data available, 48 (24%) cases were diagnosed within 3 months of arrival to Finland, 55 (27%) cases between 3 months and 2 years from arrival, and 84 (42%) cases after 2 years from arrival. Of all the foreign-born cases, 17% had been in a reception centre in Finland and 15% had been in a refugee camp abroad.

Conclusions: In addition to asylum seekers and refugees, TB screening should be considered for immigrants arriving from high TB incidence countries, since the majority of TB cases were detected among persons who immigrated to Finland due to other reasons, presumably work or study. Further evaluation of the target group and timing of TB screening is warranted to update national screening guidance.

Keywords: Tuberculosis, Screening, Immigrants, Asylum seekers, Refugees

Background

Screening of immigrants arriving from high tuberculosis (TB) incidence countries (incidence 50/100000 or more) and timely detection of TB are key actions for preventing transmission and spread of pulmonary TB. Increasing international migration is thought to be the most important factor contributing to the increase in cases and trends observed in the epidemiology of TB in high income countries in Europe [1–3]. Studies conducted since the 1990s attribute a large proportion of cases in high income countries to foreign-born residents [3–6]. Only few studies have been published concerning TB among second generation immigrants in Europe [6–9].

In Finland, the proportion of new foreign-born TB cases increased from 6% in 1995 to 46% in 2016, suggesting that the epidemiology of TB is changing in Finland. The absolute number of cases also increased from 38 in 1995 to 106 in 2016 [10]. However, the number of immigrants living in Finland also increased from

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approximately 106,000 in 1995 (2% of the population, TB incidence 36/100000) to 360,000 in 2016 (7% of the population, TB incidence 29/100000). Countries with high TB incidence such as Somalia, Afghanistan, and Vietnam were the most common birth places of foreign-born persons living in Finland in 2016 [11].

According to national guidelines, refugees and asylum seekers are screened for TB within two weeks of arrival to Finland. TB screening is offered for persons arriving from high TB incidence countries (≥50/100000), conflict areas or refugee camps or, if they have TB symptoms. Screening includes an interview and a chest x-ray. Offering screening is mandatory but participation is voluntary. TB screening is also offered to other immigrants who come from countries with a very high TB incidence (≥150/100000), and who plan to stay in Finland for 3 months or longer. Routine screening for latent tuberculosis infection (LTBI) among immigrants is not recommended in Finland. Moreover, all children born to parents from high-incidence countries receive Bacillus Calmette-Guérin (BCG) vaccine at birth.

The TB screening policy for refugees and asylum seekers has been in effect since 2009. When large numbers of asylum seekers arrived to Finland in 2015–2016, the policy was changed to include also individuals arriving from conflict areas (such as Iraq and Syria) or refugee camps. The policy concerning other immigrants has been in effect since 2014 and was modified in 2016 (TB incidence threshold was increased to 150/100000 to increase cost-effectiveness).

Second generation immigrant TB cases have not been studied earlier in Finland. In other low TB incidence countries such as Sweden, Norway, Denmark and The Netherlands [5], TB cases in foreign-born dominate the epidemiology of TB. In these countries, the proportion of immigrant cases varies between 50 and 85% of all cases. As surveillance and control of TB needs to be revised and improved in Finland to take into account the decrease in native cases and increase in foreign-born cases, enhanced TB surveillance was launched to collect detailed information of TB among migrants and their children. Our aim was to find out: 1) how TB was detected, 2) when TB was detected relative to arrival to Finland, 3) were any TB symptoms reported, and 4) what was the proportion of TB cases who were asylum seekers and refugees.

Methods

TB cases diagnosed from 1.1.2014 to 31.12.2016 were identified from the National Infectious Diseases Register (NIDR), a population-based surveillance system. All physicians and laboratories notify TB cases to the NIDR using ECDC criteria, notifying is mandatory [10]. The case definition for TB surveillance included all cases confirmed by culture, sputum smear, nucleic acid amplification or histology and also reporting category 'physician's decision to initiate full TB treatment on the basis of clinical suspicion of TB despite lack of laboratory confirmation'. Data collected from NIDR with each notification include age, gender, country of birth, nationality, date of diagnosis, and clinical presentation of TB (pulmonary/extrapulmonary). Categorical variables were compared with the $\chi 2$ test or Fisher's exact test by Statistical Analysis System Software, version 9 (SAS Institute, Inc., Cary, North Carolina) [12].

A web-based questionnaire was sent to physicians responsible for communicable disease control in regions, where foreign-born or paediatric TB cases were notified. Data was requested on country of birth, date of arrival to Finland, travel route to Finland, whether the person has lived in a refugee camp before arriving in Finland, whether the person has stayed in a reception centre in Finland, participation in TB screening, date of first symptoms (e.g. cough, night sweats, weight loss, swelling or a lump), and possible contact tracing results. For paediatric cases, the parents' country of birth was reported.

A foreign-born person was defined as a person born outside of Finland or, if the country of birth was not known, the most recent nationality was not Finnish. A paediatric case in this study was a person under 18 years old. A second-generation immigrant was defined as a person under 18 years old, born in Finland and having at least one foreign-born parent.

Results

In total, 771 TB cases were diagnosed in Finland during the study period; 314 (41%) were foreign-born and 48 (6%) were paediatric cases (foreign-born or born in Finland).

Foreign-born cases

The questionnaires were returned for 203 (65%) of 314 foreign-born TB cases notified in the NIDR during 2014–2016. The most common countries of birth were Somalia, Afghanistan and Vietnam (Table 1). The 203 patients were born in 43 different countries, and in one case the country of birth was unknown. Pulmonary TB was diagnosed in 140 cases (69%), and 9 of them (6%) had multidrug-resistant TB (MDR-TB). TB was detected in screening performed on arrival in 42 (21%) cases, 18 (9%) cases were found at contact tracing of another TB patient, and 143 (70%) cases sought care due to symptoms or were found by chance (e.g. chest x-ray taken due to an accident). The period from arrival to Finland to the date of diagnosis of TB was less than three months in 48 (24%) cases, three months to two years in 55 (27%) cases, and more than two years in 84 (42%)

Table 1 Characteristics of foreign-born TB cases, 2014–2016, Finland

	Foreign-born case ($n = 203$)[a]
Median age, years (range)	28.5 (2–83)
Male cases *n* (%)	120 (59)
Country of Birth	
Somalia *n* (%)	55 (27)
Afghanistan *n* (%)	15 (7)
Vietnam *n* (%)	14 (7)
Thailand *n* (%)	10 (5)
The Philippines *n* (%)	10 (5)
Other/unknown *n* (%)	99 (49)
Stayed in a refugee camp abroad *n* (%)	30 (15)
Stayed in a reception centre in Finland *n* (%)	35 (17)
TB found in screening *n* (%)	42 (21)
TB diagnosed within two years after arrival to Finland *n* (%)	103 (51)
Symptoms of TB *n* (%)	153 (75)
Pulmonary TB *n* (%)	140 (69)

[a]questionnaire data available

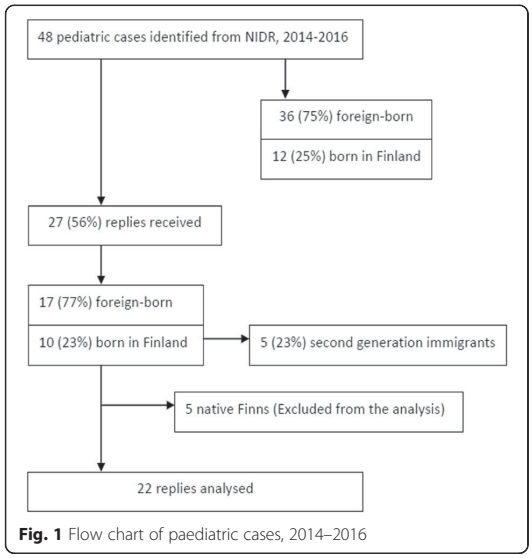

Fig. 1 Flow chart of paediatric cases, 2014–2016

cases. For 16 (8%) cases, the time of disease onset was not available. Of all the cases, 35 (17%) had stayed in a reception centre in Finland, and 30 (15%) had been in a refugee camp prior to arrival in Finland.

