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Tackling TB in migrants arriving at Europe's southern border

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ABSTRACT

Over a quarter of the individuals diagnosed with tuberculosis [TB] in the European Union region are born outside of the area and the proportion has been increasing steadily. Italy is a low TB incidence country with over 50% of TB cases in the foreign-born population primarily due to the high numbers of migrants entering the country via land or sea. As a case study to evaluate the value of screening in newly arrived migrants, the EDETECT-TB project in Italy implemented and evaluated active TB screening in the migrant population at first reception centres to ensure early diagnosis to avoid further spread. Based on a cost-effectiveness analysis from a program provider perspective, a decision tree model allowed the assessment of the value for money of case finding by estimating the cost per case of active TB detected compared with the status quo of no screening. The analysis confirmed that early case detection is a cost-effective intervention in areas with migrants arriving from high TB risk settings. Targeted post-arrival early screening of high TB risk vulnerable new entrants to Italy has a potential role in reducing the spread of TB among migrants.

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Introduction

Tuberculosis [TB] remains a major public health issue in European Union (EU) compounded by the emergence of multi-drug-resistant (MDR) and extensively drug-resistant (XDR) strains (Aldridge et al., 2014; MacPherson and Gushulak, 2006). While three-quarters of TB cases in the EU were born in European countries, low incidence in some European countries is likely the results of a decreasing trend started on centuries ago that was parallel to the improvement of social and economic conditions, while some studies also argue a lower susceptibility due to genetic predisposition of part of the population (Cai et al., 2019). Thus, new entrants now constitute a high and increasing proportion of

patients (D'Ambrosio et al., 2017). In 2019, there were 128,536 new arrivals including refugees and migrants including from high burden TB countries, who arrived by land or sea to Europe primarily via Spain, Italy, Greece, Malta and Cyprus (Ardittis and Laczko, 2020). Hence, coordinated effective and sustainable interventions for prevention, diagnosis, and treatment are essential in the EU. A 2015 survey completed by all EU/EEA countries of the WHO European Region, plus six additional EU candidate countries (Albania, Bosnia and Herzegovina, the former Yugoslav Republic of Macedonia, Montenegro, Serbia, and Turkey) showed that 19 (52.8%) systematically screen migrants for latent TB infection (LTBI), whereas 9/36 (25%) do not or 8/36 (22.2%) do not systematically (Klinkenberg et al., 2009). Approaches implemented to date include chest x-ray for active disease and tuberculin skin, and interferon gamma release assay for latent TB with varying degrees of success (Kunst et al., 2017). Furthermore, many vulnerable migrants who lack access to health care are quite often not incorporated in the screening programmes. After arrival, screening may provide a population level benefit by preventing subsequent transmission usually in the minority communities. Screening for latent TB provides a benefit directly to the individual by further progression to active disease.

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Screening for tuberculosis in Europe's southern border

In this line, EU countries have focused on two major areas; detecting prevalent TB cases in migrants to limit the onward transmission, and in some countries testing for, and treating LTBI in migrants from high-TB burden countries to avoid reactivation (Kunst et al., 2017). However, the standards for testing migrants vary across the EU with limited data on their comparative efficiency (Greenaway et al., 2018) especially in the context of screening new arrivals from high burden countries in the southern border of the EU. Two studies have recently evaluated the screening of migrants on arrival to countries on the southern border of the EU over the last decade. One study (Pasta et al., 2019) investigated migrants arriving in Lampedusa (Italy) from 2011 to 2019. Of the 775 patients hospitalised, 167 were for infectious diseases, 21 of whom were TB positive. Another study (Bertoncello et al., 2018) estimated LTBI prevalence in migrant arriving by Mediterranean Sea in 2016. Prevalence rates varied from 25–40% according to tuberculin skin test and interferon-gamma assay values. Here we present a case study using data from the E-DETECT TB project (Barcellini et al., 2019) to illustrate the cost effectiveness of screening.

Cost effectiveness of screening migrants in Italy

The EDETECT-TB project aims to contribute to the ultimate elimination of tuberculosis in the EU by utilising evidenced based interventions to ensure early diagnosis, improve integrated care and support community and prison outreach activities in low and high-incidence countries. In Italy, the project implemented and evaluated active TB screening in hard-to-reach populations, i.e. the refugee population at first reception centres to ensure early diagnosis, improve integrated care and support the community to avoid further spread (Abubakar et al., 2018). We utilised data from the E-DETECT TB project to assess the cost-effective of early detection from a provider perspective by estimating the cost per case of active TB screening method on migrants landing in Sicilian ports. In Italy, amongst over 3,000 cases of TB are diagnosed

