MASTER OF PUBLIC HEALTH (MPH THESIS)

Hochschule für Angewandte Wissenschaften Hamburg (HAW)

Hamburg University of Applied Sciences

STRATEGIES for TUBERCULOSIS CONTROL in MIGRANTS in LOW-INCIDENCE COUNTRIES

1. Examiner:	**Prof. Dr. Ralf Reintjes**
	(HAW, Hamburg)
2. Examiner:	**Prof. Dr. Dr. René Gottschalk**
	(Amt für Gesundheit, Frankfurt)

MPH Candidate: **VALENTINA DIAS-FERRAO, PhD**

Frankfurt, March 2013

DEDICATION

This study is dedicated to all the 'players' in tuberculosis low-incidence countries (in particular Germany, Switzerland and the United States of America) that permit enormous in-flows of migrants who originate from high-prevalence tuberculosis countries. The majority is driven either by severe hardships yet hope of a better tomorrow or like me by the opportunity to explore new challenges for study, work and living.

Table of Contents

1. INTRODUCTION

Tuberculosis (TB) is a disease that has been with us for ages. It is caused by the bacterium *Mycobacterium tuberculosis* and it affects all ages. It was discovered by Robert Koch, a German scientist and its treatment is standard antibiotics.

While TB incidences are falling in nearly all regions worldwide, it may be considered a re-emerging disease with multidrug resistance patterns never seen before and these multiple resistant strains are almost untreatable in some cases.

Warfare, civil unrest, violation of human rights, natural disasters, and poverty, economic incentives or striving for education, are the main reasons for people to migrate. Migration from poor countries, where the burden of TB is high, to rich countries such as Australia, Canada, Western Europe, the USA and other countries with low TB incidence is a matter of national and global concern for TB control.

This study looks at the strategies for tuberculosis control in this specific group and describes the published methods of screening, with emphasis on the strengths and limitations of screening and finally proposes an overview for future modifications in order to improve screening and TB control. In addition, it aims to compile and compare the different approaches that have been taken by other international countries and to select and recommend a pragmatic approach for Germany.

2. BACKGROUND

2.1 TUBERCULOSIS - FEATURES OF THE DISEASE

Tuberculosis is an infectious air-borne disease and is spread by droplet infection from person to person by breathing in the germs from infected persons who cough, sneeze or spit.

Those that have been infected with TB but asymptomatic are said to be latently infected with tuberculosis, or have latent tuberculosis infection (LTBI), and have a 10% risk of developing an infectious form of the disease during their lifetime **(WHO, 2012)**. The risk increases for those who are immune-compromised, for example HIV-infected persons, diabetic patients and tobacco-addicted persons.

Symptoms and Diagnosis

The early onset of symptoms for TB include persistent cough that lasts 3 weeks or longer, coughing up sputum, fatigue, fever, chills, night sweats, and loss of weight. These often mild symptoms may persist for months, going undetected. It is in this phase that these patients are most infectious and can transmit the bacteria to others (10-15 persons on average) with whom they have close contact with during the year **(WHO, 2012)**.

Persons with pulmonary TB patients may sometimes have blood in their sputum when they cough and symptoms of fever and night sweats, weight loss, no appetite, weakness and chest pains. A positive sputum smear diagnostic test (done in triplicate) can confirm infectious TB in a day and there are other, rapid diagnostic tests on the horizon. For complex types of TB (MDR-TB, HIV/TB co-infection) other diagnostic tests are used. Tuberculosis may also affect other organs like lymph nodes, skeleton, kidneys or the gut and then the patient is said to have extra-pulmonary TB. When this occurs the symptoms of TB may vary **(WHO, 2012)**.

Standard Treatment of Tuberculosis

Tuberculosis treatment should follow WHO guidelines as per their most recent expert committee recommendations. The two most powerful standard drugs for TB disease treatment are isoniazid and rifampicin and these first-line drugs are administered for 6 months and with pyrazinamide and ethambutol supplements during the initial two months **(Rieder, 1994)**.

Directly Observed Therapy under Supervision (DOTS) is central to the Stop TB Strategy promoted by the World Health Organization (WHO). It is the standard method of therapy whereby patients are given a regimen of four different types of antimicrobial drugs for duration of six months and monitored carefully for adherence by either a volunteer or Health Care Worker (HCW) who provides information, supervises and supports the patient **(WHO, 2012)**.

In order to treat latent tuberculosis infection one has to consider the bacteria's mutation rate. When a low bacteria count occurs it would be futile to do conventional therapy and the only approach would be one done for chronic disease treatment by way of a single drug regimen - mono-therapy with isoniazid (INH).

For those infected with both TB-HIV, WHO advises a 12-part integrated program for treatment and prevention; this program has been implemented successfully in several countries, and credited with saving 1.3 million lives globally (2005-2011) **(Reid, 2009)**.

Multidrug-resistant TB

Resistance to at least one anti-TB drug occurs in every country worldwide. When a TB strain is resistant to the two first-line drugs, it is said to be multidrug resistant (MDR). MDR-tuberculosis (MDR-TB) is due to resistant bacteria that do not respond to the first-line drugs, isoniazid and rifampicin, which are usually effective for TB, and it can arise in a patient due to primary infection with this strain of TB or it can arise during treatment.

When treatment is unsuccessful due to ineffective drugs or incorrect usage and moreover, treatment with the first-line drugs fails, typically with less than four drugs

simultaneously in the phase when the bacterial burden is high, MDR-TB disease arises. Persons with MDR-TB require the use of second-line drugs. Treatment duration is longer at two years and therefore more expensive and may cause severe side-effects **(WHO, 2012)**.

When the MDR-TB strain is resistant to the second-line drugs, to any of the three injectable drugs: amikacin, kanamycin, and/or capreomycin, and to any chinolone, extensively drug-resistant TB **(**XDR-TB) results and the patient has a significantly limited choice of drugs for treatment **(WHO, 2011)**.

Extensively drug-resistant TB

Extensively drug-resistant TB (XDR-TB) "is a form of TB caused by bacteria that are resistant to isoniazid and rifampicin (i.e. MDR-TB) as well as any fluoroquinolone and any of the three second-line anti-TB injectable drugs. These forms of TB do not respond to the standard six month treatment with first-line anti-TB drugs and can take up to two years or more to treat with drugs that are less potent, more toxic and much more expensive". The WHO surveillance data indicates that 58 countries have XDR-TB and 25,000 cases occur annually **(WHO, 2010).**

Totally drug-resistant tuberculosis

WHO has not yet recognized totally drug-resistant tuberculosis (TDR-TB), a not well-defined name for tuberculosis strains that are resistant to more drugs than XDR-TB and are found in several countries like India, Italy, Iran, and more recently in South Africa. This is an incurable form of TB and arises due to 'mismanagement' of treatment, by way of incorrect drug, incorrect treatment regimen and incorrect duration of drug-taking. Possible reasons are: if a patient does not complete treatment; uses the drug incorrectly; due to unavailability of drugs; or perhaps the patient is already resistant but takes the wrong treatment regimen as their type of TB-resistance was not detected before they began therapy**.** Experts in the field indicate that TDR-TB is not a new phenomenon because since the 1960s isoniazid and rifampicin have been used for treatment for decades and no new first line drugs have been discovered and therefore resistance to rifampicin after prolonged usage is inevitable. After the 1990s, incidence of MDR-TB increased a lot and so in 2006 researchers called this

resistance XDR-TB. It is complicated to treat people who have HIV-TB co-infection with effective drugs and inadequate treatment regimens may induce further resistance. Drug-susceptibility testing to test the type of drug resistance is rarely done on 95% of new cases or on previously treated cases and only 16% of drug-resistant TB patients are receiving the correct treatment **(Rowland, 2012; Klopper, 2013)**.

In summary, when TB strains are immune to first-line drugs you get MDR-TB and when TB strains are resistant to MDR-TB second-line drugs because they do not complete therapy, one gets XDR-TB. Due to the growing problem of XDR-TB, we now have the terminology 'totally drug-resistant TB' which featured in a sensational article in CDC Emerging Infectious Disease journal early this year **(Klopper, 2013)**, and can be misleading as no new germ has appeared. New diagnostics are needed to diagnose this resistance early and to assist patients in adherence to their treatment regimens because when a patient gets treated again and again there is a greater chance that resistance is amplified.

Summary of TB disease: (WHO, 2012).

1. Tuberculosis is one of the greatest killer diseases globally among preventable and curable infectious diseases.
2. Morbidity figures of 8.7million and mortality of 1.4 million worldwide alone in 2011.
3. Mortality (95%) occurs in countries where people have low or middle-income.
4. Deaths (25%) which occur in the Human Immunodeficiency Virus-TB (HIV-TB) co-infected patients are due to TB.
5. Multi-drug resistant TB (MDR-TB) is globally present. In 2011, of the 310,000 globally notified cases, 60% notifications came from the Russian Federation, India and China.
6. The Millennium Development Goal for 2015 is to reduce the transmission of Tuberculosis but the TB incidence is declining only very slowly.
7. The TB mortality rate dropped by 41% (2009-2011).
8. Latent TB affects a large number of the world's population but only 5-10% progress to active disease.

In order to reach the WHO's target for 2015, where 80% of the estimated cases of M/XDR-TB is diagnosed and treated, there is an urgent need for investments in diagnostics, care and infrastructure.

Risk Groups

Those at higher risk for developing active TB globally include such groups as homeless people, injecting drug-users, patients with chronic immunosuppression due to the intake of drugs, HIV-infected and immunosuppressed patients and migrant populations **(WHO, 2012)**.

2.2 EPIDEMIOLOGY OF TUBERCULOSIS - GLOBAL, EUROPE, GERMANY

Global Tuberculosis

Tuberculosis is prevalent all over the world and high TB incidence can be grouped into four categories: 40-99 cases/100 000, 100-249 cases/100 000, 250-499 cases/100 000 and ≥ 500 cases/100 000 **(Gilbert, 2009)**. High incidence cases are found especially in developing countries. High-incidence countries has been defined as all countries except Australia, Austria, Belgium, Canada, Czech Republic, Denmark, Finland, France, Germany, Greece, Holland, Iceland, Ireland, Israel, Italy, Luxembourg, Malta, Monaco, New Zealand, Norway, Slovakia, Sweden, Switzerland, the UK, and the USA **(Das, 2006)**.

In 2011, Asian patients contributed 60% of newly infected patients. While Sub-Saharan Africa topped with the largest proportion (260 cases per 100,000). Eighty percent of reported tuberculosis cases were found in 22 countries worldwide but countries like Brazil, China and Cambodia showed a declining trend. WHO states that overall TB is on the decline except for the European region where the disease tends to re-emerge as MDR-TB. However, due to emerging MDR-TB and XDR-TB strains, tuberculosis cure rates decreased from 73% in 2008 to 53% in 2010 **(WHO, 2012)**.

The continued flow of migrants from high-incidence to low-incidence countries has altered the epidemiology of tuberculosis in low-incidence countries. Although transmission of tuberculosis from migrant population to host country inhabitants is rare with minimal impact, transmission of TB does occur in specific ethnic migrant groups especially those with high risk factors **(French, 2007; Heldal, 2003)**. Furthermore, those carrying LTBI may develop active disease later especially

those with multidrug and extensively drug-resistant TB (M/XDR-TB) will require immediate treatment to prevent further TB transmission. Moreover, the host country, in which migrants now reside, has to bear the huge financial burden in order to protect its nationals and to avert a major public health problem.

High-TB incidence countries are those in Asia, sub-Saharan and northern Africa, and south-America. Poor immigrants from high-prevalence countries have high incidence of tuberculosis and in addition LTBI which can reactivate after several years **(Blumberg, 2010)**.

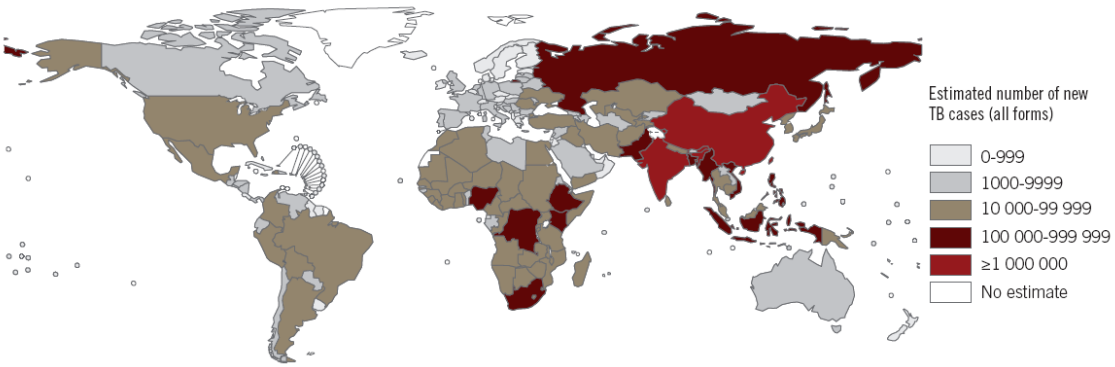
Very high TB incidence too is found in foreign nationals in UK, Norway & Sweden **(Gilbert, 2009)**. Non-UK-born and UK-born ethnic groups are at high risk of TB even after long residence period due to LTBI **(French, 2007)**.

- **Global Map of the Estimated TB incidence rates, 2011**

Of the 22 high-incidence countries (Afghanistan, Bangladesh, Brazil, Cambodia, China, the Democratic Republic of the Congo, Ethiopia, India, Indonesia, Kenya, Mozambique, Myanmar, Nigeria, Pakistan, the Philippines, the Russian Federation, South Africa, Thailand, Uganda, the United Republic of Tanzania, Vietnam and Zimbabwe), both China and India together account for an estimated 35% of global tuberculosis cases as shown in **Figure 1,** Map of estimated TB incidence rates**,** by country in 2009 **(WHO, 2011)**.

FIGURE 1. MAP OF ESTIMATED TB INCIDENCE RATES (WHO, 2011)

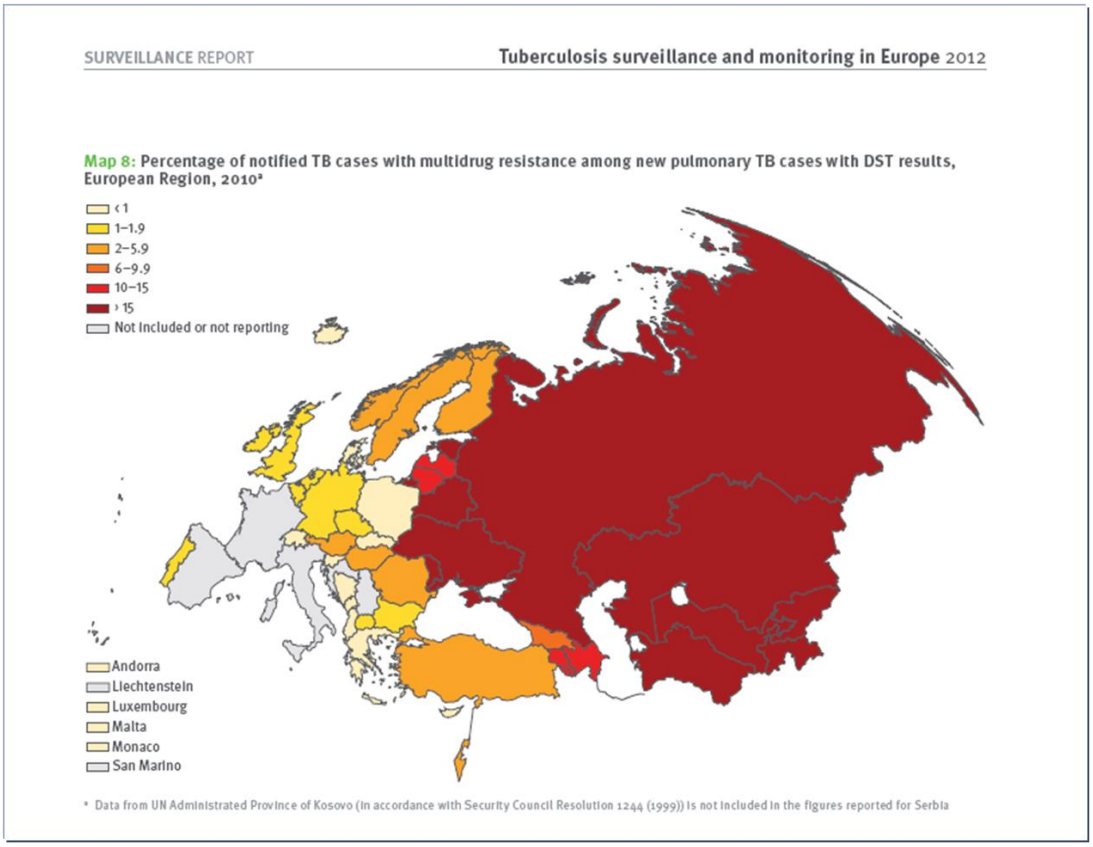
FIGURE 1 ESTIMATED TB INCIDENCE BY COUNTRY, 2009



[1] *Global tuberculosis control 2010.* Geneva, World Health Organization, 2010 (WHO/HTM/TB/2010.7). There were around 1.3 million deaths from TB among HIV-negative people and around 0.4 million deaths from TB among HIV-positive people.
[2] The 22 countries are, in alphabetical order: Afghanistan, Bangladesh, Brazil, Cambodia, China, the Democratic Republic of the Congo, Ethiopia, India, Indonesia, Kenya, Mozambique, Myanmar, Nigeria, Pakistan, the Philippines, the Russian Federation, South Africa, Thailand, Uganda, the United Republic of Tanzania, Viet Nam and Zimbabwe.
[3] Lopez AD et al. *Global burden of disease and risk factors*. New York, Oxford University Press and The World Bank, 2006.
[4] MDR-TB is defined as resistance to isoniazid and rifampicin, the two most important first-line drugs used in the treatment of TB.
[5] *Multidrug and extensively drug-resistant TB (M/XDR-TB): 2010 global report on surveillance and response.* Geneva, World Health Organization, 2010 (WHO/HTM/TB/2010.3).

