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Tuberculosis among asylum-seekers in Milan, Italy: Epidemiological analysis and evaluation of interventions

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"TAKE HOME" MESSAGE

Asylum-seekers are highly vulnerable to TB due to migration-related events and marginalization in destination countries. Coordinated screening and surveillance programmes using well-informed datasets can help reduce TB transmission, improve care and address LTBI.

INTRODUCTION

In low-incidence countries of the European Union (EU), vulnerable populations are largely responsible for the lack of a faster decline of the tuberculosis (TB) incidence rate [1]. Above all, poor and marginalized people living in metropolitan areas [2, 3] have a greater risk of developing TB. In the last few years a large proportion of TB cases in EU occurred among the foreign-born [4] at a younger median age compared to native populations with TB [1, 5].

Among the foreign-born, a particular attention must be reserved to migrants due to the increase, in recent years, in migratory flows from TB high-burden countries in Sub-Saharan Africa and the Indian subcontinent [6, 7]. This phenomenon, that also involves people seeking international protection, has led to further awareness and concern to prevent infectious disease spread, particularly at entry points [8]. Pending asylum application response, asylum-seekers (AS) may remain for months within centres increasing the potential risk for both exposure and subsequent new infection and latent TB infection (LTBI) reactivation. Both in their original countries and during the migration process, AS are a particularly vulnerable population because of their exposure to various social and economic determinants [9, 10] such as poor and crowded living conditions, mal- or under-nutrition, poverty, stress, conflicts and lack of education. In recipient countries these determinants still represent a serious concern that is worsened by cultural barriers and healthcare access difficulties [11].

Although the risk of transmission to the native population is uncommon, outbreaks may occur among migrants due to poor living conditions. For this reason, in many EU Member States different TB surveillance and screening systems, specifically built around AS, have been launched in order to detect active TB cases and prevent TB development by treating LTBI. In general, screening programmes consist of a combination of chest radiograph, symptom-based assessment and,

depending on the age and estimated TB incidence in the country of origin, LTBI detection with tuberculin skin test (TST) and/or interferon-gamma release assay (IGRA) [12, 13].

Despite the efforts made by EU countries, the average treatment success rate for active TB was 60 – 87% [14]. Important losses in screening completion have been observed for LTBI screening and management strategies [15], especially in the steps of treatment acceptance and initiation. Loss to follow-up has prevented a higher preventive treatment completion rates that were 72–80% for short regimens and 7–83% for long ones [15, 16]. Furthermore, TB unawareness and stigma play a major role in delaying early diagnosis and compromising patient adherence to treatment [17].

Notably, in Italy approximately 360,000 migrants were hosted in reception centres during the 2016-2017 study period. Among all the Italian Regions, Lombardy ranks first for number of hosted AS (13% of the national territory), and the Milan area accommodates 27% of AS present in the Region. The time spent by AS in reception facilities depends on the time required by the Territorial Commissions to make decisions about asylum application. About 40% of requests received a positive response during the study period, on average 266 days after application. Our study aimed at assessing the prevalence of both TB and LTBI among AS as soon as possible after their admission to reception centres in the city of Milan. It also investigated risk of recent transmission within receiving sites. Finally, the performance of the city screening and treatments during the biennium 2016-17 was evaluated in terms of outcome of TB treatment and acceptance of, and adherence to, LTBI treatment.

METHODS

The study focused on AS hosted within Milan's area reception centres during the period 1st January 2016 to 31st December 2017. To face the TB health problem in AS arriving from high-incidence countries a two-level active surveillance system has been developed by the Lombardy Region in order to screen this population for both disease, by using a questionnaire (QS), and LTBI, by using the tuberculin skin test (TST) [18].

Data collection and record linkage

Data sources were four: the Health Protection Agency of the Metropolitan Area of Milan; the Regional TB Reference Centre, Villa Marelli Institute, Milan; the Regional database for infectious diseases; and the Microbiological and Virologic Laboratory, Niguarda Hospital, Milan. The Health Protection Agency data collection included information on screening activities (TST and QS), as well as personal information. Villa Marelli Institute provided information on TB diagnosis, TB treatment, IGRA results and preventive therapy. The Regional database was consulted to gather information on TB diagnosis and treatment. The Microbiological and Virologic Laboratory, which holds the Regional strain collection, had provided the molecular analysis of TB culture-positive samples. Data collection included also follow-up information in the year 2018 of TB and LTBI cases diagnosed during the biennium 2016-17.

Data were first cleaned from duplicated records and transcription errors. To trace patients across the different databases, a step-wise deterministic strategy for record-linkage approach was used. In more detail, the approach began by examining the field containing "name and surname", "country of origin", "date of birth", "hosting reception centre", "TST result" and "date of TST examination" from the Health Protection Agency database. Two records were considered to match if all or at least three identifiers were identical, provided that an identical correspondence between screening identifiers ("TST result" and "date of TST examination") in the analysed datasets was observed. If

only two identifiers were matched, a further verification was performed by reviewing QS to ensure that the records identified by the electronic databases belonged to the same person. Conversely, two records were considered unmatched if the abovementioned criteria were not fully satisfied. Therefore, unmatched records were considered as losses between the first and second step of the system algorithm.

In case of one or more missing identifiers the record linkage was possible by analysing data from medical records stored at Villa Marelli confirming AS identification ("identification documents check").

