

Drug resistant tuberculosis in Italy through a global health lens

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SUMMARY

Drug-resistant tuberculosis (DR-TB) is a major global health challenge. In 2021, about one third of DR-TB patients worldwide were enrolled in treatment. In order to reach the targets set during by the 2018 UN General Assembly (UNGA) Political Declaration on Tuberculosis, a global effort must be made by both high- and low-incidence countries. Data concerning high-incidence countries are vast in the literature, but insufficient political attention has been paid in low-incidence countries to face this infectious threat. This review aims at providing an overview of DR-TB focused on different facets of DR-TB management. First, global and Italian data on the main at-risk populations for TB and DR-TB were gathered, together with the latest studies on the correlation between TB risk factors and the onset of drug resistance. Second, this review provides an analysis of obsolete Italian guidelines on the diagnosis and management of TB and DR-TB, highlighting the challenges that our country is currently facing to properly implement the latest international recommendations. Finally, some key suggestions are provided to design public health (PH) policies that can effectively tackle the DR-TB issue from a “global health” perspective.

Received March 10, 2023

Accepted March 31, 2023

INTRODUCTION

Tuberculosis (TB) represented a significant cause of illness and death globally in 2020-2021, being second only to SARS-CoV-2 as the leading cause of infectious disease mortality, with 1.4 million deaths in 2021 (World Health Organization, 2022a). TB elimination is a global challenge that needs to be tackled both in high - and low-incidence countries.

To address this challenge, in 2016 the World Health Organization (WHO) adopted the “END TB Strategy,” a package of interventions and targets set in the context of the Sustainable Development Goals (SDGs) to accelerate global efforts toward TB control and elimination (World Health Organization, 2015).

At this moment, the world is far from reaching these targets: according to the END TB milestones, by 2025 TB incidence should be reduced by 50%, and the number of TB deaths by 75%. However, as of 2021 the former decreased by only 10%, and the latter by 5.9%

(World Health Organization, 2015). Furthermore, the UN General Assembly high-level meeting set targets for the period 2018-2022 that are not on track to be met: of the 40 million people that should be treated for TB, only 26.3 million were treated as of the end of 2021, and in drug-resistant-TB (DR-TB) out of a target of 1.5 million people to be treated, only 43% were treated between 2018 and 2021 (Stop TB Partnership, 2018; World Health Organization, 2022a). Worldwide, the estimated number of DR-TB cases is increasing (450,000 incident cases in 2021), with most cases concentrated in India, the Russian Federation, and Pakistan, as well as in several countries in Eastern Europe (World Health Organization, 2022a).

Italy is a low-burden TB country with 2,378 reported cases in 2021, corresponding to an incidence of 4.9/100,000. The estimated proportion of new TB cases with MDR/RR-TB was 2.8%: 52 were rifampicin-resistant (RR-TB) or multi-drug resistant (MDR-TB, i.e., resistant to at least rifampicin and isoniazid) and 11 were laboratory-confirmed as either pre-extensively DR (pre-XDR, resistant to rifampicin, isoniazid, and to any fluoroquinolone) or extensively DR (XDR, also resistant to one of the second-line injectable drugs) (World Health Organization, 2022a).

Drug-resistant TB (DR-TB) is a global health problem for which both diagnostic tools and treatments are ei-

Key words:

Tuberculosis, global health, multidrug resistance, sustainable development goals.

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Box 1 - The eight priority actions set by WHO to address TB in low-incidence countries (World Health Organization; 2014).

1. Ensure political commitment, funding and stewardship for planning and essential services of high quality.
2. Address the most vulnerable and hard-to-reach groups.
3. Address special needs of migrants and cross-border issues.
4. Undertake screening for active TB and LTBI in TB contacts and selected high-risk groups and provide appropriate treatment.
5. Optimize the prevention and care of drug-resistant TB.
6. Ensure continued surveillance, programme monitoring and evaluation and case-based data management.
7. Invest in research and new tools.
8. Support global TB prevention, care and control.

ther inadequate or unavailable to many of those affected. In countries with few TB and DR-TB cases the capacity to provide correct clinical and social management of patients can be suboptimal due to lack of centralization and low clinical experience. Consequently, as reported by the last Global TB Report, one out of three TB patients receives a delayed diagnosis and treatment, contributing to the further spread of DR-TB (World Health Organization, 2022a). It is therefore fundamental to plan control measures that are tailored to low-burden countries. In this context,

strategies to reduce diagnostic delays, including development of new diagnostics at point-of-care, and precision drug regimens for all forms of TB to improve clinical outcomes are urgently needed.

Based on these considerations, WHO provided a framework adapting the END TB strategy to low incidence, high-resource settings, such as Italy (World Health Organization, 2014). The framework recommends eight key interventions to rapidly reduce the burden of TB in these countries, thus progressing toward elimination (Box 1).

In light of the critical importance and the high prevalence of DR-TB in many settings worldwide, and considering the WHO framework for TB control in low-incidence countries, our review aims first at assessing the at-risk populations for TB and DR-TB in Italy, and second at highlighting the DR-TB diagnostic and treatment framework and challenges in our country.

AT-RISK POPULATIONS IN ITALY: EPIDEMIOLOGICAL FEATURES AND CHALLENGES

Five conditions have been recognised as the main risk factors (RF) for TB infection: undernutrition, which may be the risk factor responsible for the highest number of TB cases worldwide, followed by HIV infection, alcohol use disorders, smoking and diabetes (World Health Organization, 2022a).