The Global Map on Estimated Percentage of MDR-TB among new TB cases illustrates the former Soviet Union as being a hotspot for Multidrug and Extensively drug-resistant TB (M/XDR-TB) as shown in **Figure 2**.

FIGURE 2. ESTIMATED PERCENTAGE OF MDR-TB AMONG NEW TB CASES IN THE EUROPEAN REGION, 2010 (ECDC, 2012)



Tuberculosis in Europe

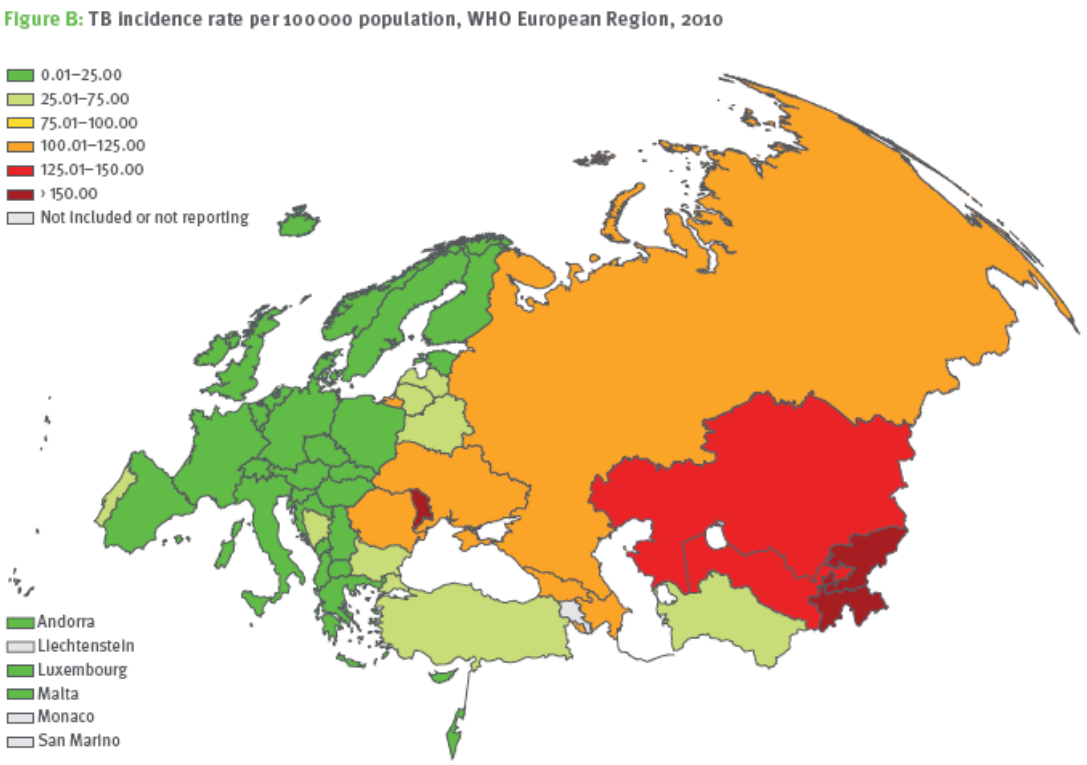
Since the countries in Europe merged to form the European Union and with the ending of the Cold War, European borders have become more porous.

Tuberculosis control in the former Soviet Union is limited and inadequate with chest radiograph (CXR) and fluorography screening of the general population.

An inefficient centrally-controlled TB network exists for diagnosis and treatment due to depleted financial systems resulting in lengthy inpatient care and high drug resistance. This issue poses a major burden to its neighbors as TB-infected migrants enter its borders **(Marx, 2009)**.

Tuberculosis surveillance and monitoring in Europe indicates that the TB incidence rate per 100,000 persons, for the WHO European Region in 2010, was again highest for the former Soviet Region which can be seen in **Figure 3**.

FIGURE 3. TB SURVEILLANCE AND MONITORING IN EUROPE (ECDC, 2012)



Tuberculosis in Germany

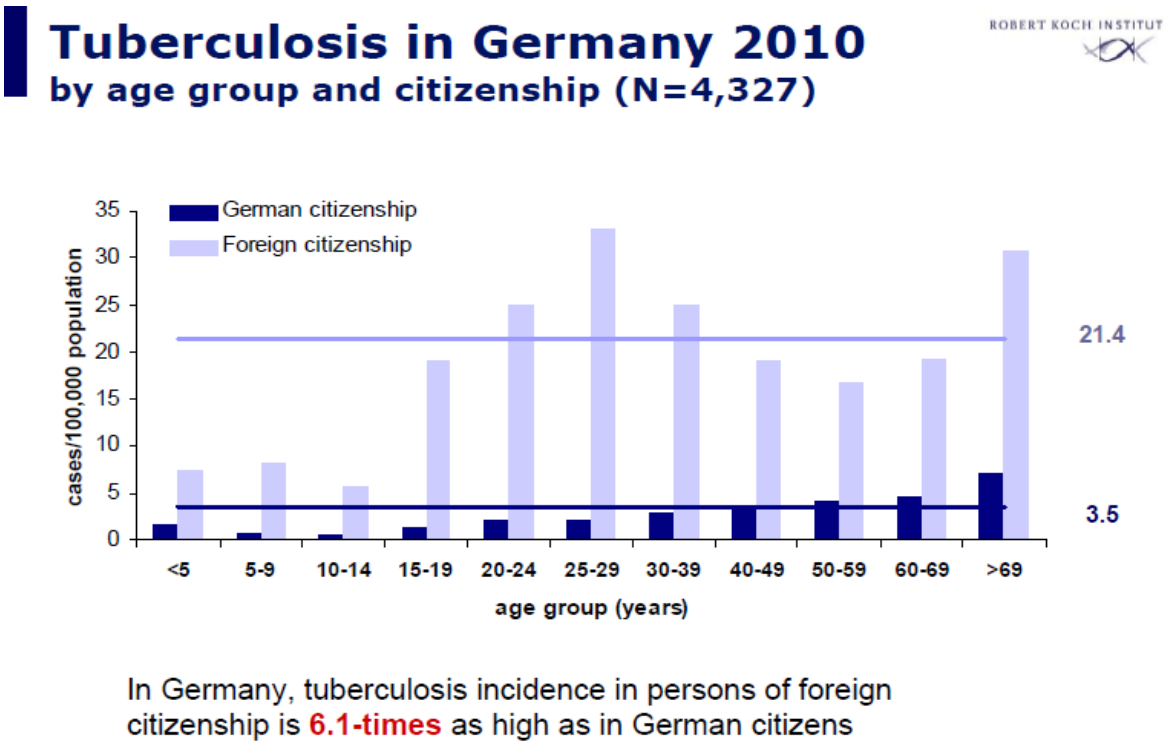
Germany, a low-incidence country has a decreasing trend for TB overall, but the incidence is above-average in large cities including Frankfurt, Hamburg and Berlin **(Diel, 2004)**. An increasing number of persons belonging to the high risk groups concentrate in big cities in hope of work and this is the reason why main German cities have higher TB incidence **(Bothamley, 2008)**.

The question arises on how to detect this disease early enough and to treat it before becoming a major health burden. In migrant populations it can be difficult to do screening early and annually. The time it takes to detect the disease in this population takes several years as this population travels back and forth to their country of origin and may become re-infected on their return to the host country **(Vos, 2004)**.

Germany is one of several countries in Europe, for example, where migrants although illegal are not deported if they are suffering from TB and disclosure to Federal officials is not compulsory **(Heldal, 2008)**.

Among the German-born population TB incidence increases with age furthermore, foreigners have 6 times higher incidence of TB compared to Germans. Adult males are mainly affected as illustrated in **Table 1**.

TABLE 1. TUBERCULOSIS IN GERMANY (RKI, 2010)



3. MIGRATION

Migrant health and the need to develop new strategies was the focus in 2007, with migrant health on the European Union agenda. In 2008, the World Health Assembly recommended that for tuberculosis control it was essential *"to formulate and implement strategies for improving the health of migrants"* **(Blumberg, 2010)**. Therefore migrants, who are a special risk group, are the focus of this current study.

Migration is mainly driven by warfare, civil unrest, violation of human rights, natural disasters and economic incentives or other incentives such as seeking education. Another reason for people to migrate is to meet a demand for specialized skills, labor work force, educational experience, language, and human resources. Migration from poor countries, where the burden of TB is high, to rich countries such as those with low TB incidence is a matter of national and global concern for TB control. Although migrants have rights to health coverage, in order to protect their own citizens and economies, Governments enforce immigration laws and policies for stricter border control. As mentioned earlier, migration occurs due to low birth rate in high economic countries and the need for skilled workers. However, in Germany, low-skilled migrants of Romas, Turks and Bulgarians who wish to survive enter the country too.

Of interest, the largest proportion of third country nationals (citizens not belonging to EU-27) who reside in EU come from Turkey, Albania or Ukraine, the second group from Africa (mainly North Africa: Morocco or Algeria), third from Asia (mainly southern or eastern Asia especially from China or India), followed by the Americas (Ecuador, Brazil, Columbia) and Oceania. The Turkish citizens were the largest non-nationals in EU followed up by Romanians and the latter keep increasing **(Eurostat, 2011)**.

European Union (EU) accession took place in 2004 and then came the influx of Eastern Europeans. Of the EU-27 countries, the United Kingdom, Spain, Italy, Germany and Switzerland ranked in descending order of those countries that accepted the majority of immigrants. The immigrants into EU were more men and

younger population. In 2009, three countries, the UK with 566,500 cases, Spain 499,000 cases and Italy with 442,900 cases comprised almost 50% of total EU Member States immigrants. In descending order in terms of the largest non-nationals who lived there, Germany, Spain, the UK, Italy and France comprised 77.4% of those living in EU-27 **(Table 2)**.

TABLE 2. IMMIGRATION BY MAIN CITIZENSHIP GROUP 2009 (EUROSTAT, 2011) (ACCESSED, JAN 2013)

	Total immigrants (1 000)	Nationals		Non-nationals					
				Total		Citizens of other EU Member States		Citizens of non-member countries	
		(1 000)	(%)	(1 000)	(%)	(1 000)	(%)	(1 000)	(%)
EU-27	*3 000*	*600*	*18*	*2 500*	*81*	*1 000*	*31*	*1 500*	*50*
Belgium	:	:	:	:	:	:	:	:	:
Bulgaria	:	:	:	:	:	:	:	:	:
Czech Republic	75.6	21.7	28.8	53.9	71.2	15.5	20.5	38.4	50.7
Denmark	51.8	19.3	37.2	32.5	62.8	16.2	31.3	16.3	31.4
Germany	347.3	79.2	22.8	267.2	76.9	126.8	36.5	140.4	40.4
Estonia	3.9	1.7	42.6	2.2	57.4	1.0	26.8	1.2	30.5
Ireland	37.4	14.7	39.4	22.5	60.1	16.0	42.7	6.5	17.4
Greece	:	:	:	84.2	:	29.5	:	54.6	:
Spain	499.0	29.6	5.9	469.3	94.1	144.9	29.0	324.5	65.0
France	:	:	:	:	:	:	:	:	:
Italy	442.9	36.2	8.2	406.7	91.8	136.1	30.7	270.6	61.1
Cyprus	11.7	:	:	:	:	:	:	:	:
Latvia	2.7	0.5	19.4	2.2	80.6	1.1	40.2	1.1	40.4
Lithuania	6.5	4.8	74.3	1.7	25.7	0.3	4.0	1.4	21.7
Luxembourg	15.8	1.1	7.1	14.6	92.7	11.9	75.7	2.7	16.9
Hungary	27.9	2.3	8.3	25.6	91.7	14.2	51.1	11.3	40.6
Malta	7.2	1.2	17.0	6.0	83.0	4.0	54.7	2.0	28.3
Netherlands	128.8	36.9	28.7	81.9	63.6	47.3	36.7	34.6	26.8
Austria	73.3	9.5	13.0	63.6	86.9	39.1	53.3	24.6	33.5
Poland	:	:	:	:	:	:	:	:	:
Portugal	32.3	18.0	55.9	14.3	44.1	4.0	12.4	10.3	31.8
Romania	:	:	:	:	:	:	:	:	:
Slovenia	30.3	2.9	9.6	27.4	90.3	1.9	6.2	25.5	84.1
Slovakia	15.6	1.2	7.7	14.4	92.3	6.9	43.9	7.6	48.4
Finland	26.7	8.6	32.3	17.8	66.7	6.5	24.2	11.3	42.4
Sweden	102.3	18.5	18.1	83.5	81.6	26.9	26.3	56.6	55.4
United Kingdom	566.5	96.0	16.9	470.5	83.1	167.4	29.6	303.1	53.5
Iceland	3.9	1.4	36.0	2.5	64.0	2.0	51.3	0.5	12.6
Liechtenstein	:	:	:	:	:	:	:	:	:
Norway	56.0	7.3	13.1	48.6	86.9	26.9	48.0	21.8	38.9
Switzerland	160.6	22.4	13.9	138.3	86.1	91.1	56.7	47.1	29.3

(1) EU-27 rounded totals are based on estimates; the individual values do not add up to the total due to rounding and the exclusion of the 'unknown' citizenship group from the table.
Source: Eurostat (online data code: migr_imm1ctz)

The Schengen Area currently consists of 26 states in Europe and all of which are EU members except for four: Iceland, Norway, Switzerland and Liechtenstein **(Dara, 2012)**.

It is estimated that migrant population make up nearly 1 billion, with three-quarters of them internal migrants and a quarter are international migrants. Majority of the latter move between developing countries and 70 million move from there to a developed country. Besides movement from south to north, migration from rural to urban can also occur within a country **(Blumberg, 2010)**.

In 2000, International Organization for Migration stated that > 150 million people are residents of a country that they were not born in. In 2010, the global number of international migrants increased to 214 million **(Dasgupta, 2005; Migration, 2011)**. WHO EU estimates that > 400,000 TB cases in Europe are mainly due to migrants.

Of the 82 million persons in Germany 9% are foreigners. Almost 50% of the total tuberculosis cases occur amongst foreigners and most were found in Turks **(Gilbert, 2009)**. Of these, data based on the country of birth indicate that 36.2% come from other countries while 8.4% originate from Former Soviet Union (3.7% from Russian Federation, 2.8% from Kazakhstan, 0.8% from Ukraine and 1.1% from the rest: Azerbaijan, Belarus, Georgia, Kyrgyztan, Moldowa, Tajikistan, Uzbekistan and the three Baltic States: Latvia, Lithuania, and Estonia.

Migration pattern changes and does have an impact on the epidemiology of TB in the host country and due to the in-and out-flow of migrants, it is inevitable that infectious diseases which respect no geographical borders, migrate too. Tuberculosis is such a disease **(Dara, 2012)**.

4. STUDY DESIGN

Information of Tuberculosis in Migrants was obtained from:

- WHO, ECDC, CDC publications
- German publications
- International publications and guidelines

A systematic literature search of the peer-reviewed literature was undertaken. PUBMED was the literature database selected in order to search for internationally published, peer-reviewed publications.

The search terms /keywords for the peer-reviewed literature search were:

- **Prevention AND Tuberculosis AND Migrants**
  and
- **Tuberculosis AND Migrants AND Germany**

A similar search was done with the corresponding German terms.

A PubMed systematic literature search was conducted to select peer-reviewed articles published within the time period selected from 1994 up to 19th October, 2012. The period prior to this had already been done by Dr. Dr. Oswald Bellinger for his MPH Thesis which served as a valuable resource. Articles prior to 1994 were excluded unless they were highly relevant regarding TB control strategies and pertaining to screening. In addition, international organizations publications were selected and some citations from the back of relevant articles were screened for likely inclusion too. Relevant articles that appeared in the media / press release were included as references too. Mainly English language papers were reviewed. When complete articles were not available, articles which had either an English or German abstract was also included. Two investigators scanned the titles for selection of relevant articles. After reading the abstracts, complete articles were obtained.

5. TYPES OF DIAGNOSTIC TOOLS AND SCREENING METHODS

The International Union Against Tuberculosis and Lung Disease states that in each country, every person should have access to diagnosis and free treatment of tuberculosis and undocumented migrants cannot be deported until treatment is complete in order to ensure not only public health safety but to prevent racism too**.**

Bacille Calmette-Guerin (BCG) is a vaccine for TB and it is usually given to infants and children in countries where TB is endemic, and is protective for immigrants from high-incidence countries who move to low-incidence countries and in addition for HCWS staff who work with drug-resistant TB (MDR-TB) **(Reid, 2009; Abubakar, 2012)**.

Diagnosis

Clinical symptoms of TB can be diagnosed by a physician that includes the following **(Reid, 2009)**: persistent cough that lasts 3 weeks or more, pain in the chest, coughing up blood or sputum, weakness or fatigue, weight loss, no appetite, chills, fever and sweating at night.

Diagnostic Tools

Briefly, for active tuberculosis the following tests are available: Chest radiograph (CXR), sputum culture (3-6 sputum samples), acid-fast staining, amplification tests and immunological tests - molecular assays (Gene Xpert, other PCR assays, and Line Probe Assay) **(Dasgupta, 2005)**.

