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The Impact of Tuberculosis among Immigrants: Epidemiology and Strategies of Control in High-Income Countries – Current Data and Literature Review

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Additional information is available at the end of the chapter

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Abstract

A significant reappearance of tuberculosis (TB) was observed in industrialized countries during the last two decades. This is due to the spread of HIV infection itself and to today's migratory phenomenon as a consequence of wealth disparity, poverty, wars and political persecutions. This proportion is expected to increase and represents an important cause of the overall resurgence of the TB epidemic and drug-resistant TB in Western Europe and the USA. TB is currently one of the leading causes of death worldwide and a health problem in high-income countries. Although WHO global TB report 2015 with its "STOP TB" strategy has the goal to eliminate TB as a public health problem by 2050, TB shows no signs of disappearing despite some decline in high-income countries. In order to intensify the fights against this deadly disease, further efforts should be aimed to improve examination/detection processes to accurately determine all kinds of TB, and how best to enhance TB control through a coordinated medical screening program of migrants for active TB. Migration in itself is not a definitive risk for TB. Stressful living condition, social isolation, poverty, political fear/persecution, and difficulties to access to health care can expose these individuals to the risk of TB infection during and after the migration process. This chapter aims to discuss and highlight all these issues.

Keywords: tuberculosis (TB), latent tuberculosis infection (LTBI), migrants, documented migrants, undocumented migrants, asylum seekers, refugees, Europe (EU)

1. Introduction

Tuberculosis (TB) currently represents one of the leading causes of death worldwide and, despite globally the TB incidence fell by an average of 1.5% per year since 2000 and is now

18% lower than the level of 2000, it has been declared a global health emergency in high-income countries [4]. TB is also the primary killer due to a single infectious disease and, after HIV/AIDS, is the second single disease which causes more deaths in the world [2]. The World Health Organization (WHO) estimates that one-third of the world population harbors latent TB infections (LTBI), 14.1 million people have active cases, 9 million are newly diagnosed per year (9.6 million new TB cases in 2014, of which 58% in the Southeast Asia and Western Pacific regions), and 1.5 million deaths are attributable to TB annually [1–4]. This death toll equals 2% of global mortality, even if it is a disease for which a cure has existed for 70 years.

In relation to HIV infection, more than 48% of TB patients globally had a documented positive HIV test result. In the African region, which has the highest TB/HIV burden, three out of four TB patients knew their HIV status [4].

Although the general decrease [1, 4] of TB cases (globally, the TB mortality rate fell by an estimated 45% between 1990 and 2013 and the TB prevalence rate fell by 41% during the same period) in recent decades has led the medical profession to pay less attention to the presence of high-risk patients, TB continues to be a public health concern in high-income countries, primarily among the foreign-born and migrant population [5]. In fact, a reappearance of this disease was observed since the early 1990s due to other than the spread of HIV infection and the increase in poor living conditions and immunosuppression; it is due to the migratory phenomenon, and an interplay of various push and pull factors are a consequence of wealth disparity, poverty, wars, and political persecutions [6, 7].

There are 244 million migrants worldwide, which is 41% more since 2000. Note that 76 million are in Europe, the continent with the highest number of migrants, followed by Asia (75 million), United States (54 million), Africa (21 million), Latin America and the Caribbean (9 million), and Oceania (8 million), according to the calculations of the latest International Migration Report of the United Nations [8]. Of all the immigrants living in Europe, Germany and Russia have 12 million, the United Kingdom has 9 million, France has 8 million, Spain and Italy have 6 million; while Saudi Arabia has 10 million and Canada and Australia have 7 million, respectively. According to the previous report of the UN [8], the largest number of citizens migrated abroad come mainly from India (16 million), Mexico (12 million), Russia (11 million), China (10 million), Bangladesh (7 million), Pakistan and Ukraine (6,000,000), and the Philippines and Syria with about 5 million migrants.

Immigrants from TB endemic countries account for a significant proportion of TB cases in industrialized countries. It can be anticipated that this proportion will continue to increase, and will represent an important cause of the overall resurgence of the TB epidemic in Western EU and the USA. Most migrants are healthy, but conditions surrounding the migration process can pose health risks such as inequalities in accessing health services, substandard quality of care, marginalization, and discrimination. Thus, the particular condition of “immigrant” predisposes to an increased risk of developing TB, either for increased incidence rates in their countries of origin, or the high rate of LTBI which predisposes to TB for conditions of social fragility and complexity related to the process of migration and multiculturalism found in the host country.

The chapter is structured as follows:

- Overview and epidemiological features of TB among immigrants in low-TB burden countries.
- Definition of LTBI and risk of progression toward TB.
- Management of LTBI among immigrants and screening practices.
- Essentials of diagnosis of infectious TB among immigrants in low TB burden countries.
- Management and treatment of drug-resistant TB.
- Conclusions and social issues.

2. Overview and epidemiological features of TB among immigrants in low-TB burden countries and screening practices

2.1. Overview and epidemiological features of TB among immigrants in low-TB burden countries¹

Many migrants originating from countries where TB has a high incidence, including tropical areas [9], have a high risk of acquiring TB before migration. Much of TB burden is concentrated in high-burden settings of Africa and Asia (28 and 58%, respectively) where TB continues to be a cause of morbidity and mortality [5]. Some areas of tropical countries, such as Haiti, Peru, Bolivia, and Suriname, have the highest TB incidence in the Americas (between 100 and 200 per 100,000 inhabitants) [10], whereas Brazil has a high TB burden, but this is not uniformly distributed. In sub-Saharan Africa and in some regions of India, HIV-coinfection and poverty affecting housing conditions, ventilation, nutritional status, education, and access to health care, other than growing urbanization with the consequent overcrowded living conditions, are the most important determinants of TB epidemic in tropical countries [9].