Focusing on the Italian context, the contribution of these RF changes significantly similarly to other

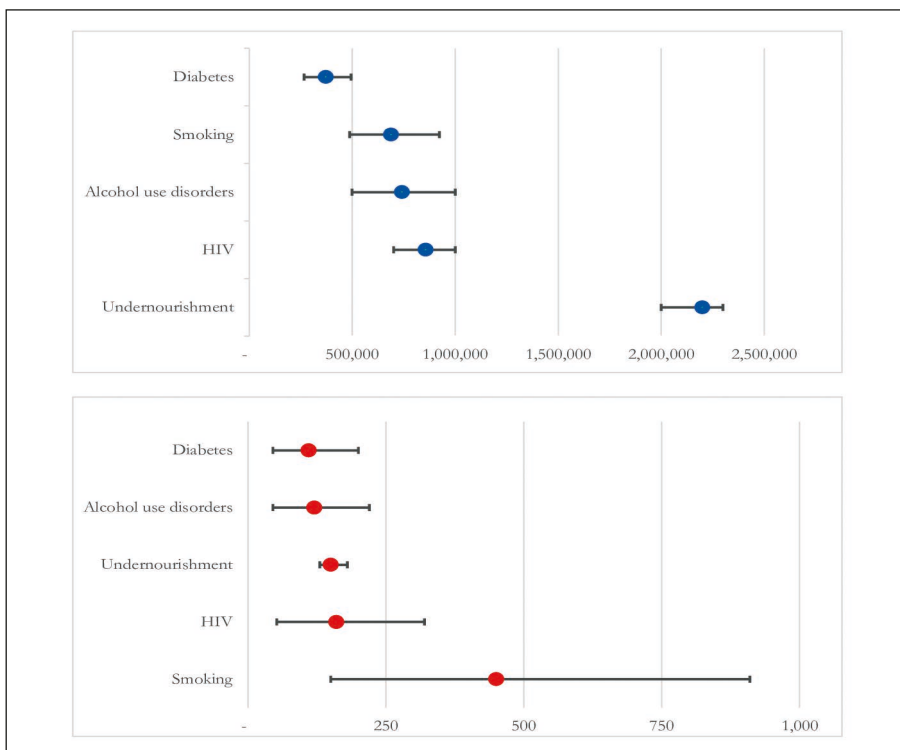


Figure 1 - Global (above) and Italian (below) total TB cases attributable to the five main TB risk factors (number). Data retrieved from: World Health Organization, Global Tuberculosis Report 2022.

low-burden and high-income countries (HIC): the major RF for TB is smoking, followed by HIV, undernutrition, alcohol, and diabetes.

However, these conditions are related not only with TB, as they intertwine with other socio-economic conditions that favour the encounter of TB and increase the risk of developing the disease.

In this section, we will analyse the major RF for TB (smoking, HIV infection, undernutrition, alcohol use disorders, diabetes), while at the same time providing an overview of some additional at-risk populations for TB and DR-TB relevant in the Italian context: international migrants, the elderly, people who use and abuse drugs, people who are incarcerated, trans and gender non-conforming people, and patients undergoing immunotherapy (Figure 1).

Tobacco smoking

Tobacco consumption is one of the biggest PH threats globally: the tobacco epidemic is estimated to kill directly and indirectly more than 8 million people a year, of which 1.2 million are due to exposure to second-hand smoke (World Health Organization, 2022b). In Italy, 24.2% of the population smokes, with a mean of 11.5 cigarettes per day (Istituto Superiore di Sanità, 2022a).

Smoking is also a social issue: according to the “Tobacco and inequities” report issued by the WHO European Regional Office, people of a lower socioeconomic status have a higher rate of smoking; they also start smoking at a younger age, and smoke more cigarettes per day (Loring, 2014).

Smoking tobacco is one of the main risk factors linked with TB. In 2020, the TB proportional attributable factor for smoking was 7.1%; therefore, approximately 0.73 million TB cases (UI 0.25-1.5) were estimated to be directly caused by exposure to tobacco (World Health Organization, 2021b). Focusing on the Italian context, smoking has by far the highest population attributable factor among the main RF for TB, \approx 450 TB cases (UI 150-910) (World Health Organization, 2022a).

Smoking may be seen as a confounder, as it is correlated with other social risk factors which, being linked to a lower socio-economic status, increase the risk of TB infection. However, it has been proved that tobacco directly tampers with innate barrier defences, as well as with the immune adaptive system, therefore having a primary role in the development of TB disease (Quan *et al.*, 2022).

Many studies have been conducted on the association between smoking and negative outcomes, both in high-incidence and in low-incidence settings (Amere *et al.*, 2018; World Health Organization, 2014). Tobacco consumption has a negative impact on all steps of TB infection, from increasing the risk of TB infection (Lindsay *et al.*, 2014), to delaying the healing process and the conversion of the smear culture (Wang *et al.*,

2020). The impact of smoking on TB death rate has been well documented in the literature: a qualitative systematic review conducted by the WHO on the association between tobacco and TB corroborated the connection between TB deaths and smoking, with risk ratios ranging between 1.02 and 6.62 (World Health Organization, 2007). However, higher risk ratios have been described in the literature: a study conducted among more than 400,000 Chinese TB patients found a nine-fold risk of TB associated death compared to TB patients who never smoked; the risk dropped by 65% in TB patients who quit smoking (Wen *et al.*, 2010).

As the link between tobacco and TB has been widely recognized, the correlation between smoking and DR-TB needs more evidence.

A positive correlation between smoking and the incidence of DR-TB among TB patients has been described: a systematic review and meta-analysis by Wang *et al.* showed that smokers with TB were 1.57 times more likely to develop some form of DR-TB and 1.45 times more likely to develop MDR-TB (Wang *et al.*, 2018).