Sputum Smear Microscopy

This came into use 100 years ago and is the standard diagnosis test recommended by The WHO. However, the test is slow and the results come out in several weeks, with false negatives, and data on drug susceptibility is lacking. So if a patient is indeed positive unknowingly this patient may transmit the disease to others during this period. A novel, rapid diagnostic test, Xpert, which detects resistance to rifampicin was approved by WHO in 2010 and 26 countries have used it in 2011 **(Rowland, 2012)**.

Sputum Culture

When culture confirmation is lacking, 'cases meeting the following criteria: a) a clinician's judgement that the patient's clinical or radiological signs are compatible with tuberculosis and b) clinician's decision to treat the patient with a full course of anti-tuberculosis treatment' **(French, 2007)**.

Tuberculosis cases are mainly diagnosed clinically by the patient's physician, next confirmed by the laboratory culture isolation of *M. tuberculosis complex* or microscopy detection of acid-fast bacteria in the sputum and a positive PCR of the specimen with drug susceptibility testing for resistance strains **(RKI, 2010)**. Screening via sputum culture is a more specific test with less number of false positives **(Dasgupta, 2005)**.

Chest radiography

Chest radiography screening results for active tuberculosis disease varies depending on place of testing (prior to, at or after entry), and if the migrant comes from a high-prevalence country. However, CXR does not pick up extra-pulmonary TB **(Erkens, 2008)**.

Furthermore, in order to determine the cause of the disease two tests detect tuberculosis bacteria: Tuberculin skin test (TST) and Blood tests. If the results are positive, it only indicates that the person has been infected with the bacteria, and not necessarily with latent bacteria or active TB disease. In order to confirm this, one uses the CXR test and takes a sputum sample for further bacterial analysis.

Tuberculin Skin Test (TST)

This test is also called the Mantoux tuberculin skin test whereby tuberculin (a fluid) is injected into the lower part of the arm and the person is required to have a trained HCW to test the skin reaction for the size of swelling, raised and hard skin results, between 48-72 hours, taking into account the person's risk factors and if already actively infected, their TB disease progression too. If the TST is positive, it confirms that the person was infected with TB and must do further blood tests, in order to confirm if the person has either active TB disease or latent TB. On the

other hand, if the TST is negative, it means that the person was not responsive to the TST test and one could rule out LTBI and TB disease **(Reid, 2009)**.

Blood tests for TB confirmation (IGRAs)

The interferon-gamma release assays (IGRAs) are the blood tests that reveal how the patient's immune system has reacted to the invasion of the TB pathogen. There are two IGRAS that have been approved: QuantiFERON-TB Gold In-Tube test (QFT-GIT) and the T-SPOT.TB test (T-Spot). A positive IGRA indicates that the person has been infected with the TB bacilli and other tests are needed to confirm if the person has active TB disease or LTBI. On the other hand, if the IGRA test is negative, one could rule out LTBI and TB disease **(Reid, 2009)**.

The QuantiFERON-TB Gold In-Tube (QFT-GIT assay) detects interferon-gamma which is released by infected cells in presence of secreted *Mycobacterium tuberculosis*–specific early protein antigens. As QFT-GIT is independent of prior-BCG vaccination or non-TB bacteria, it has higher specificity than TST test in detecting LTBI **(Mulder, 2012)**.

Confirmed Diagnosis

In order to confirm the diagnosis of active TB diagnosis – any one of the following few criteria have to apply, and these methods are utilized for TB screening in migrants **(Marks, 2000)**:

1. Positive culture of Mycobacterium tuberculosis (Mtb) is the golden standard to detect TB disease
2. Positive direct smear for acid-fast bacilli (AFB) and the patient is not 'atypical'
3. Histopathological report of caseating granulomas or TB findings
4. CXR pulmonary infiltrate that regressed after anti-TB drug treatment and is used in combination with symptom screening
5. A positive TST, clinical features of extrapulmonary-TB and response to treatment. After a positive TST, CXR is used. TST is used to identify LTBI but TST is less specific as it cross-reacts with atypical bacteria and BCG antigens found in those vaccinated from high-incidence countries. Therefore TST is also used in combination with CXR too (as proof of previous TB infection) to detect LTBI.

6. Interferon gamma release assays (IGRAs) are now used for LTBI and more applicable for migrants as they do not cross-react with BCG and only a little with atypical mycobacteria.

With regard to screening tools, they are characterized as having sensitivity or specificity. Definition of Predictive Value of a positive finding is the probability that a positive test result reflects the true condition. Chest radiograph and TST have high sensitivity but low specificity for pulmonary-TB **(Rieder, 1994)**.

In Germany, for data analysis and reporting, the results are faxed within 24 hours by the clinician to a laboratory and simultaneously the Local Health Authority is notified and receives follow up confirmatory laboratory results. The Local Health Authority notifies the State Health Department which in turn notifies Robert Koch Institute which reports annually to the European Centre for Disease Prevention and Control (ECDC), the WHO Regional Office for Europe. Reporting uses key variables of TB cases which are collected: age, sex, country of birth, prior treatment, start of treatment, major site of disease, positive acid fast bacteria (AFB) microscopy result, culture and drug susceptibility testing results and treatment outcome **(RKI, 2010)**.

Screening Programs & Location

The purpose of medical screening is to determine if a person has a disease for preventive measures as the person may not be aware of their illness and may not have symptoms yet of the disease **(Rieder, 1994)**. The reason to screen is due to the increase in TB rates in new arrivals and for immigration purposes **(Lillebaek, 2002)**. Screening is done for a common and treatable disease and it should be inexpensive, easy, causing no discomfort with high sensitivity and specificity **(Dasgupta, 2005)**.

For TB control, screening is targeted on the following group **(Rieder, 1994; (Pareek, 2012)**:

1. Groups that have a high risk for TB and who need a cure (with active TB)
2. Groups who would develop TB in the absence of a preventive intervention (with LTBI)

Questions remains: which groups to target? When should screening be conducted? What type of screening tools to use?

Screening is done mainly to detect active disease before it can spread to others in the general population. It can take place at different locations: pre-departure, at entry or after arrival **(Abubakar, 2012)**.

Criteria for screening for example would be, if they originated from high-TB incidence countries, temporary versus permanent residents, type of HCW's occupations **(Alvarez, 2011; IOM, 2011)**.

Screening strategy was defined as '*the set of regulatory actions and regulations that act to regulate the screening of individuals for the presence of a disease".* The six categories are **(Klinkenberg, 2009)**:

1. Pre-entry/pre-migration screening
2. Port of arrival screening
3. Reception/holding/transit center screening
4. Community post-arrival screening
5. Occasional screening
6. Follow-up screening

Contact tracing (CT) can also be considered as a screening method in in order to reduce further transmission of Latent TB infection in migrants **(Mulder, 2009)**.

6. RESULTS OF THE SYSTEMATIC LITERATURE SEARCH ON TB CONTROL STRATEGIES AND SCREENING IN MIGRANTS

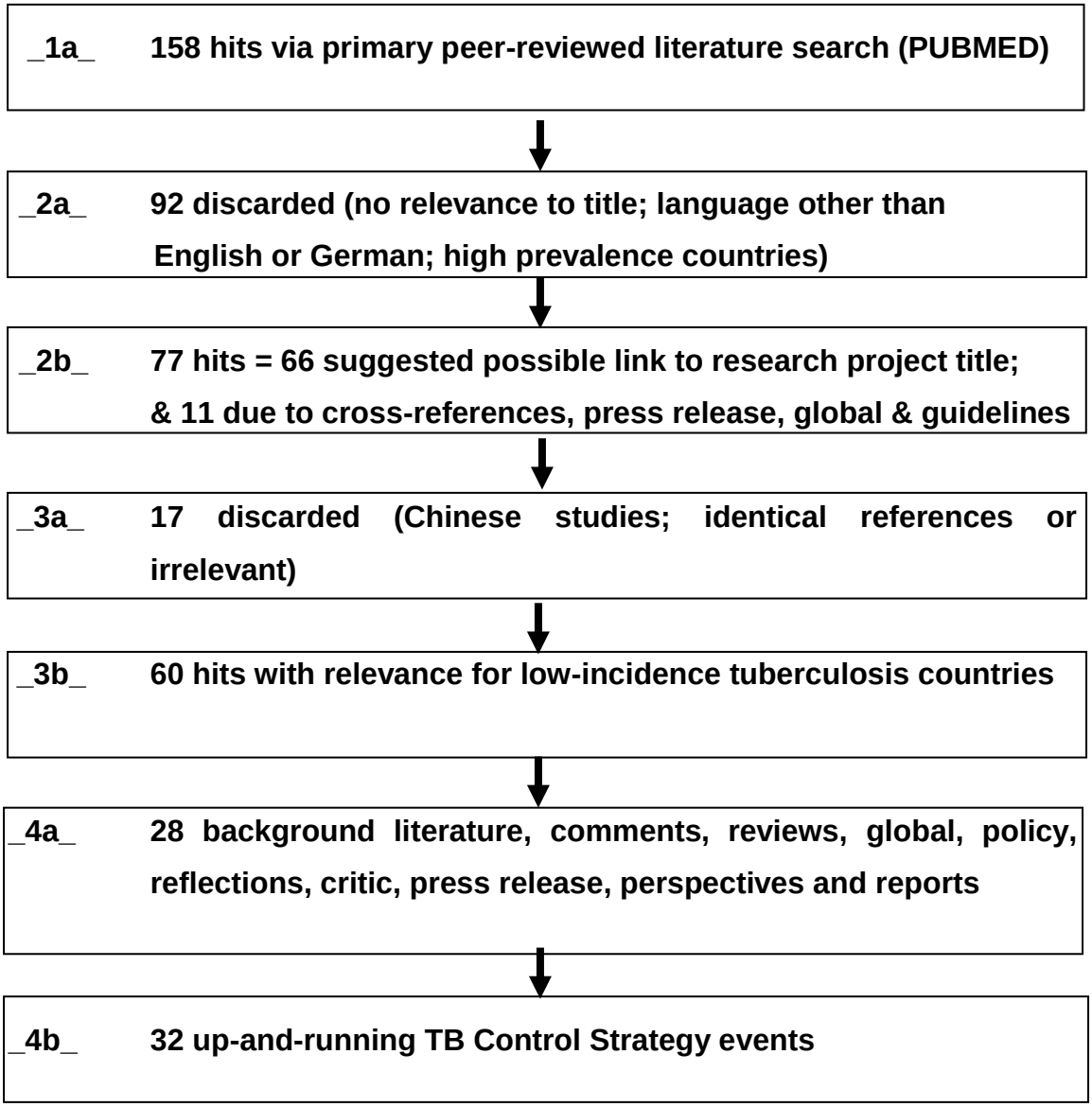
The compilation of the data from the systematic review of the 60 articles gives an outline on the type of publication, the country where the study was undertaken, an overview of the types of screening methods used, and/or point of location for the screening method, the strengths and limitations of each study, and future prospects for TB control strategies **(Appendix, Table 9)**.

The Flow Diagram for TB Control Strategies events illustrated in **Chart 1,** indicates that the articles which were mainly in English had relevance for low-incidence TB countries. Of the 60 articles selected in this systematic search, many of the articles were from individual countries in Europe that bear the major burden of the influx of migrants in decreasing order: The UK, Germany, Netherlands, Denmark, France, Switzerland, Italy, Norway & Austria. On the other hand, 22% of the articles originated from USA, Australia, Canada and New Zealand **(Appendix, Table 9)**.

The citations mainly spanned the years 2001 to 2007 with an average of 3 studies each year on this topic, however, from 2008 to October 19th, 2012 there were double number of citations, at 7 studies / year indicating that due to globalization and migrant movement from high-incidence countries, TB disease control is an important issue for low-incidence Western countries. Those countries that bear the burden of TB disease from migrants publish more on this topic **(See Chart 1 and Appendix, Table 9)**.

There were several types of references: editorial comments, perspectives, reflections, theory, supplement article, policy, simulation, press release**,** critic and addressing controversial issues**,** task force or workshop recommendations or statements**,** review articles**,** descriptive analysis**,** surveillance data analysis, global reports and a fact sheet **(Appendix, Table 9)**.

CHART 1: FLOW DIAGRAM FOR TB CONTROL STRATEGY EVENTS



Screening methods

The screening methods used in the study were overall the standard methods for screening. Most studies used a combination of screening tools; BCG, DOTS Strategy **(Schwartzman, 2005)**, however, some studies used a single screening method: clinical symptoms **(Gagliotti, 2006)**, CXR or mobile units **(Hargreaves, 2009; Das, 2006; MacPherson, 2006; Kehr, 2012; Vos, 2004)**, sputum -smear, TST **(Cain, 2008),** culture confirmation, and IGRA and QFT-GIT **(Mulder, 2012)**,

contact tracing, RFLP screening (**Heldal, 2003; Lemaitre, 1998; Escombe, 2008)**.

Diagnostic tools: clinical symptoms, CXR, sputum smear analysis, TST, IGRAs:

The minimum standard for active case finding is to look out for symptoms, those with an abnormal CXR send their sputum for analysis and then screen all sputum smear positive TB cases **(Bothamley, 2008)**.

Active TB can be ruled out by physician examination, clinical symptoms and CXR. However, with a TST positive skin reaction of > 15mm, then chemoprophylaxis is required with rifampicin (RMP) and isoniazid (INH) for 3 months. When culture or biopsy (lymph node or bronchial biopsies) are negative then diagnosis is based on clinical, radiological and epidemiological grounds. Smear positive cases does transmit TB infection **(Valin, 2002)**.

In their paper, Abubakar, et al., further outline the methods and specify the diagnostic accuracy and cost effectiveness of diagnostic tools used for screening of migrants and states the sensitivity and specificity of each of the screening tests which is shown in **Table 3**.

Chest radiograph abnormalities are a risk factor and predictor of TB disease and therefore this is an important risk group for TB intervention. Fibrotic lesions are a result of healed TB and can reactivate later **(Erkens, 2008)**.

Overall, studies from Europe, Canada and the USA indicate that CXR type of screening method is not cost-effective. Tuberculosis case detection on the other hand, is better accurately diagnosed with sputum smears and culture compared to molecular tests **(Erkens, 2008)**.

The Tuberculin skin test and IGRA (QuantiFERON or TSPOT.TB) are tests for latent tuberculosis. When QFT-GIT test is used on newly arriving migrants and the result is positive, than one can consider this new risk group for prophylactic treatment. For recently TB-infected-HIV-negative patients who show abnormalities in CXR, the Dutch treat either 6 months with daily isoniazid or 3 months with daily isoniazid *and* rifampicin **(Mulder, 2012)**.

TABLE 3. DIAGNOSTIC ACCURACY AND COST EFFECTIVENESS OF DIAGNOSTIC TOOLS FOR TUBERCULOSIS SCREENING OF IMMIGRANTS (ABUBAKAR, 2012).

Diagnostic Tool	Diagnostic Accuracy	Cost Effectiveness
Latent tuberculosis		
Tuberculin skin test		Screening less cost effective than single IGRAs, except as part of a 2-step approach
	Sensitivity: 77% (95% CI, 71%-82%)	
	Specificity: 97% (95% CI, 95%-99%), non-BCG vaccinated populations	
IGRA		Linas et al report that IGRAs are more cost effective; UK NICE guidelines identified a 2-step approach as the most cost-effective screening method. Other cost-effectiveness analyses support IGRAs as a more efficient tool for screening in Germany, France
	QuantiFERON	
	Sensitivity: 76% (95 CI, 72%-80%)	
	Specificity: 98% (95% CI, 96%-99%)	
	TSPOT.TB	
	Sensitivity: 90% (95 CI, 86%-93%)	
	Specificity: 93% (95% CI, 86%-100%)	
Active Tuberculosis		
Chest Radiograph		The main tool used by most low-tuberculosis-burden countries to screen immigrants; conflicting cost-effectiveness data largely determined by the underlying prevalence of tuberculosis in screened groups
	Sensitivity: 59%-82%	
	Specificity: 52%-99%	
Smear and culture		Increased case detection as part of package ot tests in pre- and postentry screening
	Smear	
	Sensitivity: 50%-80%	
	Specificity: 95%	
	Culture x 3	
	Sensitivity: 80%-100%	
	Specificity: 98%	
Molecular assays		Trial and cost-effectiveness data for immigrant screening limited; potentially cost effective as part of a diagnostic algorithm where individuals are first tested with smears
	Gene Xpert	
	Sensitivity: 90%	
	Specificity: 99%	
	Other PCR assays	
	Sensitivity: 50%-95%	
	Specificity: 98%	
	Line Probe Assay	
	Sensitivity: 82%-100%	
	Specificity: 92%-100%	

Abbreviations: CI, confidence interval; IGRA, interferon-γ release assay; NICE, National Institute for Health and Clinical Excellence; PCR, polymerase chain reaction.

***Defined using sensitivity and specificity. Presented as either a full range from published studies or, where a systematic review is available, a pooled point estimate with 95% CIs.**

The sensitivity and specificity of the diagnostic tools for tuberculosis: CXR, microbiological smear-sputum and culture, PCR amplification tests, immunological tests like TST, serology and cell-mediated immunity**,** are shown in **Table 4** below: **(Dasgupta, 2005)**.

TABLE 4. SENSITIVITY, SPECIFICITY AND POSITIVE PREDICTIVE VALUES (PPV) OF COMMONLY USED TESTS FOR THE DIAGNOSIS OF TUBERCULOSIS (TB) DISEASE (DASGUPTA, 2005).