TB remains one of the major public health challenges in North Africa with decreasing gradient incidence from Morocco (the highest) with more than 27,000 new cases per year, to intermediate in Algeria and lowest in Tunisia and Egypt (30 and 17 cases per 100,000, respectively) [11]. In the European Economic Area (EEA), the majority of subjects of foreign origin with TB in 2009 originated from Asia, Africa, and other European countries (34, 28, and 9.5%, respectively) [9, 10, 12]. This proportion continues to increase, and represents an important cause of the overall resurgence of the TB epidemic in the USA and Western Europe (EU) [12]. It can be anticipated that, despite efforts of the industrialized countries to conquer the disease, the incidence of new TB cases in EU varies from very low rates in Scandinavian countries (6–8 cases/100,000 population) to rates as high as 231 cases/100,000 populations in Tajikistan; the Russian Federation is eleventh among the 22 high-burden TB countries [12]. In Italy, where

¹Low TB burden or low TB incidence countries are defined as those with a TB notification rate of ≤ 100 cases (all forms) per million population a year. The high-TB burden or incidence countries are countries with the highest estimated numbers of incident TB cases that account for 80% of the global total.

over the last decade the TB notification has been stable at approximately 7 cases per 100,000 people annually, the immigrant population has a relative risk of suffering from TB, 10–15 times higher than the Italian-born population [4]. In fact, the proportion of TB cases of foreigners increased from 22% in 1999 to 46% in 2008 of the total [13]; at the same time, the proportion of drug-resistant TB cases rose to 83% [14]. Almost two-thirds of the cases of TB in foreigners in 2008 occurred in northern Italy, where immigration is more prominent than in other areas of the country [13]. The most affected age group was of young adults [13]. Concurrently in Italy, while the proportion of African-born persons with TB decreased from 51 to 30%, the proportion of cases with TB born in Eastern EU, including former Soviet Union countries, increased from 16 to 33% [14, 15]. In the Italian population, the two most affected population groups are the elderly and the foreign born. The elderly population, due to progressive weakening of both, their general conditions and their immune system, caused by the aging process itself, is at increased risk of reactivation of LTBI. Foreign-born residents, which are at increased risk of developing TB either because of the high incidence rates of TB in their countries of origin or because of the social fragility deriving from the migration process itself [16], account for the increase of TB in people less than 65 years of age and for the great majority of drug-resistant TB cases.

Summarizing, the European countries share a TB epidemiology which is characterized by a decrease of TB incidence in natives but an increasing incidence in foreign-born persons; occurrence of the majority of TB cases in recent migrants and younger age groups, especially those experiencing inadequate living and health conditions; and high percentage of drug-resistant TB among immigrants and previously treated patients [11].

Factors that influence the risk of TB reactivation among immigrants in low TB burden countries include the prevalence of TB in the country of origin, the duration of residence in the host country, and the efficiency and quality of curative and preventive services. As mentioned previously, after the actual migration process, immigrants are exposed to additional risk of acquiring reactivated TB infection because of stressful living in overcrowded conditions, social isolation, poverty, malnutrition, unemployment, and difficulties to access to health care. Generally, TB in immigrants in low-burden countries arises from an active TB infection which occurred overseas. There are also reactivations of remotely acquired LTBI, which occurs months to years after settlement in the host country, or acquired TB as new infection postarrival in the host country through local transmission or during a return travel to the country of origin [17]. Second-generation migrants, who often keep a link with their country of origin, or international travellers including visiting friends and relatives (VFR), especially children, are known to represent high-risk groups for TB [18]. Finally, homeless immigrants and other deprived groups in low-burden countries can have transmission rates as high as some high-burden countries [19].

2.2. Screening practices among adults

Migrants currently play an important role in determining the current epidemiology of TB in low TB burden countries where they are settled. As a consequence, although reports from different high-income countries with well-performing immigration medical screening have demonstrated that foreign-born TB patients do not contribute to the transmission of TB in the

native population [20], there is an increasing interest on how best to enhance TB control through coordinated medical screening of documented as well as undocumented migrants such as migrants or refugees that are arriving presently at the Greek and Italian coasts. Undocumented migrants have been shown to be at higher TB risk than other migrants, as their entry and TB infection is often more recent and their migration and living conditions are worse than those of documented migrants [21].

Immigration TB screening programs for high immigration and low TB incidence countries vary according to the national legislation, resource availability, and public health risk management practices. Moreover, programs differ by whether screening is done for active TB or LTBI, or both. The programs also differ in relation to arrival in the host country, i.e., the migrants' status, such as refugees or asylum seekers, the countries of origin, and tools used to screen for active TB or LTBI [22, 23]. The rationale of these programs is the early detection and treatment of active and often contagious TB cases in order to prevent *Mycobacterium tuberculosis* transmission to the host population of a low-burden country and reduce the burden of imported TB in low-incidence countries. Methods of TB control in migrant populations have historically focused on identifying active TB with accompanying contact tracing, but the yields for this remain relatively low. In this setting, screening can occur before entry (pre-entry screening), at entry (sometimes called port of entry screening), or after entry [24].

In most of cases, active TB immigrant medical screening in high-income industrialized countries for both documented migrants, refugees, or asylum seekers is performed on or soon after the entry (borders such as airport, reception centers/holding camps, migrant centers); 36% (9 of 25 countries including Australia, Canada, Israel, Jordan, New Zealand, France, the UK, and the USA) have a pre-entry TB screening in country of origin for people who intend to migrate; 20% (5 of 25 countries including Norway, Sweden, Switzerland, the Netherlands, and the UK) perform screening at entry [24, 25]. Literature shows that 88% of countries use chest X-rays (CXR) alone or in combination with clinical examination or TST [5, 24]. The sensitivity and specificity of CXR vary from 86–97% to 75–89%, respectively, and according to the criteria of imaging interpretation. CXR alone does not detect extrapulmonary TB (EPTB) which is increasing in comparison to pulmonary TB, especially in low-burden and high immigrant receiving countries [26], and in HIV-positive persons that have higher rates of EPTB compared with those who are HIV-negative.

Sputum smear and culture follow CXR only if this is found to be abnormal. The destiny of migrants to enter the host country depends on the outcome of these tests.

An interesting and original active TB finding approach was recently investigated by Schepisi [27] in Italy, a country where there is no TB national screening policy for new entrants [28]. Italy is a country with a TB incidence rate of 5.3/100,000 persons with 3.153 cases in 2013 [29]. TB cases are especially concentrated among high-risk TB groups, including migrants from high-incidence countries, homeless people, and drug and alcohol abusers. The study analyzed TB case finding intervention based on verbal symptoms screening,² conducted at primary centers for undocumented migrants, refugees, and asylum seekers in different Italian sites.

²Presence of cough, fever, fatigue, hemoptysis and weight loss.

Although only a limited number of TB cases was detected, of those screened and evaluated, the study, based on its feasible cost approach and reduced burden of medical procedures, contributed to the diagnoses and control of TB, especially among subpopulations that have difficulties to access specialized healthcare centers [27].

2.3. TB screening of migrant children

Although many countries have developed and documented immigration TB screening programs to suit the needs of adults, attention to migrant children lacks intensive studies.

Screening migrant children for TB is particularly important, as they have a higher risk of developing active disease due to recent infection. Furthermore, due to its “paucibacillary” nature, which makes it rarely infectious, when they develop the disease, it is more severe, resulting in increased morbidity and mortality compared with adults. Thus, TB screening in high-risk children from high-incidence countries should form part of all immigration TB screening programs. A recent survey compared various screening tools (history, physical examination, TST, interferon-gamma release assays (IGRAs), CXR,³ and MTB (*M. tuberculosis*) bacteriology) among migrant children [30]. The screening programs varied considerably between the various participating countries. History and physical examination was often normal in children with active TB disease, and TST emerged as a better predictor of TB infection or disease [30]. Sociocultural and behavioral factors have shown to be involved in the acceptance of LTBI treatment in these populations [31]. In pediatrics, although TB may not be of immediate public health concern, individual morbidity and mortality is high. The goal of TB screening is to identify children with LTBI who are at risk for progression to active TB, as early LTBI treatment prevents extended and disseminated disease.