Analysing the registration validity and internal completeness is crucial in order to understand the main problems in data collection. For the analysis of data registration validity, the database previously compiled by the Health Protection Agency was used to identify duplicated records (identical personal data), and after data cleaning and record-linkage, to be able to find errors (e.g. typing "01/31/2000" for date of birth instead of "31/01/2000"). Having done data cleaning and record-linkage, evaluation of internal completeness was made possible by comparing the number of completed data fields out of the total number of data fields [29].

Active TB surveillance, screening and treatment

AS hosted in receiving facilities could at any time self-report symptoms compatible with TB requiring further radiological and microbiological evaluations. Furthermore, whenever an AS with previous negative screening test reported symptoms compatible with TB, as signalled to the Public Health Agency by staff of the reception centre, a chest radiograph was obtained.

The questionnaire used to screen AS for active TB, developed with modifications from the one created by *Schneeberger Geisler et al.* [19], contained ten questions allowing scoring for a total of twenty-two points: 12 points for socio-demographic and history data (2 points if from country with TB incidence above 50/100,000; 1 point if arrived in Italy for less than a year; 1 point if homeless;

4 points if previously treated for TB and 4 points in case of TB exposure from family and household members) and 10 for symptoms (2 points for each: cough for three weeks or more, nights sweats, weight loss in the last three months, fever, and chest pain). A threshold of 5 points was arbitrarily selected to consider positive the QS.

Those with a positive result (QS ≥ 5 points) were offered a chest radiograph and medical examination at Villa Marelli, the TB reference centre of the City of Milan, or sometimes at a different facility in Milan (e.g., emergency room) accordingly with the urgency of the symptoms. In all circumstances, experienced pulmonologists and radiologists assessed the presence of clinical and radiological signs suggestive of active TB. Individuals with a positive chest radiograph underwent further microbiological evaluation (smear microscopy, nucleic acid amplification test, and culture of biological samples). If any such test was positive, or if a decision to start treatment had been made on an empirical basis, the AS was offered anti-TB treatment. Classification of the case followed the EU case definitions of "possible", with clinical criteria that include signs, symptoms, chest radiograph suggestive of TB or with a clinician's decision to treat the person with a full course of anti-tuberculosis therapy; "probable", if in addition to clinical criteria one of the microbiological criteria (positive sputum smear microscopy for acid-fast bacilli, nucleic-acid amplification test or histological appearance of granuloma) was present; and "confirmed", if confirmatory microbiological criteria (isolation for *Mycobacterium tuberculosis* from a clinical specimen or positivity for both nucleic-acid amplification test and microscopy for acid-fast bacilli) were met [20]. The presence of anti-TB drug resistance was investigated in all strains of *M. tuberculosis* through nucleic acid amplification test (Xpert® MTB/RIF) and phenotypic drug susceptibility testing (DST) for culture-positive samples [21]. Following TB diagnosis, a blood test for human immunodeficiency virus (HIV) was systematically performed to detect HIV infection. The treatment regimen was chosen according to DST results, immunological status, and disease location (pulmonary vs. extrapulmonary according to World Health Organization (WHO) definition [22]).

Anti-TB treatment regimens were selected based on DST results, patient's characteristics (i.e., adverse drug reaction), and diseases localization (e.g., long-term anti-TB regimens for skeletal TB). The standard anti-TB regimen proposed consisted of 6 to 9 months of therapy with an intensive phase based on the combination of isoniazid, rifampicin, pyrazinamide, and ethambutol (RHZE) for 2 months followed by RH(E) for 4 months, based on WHO guidelines [23].

Treatment outcomes were defined according to WHO definitions [22].

Molecular surveillance, based on 24-*locus* mycobacterial interspersed repetitive units/variable-number of tandem repeats (MIRU/VNTR) typing system, was also implemented to assess the likelihood of recent transmission. Clustering criteria for recent TB transmission classification consisted in having an exact 24-MIRU/VNTR profile in at least two different patient's sputum-samples or having 23 *loci* matches and one *locus* with one more or less repetition [24]. These criteria were assessed jointly with epidemiological data originating from contact tracing [25]. Recent transmission was considered through assessment of strain characteristics comparing the 24-MIRU/VNTR profile, while reactivation cases were defined if a unique 24-MIRU/VNTR strain type was obtained.

LTBI screening and preventive treatment

AS within reception facilities were additionally tested using TST, with Mantoux method, in order to screen them for LTBI. TST were considered positive if the induration had a diameter of ≥10 millimetres (mm), Those presenting with a positive result were offered chest radiograph and medical examination at Villa Marelli, where experienced pulmonologists and radiologists assessed the presence of clinical and radiological signs suggestive of active TB or the need for treatment of latent infection. AS with a positive TST result, without radiological and clinical evidence of TB, were subjected to further testing with IGRA and for HIV infection if under 35 years of age or in presence of specific risk factors (e.g. recent TB contact). In children under 5 years of age preventive

therapy was administered without additional tests. IGRA testing was performed using QuantiFERON-TB Gold In-Tube® (QFT-GIT) from 1st January to 13th December 2016 and QuantiFERON-TB Gold Plus® (QFT-Plus) since 14th December 2016. If IGRA were positive, AS were offered preventive therapy for LTBI [26]. The proportion of acceptance of preventive therapy was defined as the number of those initiating treatment divided by the total number of individuals to whom it was offered (all individuals IGRA-positive and those under-35 who refused IGRA even after a positive TST).