Of the 203 foreign-born TB cases 50 (25%) reported no symptoms compatible with TB. Thirteen (26%) of the asymptomatic cases were detected in screening performed at or soon after arrival, 10 (20%) due to being investigated because of an accident or death, and 12 (24%) during contact tracing. In 15 cases this information was not available. Of the foreign-born TB cases without symptoms, 42 (84%) had pulmonary TB, 9 (18%) had been living in a refugee camp on the way to Finland and 14 (28%) in a reception centre in Finland. The proportion of pulmonary TB was higher among asymptomatic cases (84%) than among symptomatic cases (54%). Forty-seven (94%) of the cases with no symptoms were born in a high TB incidence country.

Paediatric cases

Between 2014 and 2016, 48 paediatric TB cases were identified from the NIDR. Of them, 36 (75%) were foreign-born and 12 (25%) were born in Finland. We received 27 (56%) replies for the questionnaire, and in 5 cases both parents were born in Finland. These cases were excluded from the analysis (Fig. 1).

Of the remaining 22 paediatric TB cases with questionnaire data available and at least one parent born outside Finland, 17 (77%) were foreign-born and 5 (23%) were born in Finland, classified as second- generation immigrants. Their parents were born in high TB incidence countries, except two of the fathers who were born in Finland. Six (27%) children were born in Afghanistan, 3 (14%) in Somalia and one (5%) in Bahrain, Ethiopia, Malawi, Myanmar, the Philippines, South Africa, Thailand and Vietnam, each.

Pulmonary TB was diagnosed in 19 children (86%), and 2 (11%) had MDR-TB. All Finnish-born paediatric cases (5) were identified during contact tracing of another TB patient and all had pulmonary TB. Of the foreign-born paediatric TB cases, 7 (41%) were identified in screening performed on arrival, 4 (24%) cases were found during contact tracing of another TB patient and 6 (35%) cases sought care due to symptoms or were found by chance (e.g. chest x-ray taken for another reason). The period from arrival to Finland to the date of diagnosis of TB, was less than three months in 9 (53%) cases, three months to two years in 4 (24%) cases, and more than two years in 4 (24%) cases. Eight children (47%) had resided at a reception centre in Finland, and 5 (29%) had been in a refugee camp prior to arrival in Finland.

No TB symptoms were reported for 22 paediatric TB patients 13 (59%). Five (38%) of them were found in screening performed at or soon after arrival, 7 (54%) in contact tracing and 1 (8%) was found by chest x-ray taken for another reason. All had pulmonary TB, one (8%) had MDR-TB, 4 (31%) had been living in a refugee camp abroad, 3 (23%) in a reception centre in Finland, and 10 (77%) were born in a high TB incidence country.

Seeking care due to symptoms was more common among foreign-born adults than children ($p < 0.01$) (Table 2). Early detection of TB (less than three months

Table 2 Characteristics of adult and paediatric foreign-born TB cases, 2014–2016, Finland

	Adult *n* (%) (*n* = 186)[a]	Paediatric *n* (%) (*n* = 17)[a]	*p*-value
Pulmonary TB	125 (67)	14 (82)	0.198
Multidrug-resistant TB	7 (6)	2 (14)	0.099
Method TB detected			
Screening performed at arrival	35 (19)	7 (41)	0.029
During contact tracing of another TB patient	14 (8)	4 (24)	0.026
Sought care for symptoms or by chance	137 (74)	6 (35)	<0.01
Time from arrival to Finland to diagnosis of TB			
< 3 months	39 (21)	9 (53)	<0.01
3–23 months	51 (27)	4 (24)	0.73
≥ 24 months	80 (43)	4 (24)	0.119
Unknown	16 (9)	0 (0)	0.254
Person had resided in			
Reception centre in Finland	27 (15)	8 (47)	<0.01
Refugee camp abroad	25 (13)	5 (29)	0.076
No TB-related symptoms	40 (22)	10 (59)	<0.01

[a]questionnaire data available

after arrival), asymptomatic disease, and staying at a reception centre were more common among children than adults ($p < 0.01$).

Discussion

This study shows that in three quarters of cases TB was detected when a foreign-born person was seeking medical care because of symptoms. Half of the cases were diagnosed within two years of arrival to Finland. Only one fifth of the TB cases were detected among individuals who had stayed in a reception centre in Finland and were classified as refugees or asylum seekers. Most of the detected TB cases (80%) were therefore among individuals who had come to Finland for other reasons, such as work or study.

Our study shows that 25% of the foreign-born cases had not reported any symptoms but yet TB was found in a chest x-ray taken for screening or contact tracing purposes. Thus, TB was detected before any symptoms occurred, and further transmission of the disease was avoided. Surprisingly, the proportion of pulmonary TB was higher among asymptomatic cases than symptomatic cases. This might be due to many reasons. First, extrapulmonary TB may cause pain and/or abscess in the affected part of the body and for that reason, person is seeking medical care. Second, pulmonary symptoms are not always recognized as TB, since some of the TB cases are first treated as pneumonia or common cold. In addition, early stages of pulmonary TB do not always cause noticeable symptoms especially among previously healthy young individuals. Third, the foreign-born patients may be reluctant to report their TB symptoms due to fear of stigma or deportation. Large proportions (60%) of the paediatric patients were reportedly asymptomatic. TB in children often presents with atypical symptoms and it is difficult for small children to communicate their symptoms. Since children primarily stayed at reception centres where screening practices were routinely implemented, their TB was detected earlier than adults.

Approximately 20% of TB cases in this study were found by screening performed at arrival to Finland. This suggests that immigrants coming from high TB incidence countries might benefit from chest x-ray screening even if they do not have any symptoms. Chest x-ray may be used to assess asymptomatic active disease [13]. In Finland, chest x-ray is combined with an extensive interview and symptom screening of the individual. Immigrant screening policies in other low TB incidence countries vary widely and may influence observed rates of TB [14]. Some countries i.e. Australia, Canada, New Zealand, the United States and the United Kingdom have a pre-entry screening policy [5, 15]. The United Kingdom and the Netherlands also have a post-arrival latent tuberculosis screening policy with an active tuberculosis screening policy [5].

In Finland, screening of TB among refugees and asylum seekers is routinely performed at reception centres and screening coverage is good [16]. Screening of other immigrants (such as students, workers, family members) arriving from high-TB incidence countries is also recommended, but not consistently implemented [17]. Since systematic screening of all immigrants is unrealistic, public-health efforts should be aimed at situations were transmission of TB is more likely to occur or would cause more serious consequences to the affected (such as schools, day-care centres and hospitals). The Finnish TB screening policy has recently been modified to target all health-care workers and caretakers of small children arriving from very high TB-incidence countries [18].

