Early Detection and Integrated Management of Tuberculosis in Europe

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D6.5

Multi country latent and active TB in migrants databases

WP 6 – Multi country latent and active TB in migrants databases

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1	30 Oct 2020	Knut Lönnroth	First draft.
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Definitions and acronyms

CXR	Chest x-ray
ECDC	European Centre for Disease Prevention and Control
E-DETECT	Early Detection and Integrated Management of Tuberculosis in Europe
FoHM	Folkhälsomyndigheten (national public health agency), Sweden
ICER	Incremental cost-effectiveness ratio
ICD	International Classification of Diseases
IGRA	Interferon-gamma release assay
KI	Karolinska Institutet, Sweden
KNCV	KNCV Tuberculosis Foundation, the Netherlands
LTBI	Latent tuberculosis infection
OSR	Ospedale San Raffaele, Italy
PHE	Public Health England, Department of Health, UK
QALY	Quality Adjusted Life Years
TB	Tuberculosis
TST	Tuberculin skin test
UCL	University College London, UK
UNIB	Universita Degli Studi di Brescia, Italy
WHO	World Health Organization
WP	Work package

Country codes:
IT: Italy
NL: The Netherlands
SE: Sweden
UK: The United Kingdom

1 Introduction

In 2019, 272 million people were international migrants due to conflict, inequality, financial insecurity and a globalized labour and educational market. Europe was the destination continent for the highest number of migrants - more than 80 million [1]. This impacts Tuberculosis (TB) epidemiology as many migrants move from high to low TB incidence countries [2-4]. As TB rates are declining towards elimination levels in native populations in most low-TB incidence countries, the proportion of foreign-born cases increases [2-5]. This applies also in the E-DETECT TB partner countries Italy (IT), The Netherlands (NL), Sweden (SE) and the United Kingdom (UK).

Screening for active TB and latent TB infection (LTBI) in migrants in low-incidence countries are important for improving early detection and prevention. Despite international guidelines from ECDC [6,7] and WHO [8], there is no concrete recommendations on which migrant sub-groups should be eligible for screening, which screening algorithm to use, when and where to screened, or on the best approach for implementation of screening programmes to ensure optimal completion of the cascade of care from screening to completion of treatment.

The present lack of consolidated data on the process and outcomes of screening hinders the development of such guidance [4,5]. Better surveillance and more research are needed in order to inform how to best target screening and how to finetune programmatic implementation. It is particularly important to monitor screening coverage, screening yield and linkage to care, as well as to identify the main factors that determine these performance indicators and thereby influence the overall effectiveness and cost-effectiveness [2,4,5,9]. Screening programs without surveillance of key performance indicators could result in a substantial waste of resources [10,11].

Most national TB registries include data on notified cases of active TB, but neither screening data nor information about LTBI diagnosis or treatment [5]. International databases that rely on national reporting therefore have similar limitations, such as the TESSy database managed by the European Centre for Disease Prevention and Control (ECDC) and the World Health Organization´s (WHO) global TB database of nationally aggregated TB control indicators.

Therefore, the E-DETECT TB Work Package 6 (WP6) developed a multi-country database to collated and analyse data on active and latent TB screening for migrants (E-DETECT Objective 3.2).The database was intended firstly for E-DETECT TB partners, but the long term goal is to make the database available for more European countries, potentially as part of ECDCs TB surveillance. E-DETECT TB is a European research consortium for the early detection and integrated management of TB in Europe. It is purposed to contribute to the ultimate elimination of TB in the EU by means of evidence-based interventions, with a special focus on generating better evidence for screening [12].

WP6 has worked in a systematic and stepwise manner to build and populate this database. After a careful mapping of available data on LTBI/TB screening [5], WP6 partners developed a data pooling agreement (D6.1) and a protocol for data transfer and analysis (D6.2). The database was then created at the Farr Institute at UCL in 2017 (D6.3) and has since been populated with data at least annually (D6.4).

This report presents analyses based on the database[1]. The specific analytical objectives, in line with the agreed analysis protocol, were to determine screening yield and treatment uptake and completion. Moreover, the report presents preliminary results of cost-effectiveness analyses for each country. The report compares and contrasts results across the four partner countries and discusses the reasons behind important variations. In doing so, the report identifies possible ways to improve screening and linkage to care and optimize value for money.

2 Methods

2.1 Inventory of TB screening approaches and existing data sources

An online survey was conducted in the four WP6 countries as well as in countries showing interest to potentially share migrant screening data in the database in the future. Questions focused on screening policy, available data sources and possibilities to extract and report both numerator and denominator screening data [5]. National screening policies or local project approaches at the collaborating sites for the four WP6 countries are shown in table 1.