The LTBI preventive treatment regimens generally chosen by Villa Marelli pneumologists consisted in a combination of rifampicin (RIF or R) and isoniazid (INH or H) (RIF+INH; Rifinah®, Sanofi) for 3 months. Other single-drug regimens (rifampicin-only for 4 months or isoniazid-only for 9 months) were used in the presence of clinical risks such as high levels of liver enzymes, or in case of adverse drug reactions.

Treatment completion was defined as the proportion of AS who completed preventive therapy - assessed by patient self-reporting - divided by the number of those who started it.

Statistical analysis

Categorical variables were the number of AS and the corresponding percentage, whereas continuous variables were summarized through the median and the quartiles (Q1; Q3). Missing and incomplete data were considered as "unknown" during statistical analysis.

TB prevalence rates were determined performing an age and sex standardization for the total study population and for specific subsets, grouping individuals by World Health Organization (WHO) Regions, geographical areas (United Nations Regions) of origin and estimated TB prevalence in country of origin were available. The WHO Regions-specific prevalence rates observed were compared to available WHO estimates [27], using the prevalence ratio (PR). Total and subset-specific LTBI prevalence was calculated using as sample size those who underwent TST without a

diagnosis of TB. The number of individuals with LTBI was estimated using the proportion of IGRA-positive individuals out of those TST-positive who were examined at Villa Marelli. This was adjusted with the percentage of those lost after a TST-positive result assuming they had the same IGRA-positive proportion. Data were then compared with prevalence rates derived from the literature [28] using Chi-square test.

The surveillance system was assessed evaluating as indicators: completeness of medical evaluation after a positive TST and/or QS result, timing of interventions, TB treatment outcomes, proportion of acceptance and adherence to LTBI preventive therapy, database validity (duplicate records and errors) and internal completeness. Chi-square test was used to compare (1) anti-TB treatment success rates based on the country of origin; and (2) adverse side effects between those lost to follow-up and those who complete treatment.

RESULTS

Validity and internal completeness monitoring

Records included in the database, before data cleaning and record linkage procedures, amounted to 7,325. Of them, 1,975 (27.0%) were duplicates while 26 were reception centres' staff members screened with TST, therefore excluded from study analysis. Errors in data collection were detected in 2.2% of the fields analysed, mainly affecting information in the fields of country of origin (223; 31.9%) and TST result (227; 32.4%).

After comparing the first and second level screening system database, a total of 868 (2.7%) fields were found to be unfilled for the QS score (517; 59.6%) variable.

First-level surveillance and screening

During the 2016-2017 study period a total of 5,324 AS were enrolled. 53.4% belonged to the age group 20-29; most were males (84.2%) from Sub-Saharan African countries (69.1%) (**Table 1**). The most frequent countries of origin were Eritrea (583; 11.0%), Nigeria (564; 10.6%), Somalia (474; 8.9%), Pakistan (385; 7.2%) and Bangladesh (385; 7.2%). Among the AS screened with TST and QS by the health authorities of the city of Milan, 2,403 (45.1%) were positive (**Figure 1**). In particular, 2,298 (43.2%) and 270 (5.1%) were respectively positive to TST and QS, including a total of 165 AS positive for both tests.

Taking into account the main region of origin, 1,170 (48.5%) of West-Africans (Benin, Burkina Faso, Cote d'Ivoire, Gambia, Ghana, Guinea, Guinea-Bissau, Liberia, Mali, Mauritania, Niger, Nigeria, Senegal, Sierra Leone and Togo), 467 (40.4%) of East-Africans (Eritrea, Ethiopia, Kenya, Somalia, South Sudan, Tanzania and Uganda) and 407 (41.7%) of South-Asians (Afghanistan, Bangladesh, India, Nepal, Pakistan and Sri Lanka) AS were positives to TST. Whereas, the questionnaire was positive mainly in individuals coming from North Africa (Egypt, Libya, Morocco, Sudan and Tunisia) (5; 7.7%) and from West Africa (144; 6.0%).

Second-level surveillance and screening

During the study period, 69 active TB cases were diagnosed among AS (1.3% of the total AS screened). Of those, 89.9% were among young individuals aged 10-29 years; 88.4% were males; and the median time of permanence in Italy was 6 months (range 0.5 – 36) Cases came primarily from Western (47.8%) and Eastern (44.9%) African countries, mainly from Somalia (20; 29.0%), Eritrea (11; 15.9%), Senegal (7; 10.1%) and Guinea (7; 10.1%).

Of the 69 TB cases, 58 (84.1%) were pulmonary (including those with either pulmonary disease only or both pulmonary and extrapulmonary disease), while 11 (15.9%) had exclusively extrapulmonary TB, 6 (54.5%) of them having lymph node TB. Among active TB cases, 25 (36.2%) were classified as "possible", with consequent decision to start therapy, 3 (4.4%) as probable, and 41 (59.4%) as culture-confirmed who then also had a DST.

Drug resistance to at least one first-line anti-TB drug was detected in 5 (12.2%) cases; 2 (40.0%) of them, originating from Liberia and Côte d'Ivoire, were affected by multi-drug-resistant TB (MDR-TB). TB/HIV co-infection was observed in 2 (2.9%) AS.

A total of 1,350 individuals were offered IGRA testing. Among them, 10 (0.7%) refused IGRA and 1 child aged 5 was exempted. Of the 1,339 AS tested, 865 (64.6%) were IGRA-positive (274 QFT-GIT and 591 QFT-Plus) (**Table 1**). Among IGRA-positive individuals, two reported a clinical history of previously treated TB; therefore, no preventive treatment was offered.