Test	**Chest radio-graphy**	**Microbiological**			**Amplification**	**Immunological**		
		Smear	**Single Culture**	**Three cultures**	**PCR**	**TST**	**Serology**	**Cell-mediated immunity test**
Sensitivity, %								
Pulmonary TB Overall	59-82	50-80	80-85	80-100	50-95	53-90	21-90	53-77
Smear positive	80	100	85-96	90-100	95	53-73	45-96	
Smear negative	60	0	50	80	48-53	90	16-97	
Specificity, %	52-99	95	98	98	98	5**	80-100	64-100
Positive predictive value* %	2.9	11.6	29.3	31.3	26.9	<1	5.2	3.5

TST tuberculin skin test*: calculated for 1% prevalence of active TB using the mid-point of the range of sensitivity and specificity for each test; ** the specificity of positive TST is to distinguish active TB disease from latent TB infection.

IGRAs, are new T-cell interferon-gamma release assays which are better than TST in detecting contacts with a risk for TB e.g. LTBI persons with HIV-infection. One uses IGRA to confirm LTBI on those willing to be treated for 6-9 months regimen therapy with INH. Now there is evidence of resistance and so the physician has to explore with other therapeutics or use shorter regimens **(Bothamley, 2008)**.

Screening location & selection of target groups to screen

There was no consistency in the point of location of the screening methods used by the different countries **(Alvarez, 2011; Pareek, 2012)**.

It is difficult to compare screening programs as reasons for screening vary from country of origin, migrant class, occupation; migrant demography (age, source and duration of stay); and the reason for immigration screening (refugees, asylum, worker). For example, screening on the basis of TB incidence in country of origin (all countries or those outside EU, N. America, Australia and New Zealand); or which target group to screen (LTBI mainly for asylum seekers and refugees; and/or for those seeking immigration status) **(Alvarez, 2011; IOM, 2011)**.

Tables 5, 6, 7 and 8 give an overview of the results of different types of screening programs, in different countries, as stated by several authors in their citations.

TB control in Europe and international migration is depicted in **Table 5**: target groups selected for screening were foreign workers, asylum seekers, all entering foreigners; time of screening: at entrance, before residence, before employment or variable); type of screening system: active or passive; and the specific method used: radiography or TST (**Rieder, 1994)**.

TABLE 5. TUBERCULOSIS CONTROL IN EUROPE AND INTERNATIONAL MIGRATION (RIEDER, 1994).

Table 2. – Tuberculosis control among foreigners; in all countries, some refugees might be screened before entrance, if the medical procedures are organized through the International Organization for Migration

Country	Screening system	Method used for screening	Target group for screening	Time of screening	Utilization of preventive chemotherapy	Notification system
Austria	Active	Radiography Tuberculin test	Foreign workers (Asylum seekers)	At entrance	Contacts Children Adults	Mandatory for physicians
Belgium	Active	Radiography	Asylum seekers Foreign workers	At entrance	Fibrotic lesions	Mandatory for physicians
Czech Republic	Active	Radiography Tuberculin test	All entering foreigners	Before residence	Contacts Children	Mandatory for physicians
Denmark	Passive				Not used	Mandatory for physicians
Finland	Active	Radiography	Asylum seekers Foreign workers	At entrance	Children	Mandatory for physicians and laboratories
France	Active	Radiography	All entering foreigners	At entrance	Children	Mandatory for physicians
Germany	Active	Radiography	Asylum seekers	At entrance (asylum seekers)	(Children)	Mandatory for physicians and laboratories
		Tuberculin test in children	(Foreign workers)	Before residence (foreign workers)	(Adults	
Greece	Active	Radiography (Tuberculin test)	Asylum seekers Foreign workers	At entrance Before employment	Contacts Children	Mandatory for physicians
Hungary	Active	Radiography	Asylum seekers Foreign workers	At entrance	Not used	Mandatory for physicians
Iceland	Active	Radiography Tuberculin test	All entering foreigners	At entrance Before residence	Children Adults	Mandatory for physicians and laboratories
Ireland	Passive	Radiography Tuberculin test	All entering foreigners	Variable	Children Adults	Mandatory for physicians
Italy	Active	Radiography	Foreign workers	At entrance	Children Adults	Mandatory for physicians
Israel	Active	Radiography Tuberculin test	Some immigrants	After entrance	Contacts	Mandatory for physicians
Luxembourg	Active	Radiography Tuberculin test	All entering foreigners	At entrance Before residence	Contacts Children	Mandatory for physicians and laboratories
Netherlands	Active	Radiography (Tuberculin test)	Asylum seekers Foreign workers	At entrance Before residence	Contacts Children	Mandatory
Norway	Active	Radiography Tuberculin test	All entering foreigners	After entrance Before residence	No policy	Mandatory for physicians and laboratories
Poland	Passive					
Portugal	Active	Radiography Tuberculin test	Asylum seekers Foreign workers	At entrance Before residence	Contacts Children	Mandatory for physicians
Slovak Republic	Active	Radiograpy Tuberculin test	All entering foreigners	At entrance	Contacts Children Adults	Mandatory for physicians
Slovenia	Active	Radiography Tuberculin test	All entering foreigners	At entrance	Children Adults	Mandatory for physicians and laboratories
Spain	Active	Radiography Tuberculin test			Contacts Children Adults	
Sweden	Active	Tuberculin test Radiography	Asylum seekers Some foreign workers	At entrance		Mandatory for physicians, voluntary for laboratories
Switzerland	Active	Radiography (Tuberculin test)	All entering foreigners outside EU and EFTA*, North America, New Zealand and Australia	At entrance Before residence	Contacts Children Adults	Mandatory for physicians and laboratories
United Kingdom	Active	Radiography	All entering foreigners	At entrance Before residence	Children Adults	Mandatory for physicians (Laboratories)

*: EU European Union; EFTA: European Free Trade Association.

With reference to screening locations, countries combine screening programs in different ways below **(Abubakar, 2012)**:

***Pre-entry screening*:**

Screening, diagnosis and treatment can take place prior to departure in the original country but this is not applicable in temporary visitors or illegal immigrants who enter the host country. United States and Israel adopt this strategy and there is a follow-up in the host country. Australia, Canada and more recently UK also adapt this approach termed as immigration screening strategy **(MacPherson, 2006)**. Sputum cultures could further enhance the screening system together with chest radiography and smear testing**.**

At entry screening:

In the United Kingdom (UK), key airports screen entrants at port of entry**.** Screening with tuberculin skin and followed by IGRAs or IGRAs alone were similar in terms of cost-effectiveness.

Post entry screening:

After entry screening systems are linked to other services whereby active cases are diagnosed and treated and therefore loss to follow-up occurs at a low rate. In implementing post entry screening the UK does not conform to its national guidelines and gave a poor yield of tuberculosis, however, Dutch post entry programs had better results.

In **Table 6,** point of screening giving country of origin (pre-arrival), on arrival and after arrival screening is shown below:

TABLE 6. A COMPARATIVE EXAMINATION OF TUBERCULOSIS IMMIGRATION MEDICAL SCREENING PROGRAMS FROM SELECTED COUNTRIES WITH HIGH IMMIGRATION AND LOW TUBERCULOSIS INCIDENCE RATES (ALVAREZ, 2011).

Country	Immigrants			Refugees/Asylum seekers		
	Country of origin	On arrival	After arrival	Country of origin	On arrival	After arrival
United States	+	-	+	+	-	+
Germany	-	-	-	-	-	+
France	+	-	+	-	-	+
Canada	+	-	-	+	-	+
United Kingdom	+	+	+***		+	
Australia	+	-	-	+	-	+
Israel	+*	-	-	-	-	-
Jordan	+**	-	+	-	-	+
Additional Countries						
Norway	-	+	+	-	+	-
New Zeeland	+	-	+	+	-	+
Sweden	-	-	+	-	-	+
Switzerland	-	-	-	-	+	-
Netherlands	-	-	+	-	-	+

+ = Yes and - = No

- *** Ethiopia is the only country where Israel is performing CXRs and TST (1st step) for screening in the country of origin**
- **** Jordan does screen applicants from Sri Lanka, Indonesia and the Philippines abroad**
- ***** For programme refugees**

The location and selection criteria for screening immigrants for latent tuberculosis in selected OECD countries is illustrated in **Table 7 (**see **Appendix)**. This Table gives not only the timing of screening and criteria by which migrants are selected for latent tuberculosis screening, but in addition, pre-departure screening data as a point of screening location. In addition, the current screening practices for active and latent tuberculosis screening in industrialized OECD countries is shown in **Table 8 (**see **Appendix) (Pareek, 2012)**.

7. DISCUSSION - STRENGTHS AND LIMITATIONS OF TB SCREENING AND FUTURE PROSPECTS

Screening methods and point of screening location used for screening of migrants and implementation of policies were heterogeneous in different Western European countries.

Using the targeted screening program approach of high-risk groups like au-pairs **(Geerdes-Fenge, 2011)** or with mobile CXR screening units for active case-finding **(de Vries, 2007; Jit, 2011; Kehr, 2012)** or for migrants coming from high-incidence countries or foreign-birth origin **(Coker, 2001),** was more effective than screening all migrants or the general population. However, the high-turnover in shelters could make identification difficult **(Valin, 2005)**.

Active screening was found to be better than passive screening with letters giving information and advice as this may induce under-reporting and data obtained depends on quality of information **(Anderson, 2007)**.

Immigration screening policies is in tune with global health strategies and therefore can work in partnerships with the Public Health sector **(MacPherson, 2006)**. On the other hand, immigration screening for resident status once on-entry overlooked the re-entry of these ethnic groups who return to their country of origin only to be re-infected again **(Dasgupta, 2005; Littleton, 2008)**.

Although some countries adhere to mandatory testing, it was found to be ineffective as a screening choice and cost-effectiveness was doubtful, and in addition, it violated international standards **(Coker, 2001)**.

Surveillance systems and contact tracing were effective in identifying index cases and preventing further transmission **(Geerdes-Fenge, 2011; Lemaitre, 1998; Rieder, 1994)**.

Initiatives of collaboration between PH officials and management workers can be beneficial to track TB infected-persons for early treatment **(Kehr, 2012)**. Although both benefited, a high turnover of the migrant populations in factories makes this study group difficult to follow **(Kim, 2003)**.

Points of location for screening:

Pre-entry screening protected the host population, strengthened laboratory diagnosis and was deemed a useful tool for LTBI detection and early treatment however, contact tracing was more cost-effective **(Dasgupta, 2005; Mulder, 2009, King, 2011)**. In 98% of the pre-immigration screening results were normal but after one year some developed pulmonary TB as limited susceptibility testing was done overseas and so MDR-TB cases were missed on entry **(King, 2011)**. Moreover, systematic review of screening programs indicated there was no difference in entry-screening, just-after-arrival or follow-up screening but there were differences in risk factors of migrant groups **(Klinkenberg, 2009)**.

Screening at entry ports was found to be ineffective at detecting TB cases **(Hogan, 2005)**. Furthermore, screening early by CXR scanning prior-to or at-entry can miss out on early stages of TB and this has a limited impact on TB incidence, and LTBI goes undetected as TB is a disease with a long incubation period **(Littleton, 2008; Das, 2006; Watkins, 2002)**. The issue of TB latency and reactivation was also observed in another study where **i**ncidence of TB was higher for decades due to reactivation, although entry screening and biannual volunteer follow-up was in place **(Vos, 2004)**.

With post-migration screening, 66% were diagnosed in a doctor's office rather than on single border screening and the latter would be the preferred choice **(Littleton, 2008)**. Due to the screening process per se, often what is missing is the early diagnosis of TB with reference to detecting the symptoms in high risk groups and when TB gets diagnosed late more transmission of disease occurs to others in close contact **(Geerdes-Fenge, 2011)**. In yet another case post-migration screening was found ineffective and follow-up screening gave low yields **(Marks, 2001; Erkens, 2008)**.

Nevertheless, with regard to pre-departure screening it appeared to be cost-effective for Australia, Canada, USA as these countries would not have to bear the burden of treatment and it protected their nationals. Some investigators found entry-screening useful, however, several other investigators indicated that this was a poor utilization of limited resource materials. Most of the investigators preferred

follow-up screening as being more effective as tuberculosis disease often appears 5 years later due to the issue of latency (see **Table 9**, **in Appendix**).

Screening tools:

In a comparative study of the recommendations in the national guidelines of 50 WHO countries almost all used TST and 54% together with CXR too, 72% with sputum culture and 50% used symptoms as screening method **(Bothamley, 2008; Geerdes-Fenge, 2011)**.

The choice and usage of different diagnostic tools was daunting with some countries using just one tool and others using a combination of tools. Sputum culture was found to be more effective than CXR. However, as TB occurs only after 5 years, and immigrants are healthy on entry therfore CXR at this time is not useful **(Dasgupta, 2005; Bothamley, 2008)**.

Newly arrived immigrants could be considered as a 'new risk group' as QFT-GIT assay screening showed progression to active TB within two years and those with a positive test were subjected to prophylactic treatment **(Mulder, 2012)**.

Usually there is limited transmission across migrant ethnic groups as there is poor integration between these groups. Molecular genotyping however, indicated recent transmission occurred as genotypes clusters were identical and in this study transmission from native Danes to migrants occurred **(Kamper-Jorgensen, 2012)**. RFLP was used for recent infection and it did detect outbreaks in shelters, hospitals and other settings and further transmission was prevented **(Heldal, 2003; Valin, 2005; Lemaitre, 1998)**.

Comparing and drawing a conclusion was difficult as wide variation was used for screening: various screening methods, choice of screening location, and selection of group-type to screen for the different studies in this systematic search. Some studies used heterogeneous data collection, for example a combination of estimates and exact numbers and the qualitative data was not separated from the quantitative data. In addition, participating countries provide voluntary information that was not subjected to validation. Variation exists with respect to the selection criteria (when TB incidence was used as a selection criteria there was wide difference in threshold numbers >20 cases / 100,000 versus > 500 cases /

100,000 cases), migrant subgroups, screening methods and tools used **(Gushulak, 1998; Heldal et al, 2008; Klinkenberg, 2009; Mulder, 2009; Migration, 2011;Pareek, 2012)**. In another study, with 18 selected countries, not one had the same screening method due to subtle cultural and political country differences **(Alvarez, 2011)**.

Due to the lower cut-off points for positive TSTs, higher LTBI was detected so interpretation of data results in these studies was variable **(Mulder, 2009)**. Criteria and definitions for yield and coverage was not clear and different diagnostic tools and strategies were used in different studies and countries making comparisons difficult **(Klinkenberg, 2009)**. Usefulness of doing TSTs on undocumented migrants is futile as it is difficult to get them for >1 time **(Wolff, 2010)**.

There was heterogeneity in TST cut off values in the different studies. TST interpretation was different and not modified with or without BCG between countries in a comparative study of the national guidelines recommendations of 50 WHO countries (TST cut off values: 5 mm without BCG, or 10mm or better 15mm with BCG) **(Bothamley, 2008)**.

Migration screening programs should be evidenced-based and efficient but there is a lack of solid evidence which explains why some countries have such different approaches. Co-operation among countries doing research in this field should focus on cost-effectiveness of screening people from high-incidence countries. Since the risk of TB transmission to host populations is in fact low, contact tracing of active cases and latent TB infection in migrants may be more efficient and cost-effective way of managing TB among migrant population. Further studies are needed before developing this as a country policy **(Migration, 2011)**.

Germany, Netherlands, France, Switzerland and Austria have borders in Europe that are more porous for the migrants to flow in and out as the countries are small and adjacent to each other and so rigid border control is more difficult. In addition, with the Schengen treaty, migrants from high-incidence countries can freely move within Europe. On the other hand, countries which are mainly surrounded by seas: USA, Australia, Canada and New Zealand, and more recently the UK, have fewer countries next to them and it would seem easier to adapt common strategies to curtail the entry of migrants, consequently, in these countries, stringent

immigration screening are in effect. In addition, a better tool for LTBI screening is needed, and also to determine if active TB is in legal versus illegal immigrants.

Tuberculosis, like any other emerging and re-emerging disease, does not respect geographical borders and so investment in Global TB prevention strategies is the key method for successful control, emphasized too by several of the investigators in this study. When compared to an individual country's TB control interventions Global tuberculosis investment in the long run appears to be more cost-effective. Unless more high and middle-income countries invest in this routine humanitarian action, the WHO's goal of total elimination of tuberculosis by 2050 will only be wishful thinking.

The recommendations for future improvement of TB control strategies in migrants most cited by the investigators from the 60 articles of the systematic search done in this study are the following **(**see **Table 9,** in **Appendix)**:

1. Investment in regional and Global TB control (17)
2. Target LTBI for screening and treatment, research, determine persistence of TB: reactivation of prior infection, transmission in host country, acquired infection due to home visits (17)
3. Treatment and/or preventive treatment – shorter and less toxic treatment regimens (16)
4. EASY access of migrants to health facilities and information, language support, ensure confidentiality, improved living conditions, transcultural outreach activities (16)
5. Research into new drugs, diagnostics and clinical screening and direct detection techniques, vaccines, operational research, drug susceptibility testing (9)
6. Educational interventions, TB awareness and stigma (7)
7. Better case-management, strengthen active case-finding and early diagnosis (6)
8. Networks and data exchange: laboratory, migrant TB-registries, genotypic & phenotypic (6)
9. Evidence-based approach for targeted screening of high-risk groups and focused interventions to detect TB (6)
10. Community-based health promotion initiatives (3)
11. Incorporate TB screening integrated into health system/doctor clinic practice (2)

12. Cultural & social sensitivity for compliance - barriers, risk factors, lifestyle (2)

Research studies into the cause and reactivation of LTBI in the host country would be useful. Several factors that need to be addressed: SES, conditions of living, stigmatization, unemployment, racial discrimination, other underlying diseases, genetic factors, poverty and malnutrition, stress, studies on immune system and how it reactivates TB. What is the public health response to the issue of latency, re-entry of migrants into their endemic countries and furthermore contacts with high risk groups?