Table 1. National screening policies or local project approaches at the collaborating sites.

				Screening for active TB		Screening for LTBI	
Country	**Screening strategy**	**Population screened**	**Age (years)**	**WHO-estimated TB incidence in the country of origin/100 000**	**Screening method** Compulsory (●)/ Voluntary (□)	**WHO-estimated TB incidence in country of origin/100 000**	**Screening method** Compulsory (●)/ Voluntary (□)
Italy	Post-arrival, reception center/ health center	Asylum seekers	All	NA	Interview + CXR (●) CXR for those with positive TST or IGRA (●)	NA	Sequential TST and IGRA[a] (□) TST or IGRA[b] (□)
The Netherlands	Post-arrival, Public Health Services	Other migrants	<18 ≥18	>50 >50	CXR for those with positive TST or IGRA and no TB symptoms (●) CXR (●)	>50 NA	TST/IGRA or IGRA[c] (□) None
	Post-arrival, central reception center	Asylum seekers	<18 ≥18	>50 >50	CXR (●) CXR (●)	>50 NA	TST/IGRA or IGRA[c-d] (□) None
Sweden	Post-arrival, primary care center	Asylum seekers	All	>100 <100	CXR for those with symptoms or positive TST or IGRA (●) CXR for those with symptoms (●)	>100[e] NA	TST or IGRA (□) None
The United Kingdom	**Active TB:** Pre-entry, port of arrival, reception center **LTBI:** Post-arrival, primary care	Long stay migrants (>6 months)	<11[f] 11-15[f] 16-35 >35	>40 >40 >40 >40	Interview (□) CXR (□) CXR (●) CXR (●)	>40 >40 >150 NA	TST or IGRA (□) TST or IGRA (□) IGRA (□) None

a) From August 2017
b) 2015-July 2017
c) Until 2016: LTBI screening only for non-BCG vaccinated individuals <25 years
d) From December 2016
e) Including Eritrea, due to high-incidence in this group in Sweden
f) Recommended, not programmatic screening

The survey confirmed that few countries had comprehensive national health information systems in place from which TB and LTBI screening data (such as age, gender, and country of origin), the results of screening (abnormal chest radiographs, LTBI test results) and the final diagnosis (TB or LTBI) were captured and could be analysed to evaluate the yield of screening systematically. However, some

[1] The content of this report does not fully correspond to the title of Deliverable D6.5, as there was no mobile X-ray screening used in any of the sites contributing data to the database. Results of X-ray screening is reported in Deliverable 3.2 "Outreach screening evaluation in Romania", where this was used for other vulnerable groups. Moreover, the reporting on latent TB in Europe refers to migrants that are screened in the countries contributing to the database.

countries captured part of this data and there were also several pilot initiatives to improve screening surveillance. Surveillance of LTBI screening was particularly challenging since notification of this condition (which is non-symptomatic and non-infectious) is not compulsory in most countries. Special efforts were therefore required to gather such data for the E-DETECT TB project. Opportunities for collection of LTBI screening data in the WP6 partner countries are summarized in Table 2.

Table 2. Mapping of available data on latent TB screening in the current E-DETECT TB WP6 countries.

	Numerator (number diagnosed with LTBI)				**Denominator (number screened)**			**Numerator and denominator available from at least one national or sub-national source**
	National reporting / notification	ICD registry	Electronic medical record extraction	Laboratory records	Reporting number screened	Electronic medical record extraction	Laboratory records	
England	Compulsory	No	No	Yes	Compulsory	No	Yes	Yes
Italy	No	No	No	Project data	Project data	No	Project data	Yes
Netherlands	Voluntary	No	Possible sub-national	Project data	Project data	Possible sub-national	Project data	Yes
Sweden	Voluntary	Yes	Possible sub-national	Possible sub-national	No	Possible sub-national	Possible sub-national	Yes

2.2 Development of protocol for data sharing, analysis and dissemination

The WP6 partners agreed to standardize recording and reporting practices for screening and management and populate the database with case-based retrospective and prospective data. Since countries were at different levels of implementation, it was recognized that not all countries could provide data relevant to all objectives. The database was therefore divided into different modules representing the increased complexity of data collection. The modules and corresponding variables are shown in Figure 1 and Figure 2.