However, there is evidence that runs counter to this thesis. A systematic review and meta-analysis considering, among others, 11 studies with 5,545 participants reporting the primary outcome in smokers versus non-smoker TB patients, did not find a significant difference in the development of DR-TB between the two groups (Samuels *et al.*, 2018). Another similar study conducted on 28 studies, 7 of which regarding smoking habits, did not find an overt association with the insurgence of DR-TB (Xi *et al.*, 2022).

More solid evidence is found if smoking is associated with other risk factors, in particular alcohol consumption: a retrospective study considering almost 8,000 TB cases in China showed a higher risk of developing MDR-TB, with an adjusted odds ratio of 1.91 (Song *et al.*, 2022).

Data on the smoking/DR-TB correlation is lacking in the Italian context. A retrospective study conducted in an Italian hospital considering 74 patients with MDR-TB confirmed the theory of tobacco consumption as a risk factor for unsuccessful treatment (Gualano *et al.*, 2019). However, no targeted studies analysing the correlation between smoking and the insurgence of DR-TB on patients treated in Italy have been conducted to our knowledge.

Smoking is a perilous habit that undermines people’s health. TB-infected individuals are more fragile and should be offered the possibility to be included in targeted smoking cessation programs. Moreover, the role of tobacco consumption in the insurgence of DR has not yet been fully understood, therefore further studies should be conducted to monitor this association.

People living with HIV

One of the major factors influencing the risk of contracting active tuberculosis is HIV infection. Depend-

ing on the local epidemiology of HIV, it has been estimated that the incidence of TB among people living with HIV (PLWH) is 20-37 times higher than among HIV-negative people (Zeru, 2021). For this reason, the WHO End-TB strategy has set the goal to reduce the burden of TB-HIV coinfection (World Health Organization, 2015). An important strategy is to scale up and accelerate the start of antiretroviral therapy (ART) in PLWH. Both in countries with low and high TB burdens, ART lowers the chance of developing active tuberculosis (Suthar *et al.*, 2012). However, despite a lower incidence of HIV, late HIV diagnosis is still common in our country and drives TB incidence among PLWH (Girardi *et al.*, 2022).

TB and HIV are closely correlated, since the immunodeficiency caused by HIV makes it easier for TB to establish an infection and cause a more severe disease. A recent meta-analysis showed that HIV also increases the risk of DR-TB by a factor of 1.42. The same study shows that the proportion of DR-TB patients among HIV-infected people increased significantly in the period 2008-2017 (Sultana *et al.*, 2021). According to the Italian National Health Institute (*Istituto Superiore di Sanità*, ISS), in Italy, there has been a stabilization of TB case incidence in patients living with HIV. According to the ECDC's "Tuberculosis surveillance and monitoring in Europe 2022 (2020 data)," 5% of tuberculosis cases are diagnosed in people living with HIV (European Centre for Disease Prevention and Control, 2022). From 2012 to 2021, 782 cases of TB were notified in AIDS patients; of these, almost 63% were foreign-born, often coming from high DR-TB incidence countries (*Istituto Superiore di Sanità*, 2022c).

Additionally, a large retrospective cohort study conducted in Italy identified having a known contact with DR-TB and HIV co-infection as main factors for DR-TB (Riccardi *et al.*, 2021).

HIV in Italy usually occurs in younger populations: in 2021, the highest HIV incidence was among people aged 30-39 - 7.3 new cases every 100,000 residents - followed by people aged 25-29 - 6.6 new cases every 100 000 residents -; PLWH in Italy who develop TB usually also have other risk factors for TB and DR-TB (e.g., poor living conditions, being migrants, difficulties in access to healthcare, etc.) (*Istituto Superiore di Sanità*, 2022d).

Nevertheless, efforts to increase access to active HIV and LTBI screening are still needed.

Undernutrition

Undernutrition is one of the main plagues facing the world. According to the report "The State of Food Security and Nutrition in the World 2022," issued by the Food and Agriculture Organization (FAO), 821 million people (9.8% of the global population) were affected by hunger in 2021. In particular, this number has increased by 46 million since 2020 and by

150 million since 2019, mainly but not only due to the COVID-19 pandemic. Access to a healthy diet could not be afforded by 3.1 billion people globally, also due to inflation in food prices caused also by the economic impact of the pandemic (FAO, 2022).

Undernutrition is one of the main drivers of TB infection globally: in 2021, approximately 2.2 million incident cases of TB were attributable to undernutrition (World Health Organization, 2022a).

This RF has multiple effects on TB infection, spread, and virulence. Undernutrition decreases the activity of many cells involved in the immune response, both primary and adaptive; furthermore, it impacts on treatment adherence, outcome, and mortality, as reported in the literature (Sinha *et al.*, 2019), therefore indirectly increasing the risk of insurgence of DR-TB. Some studies in high-incidence countries appear to see a link between these two phenomena (Aderita *et al.*, 2017); however, to our knowledge no proper systematic review and meta-analysis on this specific subject have been conducted.

Recent literature shows that undernutrition has an impact not only on the insurgence, but also on treatment outcomes of DR-TB cases; however, evidence on the impact of nutritional impairments on drug resistance is scarce (Wagnew *et al.*, 2022). Undernutrition may also be cause of malabsorption of TB therapy in some patients, therefore causing suboptimal serum drug levels and increasing the chances of developing DR-TB. (Rao *et al.*, 2021; Patel *et al.*, 1995).

Looking at the Italian context, contrary to obesity where lots of data and studies have been published, undernutrition data in Italy are scarce: according to the World Bank, the prevalence of undernutrition in Italy is $\approx 3\%$ (World Bank Data, 2023a).