annually; over 50% occur in the foreign-born population coming from countries with an estimated TB incidence above 150/100,000 (Fattorini et al., 2016). 70% of the total migrants and refugees who arrived in Europe in 2017 landed in Italy according to the International Organization for Migration (IOM) (Ardittis and Laczk, 2020). Italy is a low TB incidence country and most of XDR and MDR TB cases (81%), which are more difficult to treat than drug-susceptible TB due to the limited and potentially toxic treatment options, occur in the migrant population (Lönnroth et al., 2015; Odone et al., 2011; Blasi et al., 2017). Departing mainly from Libya, newly arrived individuals either claim asylum or pass through Italy to move to other countries of the EU (Hamood, 2006). Once in Italy, refugees are firstly hosted in specific hotspots and, after few days, transferred to regional first-line reception centres (hubs) (Gianetto et al., 2019). In hotspots, active case-finding is based on TB symptoms screening, while in first aid reception centres interventions are often limited to passive case finding. In the latter, case findings are performed in symptomatic migrants who report themselves to health centres or who visit outpatient clinics for unrelated medical conditions. Case-finding is performed regardless of the vaccination status of the individual, which is usually unknown. Furthermore, nationwide data on TB in asylum seekers is limited mostly because of the health system that is fragmented on a regional level and due to the different approaches regarding TB testing/notification that are adopted by each region and/or healthcare facility (Campomori and Ambrosini, 2020). Active case finding for TB is a key element of the World Health Organization (WHO), European, and Italian general recommendations to tackle down TB (World Health Organization, 2013).

As part of the EDETECT program, newly landed migrants in Sicily were screened for active TB (between November 2016 and December 2017) using a smartphone application (standardised E-questionnaire was carried out by medical staff), followed in symptomatic individuals by fast molecular test (Xpert MTB/RIF Ultra) on collected sputum samples (Barcellini et al., 2019).

Asylum seekers (n = 3,787) in first line reception centres were interviewed through the use of the E-Detect App to collect demographic and clinical data. The app was also used to collect

Table 1
Inputs of the cost-effectiveness analysis: costs and probabilities.

Costs per sample and salaries per activity duration		
Activity (Staff costs) ^a	Average time (minutes)	Average hourly rates (€)
Nurse assistants presenting/administering the questionnaire	5 minutes	13.04
Nurse collecting sputum sample	10 minutes	14.02
Medical doctor clinical evaluation of positive/information	30 minutes	35.90
Activity (costs of transportation)		
Activity (costs of transportation)	Average number of samples	Average rate per trip (€)
Courier charges from Sicily to the main lab in Milan	60 per trip	50.00
Test ^b		
Test ^b		Cost per test (€)
XpertMTB/RIF Ultra		58.91
Model parameters		
Parameter	Probability (uncertainty)	Source/Reference
Presence of TB symptoms	0.24	EDETECT study
Xpert MTB/RIF sensitivity	0.85 (95% CI: 0.82–0.88)	Li et al. (2017)
Xpert MTB/RIF specificity	0.98 (95% CI: 0.96–0.98)	Li et al. (2017)
Offer and acceptance to TB screening if symptomatic	0.63	EDETECT study
Offer and acceptance to TB screening if asymptomatic	0.01	EDETECT study
TB positive in symptomatic screened	0.03	EDETECT study
TB positive in asymptomatic screened	0.11	EDETECT study

Notes: ^aStaff costs were obtained from the Lazzaro Spallanzani national institute for infectious diseases hospital. ^bPrice based on the national health system price list; Servizio Sanitario Nazionale (SSN). CI stands for Confidence Intervals.

smear Xpert MTB/RIF Ultra results and other diagnostics data as well as treatment and follow-up, (further details on <https://e-detecttb.eu/> and described in reference [Barcellini et al. \(2019\)](#). Collected data were automatically and securely transmitted to the medical staff at the reference hospital. Cost data were collected prospectively during the study period (2016-2017) including costs of staff, transportation and the Xpert MTB/RIF Ultra test according to the Servizio Sanitario Nazionale (SSN) ([Table 1](#)). Subsequently, probabilities were calculated based on the screening pathway ([Barcellini et al., 2019](#)). 3,787 individuals were screened, of which 891(24%) presented TB symptoms. Sputum samples were only collected from 592 (63%) symptomatic participants. Among those tested, 15 (3%) individuals were positive. A further 28 (1%) of 2,896 asymptomatic individuals were tested, among whom 3 (11%) were positive. We assumed Xpert MTB/RIF Ultra sensitivity and specificity of 0.85 (95%CI 0.82–0.88) and 0.98 (95%CI 0.96–0.98), respectively based on a previous meta-analysis ([Li et al., 2017](#)). Probability parameters used are summarized in [Table 1](#). Therefore, we undertook a cost-effectiveness analysis from program provider perspective to assess the value for money of case finding by estimating the cost per case of active TB detected. All analysis was carried out using the Microsoft Excel software 2019 version.