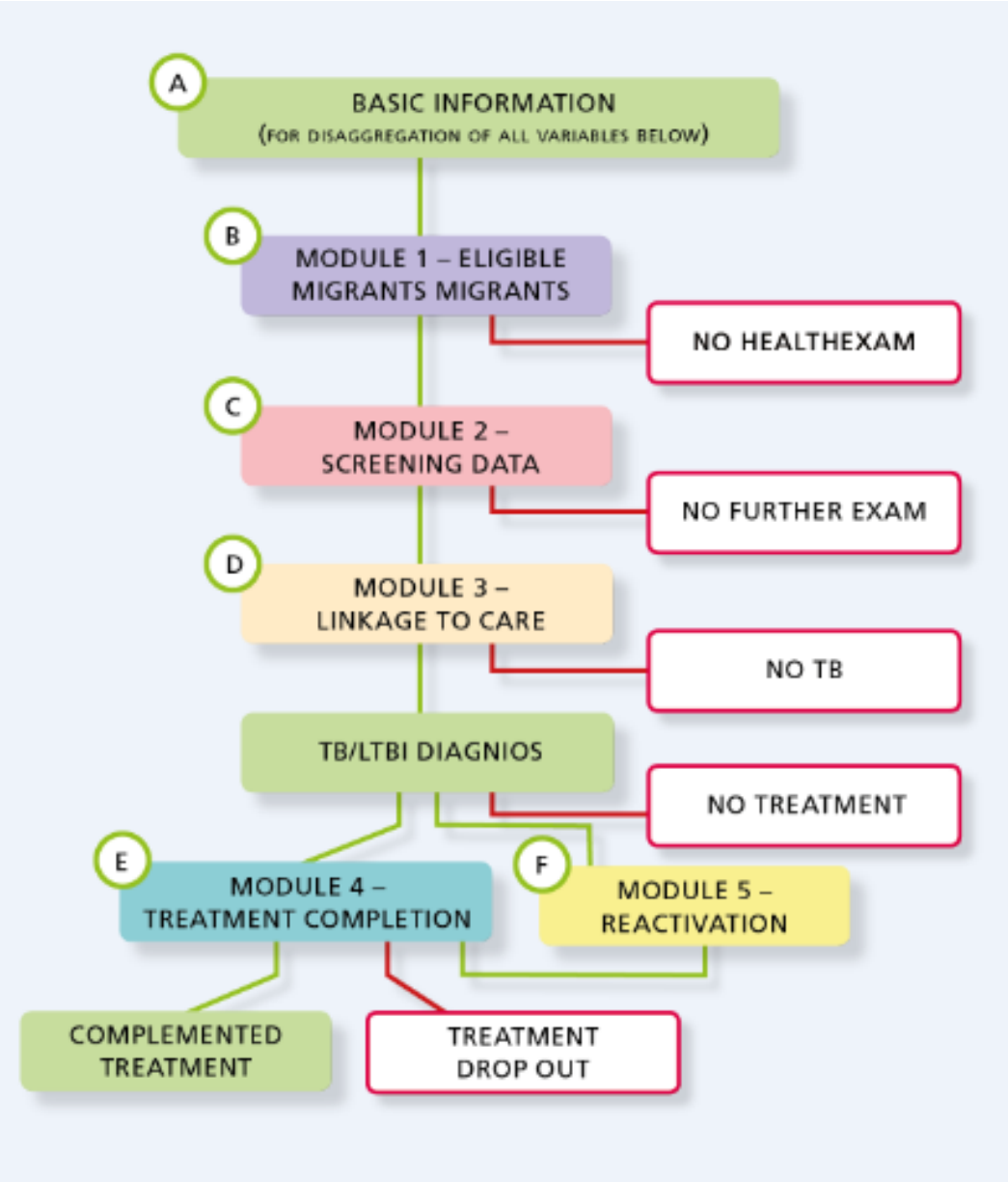

Figure 1. The screening and linkage-to-care cascade.

Figure 2. Data modules for the different steps in the screening and linkage-to-care cascade.

2.3 Preparation of data collation on national level

Within each WP6 partner country detailed mapping was done of data sources, data availability and mechanisms for data collation and sharing. UK had an existing system for data collection and collation on national level, however only for England concerning LTBI screening. The Netherlands collected routine national surveillance data on screening for active TB, while data on screening for LTBI was collected within an ongoing pilot project. For UK and Netherland, no further development of data collection and collation processes were therefore required. For Sweden, starting in in Stockholm Region, a system for TB screening data extraction from electronic medical records was developed, which could be linked to the migration authority´s database to obtain background information. An inventory of similar systems was done for all other large regions in Sweden, with a view to gradually

expand to national coverage of this model. Italy created a TB screening data recording and reporting system in selected areas, as part of the activities in E-DETECT TB WP5. The data recording and reporting model in Italy has been informed by the WP6 discussions and fully harmonized with the WP6 protocols.