Undernutrition does not represent the main RF for TB in Italy; nevertheless in 2021 ≈ 150 cases were attributable to undernutrition (World Health Organization, 2022a).

Furthermore, even if data regarding the Italian population confirm the impact of undernutrition on TB infection and outcomes, to our knowledge no systematic data has been published on its impact on DR-TB.

Notably, the WHO issued a guideline on nutritional care for patients with TB, which states that "concerns about weight loss or failure to gain weight should trigger further clinical assessment," therefore stressing the importance of nutritional status not only as a warning sign during TB treatment, but also as an RF to consider for the development of DR-TB (World Health Organization, 2013).

Alcohol use disorders

Alcohol consumption is correlated with a plethora of illnesses, both as a cause and as an RF. Globally, approximately 3 million deaths every year result from harmful use/abuse of alcohol, representing 5.3% of

total deaths. Alcohol accounts for 5.1% of the global burden of disease. Furthermore, alcohol consumption causes death and disability significantly early in life: 13.5% of total deaths among people 20-39 years of age are attributable to alcohol (World Health Organization, 2022c).

In Italy, alcohol is a significant public health issue: in 2021-2022, 54% of the Italian population age 18-69 consumed alcoholic beverages, and 15% consumed alcohol at a high-risk level for quantity and modality of consumption (Istituto Superiore di Sanità, 2023). TB has a strong correlation with alcohol consumption: it not only increases the risk of being infected and being more infectious, but also increases the chances of negative outcomes.

The impact of alcohol consumption on TB is related not only with the socio-economic RFs for TB that are linked with alcohol abuse, but evidence shows that it has a direct influence on lung immunity and on the pathogenic mechanisms used by the mycobacterium to infect the host (Wigger *et al.*, 2022).

A systematic review by Ragan *et al.* shows that alcohol consumption is associated with 1.5-2-fold increased odds of poor treatment outcomes both for drug susceptible TB (DS-TB) and DR-TB (Ragan *et al.*, 2020).

As for smoking, the relationship between alcohol consumption and the insurgence of DR-TB needs further evidence. A significant correlation between alcohol abuse and DR-TB has been found not only in high incidence settings, but also in high-income countries (Alemu *et al.*, 2022; Balabanova *et al.*, 2012).

Nevertheless, there are also systematic reviews and meta-analyses that did not find alcohol as an independent risk factor for the development of DR-TB (Samuels *et al.*, 2018), and other studies identify a correlation only if other RFs such as smoking are present.

Furthermore, looking at FBPs living in Italy, a survey conducted by the Italian Statistics Institute (*Istituto Nazionale di Statistica*, ISTAT) revealed that even if alcohol consumption in general is slightly lower among FBPs, it is highest among people from the former Soviet Union (FSU) and other central-eastern European countries such as Romania, Albania and Poland, and is more common among those groups to drink alcoholic beverages every day compared with Italian-born people (Istituto Nazionale di Statistica, 2016).

However, as of today there is no published evidence of a significant correlation between alcohol and DR-TB in Italy (Ingrosso *et al.*, 2014).

To conclude, alcohol abuse should be monitored in order to understand its trend and its possible correlations with TB and DR-TB outcomes on Italian patients, and more research is needed to understand if this RF should be taken into consideration in a patient-targeted TB or DR-TB drug regimen.

Diabetes mellitus

Diabetes mellitus (DM) is one of the most common diseases and causes of disability worldwide: approximately 10% of the world population lives with DM (Ogurtsova *et al.*, 2022). In Italy, the prevalence of people with DM has doubled since the 1980s (Istituto Superiore di Sanità, 2018) and nowadays reaches almost 5% in the general population. However, among the elderly, the prevalence of DM is greater than 20% (Istituto Superiore di Sanità, 2022b).

The relation between DM and TB is well established (Foe-Essomba *et al.*, 2021). A multicentred study conducted in Europe revealed that older patients and FBPs have the highest prevalence of DM and TB. In Italy, the prevalence of tuberculosis patients with a diagnosis of DM is between 6 and 10% (Sane Schepisi *et al.*, 2019). Additionally, a study conducted in Italy identified the socioeconomic status and biomedical risk factors associated with tuberculosis in migrants and native residents. The prevalence of comorbidities, such as DM, was lower among migrants with respect to Italian patients. In particular, diabetes prevalence in patients >65 years was significantly greater with respect to the other populations (Pittalis *et al.*, 2017).

People with tuberculosis who have DM have a poorer response to treatment, running a higher risk of treatment failure and development of DR-TB. A recent meta-analysis confirmed the association between DM and occurrence of DR-TB, suggesting that not only more robust screening and further management of DM in patients with TB is required, but also a higher level of suspicion must be present any time a person with DM presents symptoms consistent with TB (both pulmonary and extrapulmonary) (Tegegne *et al.*, 2018).

International migrants

Migrants face enormous health problems, first and foremost related to access to healthcare, depending on their status. Tuberculosis strikes this group harder for many reasons, such as increased exposure to TB risk factors (overcrowding, undernutrition, substance abuse, HIV infection), as well as the social barriers and economic issues that migrants must face. Evidence shows that the majority of active TB cases is due to reactivation of latent infection rather than new infection in the country of destination, suggesting that it is primarily socioeconomic conditions that increase the burden of TB among migrants (Pareek *et al.*, 2016).

Italy has always been a country of immigration, being in the top 4 EU countries for resident migrants, with more than 5 million people as of the end of 2020; representing almost 9% of the total population (Istituto Nazionale di Statistica, 2022a). The largest community of foreign residents in Italy is from Romania, the country with the highest incidence of TB

in Europe, with more than 15,000 cases per year (Centro studi e ricerche IDOS, 2022).