Finally, besides screening country-specific community-based and health-promotion initiatives should be encouraged for TB prevention strategies and may turn out to be more useful and cost-effective rather than screening alone.

8. LIMITATIONS OF THE PRESENT STUDY

The limitation of this study is that it was not possible to access other search engine databases like The Cochrane Library, MEDLINE, EMBASE and Scopus. We used only PubMed but were unable to access the database of the German Institute of Medical Documentation and Information (DIMDI), which includes *Medline, Global Health, Embase, Biosis Previews, Embase Alert SciSearch, Cochrane CDSR, and Cochrane CDTR*).

The Definitions were obtained from different Reference articles and were either not reported clearly in studies or the same definition had a different meaning depending on how the authors defined their study.

9. SUMMARY

The overall picture that comes out of this study is the fact that screening is necessary but not sufficient as a strategy for effective tuberculosis control. Screening in combination with another country-specific, community-based health-promotion initiative is an effective strategy for tuberculosis control in migrants in low-incidence countries.

Due to the large variation of these studies there was no uniform strategy on which to form a solid comparison across Europe or worldwide. What is needed is more consistency and consensus in the choice of methods for screening, location of screening, use of diagnostic tools and its defined cut-off points, common definitions and criteria to base the study analysis on. This consensus would facilitate a more meaningful comparison within Europe and between the other OECD countries and world-wide.

Tuberculosis has a long incubation period and so to follow up its sero-conversion using just the diagnostic tools available may not be optimal. Other less expensive and less cumbersome methods may be worthwhile exploring: medical examination and detecting early clinical symptoms at the private physician office could be a better approach. Due to the nature of TB disease it may not permit a perfect identification of those who are likely to succumb to it, however, a combination of IGRA and education of migrants with regard to early symptoms of TB may prevent and control its transmission.

One needs to consider the global versus country versus migrant epidemiology of TB disease. Several strategies have been proposed by other investigators in this study and although investment in global control is attractive and has been cited the most, in reality this is not practical.

Country-specific community-based and health-promotion initiatives should be encouraged for TB prevention strategies and may turn out to be more useful and cost-effective. Involving other in-country partners, partnerships, stake holders, besides the Public Health sector to implement TB control strategies would be welcome: industries, the transport system, humanitarian organizations and

religious institutions, health insurance companies, restaurants, socially-minded university students, educators, healthy senior citizens, and wealthy philanthropists. Volunteers from the public sector could assist in community-based interventions as it would mean more hands are available to assist in TB control initiatives for migrants.

In Germany, information documentation could be in Arabic, Russian, English or in pictorial sans-words, besides the national language, German, in order to reach out to the migrants and educate them on TB diagnosis, treatment options and screening methods giving contact information for further help available, and ensuring confidentiality. These pamphlets or advertisement with free information, advice and contact could be posted inside the local U-Bahn, S-Bahn train stations and religious and/or humanitarian institutions. Some homeless have been observed daily early morning in local trains travelling to and fro, and could avail themselves of this service if they have symptoms of TB.

.

Migrants desperate for help usually seek humanitarian institutions and religious organizations. For example, a Catholic Church is Frankfurt, daily gives out free lunch soups to the homeless and migrants who are poor. Getting some of these migrants involved, who speak the same language to assist others on TB education and would enable them to reach out to other migrants. In reward, they could get free meals or transport coupons provided by philanthropists, companies or banks or Deutsche Bahn. The Public Health department could work in partnership with charity-based organizations and both parties would benefit.

In order to promote visibility of TB control in migrants, a popular German football world cup player could address the issue in migrant newspapers, the media and on posters posted in public places.

For Germany an effective strategy for TB control in migrants would be one that utilizes the screening method of clinical symptoms and IGRA which gives a high TB detection yield, and CXR in the case of symptomatic migrants, together with a specific in-country, community-based health-promotion initiative, for example,

partnerships with volunteers from the public sector to work hand-in-hand with the German Public Health institution on educational interventions.

Perhaps the following criteria could be adapted for Germany:

1. Target better selection of migrants to screen, as few have active TB on arrival – one needs to pick up imported latent TB cases.
2. Lower the threshold of TST so that people from more foreign countries are screened; this is potentially cost-effective relative to the number of active cases prevented.
3. Treat people at the early stage (identified on screening) to prevent them from developing serious illness and becoming infectious and transmitting TB disease to others.
4. Collaborate on research with other neighboring, low-incidence countries to better educate, optimize screening, case-detection and treatment efforts.
5. Collaboration between the Immigration department and Public Health institutes in sharing information, tracking and follow-up of migrants.

10. ACKNOWLEDGEMENTS

Sincere thanks go to **Prof. Dr. Dr. René Gottschalk, Director,** Amt für Gesundheit, Frankfurt, who encouraged and kindly allowed me to access the facilities for this study at his Division.

My gratitude goes to **Dr. Dr. Oswald Bellinger** at the Amt für Gesundheit, Frankfurt, for his astute insights into the research question and the global scope of the Tuberculosis field**.**

I am indebted to **Dr. Udo Goetsch** at the Amt für Gesundheit, Frankfurt, for his valuable suggestions, assistance with extraction of publications and prints of references on an ongoing basis during this study.

This MPH thesis made it to completion due to the enduring patience and continuous support I received from my husband, **Michael Thudt.** *Vielen Dank!*

11. DEFINITIONS

A homeless person is defined as a person who frequently uses day-care, night-care, residential, or other facilities for homeless persons **(de Vries, 2007)**.

A long-term migrant is defined as a subject who moves to a nation other than that of his/her usual residence of ≥ 365 days (the country of destination becomes his/her new country of residence) **(Dara, 2012)**.

A low domestic TB incidence rate is defined as a rate of sputum smear positive PTB of < 15 cases per 100,000 population as estimated by the World Health Organization (WHO) averaged over the years 2004, 2005 and 2006 **(Alvarez, 2011)**.

A short-term migrant is defined as a subject moving to a country other than that of his/her usual residence for a period ranging from ≥ 3 months to <12 months, except for holiday, visits to friends and relatives, business, medical assistance or pilgrimage **(Dara, 2012)**.

A TB case was defined as a bacteriological or clinical diagnosis of TB based on intention to treat. TB cases refer to TB cases as reported by the authors, which implies TB cases detected through screening by chest radiography **(Klinkenberg, 2009)**.

Asylum seeker: a person wishing to be admitted to a country as a refugee and awaiting decision on their application for refugee status under relevant international instruments **(Rieder, 1994)**.

Asylum seeker: persons seeking to be admitted into a country as refugees and awaiting decision on their application for refugee status under relevant international and national instruments. In case of a negative decision, they must leave the country and may be expelled, as may any alien in an irregular situation, unless permission to stay is provided on humanitarian or other related grounds **(Pareek, 2012)**.

Contact a person who may have been exposed to the index case during the infectious phase **(Mulder, 2009)**.

Contact person with relevant exposure to an infectious or potentially infectious index case **(Leitmeyer, 2011)**.

Countries categorization of those that screened selected legal immigrants: this group included those countries that screened specific categories of legal immigrants (irrespective of the category: examples included students and pre-employment screening of workers) if they met the specific country's screening criteria in terms of country of origin/TB incidence/age **(Pareek, 2012)**.

Coverage was defined as the percentage of the target group to be screened that was indeed screened **(Klinkenberg, 2009)**.

Coverage the proportion of investigated contacts (for LTBI) relative to the total number of listed contacts **(Mulder, 2009)**.

EEA indicates the European Economic Area **(Dara, 2012)**.

Elimination phase is said to have been achieved when the incidence of all forms of active tuberculosis has fallen below 1 per 100,000 populations per year **(Rieder, 1994)**.

Ethnic group based on the Office for National Statistics classifications **(French, 2007)**.

EU indicates the European Union, composed of 27 Member States **(Dara, 2012)**.

Europe indicates the WHO European Region, composed of 53 Member States, if not specified differently **(Dara, 2012)**.

Extensively drug-resistant TB (XDR-TB) TB caused by mycobacterial strains showing *in vitro* resistance to isoniazid and rifampicin plus any fluoroquinolone and at least one of the injectable second-line drugs – amikacin, capreomycin or kanamycin **(Dara, 2012)**.

Extra-pulmonary tuberculosis is tuberculosis disease at an extra-pulmonary site only **(French, 2007)**.

Fibrotic lesions are defined as well-delineated radiographic lesions compatible with healed tuberculosis **(Rieder, 1994)**.

Foreign-born citizen: a person who is a national of the state in which they are present but who was born in another country **(Rieder, 1994)**.

Foreigner is defined as a person who is not a national of the state in which he or she is present **(Rieder, 1994)**.

HCWs: any persons working in a healthcare setting (with patients or clinical specimens) **(Anderson, 2007)**.

High Incidence groups are population segments with an incidence clearly in excess of that in the general population **(Rieder, 1994)**.

Hospital any secondary or tertiary center providing in-patient care, excluding nursing homes **(Anderson, 2007)**.

Illegal foreigner / migrant: a person whose entry, stay or work in a host country is illegal **(Rieder, 1994)**.

Illicit drug user is one who regularly uses heroin or cocaine, or receives methadone replacement therapy **(de Vries, 2007)**.

Immigrants are defined by United Nations recommendations as 'persons who change their country of usual residence. A person's country of usual residence is that in which the person lives, that is to say, the country in which the person has a place to live where he or she normally spends the daily period of rest' **(Heldal, 2008)**.

Immigrants were defined as a heterogeneous group composed of people whose origins, reasons for migration and legal and economic status vary **(Heldal, 2008)**.

Index case(s): person or persons identified as the initial case(s) reported in a chain of infection or single case with no known secondary cases **(Leitmeyer, 2011)**.

Index case the initial patient diagnosed with TB **(Mulder, 2009)**.

Infection with M. tuberculosis is defined as the subclinical, latent infection with tubercle bacilli (by common understanding including all three species of the M. tuberculosis complex), manifested by a significant tuberculin skin test reaction without any sign of clinically and/or bacteriologically and/or radiologically active disease.

Infectious TB case all cases of respiratory (pulmonary or laryngeal) TB which are sputum smear-positive and culture-positive (if culture is available).

Legal immigrant: a person who moves to a country other than that of his or her usual residence for a period of at least a year, so that the country of destination effectively becomes his or her new country of usual residence. From the perspective of the country of departure, the person will be a long-term emigrant and from that of the country of arrival, the person will be a long-term immigrant **(Pareek, 2012)**.

Low-incidence countries are usually defined as countries with an incidence of TB below 20 per 100,000 population, low and intermediate TB incidence countries are defined as countries with fewer than 50 TB cases/100 000, according to WHO 2005 estimates, which includes all Western and most Central European countries (including 22 of the 27 EU countries), USA, Canada, Australia, New Zealand, Japan, Singapore and Israel **(Heldal, 2008)**.

LTBI treatment completion rate: the proportion of infected contacts that completed LTBI treatment relative to the total number of infected contacts that started LTBI treatment **(Mulder, 2009)**.

LTBI yield the proportion of LTBI cases detected among the total number of fully investigated contacts **(Mulder, 2009)**.

Migrant is an individual who changes his/her nation of usual residence **(Dara, 2012)**.

Migrant worker is a person who is to be engaged, is engaged or has been engaged in a remunerative activity in a State of which he or she is not a national (Art. 2 (1), International Convention on the Protection of the Rights of All Migrant Workers and Members of Their Families, 1990) **(Rieder, 1994)**.

Migrant a foreigner legally admitted and expected to settle in a host country. **(Rieder, 1994)** or United Nations defines a migrant as 'any person who lives temporarily or permanently in a country where he or she was not born, and has acquired some significant social ties to this country'.

Multidrug-resistant tuberculosis (MDR-TB) TB caused by mycobacterial strains showing *in vitro* resistance to at least isoniazid and rifampicin, the two most potent first-line drugs for TB treatment **(Dara, 2012)**.

Non Infectious all cases of respiratory (pulmonary and laryngeal) TB which have two consecutive negative sputum-smear and negative culture (if culture is available) results; extrapulmonary TB does not carry any risk for transmission.

Non-nationals are people who are not citizens of the destination country. Or a person who meets the refugee definition of the 1951 Convention related to the Status of Refugees and its 1967 Protocol, or of other relevant regional instruments. Or a person wishing to be admitted to a country as a refugee, and awaiting decision on his or her application for refugee status under relevant international instruments.

Potentially infectious TB case all cases of respiratory (pulmonary or laryngeal) TB which are sputum smear-negative and culture positive.

Prevalence was defined as the total number of patients diagnosed (either through screening or passive case finding) per 100,000 individuals screened on entry **(Erkens, 2008)**.

Preventive chemotherapy is defined as treatment of subclinical, latent infection with *M. tuberculosis* to prevent progression to active tuberculosis **(Rieder, 1994)**.

Pulmonary tuberculosis is defined as tuberculosis involving the lungs and/or trachea-bronchial tree, with or without tuberculosis at an extra-pulmonary site **(French, 2007)**.

Recent infection (synonymous with "tuberculin skin test conversion") is defined as a significant skin test reaction after documentation of a negative tuberculin skin test within the preceding 2 yrs. For practical purposes children with a significant

tuberculin skin test reaction size under the age of 15 years, without Bacille Calmette-Guerin (BCG) vaccination, and close contacts of sputum smear-positive cases under the age of 50 years with a significant tuberculin skin test, are also included in this group **(Rieder, 1994)**.

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. (Art.1 (A) (2), Convention relating to the Status of Refugees, Art. 1A (2), 1951 as modified by the 1967 Protocol) **(Pareek, 2012)**.

Screening strategy was defined as the set of regulatory actions and regulations that act to regulate the screening of individuals for the presence of a disease **(Klinkenberg, 2009)**.

TB incident potential transmission of TB identified, resulting in public health action **(Anderson, 2007)**.

TB yield the proportion of TB cases detected among the total number of fully investigated contacts **(Mulder, 2009)**. (TB yield **-** various articles used different definitions for yield **(Klinkenberg, 2009)**.

Yield was defined as the number of patients detected per 100,000 individuals screened (for entry screening) and per 100,000 screenings (for follow-up screening) **(Erkens, 2008)**.

The incidence rate was defined as the total number of patients diagnosed (either through screening or passive case finding) per 100,000 persons-years follow-up in the target population. Patients detected at entry screening or passively ≤ 5 months after entry were considered to be prevalent cases. All patients diagnosed 6-29 months after entry were considered to be incident cases **(Erkens, 2008)**.

TST conversion initially negative tuberculin skin test that becomes positive. A negative TST within the first 3 weeks after exposure should elicit a second TST at the latest 8 weeks after initial exposure. If the second TST stays negative, no further investigation is needed, suggesting no evidence for infection. A positive

TST within the first 3 weeks after exposure is considered a result of previous exposure or vaccination and therefore no further TST is needed **(Leitmeyer, 2011)**.

Tuberculosis case culture confirmed case: culture confirmed disease due to Mycobacterium tuberculosis complex (*M. tuberculosis, M. bovis or M. africanum*).

Tuberculosis refers to clinically and/or bacteriologically and/or radiologically active disease **(Rieder, 1994)**.

Undocumented migrant is a person who, owing to unauthorized entry or the expiry of his/her visa, lacks legal status in a transit or host country **(Dara, 2012)**.

Undocumented migrants also known as illegal aliens, illegal resident population, illegal immigrants, undocumented immigrants. Others have defined them as 'migrants who are in an irregular situation regarding their residence status' or a group about which little is known regarding demography and TB epidemiology **(Heldal, 2008)**.

World regions based on United Nations (UN) classifications, adjusted to take into account the global epidemiology of tuberculosis and migration patterns in Western Europe. For example, the five African regions defined by the UN were grouped into two, while North America and Oceania were grouped together based on the similar epidemiology of tuberculosis in these areas **(French, 2007)**.

12. APPENDIX

TABLE 7. LOCATION OF AND SELECTION CRITERIA FOR SCREENING IMMIGRANTS FOR LATENT TUBERCULOSIS IN SELECTED OECD COUNTRIES (PAREEK, 2012).

	Timing of screening			Criteria by which migrants are selected for latent tuberculosis screening						
				Type of immigrants						
Country	Prearrival	At arrival	Postarrival	Legal	Refugees/ asylum seekers	Age	TB incidence/ 100,000 population	Target regions	duration of residence that triggers screening	Screening tools used
Belgium	No	Yes	Yes	Yes (selected	Yes	<5 y†	>50	NA	N/U	TST
Czech Republic	No	No	Yes	No	Yes	<15 y	NA	All	N/U	TST
France	No	No	Yes	Yes	Yes	<15 y		All countries except those in EU and North America, and Japan, New Zealand, and Australia	>2 mo	TST
Greece	No	No	Yes	Yes	Yes	All	NA	All	N/U	TST‡
Iceland	No	No	Yes	Yes	Yes	<35 y	NA	All countries except those in EU (except Bulgaria and Romania), and Australia, New Zealand, Switzerland, United States, and Canada	>1 y	TST
Ireland	No	No	Yes	Yes	Yes	<35 y	>40§; >500/sub-	>500/sub-Saharan Africa§	>3 mo	TST
Israel	Yes¶	No	Yes¶	Yes	No	>6 mo	NA	Ethiopia		TST
Luxembourg	No	No	Yes	Yes	Yes	All	NA	All	>3 mo	TST
The Netherlands	No	No	Yes	Yes	Yes	<12 y#	NA	All countries except those in EU, and Australia, Canada, Iceland, Israel, Japan, Monaco, New Zealand, Norway, Surinam, Switzerland, and United States	>3 mo	TST‡
Norway	No	Yes	Yes	Yes	Yes	<40 y	NA	All countries except those in EU, and United States, Canada, Australia, Japan, and New Zealand	>3 mo	TST and confirmatory IGRA
Portugal	No	No	Yes	No	Yes	All	NA	All	N/U	TST and confirmatory IGRA
Slovak Republic	No	No	Yes	Yes	Yes	All	NA	All countries except those in EU	N/U	TST and confirmatory IGRA
Slovenia	No	No	Yes	Yes (selected)	Yes	All	NA	Asia, Africa, and eastern Europe	N/U	IGRA
Sweden	No	No	Yes	No	Yes	All	>100	NA	N/U	TST
United Kingdom	No	No	Yes	Yes	Yes	<35 y	>40**	NA	>6 mo	TST and confirmatory IGRA or IGRA alone
United States	Yes††	No	Yes	Yes‡‡	Yes	2–14 y†† or >2 y§§	≥20†	All§§	N/U	TST or IGRA

*OECD, Organisation for Economic Co-operation and Development; TB, tuberculosis; NA, not applicable; N/U, not known/unclear; TST, tuberculin skin test; EU, European Union; IGRA, IGRA, interferon-γ release assay.