2.4 Data transfer, storage, access and management

The database was established at the Farr Institute of Health Informatics and Research (Farr Safe Data Haven) at University College London (UCL), 222 Euston Road, London, NW1 2DA, UK (http://www.farrinstitute.org) [13]. A data controller and manager was appointed in each WP6 partner institution country, who was responsible for each country's dataset. WP6 partners signed a data sharing agreement with UCL to enable data transfer. Anonymized data was transferred regularly (at least every 12 months) over a secured and encrypted internet link to the Farr Safe Data Haven by the data controller/manager for each WP6 partner in accordance with each country's or institution's rules for data transfer. Persons uploading or accessing data in Farr Safe Data Haven received a UCL honorary staff contract and underwent mandatory information governance training. Selected members of the WP6 steering group were able to access the dataset at Farr Institute of Health Informatics and Research through a secured, certified internet connection. Data cleaning and data management was coordinated by UCL and data analysis jointly coordinated by KI and UCL. The WP6 steering group had to approve all decisions regarding data cleaning and data analysis.

2.5 Ethical considerations and approval

All data have been transferred to Farr Safe Data Haven without unique personal identifiers. Further measures have been taken to eliminate the risk of identification of individual subjects in the pseudonymized multi-country database, including collapsing country of origin categories when there are only few screened individuals from one specific country. Each partner was responsible for legal and ethical considerations for data extraction, sharing and analysis of national or local data. The sharing of data followed the regulations of each respective participating country, the principles of GDPR [14] and the principles set out in the EC Directive on personal data protection and confidentiality (EC/2016/679). Ethics approval for UCL was granted as Provisos Project (12371/001). KI was granted two ethical approvals and one amendment for this project from the Regional Ethical Review Board in Stockholm (2016/1974-31/5, 2018/1901-32 and 2016/1648-32). Ethics approval for Italian data collection was received from the competent Ethics Committee (Comitato Etico Provinciale di Brescia) (NP 2808 and NP 2901).

2.6 Analysis

2.6.1 General approach

A retrospective multi-country cohort study of migrants eligible for LTBI/TB screening was constructed based on the data available in the database. All those included in systematic screening according to the given country´s existing national policy and local screening protocols (see table 2) and logged in the national or project databases were eligible for inclusion in the cohort. For the sake of the analysis presented in this report, inception into the cohort was at the time of screening for TB or LTBI and each individual was followed through screening, screening result, treatment initiation and treatment completion, corresponding to modules 2-4 in figure 1. Background variables for all analyses included age, sex and country of origin.

Retrospective data has been transferred from each site from the first year available up to 2019. The presented analysis in this report includes data from January 2005 to December 2018, depending on availability in each country. Upon transfer of data, an extensive cleaning, validation and harmonisation process was undertaken prior to analysis. The total number of records in the database is presently 2,331,785.

2.6.2 Screening for active TB

This analysis focused on the screening programmes for active TB across all four included countries (see table 1), to examine similarities and differences of these TB screening programmes. The available information from the database was augmented by meta-data from each of the programmes obtained through semi-structured interviews with key stakeholders using a standard questionnaire. The aim of this was to capture programme-level information (such as details of screening algorithms and timelines and timing of public health interventions) in order to provide a greater, contextual understanding of each programme and to facilitate data analysis and interpretation.

We carried out descriptive analysis along a pre-defined analysis plan, utilising demographic (age, sex, country of origin or nationality), clinical (signs and symptoms) and screening and diagnostic data (Chest X-Ray (CXR), microbiology). While we attempted to consider the entire pathway of screening and treatment, analyses were inevitably dependent on data availability, as programmes and data availability differed considerably. Data on TB treatment initiation and completion in particular is presented, insofar possible.

The main outcome was diagnosis of active TB. To define the outcome, we used a modified version of the EU TB case definition, which allows stratification into possible, probable and confirmed cases. For the most part, we present results as yield (defined as point prevalence rate) for probable and confirmed cases separately. Because of missing data on clinical history and symptoms, we applied two key alterations to the case definition, after agreement within the E-DETECT TB consortium:

a) all patients who had a verified record of TB treatment but no positive mycobacterial culture were reclassified as probable cases, independent of whether symptoms were recorded
b) patients with a verified record of a positive mycobacterial culture were reclassified as confirmed cases.