Furthermore, in 2019, along with Lithuania, Romania reported 75% of the total XDR-TB cases in the EU/EEA (European Union/European Economic Area) (European Centre for Disease Prevention and Control, 2021). As such, Romania is included in the European region priority list of EEA countries for TB and MDR-TB.

Moreover, 5 out of the top 10 countries of origin of non-Italian people residing in Italy are among the top 20 high-burden MDR and XDR-TB countries: China (4th), Ukraine (5th), India (6th), Bangladesh (7th) and Pakistan (10th) (World Health Organization, 2021a). As in other low-incidence countries, in Italy most DR-TB cases in the past few years have been detected among foreign-born people (FBPs) (European Centre for Disease Prevention and Control, 2019).

Even if migratory flows decreased significantly after the surge of the COVID-19 pandemic in 2020, the count of residency permits to non-EU citizens issued by the Italian government in 2021 reached pre-pandemic numbers (Istituto Nazionale di Statistica, 2022a). The number of refugees reaching Italy by sea has increased drastically, with 32,533 migrants versus 45,664 migrants comparing the period January-August 2021 to 2022 (Ministero dell'Interno, 2022).

Evidence shows that migrants on the Mediterranean route, especially those who are detained in migrants camp in Northern Africa before taking to sea, face conditions of extremely poor hygiene and undernutrition, therefore increasing the risk of developing active TB, as many are infected due to exposure before or during their migration process (Cañardo *et al.*, 2020; Kuehne *et al.*, 2021).

Notably, treating migrants positive to TB screening, either for active TB or TB infection, has shown sub-optimal compliance: a study conducted among ≈48,000 migrants who arrived in different ports of Sicily between 2014-2017 reported a treatment drop-out rate of 18% among those with active TB and 42.3% in the LTBI¹ group, therefore exposing them to the risk of acquiring resistance to TB drugs (Prestileo *et al.*, 2021).

Two guidelines were issued in 2017 and in 2018 to suggest how to structure migrant reception facilities and hotspots to facilitate the conducting of proper screening and clinical visits, the latter focused specifically on TB control (Tosti *et al.*, 2021; Istituto Nazionale per la promozione della salute delle popolazioni Migranti e per il contrasto delle malattie della Povertà, 2018). However, they may need to be updated, including with regard to recent discoveries in the TB field, and there has not been an assessment of their

adoption and impact, therefore making it difficult to understand the effectiveness of these documents.

Elderly population

Due to the improvement in living conditions, people worldwide are living longer: life expectancy rose significantly from 60 years in 1980 to 73 in 2021 (World Bank Data, 2023b). By 2030, 1 in 6 people will be aged 60 years or more, and the population aged 80 years is expected to triple in the next 30 years, reaching ≈426 million individuals.

This phenomenon is an expression of general societal development and wellbeing. While it started in HIC, a large increase is now experienced by low-middle income countries (LMIC): it has been estimated that by 2050, 80% of people aged ≥60 years will live in LMIC. With a mean population age of 46.2 years in 2022, Italy has one of the oldest populations in Europe (Istituto Nazionale di Statistica, 2022b). Of its ≈60 million inhabitants, almost a quarter are older than 65 years, and according to estimates by the Italian National Institute of Statistics (Istituto Nazionale di Statistica, 2022b), in 15 years this age class will represent almost a third of the Italian population (Istituto Nazionale di Statistica, 2023).

As reported by the European Centre for Disease Prevention and Control (ECDC) Surveillance Report (European Centre for Disease Prevention and Control, 2022), almost 15% of TB cases in Italy are diagnosed in patients older than 64 years. However, the majority of cases occur in foreign-born individuals who come from TB endemic countries. As this population is usually younger, the importance of TB risk in the elderly population is often underestimated (World Health Organization, 2014). Additionally, migrants who arrived in Italy from high DR-TB incidence countries in previous decades are growing old. Consequently, we can expect an increase in prevalence of DR-TB in the elderly population in the future. This warrants further attention, as older age is characterized by the arising of multiple comorbidities and a greater drug burden. Therefore, the risk of adverse drug reactions due to polypharmacy but also lower efficiency of renal and hepatic drug clearance must be considered when dealing with this population. The elderly may also have more difficulty in adhering to therapy because of a number of problems, including impaired vision, limited mobility, poor income and declining memory (Thomas & Rajagopalan, 2001). The above-mentioned issues might be associated with discontinuation of antitubercular therapy before time, and therefore, with an increased risk of unsuccessful outcome and acquisition of DR.

People who use drugs (PWUD)

Italy is among the European countries with the greatest illicit drug use (7/1000 cases of opioid use estimated in 2019, while 1.7% of the Italian popula-

¹In this article we will use the term “latent TB infection”, although today this term is often replaced by “TB infection”.

tion reported cocaine use in 2017). (European Monitoring Centre for Drugs and Drug Addiction, 2022). At a global level, PWUD have higher tuberculosis infection prevalence and disease incidence. A metanalysis conducted by Grenfell et al. showed that the prevalence of DR-TB in PWUD is among the highest in the world (Grenfell et al., 2013). The reasons behind this may be related to within-group transmission and host vulnerability. First, drug use practices and environmental factors, such as inhaling and exhaling drugs in confined and poorly ventilated spaces, might contribute to outbreaks of TB in this group. Second, the use of drugs is often linked to other at-risk behaviours, such as tobacco use and alcohol consumption, but also to other conditions such as HIV infection, homelessness and incarceration, which are commonly associated with TB (Stop TB Partnership, 2016). Additionally, PWUD have greater difficulties in accessing treatment in a timely manner. Studies show that PWUD rarely complete medical evaluations and follow-up (Carusone et al., 2019). Because of numerous barriers to care, they typically have lower rates of adherence to TB treatment than populations that do not use drugs (Deiss et al., 2009, Stop-TB Partnership, 2016).