[Figure 1](#) summarizes the TB screening pathway using a probabilistic decision tree based on the cost's parameters (per participant), and probabilities of each outcome obtained from the EDETECT study described above. We assessed the cost-per test and cost-per true-positive case, defined as total program cost divided by the number of true positive TB diagnoses due to screening program, compared with the status-quo of no intervention/screening. The total cost of the program was €41,828.2, resulting in an average cost per recruited patient of €11.05 (41,828/3,787), while there were 15 cases diagnosed. Consequently, cost per true positive case was €2,788.55. Furthermore, the total cost per single TB positive diagnosis was €81.12 (1.09 + 62.08 + 17.95).

Early case detection is a cost-effective intervention in Italy given the very low cost per true-positive case compared to other health interventions ([Woods et al., 2016](#); [Dobler, 2016](#)), and similar to

previous studies reporting between USD120 and USD23,660 ([Dobler, 2016](#); [Campbell et al., 2019](#); [Zammarchi et al., 2015](#)). Furthermore, the cost per case detected is below the median annual costs of TB per person at Italian hospitals (€8,509) in 2002 ([Bocchino et al., 2006](#)). Finally, our strategy could be even more cost-effective if the early detection programme is adopted and the samples are analysed locally avoiding having to incur in study costs such as samples transportation to the study lab and questionnaire administration which are not part of routine health expenditure. The results are in line with the WHO guidelines for countries with low TB incidence ([Lönnroth et al., 2015](#)) where active case finding is crucial to reach the pre-elimination threshold (<10 TB cases per million population) by 2035 ([World Health Organization, 2014](#)). Furthermore, the development of a national plan to manage migration-related issues (including testing for migrant specific health risk factors) and improved surveillance and TB control and surveillance at or near the point of arrival of migrants are part of the core interventions for TB elimination in Italy ([Blasi et al., 2017](#); [Ingrosso et al., 2014](#)).

The analysis has some limitations. First, we have not accounted for transmission using transmission dynamic modelling. Consequently, the intervention may be even more cost effective. Second, it is difficult to compare this intervention with a do-nothing scenario as there are costs involved in further treatments if early detection is not addressed. Third, the Gross Domestic Product (GDP) based threshold is for Disability Adjusted Life Years (DALYs) averted; however, the intervention is cost-effective when comparing our cost per true-positive TB case with other studies. Fourth, individuals were not followed-up to determine the long-term implication of early-detection or failure to identify cases. Nevertheless, the project presents a relatively simple way of analysing the costs associated with each diagnostic result, focusing public policy on a priority high risk population subgroup. The project also suggests that using cartridge based molecular test on spot (such as Xpert MTB/RIF Ultra), compared to culture, can be delivered with minimal technical support avoiding further additional costs. Future work on cost and cost-effectiveness

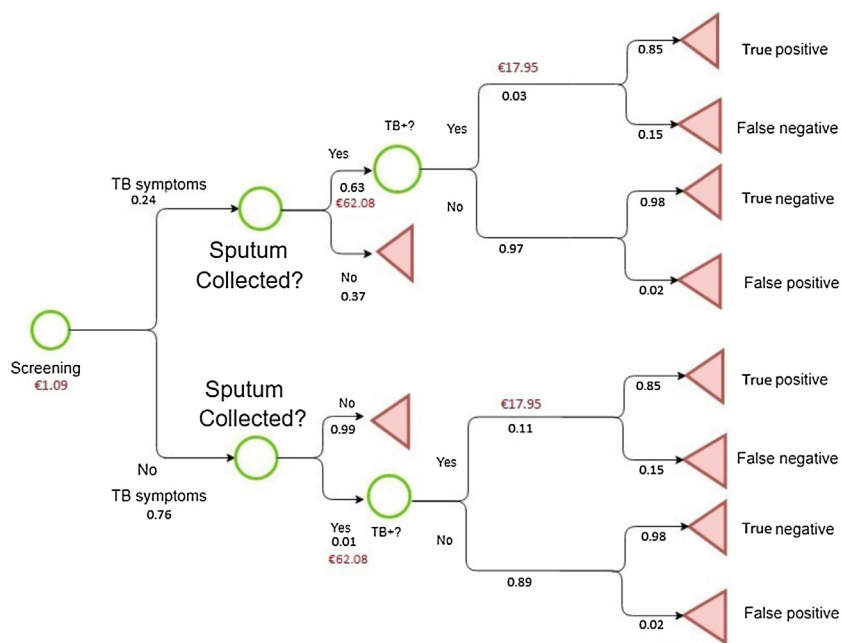


Figure 1. Active TB screening decision tree schematic.