TB clustering

TB clustering, proven through 24-MIRU/VNTR typing system (**Figure 2)**, was observed only in two clusters, including a total of five subjects, all from Eastern Africa. The first cluster included two Somalis hosted in the same reception centre, while the second included two Eritreans and one Somalian belonging to two different reception centres. Despite accurate investigations, no previous or current contact could be demonstrated between the case TB_Cluster2_A and the two others

(TB_Cluster2_B and TB_Cluster2_C). While TB case TB_Cluster2_C was assessed to be a recent contact of TB_NotClustered by the Health Protection Agency, data provided by molecular testing failed to prove any linkage.

Active TB prevalence

The observed overall TB prevalence (**Table 2**) was 1,236 per 100,000 population (95% CI: 1,210 – 1,263 per 100,000 population) with differences between WHO Regions. Prevalence was 1,033 per 100,000 population (95% CI: 1,006 – 1,060 per 100,000 population) among AS from the WHO African Region (WHO AFR) countries and 3,043 per 100,000 population (95% CI: 2,890 – 3,197 per 100,000 population) among those from the WHO Eastern Mediterranean Region (WHO EMR) countries that include Somalia (20 TB cases). The comparison between observed and estimated prevalence showed a higher TB frequency in AS compared to the general population in the WHO Region of origin: the PR were 3.1 (95% CI: 2.8 – 3.5; $p<.001$) for WHO AFR and 19.0 (95% CI: 16.2 – 22.3; $p<.001$) for WHO EMR. In particular, in Somalia and Eritrea, responsible for 44.9% of TB cases, the TB prevalence (3,800 (95% CI: 3,761 – 3,839; $p<.001$) and 1,658 (95% CI: 1,594 – 1,723; $p<.001$), respectively, per 100,000 population) is significantly higher compared with existing estimates [27]. Examining prevalence grouped into geographical regions of origin, 333 TB cases per 100,000 population was the figure for Asia, and 1,379 (95% CI: 1,343 – 2,971) and 2,971 (95% CI: 2,863 – 3,079) cases per 100,000 those for West and East Africa, respectively.

LTBI prevalence

Considering only individuals who were positive to both IGRA and TST (844; 64.8%), the LTBI prevalence (**Table 3**) was 27.9% (95% CI: 26.7 – 29.1%), differently distributed through regions. Among those from West Africa, the proportion of LTBI (747; 31.4%) was similar to that of individuals from East Africa (372; 33.1%), while a lower proportion was observed in AS from Asian Region (225; 18.6%). The countries with the highest observed LTBI prevalence were

Somalia (193; 42.5%), Guinea (123; 37.6%), Nigeria (146; 26.0%), Eritrea (144; 25.2%) and Pakistan (94; 24.5%).

Grouping data using WHO Regions, AS from WHO EMR had a prevalence of 17.4% (95% CI: 15.1 – 19.8%), consistent with 16.3% (95% CI: 13.4 – 20.5%; p=.545) estimated for their countries of origin [28]. A higher prevalence rate (31.7% (95% CI: 30.2 – 33.2%)) than the official country estimate (22.4% (95% CI: 20.6 – 24.6%; p<.001)) was observed among AS from WHO AFR [28].

Surveillance and screening participation

Examining the performance of the surveillance and screening system, 59.1% of AS positive (1,419 of 2,403) at screening activities were recorded in the second-level databases, while 984 (40.9%) subjects were lost in the transition between the first and second level of screening.

Evaluating the timing of interventions, the median delay between screening activities and second-level tests was 107 (47; 153) days. Twenty-eight (19; 80) days were necessary to receive a result and start treatment after the IGRA test. In those who received preventive treatment, the average timeframe between screening and completion was 228 (158; 280) days.

Active TB treatment outcomes

All 69 patients with an active TB diagnosis were placed on treatment and outcomes are available for 68, while 1 MDR-TB patient with HIV co-infection is still on treatment. Fifty-seven (83.8%) had a successful outcome: in 11 (19.3%), a microbiological confirmation at the end of therapy was obtained, while the remaining 46 (80.7%) completed the treatment regimen without a final microbiological confirmation, mainly due to the lack of capacity to produce sputum. Seven patients (10.3%) were lost to follow-up, and most were from East African countries (4; 57.1%). Four (5.9%) were transferred to other treatment sites outside of the study area. Focusing on the correlation between treatment success and country of origin, no statistical difference was found between West (27; 81.8%) and East African individuals (23; 74.2%) (p=.461).

In those completing treatment, 38 (66.7%) received standard anti-TB regimens of 6 to 9 months of therapy with an introduction phase with isoniazid-rifampicin-pyrazinamide-ethambutol (RHZE followed by RH(E), while 12 (21.1%) with extrapulmonary localization of the disease (i.e. disseminated and skeletal) received similar treatment but for longer periods. In 3 (5.3%) individuals the regimens were modified in the presence of adverse side effects and in 2 (3.5%) due to drug-resistance (rifampicin-resistant (RR)/MDR-TB). Two more cases (3.5%) received modified regimens in Hospitals different from the Regional Reference Centre, and we could not trace the clinical reason underlying such therapeutic choices as it was not reported in the database of the Lombardy Region.