Little data exist regarding the association between drug use and TB infection in Italy. A meta-analysis conducted in 2014 by Ingrosso et al., did not provide conclusive results, but found that the majority of cases of TB in PWUD in Italy were among Italian patients, rather than FBPs (Ingrosso et al., 2014). Therefore, further efforts are necessary to reach and screen this population to effectively face the risk of DR-TB.

Incarcerated individuals

Worldwide, prisons are considered settings in which TB can easily spread and outbreak can occur. According to the Antigone report, which collects data from Italian detention centres, more than 54,000 persons currently reside in prisons. However, what raises concern is the average detention centre overcrowding rate, which is reported to be 107% in Italy, and in some prisons, reaches up to 185% (Associazione Antigone, 2022).

Overcrowding is a recognized risk factor for respiratory transmitted infections like TB. According to data from the Italian Society of Penitentiary Medicine (*Società Italiana Medicina e Sanità Penitenziaria*, SIMPE), in 2017 more than 50% of foreign inmates resulted positive to the tuberculin skin test (TST). The risk rises to 5.7 times in inmates who had previous detentions and to 3.8 times in those who are older than 40 years (Panorama della Sanità, 2017). A study conducted in two penitentiaries in Southern Italy showed a prevalence of LTBI of 4.72%; it was of 15.69% in FBP (mainly coming from high-DR TB incidence countries). The main challenge consisted of

providing and completing TB preventing treatment (TPT), since only 38% of inmates involved completed it. The main reasons treatment was discontinued were refusal, transfer, or release of inmates (Izzo et al., 2022).

Data prove unequivocally that incarcerated people are at greater risk of getting infected because of overcrowding, as well as of failing treatment, and therefore, of acquiring and transmitting DR-strains. Recent outbreaks of DR-TB in Italian prisons mandate the implementation of screening and coordination of treatment pathways in this setting (Bedini et al., 2016).

Trans and gender non-conforming people

A particular group that has been underestimated both by national health systems and published research is trans and gender non-conforming (TGNC) people.

Evidence shows that TGNC people are more at risk of illness due to the social stigma and policies that exclude them. However, the real health burden of transgender people remains poorly studied, especially the analysis of social factors that affect the health of this underserved population (Reisner et al., 2016; Winter et al., 2016).

Regarding TB, little data have been published worldwide on this specific population. It is however well known that trans people are exposed to a considerably higher risk of being infected with HIV: a recent systematic review of global data showed a prevalence of HIV of approximately 20% among trans women and 2.56% among trans men, percentages much higher than the general prevalence: 0.7% among adults aged 14-49 (Stutterheim et al., 2021; UNAIDS, 2022).

Furthermore, TGNC people face a higher risk of poverty, abuse and stigma, making them more prone to be unemployed, or to develop habits related with a higher TB risk (such as drug abuse) or to live in poorer hygienic conditions, as well as homelessness (Fraser et al., 2019), all risk factors that exacerbate the risk not only of getting TB, but that also undermine treatment compliance and therefore increasing the chance of developing DR-TB (Oliveira et al., 2022).

The ratio of people worldwide who identify as transgender or non-conforming is approximately 2%. However, there are no precise estimates on the number of TGNC people in Italy, even if unofficial sources estimate approximately 500,000 trans people, between 0.5-1% of the general population (Matarese et al., 2019). Consequently, the real burden of TB and DR-TB among this group in Italy has not been estimated.

Due to the lack of data, it is quite complex to design public policies to tackle general trans healthcare issues, especially those concerning HIV and TB.

Other risk factors: Immunotherapy

The role of anti-TNF-alpha in the risk of reactivation of TB infection is well recognized (Keane. 2001). According to last Italian Drug Agency (*Agenzia Italiana del Farmaco*, AIFA) report, the number of patients undergoing an anti-TNF-alpha treatment is increasing, but data regarding TB prevalence in this population subset are absent (*Agenzia Italiana del Farmaco*, 2021).

Epidemiological studies conducted in other European countries with low TB prevalence show that rates of TB are higher among anti-TNF-alpha users (Ferrara *et al.*, 2012). Other biological therapies commonly used (anti-CD20, anti-CTLA-4, anti-IL) are less associated with increased TB risk (Mastorino *et al.*, 2022). Because there is little evidence in the literature, further studies are required to evaluate any association between these two conditions.

TB screening, together with correct and timely treatment, is fundamental in patients who must start an anti-TNF-alpha therapy. Furthermore, systematic data need to be collected to understand the impact of TB reactivation on patients who undergo immunotherapy in general.

DIAGNOSIS AND TREATMENT: PRESENT AND FUTURE CHALLENGES

Diagnosis

TB diagnostics is one of the most critical issues in the fight against TB, as traditional methods, such as smear microscopy and culture, either have poor sensitivity or require weeks to tell if the pathogen is present and if it is drug resistant (Alagna *et al.*, 2021). The action framework for TB elimination designed for low-incidence countries by the WHO recommends the “creation of a high-quality network of laboratories, validated by proficiency testing and other quality control and improvement mechanisms” (World Health Organization, 2014). However, the Italian TB laboratory network presents issues linked to the structure of its National Health System (NHS).