†In general, children <5 years of age are screened for latent TB although pregnant women of any age can also be screened.

‡TST is mainly used although IGRA can be used optionally if diagnosis is unclear in confirming the TST result.

§If <16 years of age; screening adults (16–35 years of age) from >500 cases/100,000 or from sub-Saharan Africa.

¶First step for TST for Jewish immigrants from Ethiopia is performed in Addis Ababa (i.e., prearrival) and the second step is performed postarrival in Israel.

#Applies to persons who were not vaccinated with *Mycobacterium bovis* BCG; in some centers in the Netherlands, immigrants <25 years of age are screened for latent TB infection.

**Previous threshold for United Kingdom was >40 cases/100,000 if <16 years of age and 500 cases/100,000 for sub-Saharan Africa if 16–35 years of age.

††In the US system, immigrants 2–14 years of age from countries with a TB incidence ≥20 cases/100,000 are screened with TST or IGRA prearrival in their country of origin. Some persons are therefore identified as having latent TB and are advised to seek medical attention on arrival in the United States.

‡‡In the US system, immigrants can be screened postarrival if their initial screening test results suggest that they have inactive TB.

§§All immigrants >2 years of age who apply to have their visa status adjusted (status adjusters) are screened by TST or IGRA.

TABLE 8. CURRENT SCREENING PRACTICES FOR ACTIVE & LATENT TB IN INDUSTRIALIZED OECD COUNTRIES (PAREEK, 2012).

Technical Appendix Table 3. Current screening practices for active and latent tuberculosis in industrialized OECD countries*

	Screening for active tuberculosis					Screening for latent tuberculosis infection				
			Groups screened for active TB					Groups screened		
			Legal immigrants		Refugees/asylum			Legal immigrants		Refugees/asylum
Country	Performed?	Compulsory?	All	Selected	seekers	Performed?	Compulsory?	All	Selected	seekers
Australia	Yes	Yes	Yes	NA	Yes	No†	NA	NA	NA	NA
Austria	Yes	Yes‡	Yes	NA	Yes	No	NA	NA	NA	NA
Belgium	Yes	No§	No	Yes¶	Yes	Yes	No	No	Yes¶	Yes
Canada	Yes	Yes#	Yes	NA	Yes	No**	NA	NA	NA	NA
Czech Republic	Yes	Yes	Yes††	NA	Yes	Yes	Yes	No	No	Yes
Estonia	No	NA	NA	NA	NA	No	NA	NA	NA	NA
Finland	Yes	No	No	Yes‡‡	Yes	No	NA	NA	NA	NA
France	Yes	Yes	Yes	NA	Yes	Yes	Yes	Yes	NA	Yes
Germany	Yes	Yes	No	Yes§§	Yes	No	NA	NA	NA	NA
Greece	Yes	Yes	Yes	NA	Yes	Yes	Yes	Yes	NA	Yes
Iceland	Yes	Yes	Yes	NA	Yes	Yes	Yes	Yes	NA	Yes
Ireland	Yes	No	Yes	NA	Yes	Yes	No	Yes	NA	Yes
Israel	Yes	Yes	Yes	NA	No	Yes	No	Yes	NA	No
Italy	No	NA	NA	NA	NA	No	NA	NA	NA	NA
Japan	No	NA	NA	NA	NA	No	NA	NA	NA	NA
South Korea	Yes	Yes	No	No	Yes	No	NA	NA	NA	NA
Luxembourg	Yes	Yes	Yes	NA	Yes	Yes	Yes	Yes	NA	Yes
The Netherlands	Yes	Yes	Yes	NA	Yes	Yes	Yes	Yes	NA	Yes
New Zealand	Yes	Yes	Yes	NA	Yes	No	NA	NA	NA	NA
Norway	Yes	Yes	Yes	NA	Yes	Yes	Yes	Yes	NA	Yes
Poland	Yes	Yes	No	No	Yes	No	NA	NA	NA	NA
Portugal	Yes	No	No	No	Yes	Yes	No	No	No	Yes
Slovakia	Yes	Yes	Yes	NA	Yes	Yes	Yes	Yes	NA	Yes
Slovenia	Yes	No	No	Yes¶¶	Yes	Yes	No	No	Yes¶¶	Yes
Spain	No	NA	NA	NA	NA	No	NA	NA	NA	NA
Sweden	Yes	No	No	No	Yes	Yes	No	No	No	Yes
Switzerland	Yes	Yes	No	No	Yes	No	NA	NA	NA	NA
United Kingdom	Yes	Yes	Yes	NA	Yes	Yes	No	Yes	NA	Yes
United States	Yes	Yes	Yes	NA	Yes	Yes	No##	Yes	NA	Yes

*OECD, Organisation for Economic Co-operation and Development; TB, tuberculosis; NA, not applicable.
†No formal screening for latent TB but immigrants may have to accept postarrival health test results (if initial chest radiograph suggests inactive TB) in which further investigations (including repeat chest radiograph, sputum examination, and tuberculin skin test) are conducted, although this may differ from country to country.
‡For work permit and refugees/asylum seekers; otherwise, screening is voluntary.
§For students, a normal chest radiographic result may be needed for additional examinations.
¶Selected screening of immigrants through school/university but this is not systematic or formal.
#Although compulsory, postarrival screening cannot be enforced, although it may affect citizenship application.
**No formal screening for latent TB but postarrival medical surveillance for persons in whom initial chest radiograph suggests inactive TB.
††Immigrants from certain countries applying for a visa of ≥90 d or long-term residence permission have to provide documentary proof that they do not have TB.
‡‡Screening is comprehensive for adopted children but informal for all other immigrants.
§§Run at state level but not national; selected screening performed for Aussiedler (ethnic Germans mainly from the former USSR who resettled in Germany).
¶¶Selected screening performed for work permit (as part of preemployment screening).
##Not compulsory for recent immigrants but compulsory for status adjusters.

Table 9. Results of systematic search on Strategies for TB Control in Migrants in Low - Incidence Countries.

No.	Reference	Year	Screening Method	Strengths	Limitations	Future prospects	Type of publication	Country of study
1	Heldal et al	2003	RFLP screening	Recent infection detected	Not specified	Better case-management, CT, preventive treatment, screening, access to health facilities.	Systematic research	Norway
2	Cain et al	2008	Target high LTBI risk with TB assays, tuberculin tests	Global TB Control	Control strategies to eliminate TB	Diagnose early & CT & treatment & target LTBI; invest in global TB control.	Editorial commentary	USA
3	Geerde-Fenge et al	2011	Sputum-smear & CT; TST, IGRA	1 MDR detected & transmission prevented	Late TB diagnosis	Look out for symptoms in this high-risk group.	Press release	Germany & Austria
4	Coker et al	2001	LTBI tool: compulsory testing & preventive treatment	Targeted intervention; draft recommended for TB elimination	International standards violated; cost-effectiveness challenged; mandatory testing	Transcultural outreach activities.	Critic /personal review	USA
5	Valin et al	2002	Sputum-smear & TST & mobile X-ray screening & RFLP & CT	Index case identified & further transmission prevented	High turnover in severe-overcrowding shelters; poor ventilation	Improve living conditions.	Systematic research	France
6	Lemaitre et al	1998	DNA fingerprinting RFLP for recent TB transmission; smear testing and culture to confirm TB	Detection of outbreaks; surveillance of nosocomial TB transmission studies with DNA finger-printing, an epidemiological tool for TB confirmatory tests.	Not specified	For early treatment: faster laboratory diagnosis & reporting system; separate TB-suspects patients and take first the immune-compromised patients for testing.	Systematic research	France

Table 9. Results of systematic search on Strategies for TB Control in Migrants in Low - Incidence Countries.

No.	Reference	Year	Screening Method	Strengths	Limitations	Future prospects	Type of publication	Country of study
7	Rieder et al	1994	Strategies for TB control; CXR, TST, culture-confirmation	Identify surveillance systems	Financial restraints	Notification systems - laboratory & physician reports; surveillance screening, cure & prevention; culture & socially-based services; follow-up treatment & implementation; evaluate screening for efficiency & efficacy.	Report	Europe
8	Hogan et al	2005	Screening at entry; CXR new entrants, TST & BCG	Lots of resources used; letters sent with information on signs and symptoms of TB; GP advised on follow-up medical appointments & HCW visits	Little active TB detected; methods used were inconsistent & CT was better; staff interpreted national policy in different ways	Community-based methods to detect & treat TB; focus on high-risk populations & target screening on refugees & asylum seekers.	Systematic research	UK
9	Dasgupta et al	2005	Strategies for TB control; sputum smear, CXR, TST, culture-confirmation, LTBI	Entry screening for LTBI , treatment offer; CT within ethnic groups	Chest radiography & entry-screening as not cost effective - as screening x1 at entry for permanent resident status versus those who re-enter again & with TB undetected! Students, labourers, visitors are not screened	Invest in Global TB control; Sputum culture to replace CXR.	Critic	Not specified

Table 9. Results of systematic search on Strategies for TB Control in Migrants in Low - Incidence Countries.

No.	Reference	Year	Screening Method	Strengths	Limitations	Future prospects	Type of publication	Country of study
10	Heldal et al	2008	Global control strategy for TB in undocumented migrants - a comparative study: Millenium Development Goals; Smear & Culture	Strengthen diagnosis & treatment; country-specific interventions	Incomplete coverage as it depended on voluntary information from countries; study was based on combination of estimates and exact numbers, and combination of qualitative and quantitative data; limitations to diagnosis & treatment; majority of countries deported TB-patients still on-treatment	Easy access to free information on diagnosis & follow-up treatment; free of fear of deportation & ensure this until treatment is complete; HCWs, authorities and NGOs adhere to confidentiality; raise awareness about TB diagnosis & free treatment independent of migration status.	Report	WHO European Region; Belgium, Canada, Israel, Spain, France, Netherlands , Norway, Switzerland, USA, Australia, Japan
11	Leitmeyer	2011	Global TB control	Not specified	Not specified	Not specified	Perspectives	Global
12	Mulder et al	2009	Symtoms screening, few sputum status, CXR, positive culture of Mtb bacteria, TST, IGRA, CT	CT was cost-effective and better than entrant screening	More data reports needed; collection and reporting data has higher herterogeneity therefore results difficult to compare - with no firm conclusions; different TST cut-off points; different definitions of close contact; no uniform CT strategy; only 6 relevant EU studies; lack reported EU evidence; Non-EU studies lower cut-off points for positive TST, so higher LTBI; large variation in studies	Need to standardize TB diagnosis and LTBI methods & BCG vaccine status; need uniform CT strategy, uniform data collection & reports; uniform CT as a high-risk screening strategy; need targeted screening & diagnostic tool.	Review ABSTRACT	EU

Table 9. Results of systematic search on Strategies for TB Control in Migrants in Low - Incidence Countries.

No.	Reference	Year	Screening Method	Strengths	Limitations	Future prospects	Type of publication	Country of study
13	Hargreaves et al	2009	New screening approaches on-arrival; CXR at entry ports	Not specified	Lack of documented data	Explore TB registries that specify migrant status and country of origin; community-based methods; new diagnostic blood tests; incorporate TB screening into general family doctor practice and clinics.	Reflection & Reaction	Europe
14	Schwartzman et al	2005	DOTS expansion strategy	DOTS more cost-effective than radiographic screening with TST	Not backed by solid research data	US-funded DOTS expansion strategy in Mexico, Haiti, the Dominican Republic - most effective long-term approach.	Theoretical	USA
15	Das et al	2006	Chest X-ray before entry & 6 weeks after arrival	TB exposure overseas, not local transmission	LTBI goes undetected	Need to screen refugee's family reunification. Open to regional TB-control in neighbouring countries; TB care-takers suspicion of TB.	Systematic research (TB surveillance)	New Zealand
16	Littleton et al	2008	Refugees TST, CXR, sputum, culture; single border screening; pre- and immigration screening; post-migration health checks (66% diagnosed in doctor's office rather than screening)	Necessary but not sufficient for TB control.	Border control is limited for TB control. Other factors needed PLUS case finding, CT, preventive treatment; mass media campaigns	Determine factors that induce reactivation of TB e.g. transnational commuting, living conditions, frequent border crossings etc.; access dial call free numbers; avoid publicity; community languages and community health promotion initiatives.	Systematic research	New Zealand
17	Kim et al	2003	TST, CXR and annual screening	No-name tracking system. Management and workers mutually benefit PH	High turnover of staff	Collaboration between health institution and industry promotes PH.	Systematic research	USA

Table 9. Results of systematic search on Strategies for TB Control in Migrants in Low - Incidence Countries.

No.	Reference	Year	Screening Method	Strengths	Limitations	Future prospects	Type of publication	Country of study
18	Watkins et al	2002	Not specified	Not Available	Screening for active disease prior-to or at entry - has limited impact on TB incidence; lack of association between migrants TB rates and estimated TB incidence in country of birth - small data size	Global approach to TB control; screening & education interventions.	Systematic research	Australia & Canada
19	MacPherson et al	2006	Radiography for pre-entry (Australia, Canada, UK and USA), on-entry & post arrival screening; medical examination for immigration screening;	Immigration policies on par with global health strategies	TST screening or new technolgies costly. LTBI goes undetected.	Support global TB control. Needed evidence-based approaches for use of resources and support of programmes. Increase free access to healthcare. Access to language, culture, social. Preventive treatment of LTBI. New diagnosis & clinical screening techniques required; direct detection of Mtb in mycobacterial cultures or clinical specimens.	Review article	Australia, Canada, USA, Western Europe, UK
20	Blumberg et al	2010	Not specified	Not specified	Not specified	Strengthen surveillance and confidentiality of immigration status; global TB control investment; strengthen national TB programs; novel drugs, diagnostics, vaccines.	Comment	Global

Table 9. Results of systematic search on Strategies for TB Control in Migrants in Low - Incidence Countries.

No.	Reference	Year	Screening Method	Strengths	Limitations	Future prospects	Type of publication	Country of study
21	Reitmanova et al	2009	Screening and surveillance	Systematic screening and surveillance in LTBI - can determine latency period	Screening and surveillance insufficient for TB control. TB continues to rise in immigrants.	Create existing registries need to include social determinants of health, SES, living conditions; systematic screening and surveillance needed as poverty & social exclusion may reactivate TB disease.	Reflection and reaction	Canada
22	Houston	1998	BCG vaccine, sputum microscopy, passive screening & DOTS	TB patients come to health center and take back benefits with cure; payment in form of livestock	Security of programme	International surveillance systems to predict conflicts that cause dispersal; preventive diplomacy - eliminate root cause of conflict with international commitment & surveillance; harmonize timing of TB implementation with host country.	Systematic research	Not specified
23	Gushulak	1998	Pre-entry screening for Australia, Canada, USA; DOTS too; refugees medical examination, CXR, sputum smear & culture, TST, positive - observe & re-evaluate; surveillance systems identify high-risk /high prevalence groups and when screened have benefit for treatment and preventive therapy; cultural & social sensitivity for compliance	Consensus-based paper	Limited availability of data; policy & practices of migrant population	Recommendations for Europe, management of refugee populations, education, better medications and delivery; monitoring & evaluation of screening methods. Maintain & standardize national notification systems (laboratory & clinical reports); address migration & population mobility. Raise awareness of screening importance, diagnosis, surveillance, treatment, prevention, education of HCWS. Support research & determine factors that reactivate latent TB.	Policy paper	Canada & Europe.

Table 9. Results of systematic search on Strategies for TB Control in Migrants in Low - Incidence Countries.

No.	Reference	Year	Screening Method	Strengths	Limitations	Future prospects	Type of publication	Country of study
24	Marks et al	2000	Chest Xray, TST, BCG scar measurement on arrival (BCG in childhood but not effective in adult TB prevention. BCG does not affect TST size after prolonged time)	Sensitivity & specificity of case ascertainment. Linear increase in TB incidence with reactivation for TST size >10mm	Reactivation was not dependent on initial BCG scar	Prognosis of TB & Isoniazid preventive therapy for refugees and S.E. Asians migrants to low-incidence countries for policy & practice.	Systematic research	Australia
25	Klinkenberg et al	2009	Screening on entry, at arrival & just after arrival & follow-up screening after arrival	No differences in 3 types of screening; differences exist in risk factors of migrant population. 14 National screening programs studied. CXR for 4-15 years, primary method of screening but used in combination with tools like symptom screening	Criteria & definitions were NOT clear and therefore comparisons was difficult; TB definitions were different, different diagnostic tools, different studies, countries, strategies. Yield factor and coverage as indicators of effectiveness was different between studies and different countries. Large variability seen between studies and limitation of data	Recommendations: Global TB control and long-term TB control strategy; Improved data on number & time period for screening, frequency & duration; assessment & improvement of cost-effectiveness; access to healthcare; management & care; caution with LTBI screening; implement screening as wider intervention part of/inclusive and integrated into the health system; Anonymous screening system using same criteria; systematic recording & reporting.	Systematic review	EU/EEA including Switzerland
26	Helbling et al	2003	N/A	N/A	N/A	Need to identify migrants barriers (lifestyle, health habits or risk factors) to access German health system & participate in prevention programs and reduce them. Need evidenced-based, sustainable & evaluated prevention programs.	Comment	Switzerland/ Germany ABSTRACT

Table 9. Results of systematic search on Strategies for TB Control in Migrants in Low - Incidence Countries.