Notes: Individuals terminate in this model in either a TB or not-TB state, indicated on the right-hand side as True positive/False negative and True negative/False positive respectively.

analysis in this population should collect costs of hospital admissions and treatment regimens, and potentially also address a societal perspective. Analysis should also investigate the population level epidemiological impact screening using transmission dynamic modelling to estimate the possible number of secondary infections averted.

Conclusions

Evidence-based interventions have a major role in reducing the spread of tuberculosis among migrants (Dasgupta and Menzies, 2005), and early detection ensures that potential transmission is averted (Lin and Flynn, 2010). We have demonstrated the importance of active case finding for TB, especially in a country with high numbers of migrant arrivals from high TB risk settings which may be a good example to take for other similar European countries. Targeted post-arrival screening for active TB in such settings may provide the most cost-effective solution to TB in Italy. Moreover, further analyses are necessary to ascertain the most cost-effective model for latent TB infections diagnosis and treatment in this population group in Italy and in other European countries experiencing high rates of incoming migrants.

Transparency declaration

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Declaration of interests

The authors declare no conflict of interests.

Contributors

Study design and analytical methods: LG, EG, HH, IA. Data analyses: LG, KA. Manuscript writing: KA, LG, IA. Data collection: DMC, LB, GS, EG. Data interpretation, critical manuscript review, edition, final approval: all authors.

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Data availability and ethics

Data cannot be shared publicly as sensitive information is contained. Essential information is included throughout the paper, and elsewhere (Barcellini et al., 2019). The present study was approved by the San Raffaele Institute Ethic Commission (agreement number 709624).

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All authors attest they meet the ICMJE criteria for authorship and have reviewed and approved the final article.

References

Abubakar I, Matteelli A, De Vries G, Zenner D, Cirillo DM, Lönnroth K, et al. Towards tackling tuberculosis in vulnerable groups in the European Union: the E-DETECT TB consortium. *Eur Respiratory J* 2018;51:1702604, doi:<http://dx.doi.org/10.1183/13993003.02604-2017>.

Aldridge RW, Yates TA, Zenner D, White PJ, Abubakar I, Hayward AC. Pre-entry screening programmes for tuberculosis in migrants to low-incidence countries: a systematic review and meta-analysis. *The Lancet Infectious Diseases* 2014;14(12):1240–9.

Ardittis S, Laczek F. Migration policy practice. *International Organization for Migration (IOM)* 2020;VII(1–3).

Barcellini L, Borroni E, Cimaglia C, Girardi E, Matteelli A, Marchese V, et al. App-based symptoms screening with Xpert MTB/RIF Ultra assay used for active tuberculosis detection in migrants at point of arrivals in Italy: The E-DETECT TB intervention analysis. *PLoS one* 2019;14(7):e0218039.

Bertoncello C, Ferro A, Ferrareso A, Mascarello M, Fonzo M, Minascorta V, et al. LTBI among migrants by Mediterranean Sea: assessing prevalence and its variations according with different thresholds and diagnostic tools. A 10-month on-field experience. *Journal of travel medicine* 2018;25(1):tay020.

Blasi F, Matteelli A, Sotgiu G, Cirillo DM, Palmieri F, Fattorini L, et al. Moving towards tuberculosis elimination: a call for action from Italy and a possible model for other low tuberculosis incidence countries. *Eur Respiratory J* 2017;49:1602242, doi:<http://dx.doi.org/10.1183/13993003.02242-2016>.

Bocchino M, Greco S, Rosati Y, Mattioli G, Marruchella A, De Mori P, et al. Cost determinants of tuberculosis management in a low-prevalence country. *The International Journal of Tuberculosis and Lung Disease* 2006;10(2):146–52.

Cai L, Li Z, Guan X, Cai K, Wang L, Liu J, et al. The research progress of host genes and tuberculosis susceptibility. *Oxidative medicine and cellular longevity* 2019;2019:..

Campbell JR, Johnston JC, Cook VJ, Sadatsafavi M, Elwood RK, Marra F. Cost-effectiveness of latent tuberculosis infection screening before immigration to low-incidence countries. *Emerging infectious diseases* 2019;25(4):661.