3. Definition of LTBI and risk of progression toward TB

Although the word LTBI should be “reconsidered” considering that both “latent” and “infection” terms indicate lack of disease and thus are redundant [32], LTBI is defined as a state of persistent immune response to previously acquired TB antigens without evidence of clinically manifested active TB disease. It is an asymptomatic and nontransmissible condition that is maintained for the lifetime of the infected person. Current tools are insufficient to measure the global prevalence of LTBI, but investigations carried out a decade ago estimated that approximately one-third of the world population (>2 billion people) is latently infected with *M. tuberculosis*.

A relatively small proportion, 5–15% of screen-test-positive patients of the estimated >2 billion people with LTBI will develop TB disease (TB reactivation) within the first 5 years after initial infection, with the remaining risk distributed over the rest of the life span [33, 34]. The likelihood of progression from LTBI to active clinical TB disease is determined by bacterial,

³Mainly employed in children ages from 11 to 16 years.

host, and environmental factors, potentially favoring TB evolution. A schematic diagram showing TB evolution following exposition is illustrated in **Figure 1**.

The risk factors for acquiring LTBI infection involve people at increased risk which include infants, children (<5 years), and adolescents who have intimate contact with high-risk adults, as well as persons who have had close contact with someone known or suspected to have active TB, health care workers, high-risk racial and ethnic minorities, prisoners, residents in nursing homes, hospitals, and homeless shelters [34]. LTBI also occurs in the migrant population coming from low-income countries with a high burden of disease, especially from the Indian subcontinent and sub-Saharan Africa (the highest burden in the world), as well as in asylum seekers and refugees, a subgroup of immigrants at particular risk for TB. Persons coming from tropical areas are also at an increased risk for developing TB. The probability of developing TB is much higher among people with cellular immunity impairment due to: human immunodeficiency virus (HIV) infection, tumor necrosis factor α inhibitors, glucocorticoids administration, and organ or hematologic transplantation. Diabetes mellitus and chronic kidney disease are also more common in migrant populations and significantly increase the risk of reactivation from LTBI to active TB [34, 35].

Among all the considered conditions, HIV infection is the most potent risk factor for progression from LTBI to active TB disease [36]. TB in fact is the leading cause of death among people living with HIV, estimated to account for around 33% of all HIV-related deaths globally [4] and individuals with both, LTBI and HIV infection, have a risk of reactivation of 10% per year of life compared with 10% for life for those who do not have an HIV infection [23]. Many HIV-positive people in developing countries develop TB as the first manifestation of AIDS [4]. The major risk factors for progression from latent infection to active disease are wide ranging and are listed in **Table 1**.

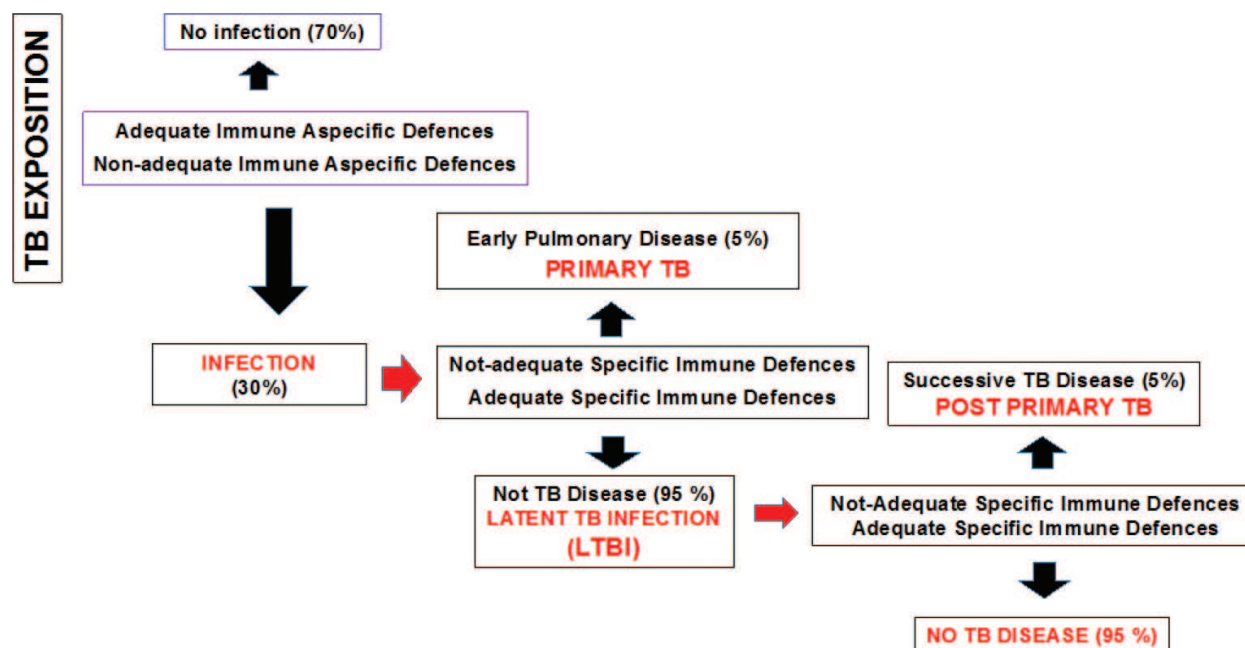


Figure 1. Evolution of TB from latent infection to active disease following exposition.

-
- Children younger than 5 years
 - Persons with immunocompromising conditions (HIV, leukemia, lymphoma)
 - Persons infected with *M. tuberculosis* within the past 2 years; persons who inject illicit drugs or use other locally identified high-risk substances (e.g., crack cocaine), tobacco, or alcohol abuse (risk of infection and active disease)
 - Persons with a history of untreated or inadequately treated TB, including those with CXR findings consistent with previous tuberculosis (e.g., apical fibronodular changes on CXR)
 - Homeless adults, elderly, health care workers, and medical students
 - Persons with recent conversion of a negative tuberculin skin test to a positive test
 - Persons with the following clinical conditions or other conditions compromising immunity: disorders requiring long-term use of corticosteroids or other immunosuppressant medications (including tumor necrosis factor-alpha antagonists), body weight 10% or more below the ideal, chronic renal failure, and end-stage renal disease requiring dialysis, diabetes mellitus*, gastrectomy or intestinal bypass, malignancy (cancer of the head, neck, or lung), silicosis
 - Tropical parasitic diseases including helminthic infestations**
 - Black race, black skin individuals***
-

*Diabetes can increase the relative TB risk (range 1.16–7.83) [37].