LTBI outcomes

Overall, 875 (64.1%) patients were eligible for LTBI treatment. The 3 months of RIF+INH regimen was used in 863 (98.6%) patients, while 12 (1.4%) were treated with either 4 months of RIF or 6 months of INH. The acceptance rate of LTBI treatment was 92.4%, since 4.3% were lost to follow-up after IGRA testing and 3.3% refused preventive therapy. The development of adverse drug reaction in those who started treatment was observed in 52 (1.9%) individuals, of which 40 (5.2%) cases among those 768 who completed treatment and 12 (30.0%) among those 40 who discontinued it ($p<.001$). The final treatment completion rate was 94.3%.

DISCUSSION

Migrants, particularly AS, are individuals at great risk of physical and social distress who need to cope with different habits and legislations in new social and cultural situations. In addition, along the migratory route, their health is jeopardised by exposure to risk factors, including violence, malnutrition and environmental challenges [30]. TB is a relevant problem among international migrants [31], and this was confirmed by our study. For all these reasons, TB national guidelines [18, 32], adopted in the metropolitan area of Milan, have been implemented to screen migrants for TB and LTBI and, as necessary, treat them.

In the absence of precise information, the number of TB cases diagnosed among AS was considered expression of prevalence, rather than incidence, although most of the individuals had arrived in Italy within 6 months from the detection of disease. However, it could be also speculated that some of the active cases emerged after arrival to Italy and therefore could represent new incident cases. The impossibility to precisely assign a date for the onset of symptoms suggests that it is more prudent to consider detected cases as prevalent ones. Thereby, TB prevalence in AS was found to be remarkably higher than the official WHO estimates [27], suggesting that in some countries the available estimates might be lower than the true TB burden [13, 33]. This may be true particularly for some African countries where information is very limited (e.g. Somalia) and estimates are made through expert opinion rather than empirical data [6, 13]. That notwithstanding, migration is likely a major driving factor for LTBI reactivation, a phenomenon that is well-known to persist for several years after arrival [34] as a consequence of marginalization and poverty. In our study, considering the lack of evidence of recent transmission while in reception sites, the majority of TB cases detected among AS were conceivably due to a state of infection acquired either in the country of origin or along the journey route. This is also supported by the fact that LTBI prevalence among AS in Milan was very similar to figures observed in previous studies [28, 35, 36].

The evaluation of the TB interventions undertaken in Milan emphasizes important achievements including the high treatment success rate, with almost no transmission documented. Similarly, the very high treatment completion rate of LTBI preventive therapy has potentially averted approximately 80 TB cases in the future (considering a 10% rate of LTBI reactivation life-time risk [37]). Furthermore, our assessment on the proportions of IGRA-positive individuals among those TST-positive (column D, **Table 3**) might suggest the need of adjustment of the current screening policy [13]. Such modifications, like the establishment of a single-step approach (TST not followed by IGRA, if positive) in some migrant populations (e.g. East Africans), could be more appropriate especially if backed by cost-effectiveness analysis. On the other hand, the study highlighted several key points for strengthening the current surveillance and screening systems. One of the major problems observed in our study was loss of candidates for preventive therapy between the first and the second step of the system. This is not unlike what has been reported in other studies [15]. In this respect, we were able to identify some of the organizational factors which jeopardise system performance. They include: 1) inadequate data quality control, digitalisation, recording and sharing; 2) high inflows of AS in Milan during the study period; 3) insufficient engagement of staff at reception centres; 4) lack of coordination due to screening activities dispersed in multiple locations; 5) logistical problems related to transportation of AS to the clinical services at Villa Marelli; and 6) insufficient coordination among agencies involved.

Correct data registration and digitalization are essential to data-sharing among agencies, preferably by using a common dataset. Therefore, it is crucial to develop a data quality control ensuring that no overestimation of losses recur in the future [29]. Undoubtedly, the existing system of combined TB control between the Health Protection Agency and the Clinical Reference Centre at Villa Marelli was overstretched once exposed to a large inflow of migrants without a corresponding increase of resources. This led to problems in the correct registration of AS and a wide time interval between the first and second level evaluations [38]. Moreover, staff of the reception centres played a key role

in the system as they were accountable for asylum-seekers attendance at Villa Marelli. To prevent any withdrawal or delayed appointment for medical evaluation, operators had been informed about the importance to prevent and detect TB in such vulnerable populations. Regrettably, there were frequent logistical and organizational problems resulting in losses or delayed appointments. Additionally, communication between the reception centres and Villa Marelli and the Health Protection Agency was weak and appointments, notification of delays and cancellations were not systematically collected in a database resulting in serious gaps in real-time monitoring of data flows and losses.

Finally, the lack of disease knowledge and other cultural issues, e.g. blood stealing/selling beliefs, mostly among West-Africans [38, 39], affected acceptance of further confirmatory testing procedures [38].

Besides the issue of clinical evaluation completion, further problems exist that limits TB and LTBI treatment success. For instance, TB treatment success, although satisfactory, could improve substantially if losses to follow-up and transfer-out were reduced. The major structural obstacle to treatment completion found in our study was short-notice in relocation/resettlement procedures of AS within Italy – 75% of those transferred out – or to other EU Member States [14].

Several interventions could be proposed to implement community-based approaches and improve structural policy. For instance, automated messages could be sent to clinicians asking to closely overlook the treatment course and report correctly the outcome [29]. Building migrant-sensitive care services and correcting the lack of cross-agency coordination [38] could allow development of a shared action plan thus minimizing attritions.