More than half of the foreign-born cases were diagnosed within two years after arrival to Finland. On the other hand, some cases had been living in Finland for ten years or more. We do not know whether these persons had travelled to their home countries or whether transmission, or reactivation of latent infection, occurred in Finland. Our previous studies using molecular genotyping methods show that TB was more often caused by reactivation of LTBI obtained in the country of origin of the patient, and that transmission of TB between Finns and foreign-born persons was rare [10, 19]. Moreover, we do not know if the diagnostic delay was due to delays in the health-care system or the patient's care seeking. It

is possible that the patient had sought help earlier but the possibility of TB was not investigated. Furthermore, persons from high TB incidence countries have a lifelong increased risk of TB. A similar scenario has been reported from Sweden where 23% of all immigrant TB cases had been living in the country for more than ten years [20].

In Finland, three quarters of children diagnosed with TB were foreign-born, 5 were second-generation immigrants and 5 cases were detected among children of Finnish origin. As the population of second-generation immigrants is much smaller, we may assume that the incidence rate among second-generation children is likely much higher than among Finnish children. [6].

A major limitation for our study was the low response rate. The questionnaire was sent to the physician in charge of communicable diseases, not directly to the clinician treating the patient. The patient data may not have been consistently recorded or requested data may have been missing. This is especially common for asylum seekers, who often move within one country and between countries, and their health records do not always follow. Moreover, asylum seekers do not receive the Finnish national identifier, which is needed for linking health records.

Conclusion

Half of the reported TB cases among foreign-born persons were detected within two years of arrival; most of them were seeking care for TB-related symptoms. As less than 20% had been seeking asylum in Finland and therefore screened, most of the cases had arrived in Finland for other reasons such as work or study. Further evaluation of the target groups and timing of TB screening is warranted to update national screening guidance.

Abbreviations

BCG: Bacillus Calmette-Guérin; Filha: Finnish lung health association; MDR-TB: Multidrug-resistant TB; NIDR: National infectious diseases register; TB: Tuberculosis; THL: National Institute for Health and Welfare

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Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due to possibility of recognition of a patient even though data does not include personal level data, but are available from the corresponding author on reasonable request.

Description of the article

Enhanced surveillance was implemented to collect detailed information of tuberculosis (TB) among migrants and their children in Finland to provide information for revising TB control policies to take into account the decrease in native cases and increase in foreign-born cases. Our aim was to find out: 1) how TB was detected, 2) when TB was detected relative to arrival to Finland, 3) were any TB symptoms reported, and 4) what was the proportion of reported TB cases who were asylum seekers and refugees.

Authors' contributions

PER, HS, PT, TV, PR, JPN and OL designed the study. PER and PT collected the data. PER, HS, TV, PR, JPN and OL contributed to data analysis and interpretation of the results. PER, HS, JPN and OL drafted and finalized the manuscript. All authors revised the manuscript critically and approved the final version for publication.

Ethics approval and consent to participate

Not applicable as data in this study were analysed within the epidemiological research purposes authorized by the Finnish Communicable Diseases Act 1227/2016, 42 §. Therefore, ethical approval was deemed unnecessary.

Competing interests

The authors declare that they have no competing interests.

Publisher's Note

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PUBLICATION III

Tuberculosis screening of asylum seekers in Finland, 2015–2016

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Tuberculosis screening of asylum seekers in Finland, 2015–2016

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Abstract

Background: In Finland, asylum seekers from countries with high tuberculosis (TB) incidence (> 50/100,000 population/year) and those coming from a refugee camp or conflict area are eligible for TB screening. The aim of this study was to characterise the TB cases diagnosed during screening and estimate the yield of TB screening at the reception centres among asylum seekers, who arrived in Finland during 2015–2016.

Methods: Voluntary screening conducted at reception centres included an interview and a chest X-ray. Data on TB screening and health status of asylum seekers was obtained from the reception centres' national health register (HRS). To identify confirmed TB cases, the National Infectious Disease Register (NIDR) data of foreign-born cases during 2015–2016 were linked with HRS data. TB screening yield was defined as the percentage of TB cases identified among screened asylum seekers, stratified by country of origin.

Results: During 2015–2016, a total of 38,134 asylum applications were received (57% were from Iraq, 16% from Afghanistan and 6% from Somalia) and 25,048 chest x-rays were performed. A total of 96 TB cases were reported to the NIDR among asylum seekers in 2015–2016; 94 (98%) of them had been screened. Screening identified 48 (50%) cases: 83% were male, 56% aged 18–34 years, 42% from Somalia, 27% from Afghanistan and 13% from Iraq. Furthermore, 92% had pulmonary TB, 61% were culture-confirmed and 44% asymptomatic. TB screening yield was 0.19% (48/25048) (95%CI, 0.14–0.25%) and it varied between 0 and 0.83% stratified by country of origin. Number needed to screen was 522.

Conclusions: TB screening yield was higher as compared with data reported from other European countries conducting active screening among asylum seekers. Half of the TB cases among asylum seekers were first suspected in screening; 44% were asymptomatic. TB yield varied widely between asylum seekers from different geographic areas.

Keywords: Tuberculosis, Screening, Asylum seekers, Foreign-born

Background

Tuberculosis (TB) remains a public health concern for low-incidence countries (< 10/100,000 population/year) primarily because of migration from high-incidence TB countries. Factors before and during migration, such as living at a refugee camp or conflict area, increase the risk of transmission [1]. During 2015 when 1.2 million asylum seekers entered Europe, Finland's public health preparedness was tested: the screening of TB among asylum seekers had to be implemented in a short period of time [2]. In 2015, the third largest number of applications in Europe was received in Finland [3, 4], 615 applications

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per 100,000 inhabitants, compared with 1727 in Sweden, 653 in Norway and 537 in Germany [5].

Similar to other European countries, Finland has adopted active TB screening protocols for asylum seekers based on WHO recommendations [6]. The aim of screening for active TB is to find infectious cases at an early stage to protect the individual's and the population health and by interrupting transmission. Despite recent recommendations by the European Centre for Disease Prevention and Control (ECDC), Finland does not currently screen for latent TB infections (LTBI) [7].

Published studies provide divergent information about yield of TB screening in European Union/European Economia Area (EU/EAA) countries [7–10]. EU/EEA countries use different screening strategies and settings: Belgium, Germany and Switzerland screen only asylum seekers and refugees, the Netherlands and Spain screen also other migrants arriving from high incidence areas, and Italy and the United Kingdom do not conduct systematic TB screenings for asylum seekers. Also, the timing and site of screening varies: pre-entry/pre-migration screening, port of arrival screening at the airport or harbour upon arrival, reception/holding/transit centre screening shortly after arrival in the country, and community post-arrival screening. In some countries TB screening is voluntary and other countries have a compulsory screening strategy [7–10]. Also, the yield of screening for active TB is presented in different ways: as percent or per 1000 asylum seekers. Screening prevalence rate (n/100000 individuals screened) is also used in parallel with yield [7].

Previous studies have reported yield of TB screening among migrants in EU/EEA countries [1, 8, 10], but only few studies have reported data on voluntary TB screening among asylum seekers in reception centres [11, 12]. The aim of this study was to characterise the TB cases diagnosed during screening and estimate the yield of TB screening at the reception centres among asylum seekers, who arrived in Finland during 2015–2016.

Methods

TB screening

All asylum seekers are given information on health, health services and infectious diseases at the reception centre [13]. Asylum seekers may also fill in a symptom-based health questionnaire on their own health including questions regarding TB, which is used to plan the urgency of the basic health check-up and infectious disease screening [2]. Attending the information session and completing the questionnaire was voluntary.