No.	Reference	Year	Screening Method	Strengths	Limitations	Future prospects	Type of publication	Country of study
27	Marks et al	2001	CXR pre-departure; BCG scar examination > 10mm, culture; post-migration TST screening	TB incidence was high in Cohort refugees	Post migration screening not effective	Early detection, diagnosis, treatment & compliance, preventive therapy; epidemiology of TB in new arrivals.	Systematic research	Australia
28	Marks et al	2001	CXR pre-departure, and follow-up after 18 months; TST, BCG, Xray, smear positive & culture; post-migration TST screening	Sensitivity & specificity of case ascertainment.	Post migration screening not effective	Passive case finding effective, raising awareness - diagnosis Public Health physicians, access to health services, treatment and management and preventive therapy.	Systematic research	Australia
29	Porco et al	2006	CXR, sputum, post entry after prior-TB pre-screening overseas	Domestic follow-up & LTBI treatment highly cost-effective - savings of LTBI intervention program	Hypothetical Cohort - accurate estimates NOT available. Transmission model - a lot of assumptions. DOTS not cost-effective for HIV negative patients	Nine months with INH - 70% efficacy rate and prevents progression to TB (latent TB isoniazid therapy and evaluate start and completion rates of INH); screen undocumented migrants, students on visas and overseas screening.	Simulation	USA
30	Gilbert et al	2009	Not specified	Increased TB rates due to immigrants from very high TB incidence countries. In 75% of foreigners (UK, Norway, Sweden) very high incidence	General OECD data. Nature of data available: birth data, foreign-born abroad, change of nationality; UK > 500cases/100,000 from S. Asia & sub-Saharan Africa	UK has limited access to health care system (exclude asylum seekers/undocumented migrants).	Descriptive analysis	OECD and 21 European countries

Table 9. Results of systematic search on Strategies for TB Control in Migrants in Low - Incidence Countries.

No.	Reference	Year	Screening Method	Strengths	Limitations	Future prospects	Type of publication	Country of study
31	French et al	2007	Sputum smear confirmed by culture	Isoniazid susceptibility	Variables missing. It is NOT possible to match causes with isolates; place of birth missing and this affects study	Global control investment; need to raise awareness of TB disease, language support, stigma, awareness of TB after after years of entry; non-UK-born and UK-born ethnic groups are at high risk of TB even after long years of residence in UK; new diagnostic tests for LTBI; diagnosis and prompt treatment.	surveillance data analysis	(UK), England & Wales
32	Gagliotti et al	2006	Symptom and smear, and epidemiology data	TB onset data in migrants - initial mild symptoms; Pulmonary TB (PTB) study	Patient vs Italian health care delays	PH intervention for migrants to access health care facilities; suspect Italians too to get TB; undiagnosed PTB is a reservoir of TB.	surveillance data analysis	Italy
33	Anderson et al	2007	Pre-employment screening (occupational), sputum smear, culture confirmed, CXR, TST; passive letters of information and advice	Country of birth of HCWs with TB (37% India, 29% sub-Saharan Africa)	Underreporting; quality of information varied; definitions and actions taken for each incident different; all new HCWs to have pre-screening is insufficient.	High suspicion of HCWs with TB symptoms; Strain-typing strategy links surveillance with outbreaks; IGRAs assays to detect LTBI and preventive treatment for hospital-based HCWS is needed.	Survey - surveillance	England & Wales

Table 9. Results of systematic search on Strategies for TB Control in Migrants in Low - Incidence Countries.

No.	Reference	Year	Screening Method	Strengths	Limitations	Future prospects	Type of publication	Country of study
34	Wolff et al	2010	General screening program, CXR screening; only free mobile out-patient clinic	Free health care to undocumented migrants - fibrotic disease was seen	Control & test sample inclusion period was NOT identical; small sample size; CXR doesnot pick up extra-pulmonary TB; being undocumented was necessary but not sufficient a determinant factor for TB, as fibrotic disease was also seen in Latin Americans independent of status; TST was not performed on undocumented migrants as its difficult to get more >1 time with this group	Regular screening; language and culture for health services participation; overcome fear & cultural barriers; Study at Mobile Unit - information leaflets in English & Portuguese, free vaccines, inform trade unions & community leaders, public social services, collaborate with charity association: Caritas, Salvation Army, social inter-active workshops, lectures and discussions, TB awareness information camps.	Systematic research	Switzerland
35	Lange et al	2008	Not specified; resistant tests	Not specified	Emergency of XDR-MTB	Urgency to develop new drugs and rapid-resistance diagnostic tests for XDR-TB (rare in Germany but present in E. Europe) and novel antibiotics.	Commentary	Germany (German Language)

Table 9. Results of systematic search on Strategies for TB Control in Migrants in Low - Incidence Countries.

No.	Reference	Year	Screening Method	Strengths	Limitations	Future prospects	Type of publication	Country of study
36	IOM (UN)	2011	Mainly TSTs done and interferon assays as confirmatory tests	Immigrants were screened only if they originated from high-TB incidence countries	Wide variation in threshold for screening - raises questions!; Various methods used for sreening, choice of location, choice of selection of group-type needed for evidence-based screening policies; better tool for LTBI screening needed; Stratify based on immigration status to determine active TB in legal vs illegal immigrants	Need to understand culture and change prejudice behaviour; multi-pronged capacity building initiatives for migrants; coordination between migrant networks; migrant-related policy; trans-border regional & intergovernmental capacity building; Screening for active disease and LTBI needed for TB control; cost-effectiveness of LTBI in migrants is needed; social change campaigns; public education and awareness raising; increase private sector engagement to give health insurance; permit migrants to pay into Government health insurance schemes. Health records/smart cards for transborder truck drivers or traffickers.	World Migration Report	Global & 31 OECD countries
37	WHO	2011	Not specified	Not specified	Not specified	Not specified	World Health Report	Global
38	United Nations	2010	Not specified	Not specified	Not specified	Not specified	Migration	Global
39	Kamper-Jorgensen et al	2012	Screening at entry and recently active case-finding of TB-risk groups	Non-clustered TB studied	Imported re-activation of ethnic sub-groups. Refugees get minimal Danish health care system information	TB control; active case-finding & treatment; education; preventive therapy for LTBI in co-infected HIV/TB; co-ordination; genotype mapping for risk patterns; post-migration access to PH systems; investment in global TB control.	Systematic Research	Denmark (ABSTRACT)

Table 9. Results of systematic search on Strategies for TB Control in Migrants in Low - Incidence Countries.

No.	Reference	Year	Screening Method	Strengths	Limitations	Future prospects	Type of publication	Country of study
40	Fears et al	2010	Not specified	Not specified	Not specified	EU needs to do drug susceptibility testing linked to TB notified cases; international molecular epidemiology MTB databases for interactive data exchange; global strategy for TB control as it is linked to social, environmental & economic issues; Lab Quality Control; Regional Reference lab network exchange data via interactive international databases of MTB genotyping & phenotyping information; research for new drugs, vaccines, diagnostics & operational research.	Report	EU (ABSTRACT)
41	Kamper-Jorgensen et al	2012	Symptom screening at arrival, sputum smear, limited culture microscopy of TB cases	Identical genomic clusters in molecular genotyping indicates recent transmission	Danes to migrants TB transmission 2.5% > vice-versa! Limited transmission across ethnic groups (country of birth) but mainly within groups e.g. Somalis	Invest in Global TB control; non-clustered cases should be studied for TB control in view of reactivation in the elderly or due to importation; focus on prevention of micro-epidemics in high risk groups (Greenlanders).	Systematic research	Denmark

Table 9. Results of systematic search on Strategies for TB Control in Migrants in Low - Incidence Countries.

No.	Reference	Year	Screening Method	Strengths	Limitations	Future prospects	Type of publication	Country of study
42	Pareek et al	2012	Screening for active vs LTBI, clinical exam, 2 TSTs, >18 CXR, clinical exam + CXR, or CXR alone	Not specified	Potential for recall / responder bias; recommendation screening may not be so in reality; data not stratified for TB cases, documented and undocumented migrants; heterogeneity exists for screening location, selection criteria, subgroup of migrants, screening methods & tools (clinical exam, TST, CXR); TB incidence as selection criteria was different in threshold numbers > cases /100,000 to > 500 cases /100,000	Evidence-based needed for which sub-group to screen; a cost-effective study on LTBI screening strategies for immigrants badly needed - screening legal immigrants for LTBI is of low priority but urgent for TB control; screening for occupational TB & LTBI; TB screening guidelines; screen & target LTBI; molecular typing of LTBI and TB drugs	Systematic Research	31 OECD countries
43	Abubakar et al	2012	BCG vaccine, sputum & culture, CXR	Duration of protection of BCG; Preventive therapy for close contacts of MDR-TB	Limitations to TB interventions in general population; BCG mandatory vs non-mandatory, no randomised trial, secondary transmission not added to economic evaluation	Target high-risk groups in urban areas; optimise tools & shorter & less toxic treatment regimens for LTBI screening & active TB; develop new anti-TB drugs; reserve new drugs for LTBI.	Systematic Research	Low burden countries (Western Europe, UK & USA)

Table 9. Results of systematic search on Strategies for TB Control in Migrants in Low - Incidence Countries.

No.	Reference	Year	Screening Method	Strengths	Limitations	Future prospects	Type of publication	Country of study
44	Jit et al	2011	Mobile screening units - Initiative 'Find & Treat'; CXR & culture	Cost-effective as it dealt with active TB cases, prevented both transmission and antibiotic resistance; targetted intervention that interrupts transmission	Not specified	Testing care - role of community-based treatment delivery.	Systematic Research	UK
45	de Vries et al	2007	Mobile X-ray screening Unit; smear positive, culture-confirmed, CT	TB transmission and yearly TB cases were reduced; 50% transmission reduced during intervention; a targeted screening program; DNA finger-printing is a useful tool to evaluate TB screening programs	Not specified	Incentives for high completion rates: public transport tickets, priority accommodation in shelters, volunteer admission to specialized TB hospitals, assistance with temporary residence permits.	Systematic research	The Netherlands
46	Eurostat	2011	Not specified	Not specified	Not specified	Not specified	Migration statistics	Europe
47	ECDC	2009	Not specified	Not specified	Not specified	Not specified	Not specified	EU

Table 9. Results of systematic search on Strategies for TB Control in Migrants in Low - Incidence Countries.

No.	Reference	Year	Screening Method	Strengths	Limitations	Future prospects	Type of publication	Country of study
48	King et al	2011	Prescreening chest X-ray, sputum culture	Applicants treated before entry and Australian population protected and pre-migration screening strengthened laboratory diagnosis	Limited susceptibility testing was done overseas so MDR-TB cases were missed on entry; data collection under-reporting bias; 98% of pre-migartion cases CXR is normal but after I year develop pulmonary TB	A new data system "cHealth" captures data for analysis; centers of excellence; improve lab diagnosis; identify selected labs for testing (India, Philippines, Vietnam & China); Improve lab capacity.	Systematic research	Australia
49	Alvarez et al	2011	Immigration screening, CXR, smear +, LTBI, TST	Medical science diagnostic techniques & therapeutics	Not one country had the same screening method! - subtle cultural & political country differences - account of participants information	Evidence-based approach to TB screening for migrants and cooperation between countries are needed; standardized information & research; Investment in Global control.	Systematic Research	18 selected countries & Canada
50	Kehr et al	2012	CXR at entry screening; screening for active-case finding and mobile X-ray unit; sociology of screening; link Public Health -to immigration - to ID; TB is linked to politics - border control	Collaboration between PH and Charity /humanitarian Institute	Restriction and inflexibility of German PH system; how political influence on immigration policy affects PH for vulnerable in society	Focus on undocumented migrants and Roma; Mobile Unit goes to Charitable Health Centre	Systematic Research	France & Germany

Table 9. Results of systematic search on Strategies for TB Control in Migrants in Low - Incidence Countries.

No.	Reference	Year	Screening Method	Strengths	Limitations	Future prospects	Type of publication	Country of study
51	Dara et al	2012	Not specified	Not specified	Not specified	Coordinated approach for TB control across countries, collaboration across borders that delivers health services, strengthened via political and financial commitments; prevention, infection control, contact management, diagnosis & treatment, psychological support.	Wolfheze Consensus Statement	WHO Euro Region
52	Erkens et al	2008	X-ray screening on entry and biannual follow-up, sputum microscopy & culture, TST	Screening at follow-up & coverage gave low yields; yield of entry screening was high	Coverage of screening & representativeness of data; selection bias as persons with symptoms report for screening & yield of screening is high	Discontinue X-ray follow-up screening for countries incidence < 200 per 100 000, low or medium incidence with no CXR abnormalities; coverage & follow 1 year & increase in high-incidence groups.	Systematic research	The Netherlands
53	Vos et al	2004	Mandatory X-ray entry screening and biannual volunteer screening 6 months for 2 years	Not specified	TB transmission within The Netherlands may have occurred: confounding with country of origin & time of immigration	Effective control policies are needed as cause of persistence is unknown; study 3 factors: reactivation of prior infection, host country transmission, acquired infection during home visits.	Systematic research	The Netherlands
54	Mulder et al	2012	QFT-GIT assay screening for newly arrived immigrants; CXR, culture confirmation, volunteer follow-up CXR at 6 months/2 years	New immigrant as a risk group! Showed progression to active TB within 2 years	Slight under-estimation of risk of progression to TB; study not for <18 years or re-migration after entry screening; assumes cases were infected at entry, estimates for risk of progession to TB not proper	QFT-GIT screening could be used for prevention and control strategies; new technique for recent/remote infection which distinguishes/measures latency antigens; QFT-GIT + for prophylactic treatment; research on barrier & facilitors of a treatment program; alternative entry-screening strategy; cost-effectiveness.	Systematic research	The Netherlands

Table 9. Results of systematic search on Strategies for TB Control in Migrants in Low - Incidence Countries.

No.	Reference	Year	Screening Method	Strengths	Limitations	Future prospects	Type of publication	Country of study
55	Bothamley et al	2008	TST screening and X-ray - active TB screened & Latent TB; symptom screening (50%) & sputum (72%) & TST & CXR (54%);	Nearly all countries did TST and half did X-ray independent of TST results Contacts screened for active TB and LTBI; 6-9 months INH treatment; agree on screening for TB control & latent treatment but differ on low detection rate & excessive screening	Immigrants are healthy on arrival so CXR not helpful on entry, TB> 5 years; TST interpretation was different between countries; not modified with/without BCG; sputum Screening not in guidelines; Tuberculin cut-off values 5mm without BCG or 10mm or 15mm (best) with BCG	Symptoms & sputum smear (should be more widely used!) for those with persistent cough for 3 weeks -go for screening active TB. Interferon-gamma release assays for targeting LTBI. treatment	Systematic Research - survey	50 countries WHO European Region
56	Diel et al	2004	Entry Screening; Symptoms, CXR, TST, culture positive TB, CT	Molecular typing indicates clustering; Recent transmission rarely occurs in migrants in Hamburg	Limitation of study: period 5 years underestimation of real transmission rate between foreign-born & German-born; Few TB cases detected when screening asylum or via CT	TB prevention: TST for all, CXR, symptom awareness.	Systematic research	Germany
57	WHO TB Fact Sheet	2012	Passive case-finding	Not specified	Not specified	Not specified	Fact Sheet	WHO
58	Robert Koch Institute	2010	Not specified	Not specified	Not specified	Geographical variation of TB in immigrants; different incidence trends on arrival; focused intervention - identify specific groups.	Survey	Germany
59	**ECDC**	2012	Not specified	Not specified	Not specified	Not specified	Report	Europe

Table 9. Results of systematic search on Strategies for TB Control in Migrants in Low - Incidence Countries.

No.	Reference	Year	Screening Method	Strengths	Limitations	Future prospects	Type of publication	Country of study
60	YearLillebaek et al	2002	Screening on arrival; CXR, TST & sputum culture	Disease of subgroups	Only gradual decline of TB incidence	For latency - vitamin deficiency, genetic, immune; surveillance of TB incidence trends in risk groups; regular check-ups, preventivechemotherapy; intervention for latent and active TB; compliance forpreventive treatment - side-effects of medications; reduce new TB incidence, reduce prevalence, arrest latent and prevent active disease.	Systematic research	Denmark

13. LITERATURE REVIEW

Abubakar, I., Stagg, H. R., Cohen, T., Mangtani, P., Rodrigues, L. C., Pimpin, L., Watson, J. M., Squire, S. B. and Zumla, A. Controversies and unresolved issues in tuberculosis prevention and control: a low-burden-country perspective. J Infect Dis 205 Suppl 2, S293-300, doi:10.1093/infdis/jir886jir886 [pii] (2012).