Campomori F, Ambrosini M. Multilevel governance in trouble: the implementation of asylum seekers' reception in Italy as a battleground. *Comparative Migration Studies* 2020;8(1):1–19.

D'Ambrosio L, Centis R, Dara M, Solovici I, Sulis G, Zumla A, et al. European policies in the management of tuberculosis among migrants. *International Journal of Infectious Diseases* 2017;56:85–9.

Dasgupta K, Menzies D. Cost-effectiveness of tuberculosis control strategies among immigrants and refugees. *European Respiratory Journal* 2005;25(6):1107–16.

Dobler CC. Screening strategies for active tuberculosis: focus on cost-effectiveness. *ClinicoEconomics and outcomes research: CEOR* 2016;8:335.

Fattorini L, Mustazzolu A, Borroni E, Piccaro G, Giannoni F, Cirillo DM, et al. Tuberculosis in migrants from 106 countries to Italy, 2008–2014. *European Respiratory Journal* 2016;47(4):1273–6.

Giannetto L, Ponzio I, Roman E. National report on the governance of the asylum reception system in Italy. CEASEVAL RESEARCH ON THE COMMON EUROPEAN ASYLUM SYSTEM 2019;21:..

Greenaway C, Pareek M, Abou Chakra C-N, Walji M, Makarenko I, Alabdulkarim B, et al. The effectiveness and cost-effectiveness of screening for latent tuberculosis among migrants in the EU/EEA: a systematic review. *Euro-surveillance* 2018;23(14):17-00543.

Hamood S. African transit migration through Libya to Europe: the human cost. *American University in Cairo, Forced Migration and Refugee Studies* Cairo; 2006.

Ingrosso L, Vescio F, Giuliani M, Migliori GB, Fattorini L, Severoni S, et al. Risk factors for tuberculosis in foreign-born people (FBP) in Italy: a systematic review and meta-analysis. *PLoS one* 2014;9(4):e94728.

Klinkenberg E, Manissero D, Semenza J, Verver S. Migrant tuberculosis screening in the EU/EEA: yield, coverage and limitations. *European Respiratory Journal* 2009;34(5):1180–9.

Kunst H, Burman M, Arnesen T, Fiebig L, Hergens M, Kalkouni O, et al. Tuberculosis and latent tuberculosis infection screening of migrants in Europe: comparative analysis of policies, surveillance systems and results. *The International Journal of Tuberculosis and Lung Disease* 2017;21(8):840–51.

Li S, Liu B, Peng M, Chen M, Yin W, Tang H, et al. Diagnostic accuracy of Xpert MTB/RIF for tuberculosis detection in different regions with different endemic burden: a systematic review and meta-analysis. *PLoS One* 2017;12(7):e0180725.

Lin PL, Flynn JL. Understanding latent tuberculosis: a moving target. *The Journal of Immunology* 2010;185(1):15–22.

Lönnroth K, Migliori GB, Abubakar I, D'Ambrosio L, De Vries G, Diel R, et al. Towards tuberculosis elimination: an action framework for low-incidence countries. *European Respiratory Journal* 2015;45(4):928–52.

MacPherson D, Gushulak BD. Balancing prevention and screening among international migrants with tuberculosis: population mobility as the major epidemiological influence in low-incidence nations. *Public health* 2006;120(8):712–23.

Odone A, Riccò M, Morandi M, Borroni BM, Pasquarella C, Signorelli C. Epidemiology of tuberculosis in a low-incidence Italian region with high immigration rates: differences between not Italy-born and Italy-born TB cases. *BMC Public Health* 2011;11(1):376.

Pasta L, Suero LAM, Filippazzo MG, Farinella EM, Gargano C, Serravalle D, et al. The Health Problems at the Landing of the Migrants in Lampedusa from 2011 to June 2019: Analysis of the Data and Revision of the Literature. *Journal of International Migration and Integration* 2019;1–14.

Woods B, Revill P, Sculpher M, Claxton K. Country-level cost-effectiveness thresholds: initial estimates and the need for further research. *Value in Health* 2016;19(8):929–35.

World Health Organization. Systematic screening for active tuberculosis: principles and recommendations. *World Health Organization*; 2013.

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World Health Organization. World Health Organization 67th World Health Assembly Gsatftp, care, and control after 2015. A67/11. Geneva: World Health Organization; 2014 Global strategy and targets for tuberculosis prevention, care, and control after 2015. 2014.

Zammarchi L, Casadei G, Strohmeyer M, Bartalesi F, Liendo C, Matteelli A, et al. A scoping review of cost-effectiveness of screening and treatment for latent tuberculosis infection in migrants from high-incidence countries. *BMC health services research* 2015;15(1):412.