TB screening consists of two phases and an asylum seeker was considered to be screened if one of the two phases was complete. First, in the initial health check-up a nurse interviews asylum seeker about their risk factors of TB, such as symptoms (including extrapulmonary TB symptoms), having stayed at a refugee camp or in a conflict area, or previous history of TB. Second, chest X-ray (CXR) is performed within two weeks of arrival. CXR is offered to asylum seekers coming from countries that have a high incidence of TB (> 50/100,000 population/year) and those with other risk factors. CXR is voluntary but highly recommended for those asylum seekers who are asymptomatic but mandatory for those who have symptoms. In 2015–2016, CXR was performed by two nationally-contracted private healthcare providers. The number of asylum seekers who had CXRs performed was obtained from the immigration and healthcare procurement registers.

Information about the country of birth of the screened asylum seekers without TB diagnosis was not available due to non-systematic recording of health and screening information to HRS.

National Health Record System of the Reception Centres.

HRS is maintained by the Finnish Immigration Service, was introduced to the reception centres in 2014 and was comprehensively used in the beginning of 2016. HRS is used for maintaining the health and screening records of all asylum seekers regardless of whether they live in a reception centre or private housing. The following HRS data was collected on asylum seekers diagnosed with TB: name, date of birth, gender, nationality, date of interview and health check-up, date and findings of CXR, TB - related symptoms, date of symptom onset and further examinations performed.

National Infectious Disease Register

All physicians and laboratories notify TB cases to the national infectious disease register (NIDR). The case definition for TB surveillance includes all cases confirmed by culture, sputum smear, nucleic acid amplification and/or histology [14]. A case is also reported based on physician's decision to initiate full TB treatment due to clinical suspicion of TB, despite lack of laboratory confirmation. Each physician's notification includes a unique national identifier, if available, name, date of birth, gender, country of birth, nationality, place of residence and treatment, date of symptom onset and diagnosis, diagnostic method and clinical presentation (pulmonary/extrapulmonary TB). The NIDR data is supplemented with details of the patient's place of residence, country of birth, nationality and possible death from the National Population Information System, if the national identifier is available. The information about the asylum status is not notified in the NIDR data. Therefore, data on foreign-born TB cases (i.e. cases not born in Finland or

unknown country of birth) notified to NIDR during 2015–2016, were linked to the HRS data by name, date of birth and origin to identify asylum seekers who had arrived in Finland during 2015–2016.

Data analysis and statistics

Aggregated data of all asylum seekers by age group and country of origin who had arrived in Finland during 2015–2016 were obtained from the Finnish immigration service [15].

Overall TB yield was defined as the percentage of TB cases identified among screened asylum seekers. Aggregated data were used as denominator to calculate the yield by country of origin. The confidence intervals (CI) were calculated according to Wald [16]. The number needed to screen (NNS) was calculated as the number of persons screened divided by the number of TB cases found in screening. Cross-tabulation was used to analyse the data. The data analysis was performed using Microsoft Excel 2010 (Microsoft, Redmont, Washington, USA) and IBM SPSS statistics 25.0 (SPSS Inc., USA).

Results

From January 1, 2015 through December 31, 2016, a total of 38,134 asylum seekers arrived to Finland (Table 1): most were men (80%) and 18–34 years of age (60%). Over 80% of asylum seekers came from Iraq, Afghanistan, Somalia or Syria. A total of 34,998 asylum seekers were eligible for CXR screening and 25,048 CXRs were performed (coverage, 72%; 95% CI, 71.1–72.0%) [2].

Altogether 386 abnormal screening results were recorded in the HRS; 210 (54%) were examined further, i.e. there was suspicion of TB, and 39 (18.6%) of them were lost to follow-up (Fig. 1). We identified 105 asylum seekers in the NIDR who had been diagnosed with TB in 2015–2016; 9 asylum seekers had arrived in Finland before 2015 and therefore were excluded from the analysis. A total of 96 asylum seekers, who had arrived in Finland during 2015–2016, received a diagnosis of TB during 2015–2016, and of them 48 (50%) were diagnosed based on screening.

Of the 48 TB cases diagnosed based on screening, 83% were male and the median age was 25 years (range, 3–62) (Table 1). The most common country of origin was Somalia (40%), Afghanistan (27%) and Iraq (12.5%). Altogether 41 (85%) had attended the health information session and/or initial health check-up; the attendance was not documented in 7 (15%) cases. All 48 cases had undergone screening CXR; 40 (83%) had abnormal findings and in 8 (17%) cases detailed CXR results were not documented. Pulmonary TB was diagnosed in 44 (92%) cases; 27 (61%) were culture-confirmed, 27 (61%) had symptoms, and 7 (16%) were sputum smear positive. The date of CXR was available for 41 cases; the median time from

Table 1 Characteristics of asylum seekers, TB cases among asylum seekers, TB cases diagnosed based on screening and yield of TB cases diagnosed based on screening, 2015–2016, Finland

		All asylum seekers; n (%),	All TB cases among asylum seekers; n (%),	TB cases diagnosed based on screening; n (%)	Yield of TB cases diagnosed based on screening; (%)
		n = 38,134	*n* = 96	*n* = 48	0.19 (48/25048)
Men[a]		30,122 (79)	71 (74)	40 (83)	
Age group[b]	0–13	5669 (15)	3 (3)	1 (2)	
	14–17	3740 (10)	13 (13.5)	9 (19)	
	18–34	22,397 (59)	65 (68)	27 (56)	
	35–64	6024 (16)	13 (13.5)	11 (23)	
	65 or above	114 (0.3)	2 (2)	0	
Origin[c]	Iraq	21,731 (57)	11 (11)	6 (12.5)	0.028[e]
	Afghanistan[d]	5968 (16)	17 (18)	13 (27)	0.22[e]
	Somalia[d]	2413 (6)	49 (51)	20 (42)	0.83[e]
	Syria	1479 (4)	2 (2)	0	0
	Other	6493 (17)	17 (18)	9 (19)	NA
Pulmonary TB			71 (74)	44 (91.7)	
MDR-TB			8 (8.3)	4 (8.3)	

[a] For 53 (0.1%) asylum seekers, information on sex was missing
[b] For all asylum seekers, age at the time of immigration; for TB cases age at the time of diagnosis. Of all the asylum seekers, 190 (0,5%) had unknown age
[c] Origin is based on country of birth, and if not available, on nationality. Of all the asylum seekers, 50 (0,1%) had unknown origin
[d] Incidence rate > 50/100000 population in 2015–2016
[e] Aggregated data were used as denominator to calculate the yield by country of origin