Alvarez, G. G., Gushulak, B., Rumman, K. A., Altpeter, E., Chemtob, D., Douglas, P., Erkens, C., Helbling, P., Hamilton, I., Jones, J., Matteelli, A., Paty, M-C., Posey, D. L., Sagebiel, D., Slump, E., Tegnell, A., Valin, E. R., Winje, B. A. and Ellis, E. A comparative examination of tuberculosis immigration medical screening programs from selected countries with high immigration and low tuberculosis incidence rates. BMC Infect Dis 11, 3, doi:10.1186/1471-2334-11-31471-2334-11-3 [pii] (2011).

Anderson, C., Abubakar, I., Maguire, H. and Sonnenberg, P. Survey of tuberculosis incidents in hospital healthcare workers, England and Wales, 2005. J Public Health (Oxf) 29, 292-297, doi:fdm042 [pii] 10.1093/pubmed/fdm042 (2007).

Blumberg, H. M., Migliori, G. B., Ponomarenko, O. and Heldal, E. Tuberculosis on the move. Lancet 375, 2127-2129, doi:10.1016/S0140-6736(10)60574-0 S0140-6736(10)60574-0 [pii] (2010).

Bothamley, G. H., Ditiu, L., Migliori, G. B. and Lange, C. Active case finding of tuberculosis in Europe: a Tuberculosis Network European Trials Group (TBNET) survey. Eur Respir J 32, 1023-1030, doi:10.1183/09031936.0001170809031936.00011708 [pii] (2008).

Cain, K. P. and Mac Kenzie, W. R. Editorial commentary: Overcoming the limits of tuberculosis prevention among foreign-born individuals: next steps toward eliminating tuberculosis. Clin Infect Dis 46, 107-109, doi:10.1086/523732 (2008).

Coker, R. and van Weezenbeek, K. L. Mandatory screening and treatment of immigrants for latent tuberculosis in the USA: just restraint? Lancet Infect Dis 1, 270-276 (2001).

Dara, M., de Colombani, P., Petrova-Benedict, R., Centis, R., Zellweger, J., Sandgren, A., Heldal, E., Sotgiu, G., Jansen, N., Bahtijarevic, R. and Migliori, G. Minimum package for cross-border TB control and care in the WHO European region: a Wolfheze consensus statement. Eur Respir J 40, 1081-1090, doi:10.1183/09031936.0005301209031936.00053012 [pii] (2012).

Das, D., Baker, M., Venugopal, K. and McAllister, S. Why the tuberculosis incidence rate is not falling in New Zealand. N Z Med J 119, U2248 (2006).

Dasgupta, K. and Menzies, D. Cost-effectiveness of tuberculosis control strategies among immigrants and refugees. Eur Respir J 25, 1107-1116, doi:25/6/1107 [pii] 10.1183/09031936.05.00074004 (2005).

de Vries, G., van Hest, R. A. and Richardus, J. H. Impact of mobile radiographic screening on tuberculosis among drug users and homeless persons. Am J Respir

Crit Care Med 176, 201-207, doi:200612-1877OC [pii]10.1164/rccm.200612-1877OC (2007).

Diel, R., Rusch-Gerdes, S. and Niemann, S. Molecular epidemiology of tuberculosis among immigrants in Hamburg, Germany. J Clin Microbiol 42, 2952-2960, doi:10.1128/JCM.42.7.2952-2960.200442/7/2952 [pii] (2004).

ECDC / WHO Regional Office for Europe: Tuberculosis surveillance and monitoring in Europe. (http://ecdc.europa.eu/en/publications/publications/1203-annual-tb-report.pdf). (2012).

ECDC, E. C. f. D. P. a. C. Migrant health: background note to the 'ECDC Report on migration and infectious diseases in the EU'. (http://www.ecdc.europa.eu/en/publications/Publications/0907_TER_Migrant_health_Background_note.pdf) (2009). (Accessed Jan 2013)

Erkens, C., Slump, E., Kamphorst, M., Keizer, S., van Gerven, P. J. H. J., Bwire, R., Berkel, M., Borgdorff, M. W. and Verver, S. Coverage and yield of entry and follow-up screening for tuberculosis among new immigrants. Eur Respir J 32, 153-161, doi:10.1183/09031936.0013790709031936.00137907 [pii] (2008).

Escombe, A. R., Moore, D. A. J., Gilman, R. H., Pan, W., Navincopa, M., Ticona, E., Matinez, C., Caviedes, L., Sheen, P., Gonzalez, A., Noakes, C.J., Friedland, J. S. and Evans, C. A. The infectiousness of tuberculosis patients coinfected with HIV. PLoS Med 5, e188, doi:10.1371/journal.pmed.0050188 07-PLME-RA-0563 [pii] (2008). http://dx.doi.org/10.1371/journal.pmed.0050188.

Eurostat, E. C. and Migration and migrant population statistics. (2011).http://epp.eurostat.ec.europa.eu/statistics_explained/index.php?title=File:Immigration_by_main_citizenship_group_2009.png&filetimestamp=20120924101729 (Accessed Jan 2013)

Fears, R., Kaufmann, S., Ter Meulen, V. and Zumla, A. Drug-resistant tuberculosis in the European Union: opportunities and challenges for control. Tuberculosis (Edinb) 90, 182-187, doi:10.1016/j.tube.2010.03.008S1472-9792(10)00029-6 [pii] (2010).

French, C. E., Antoine, D., Gelb, D., Jones, J. A., Gilbert, R. L. and Watson, J. M. Tuberculosis in non-UK-born persons, England and Wales, 2001-2003. Int J Tuberc Lung Dis 11, 577-584 (2007).

Gagliotti, C., Resi, D. and Moro, M. L. Delay in the treatment of pulmonary TB in a changing demographic scenario. Int J Tuberc Lung Dis 10, 305-309 (2006).

Geerdes-Fenge, H. and Loytved, G. [Tuberculosis in 22 Au-pairs in Germany and Austria - diagnosis reduces risk of infection for host families]. Dtsch Med Wochenschr 136, 1837-1841, doi:10.1055/s-0031-1286353 (2011).

Gilbert, R. L., Antoine, D., French, C. E., Abubakar, I., Watson, J. M. and Jones, J. A. The impact of immigration on tuberculosis rates in the United Kingdom compared with other European countries. Int J Tuberc Lung Dis 13, 645-651 (2009).

Gushulak, B. D. Tuberculosis control in refugees--policy and practices. Int J Tuberc Lung Dis 2, S87-93 (1998).

Hargreaves, S., Carballo, M. and Friedland, J. S. Screening migrants for tuberculosis: where next? Lancet Infect Dis 9, 139-140, doi:10.1016/S1473-3099(09)70026-X S1473-3099(09)70026-X [pii] (2009).

Helbling, P. G. U. R. T. Z. J.-P. Die Tuberkulose in der Schweiz: Epidemiologie, Überwachung und Meldung. Schweiz Med Forum 21, 487-491 (2003).

Heldal, E., Dahle, U. R., Sandven, P., Caugant, D. A., Brattaas, N., Waaler, H. T., Enarson, D. A., Tverdal, A. and Kongerud, J. Risk factors for recent transmission of Mycobacterium tuberculosis. Eur Respir J 22, 637-642 (2003).

Heldal, E., Kuyvenhoven, J. V., Wares, F., Migliori, G. B., Ditiu, L., Fernandez de la Hoz, K. and Garcia, D. Diagnosis and treatment of tuberculosis in undocumented migrants in low- or intermediate-incidence countries. Int J Tuberc Lung Dis 12, 878-888 (2008).

Hogan, H., Coker, R., Gordon, A., Meltzer, M. and Pickles, H. Screening of new entrants for tuberculosis: responses to port notifications. J Public Health (Oxf) 27, 192-195, doi:fdi019 [pii] 10.1093/pubmed/fdi019 (2005).

Houston, S. Tuberculosis in refugees and displaced persons. Int J Tuberc Lung Dis 2, S94-97 (1998).

Jit, M., Stagg, H. R., Aldridge, R. W., White, P. J. and Abubakar, I. Dedicated outreach service for hard to reach patients with tuberculosis in London: observational study and economic evaluation. BMJ 343, d5376, doi:10.1136/bmj.d5376bmj.d5376 [pii] (2011).

Kamper-Jorgensen, Z., Andersen, A. B., Kok-Jensen, A., Bygbjerg, I. C., Thomsen, V. O. and Lillebaek, T.. Characteristics of non-clustered tuberculosis in a low burden country. Tuberculosis (Edinb) 92, 226-231, doi:10.1016/j.tube.2012.02.001S1472-9792(12)00026-1 [pii] (2012).

Kamper-Jorgensen, Z., Andersen, A. B., Kok-Jensen, A., Kamper-Jorgensen, M., Bygbjerg, I. C., Andersen, P. H., Thomsen, V. O. and Lillebaek, T. Migrant tuberculosis: the extent of transmission in a low burden country. BMC Infect Dis 12, 60, doi:10.1186/1471-2334-12-601471-2334-12-60 [pii] (2012).

Kehr, J. Blind spots and adverse conditions of care: screening migrants for tuberculosis in France and Germany. Sociol Health Illn 34, 251-265, doi:10.1111/j.1467-9566.2011.01415.x (2012).

Kim, D. Y., Ridzon, R., Giles, B., Mireles, T., Garrity, K., Hathcock, A. L., Crowder, D., Jackson, R. and Taylor, Z. A no-name tuberculosis tracking system. Am J Public Health 93, 1637-1639 (2003).

King, K., Douglas, P. J. and Beath, K. Is premigration health screening for tuberculosis worthwhile? Med J Aust 195, 534-537, doi:kin11395_fm [pii] (2011).

Klinkenberg, E., Manissero, D., Semenza, J. C. and Verver, S. Migrant tuberculosis screening in the EU/EEA: yield, coverage and limitations. Eur Respir J 34, 1180-1189, doi:10.1183/09031936.00038009 34/5/1180 [pii] (2009).

Klopper, M., Warren, R. M., Hayes, C., Gey van Pittius, N. C., Streicher, E. M., Müller, B., Sirgel, F. A., Chabula-Nxiweni, M., Hoosain, E., Coetzee, G., van Helden, P. D., Victor, T. C. and André Phillip Trollip, A. P. Emergence and Spread of Extensively and Totally Drug-Resistant Tuberculosis, South Africa. Emerg Infect Dis, 19, (2013).

Lange, C., Grobusch, M. P. and Wagner, D. [Extensively drug-resistant tuberculosis]. Dtsch Med Wochenschr 133, 374-376, doi:10.1055/s-2008-1046724 (2008).

Leitmeyer, K. European risk assessment guidance for infectious diseases transmitted on aircraft--the RAGIDA project. Euro Surveill 16, doi:19845 [pii] (2011).

Lemaitre, N., Sougakoff, W., Truffot-Pernot, C., Cambau, E., Derenne, J.-P., Bricaire, F., Grosset, J. and Jarlier, V. Use of DNA fingerprinting for primary surveillance of nosocomial tuberculosis in a large urban hospital: detection of outbreaks in homeless people and migrant workers. Int J Tuberc Lung Dis 2, 390-396 (1998).

Lillebaek, T., Andersen, A. B, Dirksen, A., Smith, E., Skovgaard, L. T. and Kok-Jensen, A. Persistent High Incidence of Tuberculosis in Immigrants in a Low-Incidence Country. Emerg Infect Dis 8, 679-684, (2002).

Littleton, J., Park, J., Thornley, C., Anderson, A. and Lawrence, J. Migrants and tuberculosis: analysing epidemiological data with ethnography. Aust N Z J Public Health 32, 142-149, doi:10.1111/j.1753-6405.2008.00191.x AZPH191 [pii] (2008).

MacPherson, D. W. and Gushulak, B. D. Balancing prevention and screening among international migrants with tuberculosis: population mobility as the major epidemiological influence in low-incidence nations. Public Health 120, 712-723, doi:S0033-3506(06)00106-5 [pii] 10.1016/j.puhe.2006.05.002 (2006).

Marks, G. B., Bai, J., Simpson, S. E., Stewart, G. J. and Sullivan, E. A. The incidence of tuberculosis in a cohort of South-East Asian refugees arriving in Australia 1984-94. Respirology 6, 71-74, doi:res300 [pii] (2001).

Marks, G. B., Bai, J., Simpson, S. E., Sullivan, E. A. and Stewart, G. J. Incidence of tuberculosis among a cohort of tuberculin-positive refugees in Australia: reappraising the estimates of risk. Am J Respir Crit Care Med 162, 1851-1854 (2000).

Marks, G. B., Bai, J., Stewart, G. J., Simpson, S. E. and Sullivan, E. A. Effectiveness of postmigration screening in controlling tuberculosis among refugees: a historical cohort study, 1984-1998. Am J Public Health 91, 1797-1799 (2001).

Marx, F. M., Skachkova, E. I., Son, I. M., Strelis, A. K., Urazova, O. I., Hahn, H., Kramer, A. and Ulrichs, T. [Control of tuberculosis in Russia and other countries of the former Soviet Union]. Pneumologie 63, 253-260, doi:10.1055/s-0028-1119571 (2009).

Migration, I. O. f. (2011). International Organization for Migration. www.iom.int/ iomwebsite. (Accessed Jan 2013)

Mulder, C., Klinkenberg, E. and Manissero, D. Effectiveness of tuberculosis contact tracing among migrants and the foreign-born population. Euro Surveill 14, doi:19153 [pii] (2009).

Mulder, C., van Deutekom, H., Huisman, E. M., Toumanian, S., Koster, B. F. P. J., Meijer-Veldman, W., van Loenhout-Rooyackers, J. H., Appel, M., Arend, S. M., Borgdorff, M. W. and van Leth, F. Role of the QuantiFERON(R)-TB Gold In-Tube assay in screening new immigrants for tuberculosis infection. Eur Respir J 40, 1443-1449, doi:10.1183/09031936.00010612 09031936.00010612 [pii] (2012).

Pareek, M., Baussano, I., Abubakar, I., Dye, C. and Lalvani, A. Evaluation of immigrant tuberculosis screening in industrialized countries. Emerg Infect Dis 18, 1422-1429, doi:10.3201/eid1809.120128 (2012). http://wwwnc.cdc.gov/eid/article/18/9/12-0128_article.htm

Porco, T. C., Lewis, B., Marseille, E., Grinsdale, J., Flood, J. M. and Royce, S. E. Cost-effectiveness of tuberculosis evaluation and treatment of newly-arrived immigrants. BMC Public Health 6, 157, doi:1471-2458-6-157 [pii] 10.1186/1471-2458-6-157 (2006).

Reid, M. J. A. and Shah, S. N. Approaches to tuberculosis screening and diagnosis in people with HIV in resource-limited settings. Lancet Infect Dis 9, Issue 3, 173-184, (2009).

Reitmanova, S. Immigrant tuberculosis: beyond screening and surveillance. Lancet Infect Dis 9, 584-585, doi:10.1016/S1473-3099(09)70237-3 S1473-3099(09)70237-3 [pii] (2009).

Rieder, H. L., Zellweger, J. P., Raviglione, M. C., Keizer, S. T. and Migliori, G. B. Tuberculosis control in Europe and international migration. Eur Respir J 7, 1545-1553 (1994).

RKI, Data of the Tuberculosis Report (2010)

Rowland, K. Totally drug-resistant TB emerges in India. Nature/News. DOI:doi:10.1038/nature.2012.9797 (2012).

Schwartzman, K., Oxlade, O., Barr, G. R., Grimard, F., Acosta, I., Baez, J., Ferreira, E., Melgen, R. E., Morose, W., Salgado, A. C., Jacquet, V., Maloney, S., Laserson, K., Mendez, A. P. and Menzies, D. Domestic returns from investment in the control of tuberculosis in other countries. N Engl J Med 353, 1008-1020, doi:353/10/1008 [pii] 10.1056/NEJMsa043194 (2005).

United Nations. Recommendations on statistics of international migration. http://unstats.un.org/unsd/cdb/cdb_dict_xrxx.asp?def_code=336. (Accessed Jan 2013) http://www.un.org/esa/population/migration/data-analysis-undesa-bpaper.pdf (Accessed Jan 2013)

Valin, N., Antoun, F., Chouaid, C., Renard, M., Dautzenberg, B., Lalande, V., Ayache, B., Morin, P., Sougakoff, W., Thiolet, J. M., Truffot-Pernot, C., Jarlier, V. and Decludt, B. Outbreak of tuberculosis in a migrants' shelter, Paris, France, 2002. Int J Tuberc Lung Dis 9, 528-533 (2005).

Vos, A. M., Meima, A., Verver, S., Looman, C. W. N., Bos, V., Borgdorff, M. W. and Habbema, J. D. F. High incidence of pulmonary tuberculosis persists a decade after immigration, The Netherlands. Emerg Infect Dis 10, 736-739, doi:10.3201/eid1004.030530 (2004).

Watkins, R. E., Plant, A. J. and Gushulak, B. D. Tuberculosis rates among migrants in Australia and Canada. Int J Tuberc Lung Dis 6, 641-644 (2002).

WHO, Tuberculosis - Fact sheet No 104. www.who.int. [October 2012]

WHO. Multidrug and extensively drug-resistant TB (M/XDR-TB): 2010 Global Report on Surveillance and Response. http://www.who.int/tb/publications/2010/mdrtb2010report_executive_summary.pdf (2010).

Wolff, H., Janssens, J., Bodenmann, P., Meynard, A., Delhumeau, C., Rochat, T., Sudre, P., Costanza, M., Gaspoz, J. and Morabia, A. Undocumented migrants in Switzerland: geographical origin versus legal status as risk factor for tuberculosis. J Immigr Minor Health 12, 18-23, doi:10.1007/s10903-009-9271-6 (2010).

World Health Organization. Global tuberculosis control 2011. http://www.who.int/tb/publications/global_report/2011/en/index.html.(Accessed January 2013)