**These can negatively impact on TB disease inducing immunological weakening throughout Th1 impairment [38].

***Black skin individuals are constitutively more susceptible than white skin persons owing to environmental and genetic factors [39].

Table 1. Groups at increased risk of progression from LTBI to active tuberculosis.

4. Management of LTBI among immigrants and screening practices

Given that the majority of active TB in foreign-born persons in low-incidence countries arises from reactivation of LTBI, acquired many years previously in the country of origin, as also demonstrated by epidemiological studies based on *M. tuberculosis* strain isolates by molecular genotyping that found that 55–90% of TB cases in foreign-born persons are due to LTBI reactivation [40–41]. Screening new entrants for LTBI remains the cornerstone for controlling imported TB. While most developed countries screen for active TB, screening for LTBI is much less commonly performed [24, 42].

Guidelines for LTBI screening among immigrants are not homogenous and vary among regions; moreover, evidence supporting their effectiveness is lacking and identifying models of best practice remains difficult, so that there are no perfect methods for the diagnosis and management of LTBI [43–45] whose identification provides opportunity for early treatment and the prevention of significant health sequelae for the individual. Diagnosis of TB is currently based on a positive result of either a tuberculin skin test (TST) or IGRA test indicating an immune response to *M. tuberculosis*. The TST is widely used and inexpensive, but requires a repeat visit to the physician and has low performance in persons recently vaccinated with BCG (e.g., immigrants arriving in industrialized countries), or who are infected with HIV. With the TST, an induration of 15 mm or more is considered positive in persons without risk factors, 10 mm or more is positive for those at higher risk, such as immigrants from high TB-endemic countries with no history of TB, and 5 mm or more is positive for certain high-risk persons (e.g., immunocompromised patients, those exposed to

active TB). The more expensive IGRAs overcome some of the TST performance issues [46]. IGRAs require a single patient visit to conduct the test and results can be available within 24 hours. IGRAs, however, are not the preferred testing method for use in children younger than 5 years old, persons recently exposed to TB, immunocompromised persons, and those who will be tested repeatedly [47]. To test immigrant and refugee children with LTBI who are probably vaccinated with BCG, IGRAs may limit the number of children targeted for preventive therapy [48]. The use of one-step IGRA has also demonstrated to be the best option for young migrants [9]. Although in the last decade, IGRAs have increasingly replaced the use of TST, these tests have also limitations, both cannot verify the presence/absence of dormant bacteria still able to reactivate and thus they do not reliably predict who will progress to active TB [2, 3]. Moreover, strong positive tests do not suggest a higher TB risk reactivation, and in children under 5 years of age and immunocompromised patients, including HIV-infected subjects, the test performances are particularly poor, thus needing a better detection test for LTBI [49, 50]. The comparative performance of the TST and IGRAs also varies between high-incidence and low-incidence countries, possibly because of the effects of BCG vaccination and reinfection [51]. In this setting, WHO strongly recommend that either TST or IGRA be used to test for LTBI in special risk populations (i.e., HIV persons, transplant patients, patients initiating anti-TNF treatments, household members or close contacts, including children of pulmonary TB cases). A positive IGRA or TST test is required to diagnose LTBI and to start specific therapy according WHO guidelines [4]. In high TB burden countries a LTBI test is not required prior to LTBI treatment, but it is encouraged for HIV-positive persons.

4.1. Screening practices

Individuals should be asked about symptoms of TB before being tested for LTBI. In this setting, WHO guidelines [4] suggest an algorithm for targeted diagnosis and treatment of LTBI in individuals of risk groups (**Figure 2**).

A recent survey found that only 55.2%, 16 out of the previously mentioned 29 countries (see p. 6), screen for LTBI most frequently postarrival in their country using TST in 68.8% of cases, TST plus a confirmatory IGRA in 25%, and IGRA alone in 18.8%. In 11 of these countries, the screening is compulsory for documented migrants [5, 24, 25].

The screening may decrease the period of infectiousness by as much as 33% in some situations [5]. LTBI screening is effective in persons at risk of contracting *M. tuberculosis* or of progressing from LTBI to active TB. It is generally thought that routine screening outside these high-risk groups wastes resources and leads to high false-positive test rates. According to the WHO 2015 Guidelines on the Management of LTBI [4], systematic testing and treatment of LTBI is highly recommended in immigrants from high TB burden countries; prisoners, homeless persons, and illicit drug users should be treated according to TB epidemiology and resource availability. This procedure has shown to lead to early detection of cases, resulting in a shorter duration of symptoms, and fewer hospitalizations.

The decision to screen for TB is a decision to treat. LTBI can be effectively treated in order to prevent progression to active TB, thus resulting in a substantial benefit for both the individual and the community. Currently available treatment options allow to reduce the risk of