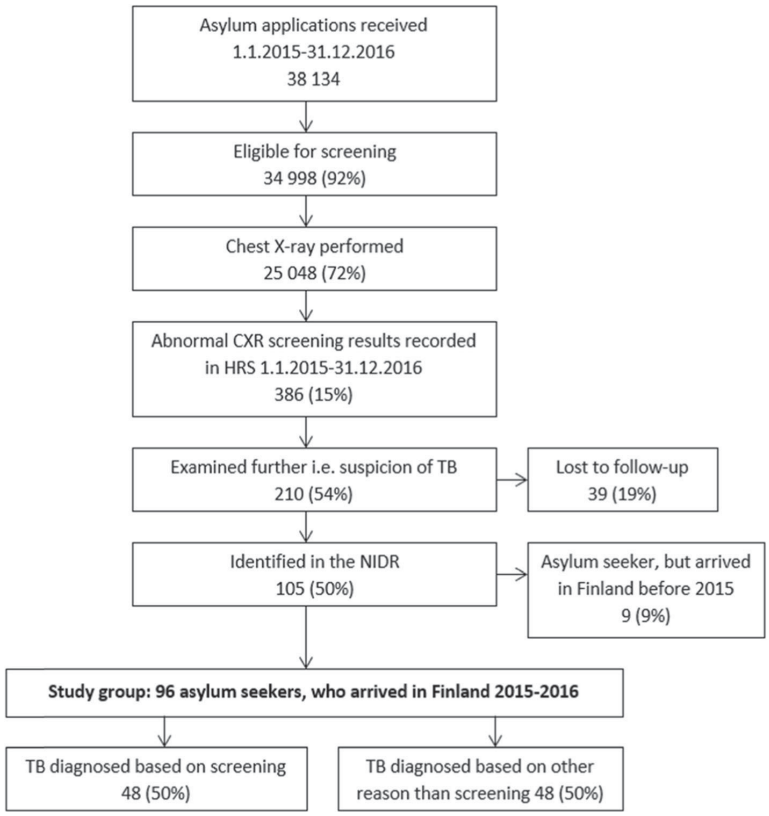

Fig. 1 Flow chart of the screening process and study groups

CXR screening to the time of diagnosis was 18 days (range 1–376 days). Two of the cases had a long diagnostic delay; one case was due to pregnancy (180 days); in the other case (376 days) the reason was unknown.

Of the 48 TB cases diagnosed based on other processes than screening, 73% were male and the median age was 22 years (range, 5–82). The most common country of origin was Somalia (56%), Iraq (8%) and Afghanistan (6%). In 40 (83%) cases TB suspicion arose because of symptoms which appeared after screening, for 5 (10%) cases the reason of TB suspicion was unknown, 2 (4%) were found before screening and 1 (2%) in contact tracing. Altogether 36 (75%) had attended the health information session and/or initial health check-up; the attendance was not documented in 12 (25%) cases. A total of 46 (96%) cases had undergone screening CXR; 5 (11%) had abnormal findings and 41 (89%) cases' detailed CXR results were not documented. Pulmonary TB was diagnosed in 27 (56%) cases; 24 (89%) were culture-confirmed, 24 (89%) had symptoms, and 6 (22%) were sputum smear positive. The date of CXR was available for 14 cases; the median time from CXR screening to the time of diagnosis was 230 days (range 97–395 days).

TB yield among individuals screened was 0.19% (95%CI, 0.14–0.25%) and NNS 522. When assuming that all asylum seekers from the same country of origin were screened, TB yield ranged from 0 to 0.83% by country of origin, being highest for Somalia (Table 1). Accordingly, screening prevalence rate among asylum seekers was 191/100000 and ranged from 0 to 828 cases/100000 by country of origin.

Discussion

We evaluated the screening of active TB in asylum seekers arriving in Finland during the large influx in 2015–2016. A total of 96 TB cases were diagnosed among asylum seekers and reported to the NIDR during this time period. Half of them were first suspected in

screening and over 40% of these cases were asymptomatic. Pulmonary TB was more common among those diagnosed based on screening. There was a 40-fold difference in TB prevalence among asylum seekers from different geographic regions. For those originating from Iraq, the prevalence of TB was low. On the other hand, individuals of Somali background, who constituted only 6 % of the asylum seekers, constituted half of the TB cases.

During the 2015–2016 influx of asylum seekers, other European countries also conducted TB screening at reception centres. We found that the yield in Finland was higher than the average yield reported from other European countries (0.19% vs. 0.12%) [8]. That said, the screening prevalence rate of TB (191/100000) and NNS (522) in Finland differed greatly from Italy and Germany [1, 12]. In Italy, post-entry screening prevalence rate of TB in asylum seekers was 535/100000 and NNS 187, among the highest in Europe. In Italy, most of the asylum seekers (82%) originated from very high TB prevalence countries in Africa, contributing to the higher screening yield. In Germany, where TB screening is mandatory, the prevalence was 347/100000 and NNS 288. This variability may be associated with differences in countries of origin and migration routes of asylum seekers as well as implementation of screening policies [1, 12].

Somalis represented over half of all TB cases in asylum seekers and over 40% of TB cases found by screening. In our previous studies [17, 18], persons of Somali origin accounted for approximately 30% of TB cases among migrants in Finland. Furthermore, it is also of note that 76% of all TB cases in persons from Afghanistan were found in screening, suggesting that Afghan asylum seekers may have had advanced TB disease at the time of arrival to Finland.

The delay from CXR to TB diagnosis ranged from 1 to 376 days (median, 18 days), which is in line with the findings in a recent systematic review and meta-analysis (the median diagnostic delay ranged from 30 to 366.5 days) [19]. In a previous Finnish study [2] of the same study population, the median delay from arrival in Finland to performing CXR for an asylum seeker was 43 days for children and 74 days for adults. Adding up the previous finding from arrival to CXR with our finding of median delay from CXR to TB diagnosis (18 days), the total median delay from arrival in Finland to TB diagnosis was estimated to be two to three months.

There are several limitations that should be considered when interpreting our findings. First, during 2015, the national health record system (HRS) was not fully implemented at all reception centres. Therefore, all health records were not entered systematically in the HRS. In addition, all of the screened asylees' backgrounds or countries of birth were not recorded which may have led to incomplete electronic records, too small denominator and potential underreporting of screening and yield. Second, all asylum seekers did not have the unique national identifier, because they were not assigned it during the asylum process. Furthermore, due to unavailability of national identifier, misspelling of asylum seekers' names and varying dates of birth in different databases caused difficulties in linking HRS and NIDR. Taken together, this means that the numerator in the yield calculation might be too large, leading to overestimation of screening yield. Third, it is possible that TB was not always detected by CXR at the time of screening; almost 20% of the asylum seekers with abnormal screening results were lost to follow-up before further examinations. Finally, we were unable to assess the sensitivity and specificity of screening as it was not possible to detect false-positive cases, since abnormal CXR result due to other diagnoses than TB were also documented in the HRS CXR results section. The reporting system could be improved by assigning the unique national identifier to asylum seekers at the border when arriving to Finland. This would make electronic screening documentation available at all healthcare centres and reduce loss to follow-up. Also, the national identifier would help linking records between registers. Mandatory screening of all asylum seekers, however, has not been found cost-effective in the Finnish context [2, 18].

Conclusions

In conclusion, the yield of TB screening was not as high as expected, since the asylum seekers during 2015–2016 originated more often from conflict areas with a low or moderate TB incidence than countries with high TB incidence. Even if the current guidelines seem adequate for screening active TB in Finland, interventions with screening and treatment of latent TB infection, as recommended by the ECDC, could be considered [7]. Careful prioritization of resources and TB screening criteria, combined with efficient reporting of data, are needed when there is an unusual pressure on limited services.

Abbreviations

CI: Confidence interval; CXR: Chest X-ray; ECDC: European Centre for Disease Prevention and Control; EU/EEA: European Union/European Economic Area; HRS: National Health record system of asylum seekers; LTBI: Latent Tuberculosis Infection; Migri: Finnish Immigration Service; NIDR: National Infectious Disease Register; NNS: Number Needed to Screen; TB: Tuberculosis; WHO: World Health Organisation

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Authors' contributions

PER, HS, PT, JPN, OS and OL designed the study. PER and PT collected the data. PER, HS, PT, JPN and OL contributed to data analysis and interpretation of the results. PER, HS, JPN and OL drafted and finalized the manuscript. All authors revised the manuscript critically and approved the final version for publication.