In fact, the Italian NHS has been decentralized, and this process has gradually transformed it into a group of uneven regional health services (Garattini *et al.*, 2020).

TB management in Italy is regulated by a ministerial decree that took effect in 1998 (Ministero della Salute, 1998). As for TB diagnostics, this law identified three different types of laboratories for TB management: (i) I level laboratories, for microscopy and cultural exams only; (ii) II level laboratories, also with capacity for antibiogram and identification of human MTB (catchment area: 1 million people); (iii) reference laboratories, with type II competences plus use of high technology, coordination with other labo-

ratories for quality control, storage of strains, staff retraining (catchment area: 5-10 million people). This system is coordinated by the WHO Supranational Reference Laboratory for anti-TB drug resistance surveillance led by ISS, the technical-scientific body of the Italian NHS, which however has only a supportive role in the coordination of the TB laboratories (*Istituto Superiore di Sanità*, 2019). Finally, outside of this system, there are two III level WHO collaborating laboratories for the management of TB that aid the WHO in supporting and providing technical assistance to high-incidence countries on modern TB diagnostics implementation (WHOCC - WHO Collaborating Centres, n.d.).

This system is not designed as an official laboratory network since, due to the fragmentation of the Italian NHS, it does not provide a proper national control system that is able to monitor issues like the efficacy of the laboratory network inside the single regions or the fitness of the analysis conducted according to national and international guidelines.

It is important to mention SMIRA (*Studio Multicentrico Italiano Resistenze Antitubercolari*), a project started in 1996 thanks to grants issued by the Italian National Institute of Health (*Istituto Superiore di Sanità*, ISS) with the aim of collecting data of DR towards I and II-line drugs. Nowadays the SMIRA network has 46 different laboratories located in 19 Italian regions; however this system is based on voluntary participation and does not rely on institutional regulation and control.

According to the results of a survey circulated among National Reference Laboratories (NRL) all over Europe, unofficial laboratory networks may lead not only to a lack of knowledge of the methods used in peripheral laboratories, but also to technical difficulties in the implementation of novel diagnostic tools due to lack of central support. Furthermore, a challenge to NRL without a proper network is that it may have a consultative role without authority, therefore impacting on their performance and the performance of public health interventions on TB outbreaks (Klaos *et al.*, 2022). This was proven to be true in Italy, as inefficiencies in investigating DR-TB due to the structure of its TB laboratory network in certain areas of the country has already been witnessed in recent years (Gillini *et al.*, 2015).

The development of molecular biology-based technologies (such as GeneXpert Ultra) represented a significant step forward for improving the diagnosis and detection of drug resistance of TB. One of the main new tools, such as Xpert MTB/RIF Ultra, relies on amplification of nucleic acids using the polymerase chain reaction (PCR) method.

Not only do these new tools provide good sensitivity in detection of *M. tuberculosis*, but some rapid TB diagnostic tools also inform whether a particular strain is resistant to rifampicin and/or isoniazid plus

several 2nd line drugs in less than 2 hours, significantly accelerating the diagnosis of DR-TB (World Health Organization, 2021c). For this reason, the WHO has included universal drug susceptibility testing (DST) among the key components of the 1st pillar, regarding integrated and patient-centred care and prevention (World Health Organization, 2015).

Rapid molecular tests are recommended by the WHO guidelines on TB diagnosis not only for high-burden countries, but also for low-incidence countries (World Health Organization, 2021b): in fact, it has been shown that these new technologies are cost-effective in low-incidence settings as well (Hao *et al.*, 2020; Hickey *et al.*, 2022).

However, according to the latest WHO 2022 TB report, in EU/EEA countries only 28.3% of total TB cases were diagnosed with a WRD (WHO recommended diagnostic), and in Italy this data is even worse, with only 9.9% of cases. Quite surprisingly, Italian data on TB cases diagnosed with rapid tests were not available at least in the five past Global TB reports (World Health Organization, 2022a).

This issue may be due to the lack of updates on the national TB guidelines that still support traditional methods, in direct contrast with the guidelines issued by international health institutions such as the ECDC (European Centres for Disease Prevention and Control, 2018), as well as the absence of an implementation guideline that may help peripheral laboratories be up to date on the proper TB diagnostics to perform case by case.

The lack of bold policies that implement the recommendations issued by international health authorities, the lack of clear guidelines and implementation strategies for rapid diagnostic testing, and the lack of data and data reporting represent the main obstacles to efficient DR-TB testing in Italy.

Treatment

In 2022, WHO, based on the most recent evidence available, released an updated edition of evidence-based recommendations on the management of DR-TB cases.

According to these consolidated guidelines, the 6-month BPaLM and BPaL novel treatment regimens comprising bedaquiline, pretomanid, and linezolid with or without moxifloxacin can be used in patients aged 15 years or more with MDR/RR-TB or pre-XDR-TB who have either had no previous exposure to bedaquiline and linezolid or have been exposed for no more than 2 weeks (World Health Organization, 2022d).

The Italian Drug Agency approved bedaquiline in 2014 and pretomanid just a year ago (Osservatorio Malattie Rare, 2022). Before that, the treatment of DR-TB lasted at least 18 months, the medication burden was high (with patients receiving up to seven medications, among which injectable drugs), as was

the incidence of side effects (45% of patients reported moderate-to-severe adverse events).

The introduction of the new BPaL regimen in WHO guidelines might lead to better treatment outcomes, as well as to greater safety. However, despite promising results, challenges in the management of patients with DR-TB are still evident, both in high- and in low-incidence countries.