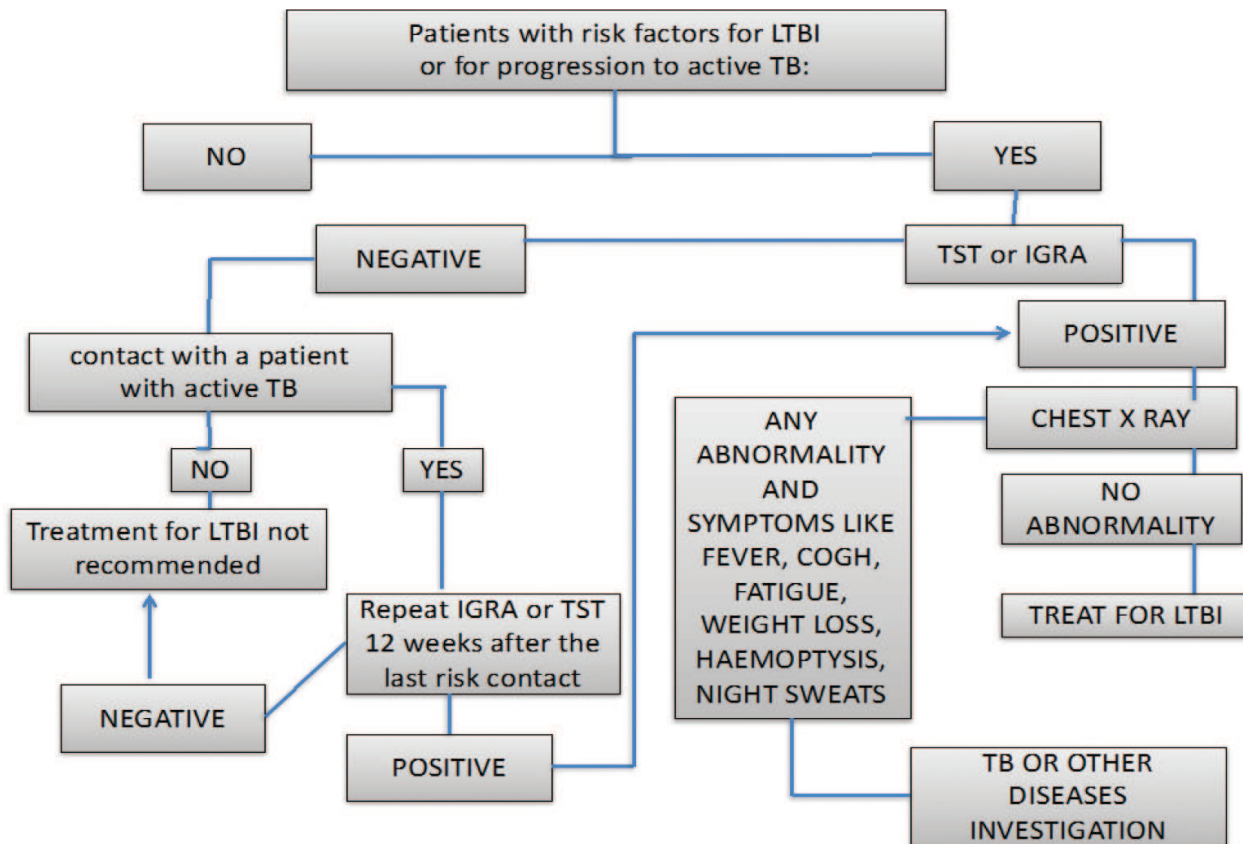


Figure 2. Algorithm for the management of LTBI in individuals at risk for TB. Modified and adapted from Guidelines on the Management of Latent Tuberculosis Infection. Available from: www.who.int/tb/areas-of-work/preventive-care/lbti/en/

developing active TB by at least 60%. However, safety concerns exist, mainly related to the development of drug-related adverse events including hepatotoxicity. The following regimens recommended by the WHO TB Report 2015 [4] for the treatment of LTBI are: daily therapy with INH for 6–9 months; 12 weeks rifampentine plus INH weekly; 3–4 months INH plus rifampicin daily; rifampicin plus pyrazinamide for 2 months or 3–4 months RIF alone. While the safety of 2 months of RIF and PZA has shown to be acceptable in HIV-infected persons and children, in non-HIV-infected adults, this regimen has demonstrated a high rate of severe liver toxicity [52].

Identification of latently infected individuals and their treatment has lowered TB incidence in rich, advanced countries. Similar approaches also hold great promise for countries with low to intermediate rates of TB incidence. Wide variations are observed for the cost of screening of eligible candidates for LTBI treatment and the costs for treatment. For reasons of practicality and cost effectiveness, most high-income countries consider and check as eligible population refugees or asylum seekers or those individuals arriving from high TB burden settings. The available evidence suggests that screening for and treatment of LTBI may be a cost-effective intervention in population groups characterized by high prevalence of LTBI and/or high risk of progression to active TB, such as persons migrating from high TB incidence countries, contacts with active TB cases, and persons living with HIV.

5. Essentials of diagnosis of infectious TB among immigrants in low TB burden countries

Owing to difficulties in access to the health system, TB diagnosis and treatment are lower in migrant populations compared to native subjects. This is in part due to the fact that migrants, in general, have a longer patient diagnostic delay for TB (time elapsed from the onset of symptoms and the first medical visit) possibly due to a combination of reasons including language barriers, unemployment, or interruption due to lack of medical insurance that hinders migrants from using the available health TB services, while natives have a longer health care diagnostic delay (defined as the time elapsed between the first medical consultation and the initiation of treatment) [53]. Although the reliability of epidemiological assessments has progressively improved in recent years, no more than 30% of the estimated number of people suffering from TB, including migrants, is actually diagnosed with a method of proven efficacy [54]. Moreover, current diagnostic tests have poor performance on forms of TB which are intrinsically difficult to diagnose, such as childhood TB, smear-negative pulmonary TB and EPTB, TB in HIV/AIDS patients, and drug-resistant TB.

5.1. Conventional diagnostic methods

To date, the most common methods for diagnosing TB worldwide which constitute the backbone of TB diagnosis remain the “old” sputum smear microscopy test and bacteriological culture which is also the test necessary for monitoring patients’ response to treatment [2, 3]. These methods, however, represent a major constraint even in high-tech, high-resources western countries, when the mycobacterial load is low or the district of infection is not easily accessible. TB diagnosis includes suspicion as the first step. All patients with TB, including migrants, can present with almost any symptom including cough, shortness of breath, chest pain, hemoptysis, together with the presence of constitutional symptoms (weight loss, fever, fatigue, and night sweats) which meet the definition of a suspected TB case according to WHO [55]. These symptoms must be considered in differential diagnosis in patients with epidemiologic risk (exposure to infectious patients, travel to or residence in a high prevalence area, previous TB) [2, 54]. The clinical suspicion of TB is then investigated through radiographic imaging, microbiology, and histopathology. Radiology could also have an important role in the diagnosis of TB in low-resource countries, especially as pre-entry TB screening in the country of origin for those migrants who intend to migrate and refugees. However, the equipment is expensive and it needs qualified and experienced staff to be able to interpret the radiological signs—they are not always available in these settings [23, 45, 56, 57]. Moreover, CXR cannot provide a conclusive diagnosis on its own and needs to be followed by sputum testing. Although inexpensive and potentially easy to perform, conventional smear microscopy has a number of limitations including the variable (from 20 to 80%) sensitivity which is low, particularly among all persons coinfecting with TB and HIV, including migrants and children, due to the reduced pulmonary bacillary load in these subjects [58]; it cannot distinguish between MBT complex and non-TB mycobacteria and it does not provide information on the resistance profile of the bacilli. In this setting, phenotypic drug-susceptibility testing (DST) on cultured specimens is the conventional method used to detect resistance to first- and SLD-TB drugs in

MDR-TB and monitoring patients' response to treatment [4]. Finally, the challenge of TB diagnosis in the low-income countries including the tropics, must also take into account the differential diagnosis with a wide spectrum of microbial agents causing respiratory infections of which migrants can be affected and include viruses, bacteria (*Actynomicetes*), and parasites (*paracoccidioidomycosis*, *paragonimiasis*, *dirofilariosis*), which can mimic TB [2, 3, 9], and other diseases such as sarcoidosis and cancer. In these settings, basic radiography and other analyses are of considerable use but are not available in all centers [9].