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Availability of data and materials
The datasets generated and/or analysed during the current study are not publicly available due to possibility of recognition of a patient even though data does not include personal level data but are available from the corresponding author on reasonable request.

Ethics approval and consent to participate
The study was approved by the Ethics Committee of the Hospital District of Southwest Finland (§326, 9.8.2018) and by the Finnish Immigration Service (permission number MIG-1815473, 3.9.2018).

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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Publisher's Note

PUBLICATION IV

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RESEARCH ARTICLE

Transmission of tuberculosis between foreign-born and Finnish-born populations in Finland, 2014–2017

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Abstract

We describe the epidemiology of tuberculosis (TB) and characterized Mycobacterium tuberculosis *(M. tuberculosis)* isolates to evaluate transmission between foreign-born and Finnish-born populations. Data on TB cases were obtained from the National Infectious Disease Register and denominator data on legal residents and their country of birth from the Population Information System. *M. tuberculosis* isolates were genotyped by spoligotyping and Mycobacterial Interspersed Repetitive Unit Variable Number Tandem Repeat (MIRU-VNTR). We characterized clusters by age, sex, origin and region of living which included both foreign-born cases and those born in Finland. During 2014–2017, 1015 TB cases were notified; 814 were confirmed by culture. The proportion of foreign-born cases increased from 33.3% to 39.0%. Foreign-born TB cases were younger (median age, 28 vs. 75 years), and had extrapulmonary TB or multidrug-TB more often than Finnish-born cases (P<0.01 for all comparisons). Foreign-born cases were born in 60 different countries; most commonly in Somalia (25.5%). Altogether 795 isolates were genotyped; 31.2% belonged to 80 different clusters (range, 2–13 cases/cluster). Fourteen (17.5%) clusters included isolates from both Finnish-born and foreign-born cases. An epidemiological link between cases was identified by (epidemiological) background information in two clusters. Although the proportion of foreign-born TB cases was considerable, our data suggests that transmission of TB between foreign and Finnish born population is uncommon.

Introduction

Tuberculosis (TB) is a worldwide disease, and the most affected areas are the South-East Asia, Western Pacific regions, and Africa [1]. Increasing migration from high TB incidence countries is a challenge for national TB programmes in low TB incidence countries (<10/100 000 population), such as Finland. Our previous nationwide, population-based study showed that

permission to share the data. Qualified researchers can apply for access to the data through the Health and Social Data Permit Authority (Findata) (https://www.findata.fi/en/ or https://www.findata.fi/en/services/data-permits/) and by following the protocol outlined in the Methods section.

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during 1995–2013 the number of notified TB cases in foreign-born persons tripled as the foreign-born population from high-incidence countries grew [2]). The proportion of all TB cases who were foreign-born increased more than fivefold reflecting both increased migration and the decrease in the number of Finnish-born TB cases in Finland. Somali-born population represented over 30% of the foreign-born TB cases while Somalis were the fourth largest group of migrants in Finland [2]. In 2015–2016, when the large influx of asylum seekers reached Europe, Finland received approximately 35,000 asylum seekers and the majority of them were born in Iraq, Afghanistan, Somalia or Syria [3].

Genotyping has provided important insights into the molecular epidemiology of TB in many low-incidence countries [4–6]. The risk of transmission from migrant to native populations is generally considered low [7, 8]. In low-incidence countries, TB transmission mainly occurs within households [9–11]. Studies suggest that the risk of transmission is increased within migrant households and migrant communities, but not in host populations. A previous study conducted in Finland in 2013 showed that only 10% of clusters included both foreign- and Finnish-born cases [12].

In this study, we describe the epidemiology of TB in Finland during 2014–2017 and characterize Mycobacterium tuberculosis *(M. tuberculosis)* isolates by genotyping methods to evaluate transmission between foreign- and Finnish-born populations.

Materials and methods

National Infectious Disease Register

In Finland, clinical microbiology laboratories notify new *M. tuberculosis* isolations directly to the National Infectious Disease Register (NIDR), maintained by the Finnish Institute for Health and Welfare (THL), and submit isolates to the Mycobacterial Reference Laboratory at THL for drug susceptibility testing and genotyping. In addition, physicians notify clinically confirmed TB cases to NIDR; reporting is mandatory. All cases notified to NIDR during 2014–2017 were included in the study. The TB surveillance case definition includes all cases confirmed by culture, sputum smear, nucleic acid amplification and/or histology, as well as clinically diagnosed TB, if a decision to give full TB treatment is made [13]. Each notification includes a unique national identifier if available, name, date of birth, gender, and the notification of the physician includes in addition country of birth, nationality, place of residence and treatment, dates of symptom onset and diagnosis, diagnostic method, clinical presentation (pulmonary/extrapulmonary TB), and additional information on the contact tracing (free text column on the notification form). A foreign-born in this study is defined as a person whose country of birth is not Finland and if the data is not available the most recent nationality is not Finnish.

Laboratory methods and identification of clusters

Culture-positive *M. tuberculosis* isolates are routinely sent to the THL Mycobacterial Reference Laboratory for drug susceptibility testing and genotyping by spoligotyping and Mycobacterial Interspersed Repetitive Unit Variable Number Tandem Repeat (MIRU-VNTR) (24 loci) according to standard protocols [14, 15]. DNA was extracted from bacterial colonies grown on solid medium using the CTAB (cetyl trimethylammonium bromide) method [16, 17]. Spoligotyping was performed using spoligotyping membranes obtained from Ocinum Biosolutions (Hyderabad, P.A., India) or produced in-house as previously described by Kamerbeek *et al.* [15]. The MIRU-VNTR analysis was performed at GenoScreen (Lille, France) using the MIRU-VNTR Kits of the same company.

The resulting spoligotype patterns were compared to the data in the international SITVIT-WEB 2 database [18]. An isolate was assigned a shared type (SIT) and a lineage if the same spoligotype was found in the database. The MIRU-VNTR results were analysed by the MIRU-VNTR plus database [19] using the Bionumerics 6.6 software (Applied Maths, Sint-Martens-Latem, Belgium). When two or more *M. tuberculosis* isolates matched by genotyping methods (i.e., identical spoligotype and MIRU-VNTR patterns), they were considered a genotype cluster. Clustering of isolates with incomplete MIRU-VNTR profile due to missing/undetectable, double, or non-numerical (e.g. 3s) results was performed with help of UPGMA (unweighted pair group method with arithmetic mean) tree generated in the Bionumerics software. Clusters which included Finnish- and foreign-born cases were evaluated by using the additional information on contact tracing: type of social contacts such as schoolmates, friends, relatives, and family members. The genotypes of the mixed clusters were compared with a local genotyping database obtained from *M. tuberculosis* strains isolated in Finland to determine whether the clusters had been detected in Finland earlier.

Population data

The number of people residing legally in Finland by year and country of birth was obtained from the National Population Information System [20].

Data analysis and statistics

Statistical significance for categorical variables was analysed with the $\chi 2$ test or Fisher's exact test. Continuous variables were analysed using the Mann–Whitney U test. P-value of <0.05 was considered statistically significant.

The annual incidence rate was calculated by the annual number of cases divided by population at the end of the year. A Poisson regression model was used to assess the log-linear trend in annual incidence rates.

IBM SPSS v. 25.0 (SPSS Inc., USA) and Microsoft Excel (Microsoft Corp., USA) were used to analyse the data.

Ethical approval was not applicable as data in this study were analysed within the epidemiological research purposes authorized by the Finnish Communicable Diseases Act 1227/2016, 42 §. Therefore, ethical approval was deemed unnecessary.