First, access to treatment must be guaranteed to all subjects with a diagnosis of tuberculosis. According to the last ECDC Surveillance and Monitoring report, Italy is among the countries which did not report drug resistance surveillance data (or gave incomplete data²). With the available data, it appears that of all reported pulmonary TB cases, only 72% had DST results (European Centre for Disease Prevention and Control, 2022). This, in turn, implies that a significant proportion of drug-resistant cases remains undiagnosed, and therefore, untreated. In general, patients with DR-TB are subject to long treatment duration, frequent side effects and, as a consequence, loss of adherence. As mentioned, the individuals who are more at risk of developing drug-resistant forms of TB are also the ones who are more fragile and vulnerable. At-risk groups encounter greater barriers in access to care and, therefore, to tuberculosis diagnosis and treatment. In a qualitative research study carried out in 4 European countries, the ECDC reported that one of the factors contributing to negative treatment outcomes was difficulty in providing continuation of treatment and care for migrants and other vulnerable groups (European Centre for Disease Prevention and Control, 2014). Additionally, a retrospective study carried on an Italian cohort of DR-TB patients showed a high rate of lost to follow-up (20%) (Gualano *et al.*, 2019).

Even in low-incidence countries, improved cooperation among healthcare providers, drug delivery services and laboratories, is now mandatory. Moreover, relationships with actors from the civil society need to be fostered and enhanced to obtain a global person-oriented approach.

Second, in low-prevalence settings like Italy, experience on DR-TB management is scarce.

In the above-mentioned qualitative research carried out by the ECDC, it emerges that despite the availability of global recommendations, clinicians usually rely on recent literature and/or professional experience. Limited experience in DR-TB care is likely to result in inappropriate case management and further

²Data were not collected nationwide, culture results were available for less than 90% of cases, less than 50% of cases were culture positive, less than 75% of all culture-positive cases had DST results available for isoniazid and rifampicin, less than 95% of external quality assessment results were confirmed by a supranational reference laboratory.

contributes to the emergence of resistance (European Centre for Disease Prevention and Control, 2014). Accurate monitoring of TB drug safety, by documenting and managing adverse events and reporting of treatment outcome, is therefore warranted. It is worrisome that no official data reported to the WHO and/or ECDC are available for DR-TB outcomes in Italy. Only a large retrospective cohort study conducted in different Italian centres demonstrated that the success rate in DR-TB is highly variable in our country, ranging from 55% in Southern Italy to 81% in Northern Italy (Riccardi *et al.*, 2021). Reporting data on treatment outcome and drug-safety in low-incidence settings is therefore of mandatory importance to obtain more coordinated and evidence-based management of DR-TB.

Finally, the economic impact of a correct and personalized therapy in DR-TB cases must be considered. Cost-efficacy studies carried out in Europe estimated that the average cost for treating drug-susceptible TB in HIC reaches €280, whereas for DR-TB, regimen costs range from € 29,765 for MDR-TB to € 217,591 for XDR-TB (Günther *et al.*, 2023).

Unfortunately, the available studies do not consider costs related to use of the new BPaL regimen, which has recently been approved. Just recently, in Italy, an analysis carried out by Codecasa *et al.* (2016) estimated that regimens containing bedaquiline for the treatment of DR-TB are more cost-effective than basic regimens, considering both hospitalization and outpatient costs (Codecasa *et al.*, 2016). However, further studies are required to analyse the cost-efficacy of new anti-TB drugs. The actual enormous costs of DR-TB drug regimens warrant further attention in preventing the spread of drug-resistant TB strains.

CONCLUSIONS

The spread of DR-TB in all countries, including low-incidence ones, is a major challenge toward accomplishment of the WHO End-TB strategy. One of the WHO's main goals in low-incidence countries is to pre-eliminate TB by 2035, therefore reaching fewer than one case every 100,000 inhabitants. However, rapid progress is urgently needed to reach this ambitious goal. Several reasons contribute to the stagnant burden of TB in Italy, including: the unprecedented flow of migrants coming from high-incidence countries and their associated vulnerability, an older population with a higher prevalence of comorbidities, poor management and control of the disease in specific populations and contexts (e.g., prisons, PWUD...).

In order to tackle TB in these vulnerable populations, a greater effort is urgent. The most important way to prevent the spread of TB is to identify cases as soon as possible, placing them on effective and tailored

treatment, and support the care of people with TB until cure. Healthcare providers are crucial for preventing DR-TB by quickly diagnosing cases with rapid DST followed by the adoption of recommended treatment guidelines, supporting patients' response to treatment, and making sure therapy is completed. According to the principles of Global Health, for interventions involving at-risk populations one must consider their peculiar features and frailties, which increase their risk of contracting and developing DR-TB. This can be achieved only with a proper surveillance and monitoring system that constantly provides up-to-date information on these populations. It requires a system that is able to design focused and robust technical guidelines and bold policies to tackle the socio-economic determinants that constitute the roots of TB and DR-TB in Italy, as well as in other low-incidence countries.

More research is needed to design algorithms that are able to provide tailored DR-TB regimens that take into consideration the habits and risk factors of patients to further improve the treatment successful rate. Appropriate funding for TB research and governmental support is needed to acquire new tools to fight TB and DR-TB.

As TB represents an uncommon disease in low-burden countries such as Italy, and because the resources granted by the national government are limited, a more targeted effort is needed to design a robust and well-organized network of laboratories and clinics properly trained to treat at-risk populations for TB and DR-TB.

All these ambitious goals, adopted by Italy as part of resolutions and declarations during policy and political events in the last decade, must now be pursued assertively. It is only by increasing awareness and political commitment, besides improving services for the most vulnerable people, that TB will eventually be eliminated in the years to come.

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