5.2. Advanced diagnostic techniques

Current-generation MTB-specific nucleic acid amplification tests (NAATs) can be a valid surrogate to direct observation or isolation of tubercular bacilli and to replace culture [33] and detect new TB cases within few hours. Although NAATs are widely used in Europe [33, 59], their high cost and level of technical support hindered the widespread adoption in TB endemic countries. Improving diagnosis in high-income countries is a strategic goal in TB research, and the pipeline of diagnostic tools is rapidly growing: new ways of performing sputum smear microscopy and innovative technologies for molecular diagnosis have already been endorsed by WHO, or are under investigation [60]. To respond to the urgent need for simple and rapid diagnostic tools at the point of treatment in high-burden countries, a fully automated molecular test for *M. tuberculosis* detection and resistance to RIF testing was developed (Xpert®MTB/RIF) and has been endorsed by WHO in December 2010 [56]. Its capability to simultaneously detect mutations conferring resistance to RIF extends its usefulness beyond the diagnosis of TB (sensitivity 98.2 and 72.5% respectively for smear-positive and smear-negative samples; specificity 99.2%), also to first-line assessment of RIF resistance (99.1% sensitivity and 100% specificity) and prediction of multidrug resistance (99% sensitivity) [61]. Xpert®MTB/RIF system has the advantage to provide accurate results in less than 2 hours as it requires minimal biosafety supplies and training, so that patients can receive treatment from the same day on. According to WHO recommendations, Xpert®MTB/RIF, which is less sensitive than culture but more sensitive than microscopy [62], should be especially used as the initial diagnostic test in all individuals including migrants suspected of multidrug-resistant (MDR) TB or HIV-associated TB and in testing cerebrospinal fluid specimens from patients presumed to have TB meningitis; it may be used as a follow-on test to microscopy in settings where MDR and/or HIV is of lesser concern, especially in smear-negative specimens (conditional recommendation, recognizing major resource implications). With the introduction of Xpert®MTB/RIF, there has been an increase of the number of microbiologically confirmed TB in children [63], thus offering in low-income and middle-income countries, an opportunity for investigators to provide access to diagnosis for children beyond smear microscopy, and an increase of the number of pulmonary TB cases detected in HIV-positive patients when compared with microscopy [62]. Although with high specificity, Xpert®MTB/RIF has shown limited sensitivity for the detection of EPTB especially in HIV-positive individuals and among migrants in whom it can mimic cancer, bacterial and fungal infections [4, 64]. Other than Xpert®MTB/RIF test, new TB diagnostic tests may enhance diagnostic algorithms by offering rapid, point-of-care, or near-care detection of TB. One of these is the urine tests for lipoarabinomannan (LAM) and is detectable in the urine of all individuals with active TB [65]. Urine-based testing has

advantages over sputum-based testing because urine is easy to collect and store, and lacks the infection control risks associated with sputum collection. The test is easy to perform, rapid (less than 30 minutes), and may be used at the point at which care is provided for TB or HIV. The urinary LAM assays currently available are unsuitable as general diagnostic or screening tests for TB, due to suboptimal sensitivity. The test was found to be cost-effective in sub-Saharan Africa when used for HIV-positive patients with CD4 counts of less than 100 per mm³ [66], but lacks accuracy if used in patients with CD4 counts over 200 or in children. WHO recommends that LAM assay should be used for the diagnosis of TB in all HIV-positive persons with low CD4 counts or in those who are seriously ill,⁴ and to assist in the diagnosis of TB in HIV-positive adult inpatients with signs or symptoms of TB (pulmonary and/or EPTB) who have a CD4 cell count less than or equal to 100 cells/L [4]. Other new generation NAAT kits have been released for research use [67], but further data are needed before their potential to assist TB control can be judged. Independent studies are required in settings representative of the intended use of the device.

6. Management and treatment of drug-resistant TB

So far TB treatment in migrant populations represents a challenge as it contributes considerably to illness and death especially in western countries. There are not only the economic but also the social costs. A number of social determinants, such as limited language, sociopsychological barriers, lack of employment, fear of expulsion, and access to health care facilities, often lead to a protracted diagnosis. Thus, TB treatment of these patients can be limited or inadequate and this is fundamental for conferring TB drug resistance.

6.1. MDR and XDR-TB management issues

The current standard of care of drug-susceptible MTB requires 6–9 months of combination therapy which includes a 2-month “intensive” phase of a four-drug cocktail containing RIF, INH, PZA, and EMB; followed by a longer “continuation” phase of RIF and INH to eradicate the remaining bacilli that have entered a dormant, slowly replicating the latent phase. Currently, standardized regimens require that patients’ daily ingest up to four drugs under direct observation of a healthcare worker for a period of 6–9 months. In this setting, directly observed treatment (DOT) of TB reduces TB-related death, disability, and transmission; it is a highly cost-effective intervention, even in the lowest income countries [54]. Treatment of TB represents a therapeutic challenge because of not only the natural level high resistance of *M. tuberculosis* to antibiotics, but also because of the occurrence of new mutations that confer additional resistance as well as multidrug strains. The drug-resistant TB represents a constant threat to some groups of patients, including migrants, who do not take the medication once they start to feel better. Indeed, an increasing number of MDR-TB strains are isolated because of the poor compliance to treatment that characterizes migrants themselves. Nowadays, the insufficient treatment regimens, nonadherence, and poor availability of drugs are a major

⁴Respiratory rate >30/min, temperature >39°C, heart rate >120/min, severe difficulty to walk unaided.