Results

From 2014 to 2017, a total of 1015 TB cases were identified in the NIDR; 814 were confirmed by culture. Of the cases, 579 (57.0%) were Finnish-born, 415 (40.9%) were foreign-born and 21 (2.1%) had no information on country of birth or nationality. Of the 415 foreign-born TB cases, 25.5% were born in Somalia, 7.0% in Afghanistan, 6.3% in Thailand and 5.3% in Vietnam; the remaining 232 cases were born in 56 different countries. Foreign-born TB cases were significantly younger compared to Finnish-born cases ($P<0.01$) (Table 1). Extrapulmonary TB and multidrug-resistant TB (MDR-TB) were more common among foreign-born cases ($p<0.01$).

The annual incidence of TB decreased from 4.8/100 000 population in 2014 to 4.5/100 000 population in 2017, being highest 5.0/100 000 population in 2015, but the decreasing trend was not statistically significant ($p = 0.16$) (Table 2). However, there was a significant decreasing trend among Finnish-born population (average annual decrease, 8.7%; $p<0.01$). The number and the incidence of foreign-born TB cases increased from 2014 to 2015 but fluctuated thereafter during 2015–2017 ($p = 0.72$). The proportion of foreign-born cases was highest (47.6%) in 2016.

Table 1. Characteristics of Finnish-born and foreign-born TB cases in Finland, 2014–2017.

		Finnish-born (n = 579)	Foreign-born (n = 415)	*P*-value
Median age, years (range)		75 (0–101)	28 (2–87)	<0.01
Age group, years n (%)				
	0–14	13 (2.2)	19 (4.6)	
	15–29	17 (2.9)	203 (48.9)	
	30–44	28 (4.8)	119 (28.7)	
	45–59	62 (10.7)	49 (11.8)	
	60–74	167 (28.8)	14 (3.4)	
	75-	292 (50.4)	11 (2.7)	
Male cases, n (%)		346 (59.8)	235 (57.8)	0.543
Pulmonary TB, n (%)		448 (77.4)	288 (72.1)	<0.01
	Smear positive, n (%)	150 (33.5)	107 (37.2)	0.02
Extrapulmonary TB, n (%)		131 (22.6)	127 (30.6)	<0.01
MDR-TB, n (%)		5 (0.9)	21 (5.3)	<0.01

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A total of 795 isolates from culture-positive cases were characterised by spoligotyping and MIRU-VNTR. Of the isolates, 248/795 (31.2%) belonged to 80 different clusters (range, 2–13 isolates/cluster): 42 (52.5%) clusters included isolates only from Finnish-born cases and 24 (30%) only from foreign-born cases, 13 of these having only cases born in the same country within a cluster. A total of 14 (17.5%) clusters included Finnish- and foreign-born cases, i.e. were mixed clusters, consisting of 9.6% (76/795) of the cases. Overall, 25.0% and 24.1% of the Finnish-born and foreign-born-cases were clustered, respectively.

Based on the spoligotyping results, 7 different lineages were detected among the mixed clusters. Beijing, Latin American & Mediterranean (LAM) and T lineages were the most common, including 5, 3 and 3 clusters, respectively. Altogether 81.6% isolates belonged to these most common lineages.

Altogether 76 isolates belonged to the 14 mixed clusters: 39 (51.3%) were from Finnish-born cases, 36 (47.4%) from foreign-born, and one of unknown origin. Foreign-born cases originated from Europe (9 cases), Asia (13 cases) and Africa (14 cases, 6/14 from Somalia) (Table 3). The majority of the isolates, 53 (70%) were from male cases and the median age of the cases was 42 years (range, 13–86). Five cases (6.6%) were under the age of 18. Out of the 76 isolates, 69 (91%) were from pulmonary TB cases, and 38 (55%) of these were smear positive.

Table 2. Incidence of TB cases in the whole, Finnish-born and foreign-born populations in Finland, 2014–2017.

	All cases			Finnish-born cases			Foreign-born cases		
Year	Population in Finland	No. of cases*	Incidence (95%CI)	Finnish-born population in Finland n (%)	No. of cases (%)	Incidence (95%CI)	Foreign-born population in Finland n (%)	No. of cases (%)	Incidence (95%CI)
2014	5 471 753	264	4.8 (4.3–5.4)	5 149 776 (94.1)	172 (65.2)	3.3 (2.9–3.9)	321 977 (5.9)	88 (33.3)	27.3 (22.2–33.7)
2015	5 487 308	272	5.0 (4.4–5.6)	5 150 146 (93.9)	151 (55.5)	2.9 (2.5–3.4)	337 162 (6.1)	115 (41.9)	34.1 (28.4–40.9)
2016	5 503 297	233	4.2 (3.7–4.8)	5 145 756 (93.5)	117 (50.2)	2.3 (1.9–2.7)	357 541 (6.5)	111 (47.6)	31.0 (25.8–37.4)
2017	5 513 130	246	4.5 (3.9–5.1)	5 140 328 (93.2)	139 (56.5)	2.7 (2.3–3.2)	372 802 (6.8)	101 (39.0)	27.1 (22.3–32.9)
Total		1015			579 (57.0)			415 (40.3)	

* Including cases with unknown country of birth.

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Table 3. Characteristics of TB transmission patterns in clusters including both Finnish-born and foreign-born cases in Finland, 2014–2017.

Spoligotype + MIRU-VNTR	No of cases	Males n	Age range, years	Pulmonary/ Smear positive	Foreign-born (%)	Foreign area of birth	Diagnosis time frame	District	Epidemiological background information	Lineages/Notes
SIT53 +1112–15[a]	13	8	24–86	10/5	7,7	Europe: 1	2014–2017	Several regions	Unknown	T1 lineage, the most common in Finland
SIT1 +94–32[a]	8	5	18–63	8/5	62,5	South-Asia: 2 North-Asia: 3	2014–2017	Several regions	Unknown	Beijing lineage, very common in Finland
SIT149 +594–15[a]	8	7	17–63	8/4	75	East Africa: 5 South-East Asia: 1	2014–2017	Several regions	5 cases from the same city	T3-ETH lineage, common in Finland
SIT42 +1119–52[a]	8	5	30–69	8/6	25	Europe: 2	2014–2015	Several regions	5 cases from the same city	LAM9 lineage, very common in Finland
SIT1 +100–32[a]	7	5	34–78	6/3	71,4	Europe: 3 North Asia: 2 Unknown: 1	2014–2017	Regional	6 cases from the same city	Beijing lineage, very common in Finland MDR cluster (one case is not MDR)
SIT1 +342–32[a]	7	4	16–83	7/3	57,1	East Africa: 2 South-East Asia: 2	2015	Several regions	5 cases from the same school	Beijing lineage, very common in Finland
SIT381 + 18194–32[a]	7	5	13–34	7/3	42,9	East Africa: 3	2015–2017	Local	household and friendship	CAS1-Delhi lineage, not common in Finland
SIT50 +172–69[a]	4	4	19–36	3/2	75	Southwest Asia: 1 West Africa: 2	2015–2017	Several regions	Unknown	Harlem3 lineage, very common in Finland
SIT254 + 9118–52	3	3	37–46	3/2	66,7	Europe: 2	2014	Several regions	Unknown	LAM-RUS lineage, not common in Finland
SIT2028 + 1481–66[a]	3	2	15–61	3/3	33,3	Europe: 1	2014–2015	Local	3 cases from the same city	Unknown lineage
SIT1 +3882–32	2	0	28–43	2/1	50	South-East Asia: 1	2014–2016	Several regions	Unknown	Beijing lineage, very common in Finland
SIT42 +5014–218	2	2	31–71	2/0	50	East Africa: 1	2015	Several regions	Unknown	LAM9 lineage, very common in Finland
SIT1 +3894–32[a]	2	1	39–51	2/1	50	South-East Asia: 1	2016	Several regions	Unknown	Beijing lineage, very common in Finland
SIT928 + 18673–15	2	2	19–57	0/0	50	East Africa: 1	2016	Several regions	Unknown	T lineage, common in Finland
Total	76 (2–13)	53 (70%)	13–86	69/38	47,4		2014–2017			

[a] The cluster detected in Finland before the year 2014.