In low-incidence settings aiming at TB elimination LTBI treatment is essential. A critical step is ensuring completion of therapy once started, as important losses have been observed in several studies [15]. Overall, these studies have reported that only half of migrants and other marginalized

groups with a medical indication start treatment, usually with very low completion rates. Despite the initial losses during screening, once treatment was started all the efforts were focused on completion through a migrant-sensitive approach focusing on counselling about the importance of the treatment, directly dispensing medications, and involving the reception centres' operators in supporting the intervention [38, 40]. An important factor for treatment adherence is the adoption of the short-course (3 months of combined RIF+INH/Rifinah®, Sanofi) treatment [15, 16, 41].

Our results prompt a consideration on the best future perspectives to approach hard-to-reach populations in a metropolitan area. These may include the creation of a single-centre multi-disciplinary service that combines the two steps of the actual screening system, leading to a reduction of dilution of health interventions and providing a better standardized method of collection, recording and sharing of data. A mobile system able to bring healthcare workers together with first- and second-line screening activities such as TST, chest radiograph and blood tests (including IGRAs), within reception centres would better fit with a vulnerable and mobile population. This option may improve completion of clinical evaluation by substantially reducing waiting time and permitting more effective approaches to hard-to-reach communities [15, 31] that are heterogeneously distributed within metropolitan areas. A national web-based database would also contribute to reduce losses and duplications and would provide un-interrupted care in mobile populations.

In conclusion, this study shows that well-coordinated screening measures are critical to early diagnosis and treatment among a high-risk, vulnerable and marginalised migrant population in a large metropolitan area. It also proves that rolling out successful at-scale interventions for both preventive therapy and active disease management, and maximising effectiveness through digital innovations allowing better inter-connectivity among involved services, are critical innovations to pursue.

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TABLES

Table 1. Baseline characteristics of asylum-seekers population within reception centers in Milan participating in screening activities.

	A	***B***	***C***	***D***
	Total	**TST-positive**	**QS-positive**	**IGRA-positive / IGRA tested**
	n (%)	**n (% A)**	**n (% A)**	**(%)**
Total	5,324 (100.0)	2,298 (43.2)	270 (5.1)	865 / 1,339 (64.6)
Sex				
Male	4,482 (84.2)	2,003 (44.7)	236 (5.3)	760 / 1,189 (63.9)
Female	734 (13.8)	260 (35.4)	28 (3.8)	105 / 150 (70.0)
Unknown	108 (2.0)	35 (32.4)	6 (5.6)	-
Age				
0-9	60 (1.1)	12 (20.0)	1 (1.7)	2 / 5 (40.0)
10-19	1,375 (25.8)	580 (42.2)	67 (4.9)	232 / 367 (63.2)
20-29	2,843 (53.4)	1,215 (42.7)	153 (5.4)	494 / 766 (64.5)
≥ 30	985 (18.5)	464 (47.1)	35 (3.6)	137 / 201 (68.2)
Unknown	61 (1.1)	27 (44.3)	27 (44.3)	-
Geographical Region of origin				
North Africa	299 (5.6)	65 (21.7)	5 (7.7)	14 / 24 (58.3)
East Africa	1,155 (21.7)	467 (40.4)	43 (3.7)	180 / 221 (81.4)
West Africa	2,415 (45.4)	1,170 (48.5)	144 (6.0)	493 / 757 (65.1)
South Asia	975 (18.3)	407 (41.7)	42 (4.3)	132 / 260. (50.8)
Others	350 (6.6)	124 (35.4)	12 (3.4)	46 / 77 (59.7)
Unknown	130 (2.4)	65 (50.0)	24 (18.5)	-
WHO Region of origin				
WHO AFR	3,741 (70.3)	1,711 (45.7)	188 (5.0)	711 / 1,022 (69.6)
WHO EMR	1,041 (19.6)	309 (29.7)	39 (3.8)	98 / 175 (56.0)
Others	542 (10.2)	213 (39.3)	19 (3.5)	56 / 142 (39.4)
Unknown	130 (2.4)	65 (50.0)	24 (18.5)	-

Missing data for one or more variable are collected as “not known”, except for missing result of one screening test (TST or QS) in presence of a positivity in the remaining test.

The columns B and C include data of asylum-seekers positive to both TST and QS.

Table 2. TB prevalence among asylum-seekers grouped into WHO and geographical Regions.

	Total TB cases	TB prevalence
	n (%)	rate per 100,000 (95% CI)
Total	69 (100.0)	1,236 (1,210 – 1,263)
Geographical Region of origin		
West Africa	33 (47.8)	1,379 (1,343 – 2,971)
East Africa	31 (44.9)	2,971 (2,863 – 3,079)
Asia	4 (5.8)	333 (315 – 352)
Others	1 (1.4)	-
WHO Region of origin		
WHO AFR	44 (63.8)	1,033 (1,006 – 1,060)
WHO EMR	24 (34.8)	3,043 (2,890 – 3,197)
Others	1 (1.4)	-

Table 3. Positivity to TST and IGRA test and LTBI estimation:

	A	*B (B/A)*	*C (C/B)*	*D (D/C)*	*E (E/A)*	*F*
	Total	**TST-positive**	**TST-positive at 2nd level of screening ‡**	**IGRA-positive**	**Estimated LTBI cases§**	**Literature estimates for LTBI prevalence†**
	N	***n* (% A)**	***n* (% B)**	***n* (% C)**	***n* (% A)**	**%**
Total	5,255	2,259 (43.0)	1,302 (57.6)	844 (64.8)	1,464 (27.9)	-
Geographical Region and country of origin						
West Africa	2,380	1,153 (48.4)	741 (64.3)	480 (64.8)	747 (31.4)	19
Guinea	327	178 (54.4)	90 (50.6)	62 (68.9)	123 (37.6)	22
Nigeria	562	217 (38.6)	149 (68.7)	100 (67.1)	146 (26.0)	18
East Africa	1,124	448 (39.9)	212 (47.3)	176 (83.0)	372 (33.1)	22
Eritrea	572	182 (31.8)	62 (34.1)	49 (79.0)	144 (25.2)	7
Somalia	454	221 (48.7)	126 (57.0)	110 (87.3)	193 (42.5)	22
Asia	1,213	465 (38.3)	291 (62.6)	141 (48.5)	225 (18.6)	27
Bangladesh	384	192 (50.0)	124 (64.6)	48 (38.7)	74 (19.3)	28
Pakistan	383	156 (40.7)	90 (57.7)	54 (60.0)	94 (24.5)	29
Others	408	133 (32.6)	58 (43.6)	47 (81.0)	108 (26.5)	-
Unknown	130	68 (52.3)	-	-	-	-
WHO Region of origin						
WHO AFR	3,697	1,688 (45.7)	997 (59.1)	693 (69.5)	1,173 (31.7)	22
WHO EMR	987	294 (29.8)	166 (56.5)	97 (58.4)	172 (17.4)	16
Others	441	217 (49.2)	139 (64.1)	54 (38.8)	84 (19.0)	-
Unknown	130	68 (52.3)	-	-	-	-

Missing data for one or more variable are collected as "unknown", except for missing result for TST.

‡ The second level of screening include both chest radiography and IGRA testing, performed at Villa Marelli.

§ The total number of individuals (**A**) was calculated as the total number of subjects who underwent TST minus those with active TB. The estimated prevalence of LTBI (**E**) was calculated using the % of IGRA-positive among the TST-positive people who underwent further testing with IGRA at the Regional Reference Centre (**D**/**C**) applied to the number of those lost between TST and IGRA evaluations **(×(B minus C))**, and assuming they had the same level of positivity as those tested with IGRA. This figure was then added to those who tested positive at IGRA (**D**) to derive the numerator.

† Literature estimates are taken from *Houben et Dodd* [28].

Table 4. Treatment outcomes and regimens used for active tuberculosis cases (N = 69):

	A	***B***	***C***
Anti-TB regimens	**Treatment success** ***n***	**Lost to follow-up** ***n***	**Transfer out** ***n***
	57 (83.8)	**7 (10.3)**	**4 (5.9)**
Standard anti-TB regimens	38 (66.7)	-	-
Modified anti-TB regimens for:			
- Adverse drug reaction	3 (5.3)	-	-
- Particular forms of EPTB	12 (21.1)	-	-
- RR/MDR-TB	2 (3.5)	-	-
- No reason reported	2 (3.5)	-	-

Standard TB regimens refers to those with at least 6 months of rifampicin-containing treatment regimen. A modified and extent regimen was used for those having particular forms of EPTB (i.e., skeletal, neurological tuberculosis).