cause of treatment failure, relapse of disease, and TB drug-resistance especially in migrants. Eastern European countries are among those with the highest rates of MDR-TB and have also the most drug-resistant (XDR) strains in the world⁵ [15]. By the end of September 2009, at least one case of XDR-TB had been reported by each of the 25 countries in the European continent. The majority of European and other low prevalence countries, excluding some of the high priority countries in the WHO European Region (such as Latvia, Lithuania, Bulgaria, and Estonia), also reported higher prevalence of MDR-TB cases in migrants when compared to the native population [68]. The number of cases of XDR-TB diagnosed globally is rising as expected because of improved laboratory testing and reporting. The diagnosis of XDR-TB is equivalent today to a death sentence. Factors contributing to higher mortality rates in patients with XDR-TB include: resistance to six or more drugs, delayed diagnoses, prescribing ineffective drug therapies due to the lack of DST, and deprivation of programmatic access to effective SLD. During 2015, 105 countries reported cases of XDR-TB to the WHO [4]. However, the highest numbers were registered in 2014 and included India, Ukraine, South Africa, Belarus, and Kazakhstan [4]. In the United States, 15 cases of XDR-TB were reported to the CDC between 2009 and 2014 [4]. In Italy, the proportion of TB cases notified in foreigners increased from 22% in 1999 to 46% in 2008, paralleling the proportion of MDR-TB cases which consistently grew to 83% [13, 69]. A recent retrospective study conducted over the period 2008–2010 aimed to investigate drug-resistance proportions and drug-resistance profiles of *M. tuberculosis* strains circulating among immigrants and natives. It showed that the five countries mainly contributing to the TB resistance in foreigner groups in Italy were Romania (28.7%), Morocco (9.9%), Peru (5.8%), Pakistan (5.8%), and India (5.6%). Moreover, the MDR-TB prevalence in immigrants was consistent with that of their native countries (e.g., in 2009: Romania, 11.2%; Ukraine, 19%; Moldova, 44.3%). Differences in culture may impact significantly on TB prevention, diagnosis, and treatment in immigrants which, unlike the general population, are also at greater risk of having an infection with MDR-TB [14]. In general, patients who do not respond to previous TB therapy have an up to a 50-fold higher risk of having MDR- and XDR-TB. Other prominent risk factors include close contact to a patient with MDR-TB, migration, HIV infection, and young age. Moreover, as infection control policies are problematic in many developing countries, nosocomial transmission of MDR- and XDR-TB is 3–6 times higher in patients hospitalized for more than 14 days [70]. In particular, the risk increases in open hospital wards where advanced HIV-infected with low CD4 cell counts can facilitate the nosocomial spread of infection. The management of patients with MDR-TB, XDR-TB, or total resistant TB requires an appropriate and rapid diagnosis. After identification of high-risk groups, microbiological confirmation and appropriate treatment should be started [71, 72]. Confirmation of resistant-TB and identification of potentially effective drugs in an optimized combination treatment regimen should be done on the basis of antimicrobial DST. However, only 22% of countries worldwide routinely perform cultures and DST, and only 48% of the 46 countries in the WHO Africa region have ever undertaken a drug-resistance survey [4, 73]. Moreover, DST is often too expensive, especially in high-burden countries, and in many settings it is neglected because

⁵That is, MDR strains resistant to any FC and to at least one of three injectable SLD: KM, CM, AK.

of the lack of SLD [73, 74]. In general, treatment for MDR-TB can extend up to 2 years after microbiologic culture conversion and relies on more toxic, less efficacious second- or third-line agents, many of which are even more scarce than frontline drugs in affected areas [75].

6.2. Therapeutic concerns of MDR and XDR-TB in different population groups including migrants

Patients with MDR-TB strains should receive therapy based on individual DST including residual first-line (SM), EMB, PZA drugs, and SLD such as oxacin, KM, CM, ET, PAS, and CS. As with other antimicrobial agents, the use of SLD can generate resistant mutants. DST often shows poor reproducibility and lack of correlation with clinical response. The initial intensive phase of therapy should last 6–8 months and includes at least 4 months after culture conversion. Compared with the treatment of drug-susceptible TB, the treatment of MDR- and XDR-TB requires more drugs that are less well tolerated for a more prolonged duration. The available TB drugs against MDR/XDR-TB are included among a hierarchy of five groups, with first-line TB drugs listed in Group 1 and second-line drugs in Groups 2 through 5 [76]. Group 1 is composed of first-line TB drugs RIF, INH, PZA, and EMB; Group 2 contains the injectable agents embracing the bactericidal aminoglycosides (SM, AK, and KM) and CM, whereas Group 3 consists of FC including gatifloxacin and moxifloxacin. The remaining SLD ethionamide/prothionamide, CS, and PAS are inside Group 4 and are considered less potent and often less well tolerated by patients. Group 5 contains new antimicrobial agents, those with less clinical experience, and drugs with less proven efficacy in the management of drug-resistant TB such as clofazimine, developed in the 1950s to treat leprosy. Bedaquiline, delamanid, linezolid, clofazimine, meropenem, amoxicillin-clavulanate, and clarithromycin are included in this category. Although adherence to therapeutic programs is often impossible for immigrants as they are often lost in follow-up, at least five drugs (including an injectable agent) should be given for an “intensive phase” of up to 8 months. The specific drugs chosen depend on a patient's previous TB drug therapies and individual DST results. Thereafter, a “continuation phase” of least four oral drugs should be continued until a total minimum duration of 20 months. Prolonged therapy presents a range of practical challenges including prolonged hospitalization with conspicuous health care cost, toxicity (i.e., nephro- and ototoxicity with aminoglycoside drugs), and high loss to follow-up during continuation therapy. Finally, drug-resistant TB can represent in Africa a particular risk to individuals with HIV with high transmission of infection and high mortality [77]. Treatment success rates of MDR/XDR-TB vary between 36 and 79% [78, 79]. Surgery can have a positive adjunctive role with combination of antimicrobial drug therapy in the management of drug-resistant TB, but does not allow for shortening the duration of therapy [80].

Three groups of people deserve special attention in MDR/XDR TB management: children, pregnant women, and HIV-positive patients.

There are not enough data regarding optimal duration of MDR/XDR-TB treatment in children which may vary from case to case. Depending on the extent of the disease, the TB DST pattern and the immune status of the child, a total duration of treatment between 12 and 18 months following culture conversion could be acceptable, with the recommendation to continue the

treatment only in particular cases to avoid relapse [30]. However, the clinical trials in children so far carried out are not enough to supporting this approach.

Regarding pregnancy, there is consensus that neither LTBI following contact of a patient with MDR/XDR-TB nor active MDR/XDR-TB requires cessation of pregnancy [81]. While safety of many drugs for the unborn child is unknown, treatment of pregnant females who develop MDR/XDR-TB or become pregnant during treatment can be successful without adverse events for the newborn, although aminoglycosides/polypeptides are not recommended for MDR/XDR-TB treatment during pregnancy [82]. Theoretically, breastfeeding should be recommended only in females who are not infectious. However, the known and theoretical benefits of continuing treatment seem to outweigh theoretical risks to the mother and fetus.

Being TB and HIV strictly related, HIV exacerbates TB and the phenomenon of MDR/XDR-TB is somehow increasing in these patients in whom HIV testing is not always evaluated especially in particular countries, thereby delaying the initiation of antiretroviral therapy (ART) which could significantly reduce mortality, relapse rates, and development of resistant strains [83]. This is especially true for immigrants in whom not only it is difficult the access HIV testing, but also ART testing. A large body of research has in fact shown that migrants are more likely to enter into the healthcare system late and are less likely to be retained at successive stages of the HIV treatment cascade.

MDR/XDR-TB has higher mortality rates especially in South Africa [83, 84] among MDR/XDR-TB and HIV coinfecting cases with very low CD4 cell counts and limited access to ART. Timely diagnosis based on molecular assays is crucial to reduce the mortality associated with MDR/XDR-TB patients among HIV-infected persons. Owing to high case detection rates compared to smear microscopy, WHO recommends Xpert®MTB/RIF as a primary diagnostic test for TB in persons living with AIDS [4].