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Based on the date of symptom onset or diagnosis, the first case in 7 (50%) mixed clusters was foreign-born and in 7 (50%) Finnish-born. In 13 clusters the first case had pulmonary TB, and in one cluster both cases had extrapulmonary TB. A total of 67 (88%) cases in 10 mixed clusters were

in clusters that had been detected before the year 2014 in Finland (based on the genotype of the cluster). The remaining four mixed clusters had not been detected in Finland earlier (Table 3).

Based on the epidemiological background information, in two mixed clusters the epidemiologic link was definite (same school or household/friendship) between Finnish- and foreign-born cases. In both clusters, the foreign-born case was the first case diagnosed. In four clusters, the links were less clear: one cluster included cases from the same city and in three clusters most of the cases were living in the same city. In the remaining eight clusters cases lived in several different regions in Finland. A phylogenetic tree was constructed based on MIRU-VNTR typing data to show the relatedness among mixed clusters (S1 Fig).

Discussion

Our nationwide, population-based study showed that during the study period (2014–2017) the total number of foreign-born TB cases increased while TB incidence first increased and then decreased to its lowest level in 10 years [2]. Although a large proportion of TB cases were among foreign-born individuals, our data suggest that transmission from the foreign-born to Finnish-born population was less frequent (17.5% vs. 32% of the TB clusters were part of mixed clusters) than the median in the European Union/European Economia Area (EU/EEA) countries during 1992–2007, shown by a systematic review published in 2014 [7]. To our knowledge, recent studies of the extent of transmission including cases of the 2015–2016 major influx of asylum seekers between foreign- and native-born populations have not been published from EU/EEA countries.

Our study shows that over 50% of the clusters included isolates from Finnish-born cases only, and 30% from foreign-born cases only. Furthermore, more than half of the foreign-born clusters included cases originating only from one country. This finding is in line with other studies conducted in low-incidence countries which suggest that the risk of transmission is elevated within migrant households and migrant communities, but not between host and migrant populations [7, 8].

In a previous study conducted in Finland between 2008–2011, only 10% of clusters included both Finnish-born and foreign-born cases [12]. The increase might be due to increase in the number of foreign-born people living in Finland, and also of the assumption that Finnish-born and foreign-born are interacting more with each other [21]. It has been shown that more than half of the foreign-born TB cases are diagnosed within two years of arrival to Finland [22], which supports the suggestion that TB in foreign-born cases in Finland is often caused by a reactivation of TB obtained in their country of birth [12].

No difference was found in proportions of clustered isolates among Finnish-born and foreign-born populations as 25% of the Finnish-born cases and 24% of the foreign-born cases were part of a cluster. The clustering rate of foreign-born cases is similar in Spain, where 22–28% of the foreign-born TB cases were part of a cluster [23, 24], but other European countries have reported higher proportions; 30% in Norway [25], 35% in France [26], 46% in Italy [27] and 56% in Sweden [28]. These countries have had more immigrants for a longer period of time than Finland [29], resulting in more interaction between natives and immigrants [26] which may explain the difference.

Only 6 out of 14 mixed clusters had a definite or possible epidemiologic link between the cases. Two clusters had a definite link; one cluster was transmitted in a school and another between friends and family. In four clusters, living in the same region was the possible link. In eight clusters without a known epidemiological link the cases in the same cluster were diagnosed in several regions in Finland. It is known that migrants are very mobile leading to clusters spreading to wider geographical areas [30].

The full size of the clusters is not captured due to the fact that TB transmission chains are building up slowly, TB has a long exposure and incubation time and delays in diagnosis can be substantial. In this study, the vast majority of the mixed clusters had a genotype that had been seen in Finland earlier. The proportion of Finnish and foreign-born varied within the mixed clusters. The largest mixed cluster consisted of 13 cases, 12 of which were Finnish-born. This cluster had a genotype that is very common in Finland and has caused local outbreaks. Thus, the infection of the foreign-born case in this cluster had probably been acquired from a Finnish-born case, although this genotype is common also elsewhere. The greatest proportion of foreign-born cases were found in widely spread (MDR) clusters SIT1+100–32 and SIT1+94–32 belonging to the Beijing genotype [31].

Approximately half of the cases of the mixed clusters were Finnish-born and half foreign-born. Thus, we can assume that both Finnish-born and foreign-born cases contribute to the same extent to TB transmission in mixed clusters and the cross-transmission among foreign- and native-born populations is bidirectional in Finland, as reported also in a systematic review in the EU/EEA countries [7]. To verify this assumption, whole genome sequencing (WGS) with thorough data analysis [32] and contact tracing should be performed to get more detailed information about direction of transmission chains.

In Finland, the majority of TB cases are still reported in the Finnish-born population. Despite of the increase in number of foreign-born people, Finland has not reached the epidemiological situation reported from Sweden, Norway, Denmark and The Netherlands, where most of the TB cases are foreign-born [33–38]. It appears that the large influx of asylum seekers had a short-term influence on the number and the incidence of foreign-born TB cases. However, it did not have a major impact on the overall annual incidence of TB in Finland.

The characteristics of TB cases have remained rather stable over the years, when compared to our previous study [2]. However, some differences to the previous period can be seen: Finnish-born cases are older, foreign-born cases are younger, the proportion of cases with Somali origin has decreased and, furthermore, the frequency of smear positive pulmonary TB cases has decreased, resulting in fewer highly infectious TB cases.

There were several limitations in our study. First, while asylum seekers and other migrants, who do not have a residency permit in Finland, are waiting for a decision on the residency permit application, they are not considered permanent residents in Finland and are not registered in the population information system [39]. In 2015–2016 there were approximately 35,000 asylum seekers [38] and an unknown number of paperless people who were not registered into the population information system. For that reason, the incidence of TB among immigrants may be an overestimate as these migrants who do not have a residency permit are not counted in the population denominator in Finland. Second, we used spoligotyping and MIRU-VNTR as genotyping methods to detect the clusters. WGS method with higher discriminatory power probably would have detected less clustered cases [40, 41] or possibly could have identified more clusters by splitting clusters smaller [42]. Third, our study may underestimate transmission due to the limited time of observation. Fourth, the definitions of foreign-born was made according to the country of birth, and if not available, the most recent nationality. With the data available, we were not able to identify second-generation immigrants who have been born in Finland: this could give a clearer understanding of the transmission within the immigrant community.

Conclusion

While both the number of immigrants and the number of TB cases among foreign-born individuals is increasing in Finland, our study suggests that transmission of TB from foreign- to

Finnish-born population is uncommon, as some 17.5% of clusters and 9.6% of the cases were part of clusters with isolates from both Finnish-born and foreign-born cases.

Supporting information

S1 Fig. Phylogenetic tree of the mixed clusters. The tree was generated with Bionumerics 6.6 using the UPGMA (unweighted pair group method with arithmetic mean) method on the categorical values of the similarity matrix of the MIRU-VNTR results.
(PDF)

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