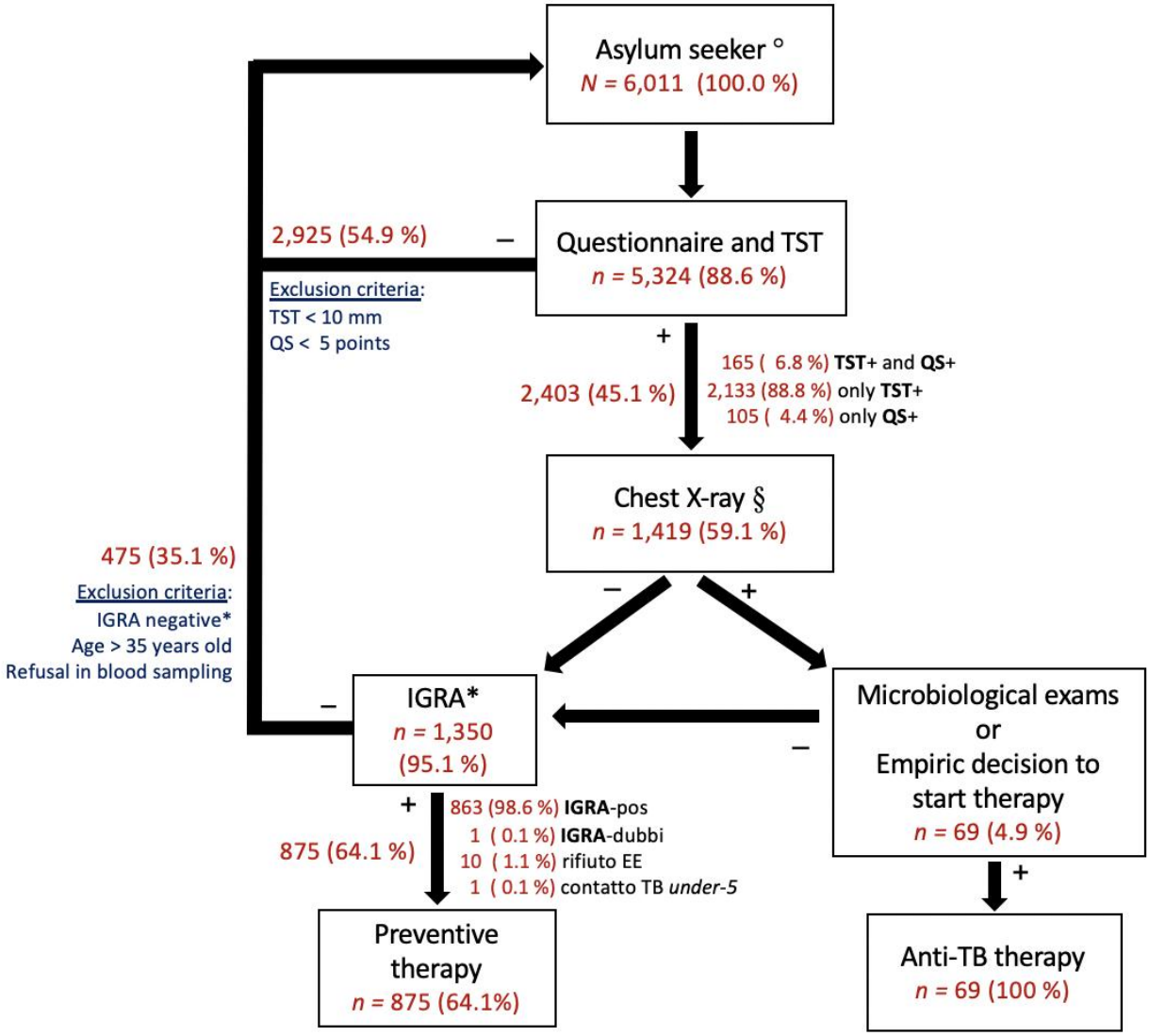

Figure 1. Sequence of interventions in screening activities for the diagnosis and therapy of TB and LTBI. Those considered negative during screening activities include also those without data collected in databases. ° Estimated by the municipality of Milan (Comune di Milano)."§ Data on CXR are not routinely collected in the analyzed databases, but the number indicated reflect the sum between people tested with IGRA and those with diagnosis of TB. "* IGRA were performed in people under 35 of age in the absence of further risk factors (e.g. recent TB contact).

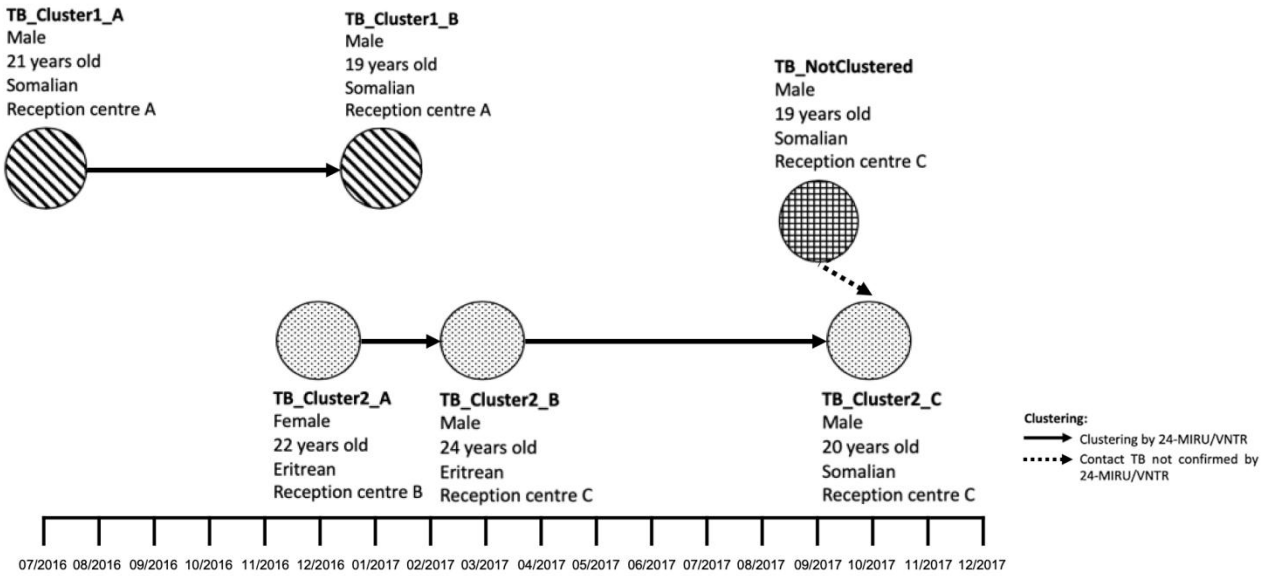

Figure 2. TB transmission dynamic within Milan reception centres. %"Using the 24-MIRU/VNTR typing system we were able to find five TB cases linked by transmission. However, one individual ("TB_Cluster2_C") was found to be a recent contact of another one ("TN_NotClustered"), although spread between them was excluded by molecular epidemiology.

Table: TB screening tools

Type of symptoms	TB cases	Specific sub-groups		Prevalence rate *per 100,000*
No symptoms (QS-negative TST-positive)	16	QS-negative TST-positive	2,133	750
		QS-negative with TST	5,054	317
Mild symptoms (QS- and TST-positive)	23	QS-positive TST-positive	165	13,939
		QS-positive with TST	240	9,583
		TST performed	5,294	432
Severe symptoms (QS-positive without TST)	30	QS-positive	270	11,111
		QS performed	5,324	564

Considering both groups of symptomatic individuals (53 AS) among a total of 270 asylum seekers with positive QS we found a prevalence rate of 19,630/100,000; whereas considering both TB groups with positive TST (39 AS) among a total of 2,298 TST-positives prevalence was 1,697/100,000.