In conclusion, treatment for MDR/XDR-TB is far from optimal at present. In particular, treatment of MDR/XDR-TB in migrants living in high-income countries is associated with increased risk of therapy nonadherence, loss to follow-up, and in general, noncontinuity of anti-TB care that worsens drug-resistant TB. Migrants' slow progression through the TB or HIV treatment cascade can be attributed to feelings of confusion, inability to effectively communicate in the native language, and poor knowledge about administrative or logistical requirements of the healthcare system.

Novel therapeutic interventions with shorter treatment regimens with higher efficacy and better tolerability than those currently available are required. In addition, new drugs need to be developed and existing drugs for anti-TB properties should be reevaluated for their potential efficacy in the treatment of MDR/XDR-TB. In receiving high-income countries, the international community has responded with financial and scientific support, leading to new drugs [85] and regimens in advanced clinical development and an increasingly sophisticated understanding of resistance mechanisms and their application to all aspects of TB control and treatment. In the absence of a preventive vaccine, more effective diagnostic tools, and novel drugs, the control of MDR/XDR-TB will be extremely difficult. Moreover, the increasing rates

of drug-resistant TB in Eastern EU, Asia, and sub-Saharan Africa is now threatening the gains made by TB control programs worldwide.

7. Conclusions and social issues

Although the WHO Report 2015 [4] with its "STOP TB" strategy has the goal to eliminate TB as a public health problem (defined as <1 case per 1 million population per year) by 2050, TB shows no signs of disappearing in the near future despite declining incidence in most high-income countries. TB is still one of the top three infectious killing diseases in the world, after HIV/AIDS that kills 3 million people each year, TB kills 2 million, and malaria kills 1 million [4]. In order to intensify the fights against this deadly disease, further efforts aimed to strength surveillance programs to accurately estimate the burden of all kinds of TB are of great significance. Considering the enormous number of migrants around the world [8] with its high rates in the USA and Europe (54 and 76 million, respectively), particularly in Germany, Russia, the UK, France, Spain, and Italy, other than Saudi Arabia, Canada, and Australia, the problem of TB is of foremost importance and deserves great attention in order to act promptly to find solutions.

Although migration in itself is not a definitive risk for TB, several factors can put migrants in vulnerable situations that push factors (desertification, famine/drought, political fear/persecution, poor medical care, loss of wealth, and natural disasters), and pull factors (search of job opportunities, better living conditions, better medical care, political and/or religious freedom and security) migrant people in and out of TB-endemic areas [86]. Social fragility of migrant populations, despite its heterogeneity, shows areas of health suffering in large part due to highly uncertain circumstances and integration policies in receiving countries, especially at the local level, difficulties in access to services, and to relational communicative problems. In fact, the slow or less rapid deterioration of the migrant health in the host country creates serious problems, both to the person who is sick, and to the community which is forced to support the social and economic costs that this entails. Therefore, understanding the changing socioenvironmental situation as well as population movements and their associated risks for TB infection is critical for control, containment, and elimination of this disease which still poses infection-control and public-health challenges in the twenty-first century. Providing services aimed to identify and treat TB in migrants, refugees, or asylum seekers who are at high TB risk is challenging and requires a multidisciplinary approach and a high rate of investment of resources, human, structural, and material [87]. In immigrants living in high-income countries there are crucial factors that play an important role in TB-drug adherence which include length of treatment course, complex regimens, medication side effects, poor access to health care services, poor communication with health care providers, lack of social support, negative perceptions, stigma, and discrimination. The lack of laboratory facilities in their country of origin made the laboratory diagnosis of infectious diseases, including TB, difficult in many parts of the African continent as well as in the majority of other poor and low resource countries, where the diagnosis continues to rely on century-old sputum microscopy. In recent years, a growing number of rapid and more sensitive tests for TB and drug-resistant TB, based on molecular methods, including Xpert®MTB/RIF, have become available to replace or parallel exist to conventional tests; however, current TB

diagnostics are still suboptimal in their performance for childhood TB, smear-negative TB, EPTB, HIV-TB, and drug-resistant TB. Furthermore, there is no standard test for the identification of LTBI, which, if correctly identified in particular risk groups including migrants, could be appropriately treated in order to prevent the onset of TB. So far, neither test can reliably predict future disease among persons with positive tests, and strong positive tests do not suggest a higher risk.

Looking at the movement of people today, at world politics, and at the increasing gap between the rich and the poor, it is expected that the number of immigrants will increase and with it health risks of those on the move and, to a lesser extent, the risk of those in the receiving countries can also be anticipated. It is argued here that a substantial increase in funding for TB research is required. There is no vaccine with adequate effectiveness, and TB treatment regimens are protracted and have a risk of toxic effects. Moreover, fundamental understanding of the pathogenesis of this disease is inadequate. In order to achieve the ambitious targets of the End-TB strategy 2035 (95% reduction in TB deaths, compared with 2015), 90% reduction in TB incidence rate (less than 100 TB cases per million population, no affected families facing catastrophic costs due to TB), greater efforts are needed also regarding migrants interventions, such as support services to receive and treat migrants, improving their access to health facilities, preventing the development of drug resistance through high quality treatment of drug-susceptible TB, improving adherence to anti-TB treatment, and offering vaccination for TB especially to prevent TB meningitis in children in endemic areas. Control strategies need to be adapted to local realities after evaluation of data prevalence/incidence, feasibility, and cost effectiveness. TB transmission among immigrants and natives is still rare, although it could increase in case of limited TB control. Thus, interventions such as expansion of the free service package and education about TB diagnosis among community health personnel are urgently required for early LTBI or case detection among migrants, particularly those born in a country with a high incidence of disease or in those persons exposed to the contact with TB, like close relatives of infectious patients [87]. It is recommended that high-income countries and their institutions cooperate in the near future with high-burden countries [4]. One important goal inside the “Global Action Framework for Research towards TB Elimination,” developed by WHO [4] for the period 2016–2025 will be in fact to translate the new technologies and innovative approaches into policies and practices and then adapt to particular country contexts as appropriate. This is only another rational approach that in future will help to reach some of the ambitious targets to control, perhaps stop TB, in the coming decades.

Abbreviations

RIF	Rifampicin
INH	Isoniazid
PZA	Pyrazinamide
EMB	Ethambutol
KM	Kanamycin
CM	Capreomycin

AK	Amikacin
CS	Cycloserine
PAS	P-aminosalicylic acid
FC	Fluoroquinolones
MDR-TB	Multi drug-resistant tuberculosis
XDR-TB	Extensive drug resistant-TB
SLD	Second-line drugs

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