Stratified analysis was done by type of screening programme, as well as by demographic variables (age, sex, country of origin or nationality and migrant typology).

We used simple cross tabulations and graphics to analyse proportions, using simple univariate statistics, such as χ^2 or Fisher exact tests as appropriate. Stratified analysis was utilised to explore how programmes and populations vary in their outcomes and to describe patterns of TB case yield variation. Statistical analysis was carried out with STATA 16.1 (Statacorp, Texas, USA), simple figures and tables were produced using Microsoft Excel for Mac version 16.30.

2.6.3 Screening for latent TB infection

The latent TB infection study included data from the screening programs in each setting , see table 1. Descriptive analysis was performed according to the pre-defined analysis plan and its modules for each different step in the screening and linkage-to-care cascade presented in figure 2. Data availability differed considerably between countries and therefore all the data modules could not be populated for all countries. All data were disaggregated by age, sex and TB incidence per 100,000 in country of origin or nationality.

The main outcomes analysed were the yield of positive tests and the rates of completion of key steps in the cascade of care: LTBI treatment initiation and treatment completion. The definition used for a positive latent TB infection was a positive TST or IGRA test and no active TB diagnosis.

We used cross tabulations and graphics to analyse proportions, using simple univariate statistics, such as χ^2 or Fisher exact tests as appropriate. Stratified analysis was utilised to explore how countries and populations vary in their outcomes. Analysis was carried out with SAS Enterprise Guide 7.1 (SAS Institute Inc, Cary, NC, USA). Figures and tables were produced using Microsoft Excel.

2.6.4 Cost-effectiveness analysis of LTBI screening

Given the variation in the yield of LTBI screening between different countries as well as within the same country depending on target groups, an economic analysis was performed to assess the cost effectiveness of LTBI screening strategy compared to a scenario of no screening, in each respective setting. The aim of the economic modelling was to inform policy about whether allocating recourses for LTBI screening is justified in general or for specific subgroups of migrants. An additional aim was to identify and compare major cost drivers in order to explore how cost-effectiveness could be improved.

A Markov model was developed to model the costs and effects of the LTBI screening usin a time horizon of 20 years. Two options were assessed: 1) the current LTBI screening strategy 2) No screening. The second arm represents the hypothetical scenario in which LTBI screening would not be implemented and none of the LTBI cases would be detected or treated.

A healthcare perspective was adopted to estimate the costs of LTBI screening and treatment, as well as the costs of TB diagnosis and treatment, with a focus on direct costs (test costs, treatment cost, staff costs for consultations, interpreter cost, etc). Indirect costs in term of productivity loss were not included due to the health-care perspective used for this analysis. The different cost components were quantified through published cost studies, hospital records and national tariffs published by the national health services. These values were discussed and agreed upon with experts from each country. Effects were estimated in term of Quality Adjusted Life Years (QALYs). All costs and effects were discounted with 3%. Incremental cost-effectiveness ratios (ICER) were calculated to obtain the marginal cost per QALY gained.

LTBI prevalence and the cascade of care indicators are critical epidemiological parameters for the economic modelling and were obtained from the database of this project. Other important parameters were obtained from the published literature based on the most recent evidence. Assumptions were made about partial efficacy of LTBI treatment, adverse drug reactions and success of TB treatment. Parameters and assumptions used for the economic analysis are summarized in Table 3.

Table 3. Parameters used in the economic modelling of LTBI screening

Parameter	Estimation
LTBI treatment	• Prevalence: age and country dependent (from the database) • Cascade of care: age and country dependent (from the database) • Treatment efficacy: 90% • Partial efficacy: 0% • Adverse drug reactions: excluded from the analysis
Active TB	• Treatment Efficacy:100% • Reactivation rate: 0,25% first 2 years and 0,1% for the rest of the cycles (10% lifetime risk of activation) • Adverse drug reactions: excluded from the analysis Increased risk of death due to TB: 7% • Secondary transmission: 0,1 per active case
HRQoL	• LTBI decrement: 0 • TB decrement:0,28

HRQoL, Health-related Quality of Life; LTBI, Latent Tuberculosis Infection; TB, Tuberculosis.

3 Results

3.1 Screening for active TB

3.1.1 Profile of persons screened

Across all programmes and years, there were a total of 2,331,785 screening episodes from 2,136,786 individuals. As can be seen from figure 3, there were overall slightly more screening episodes in men than women (overall male to female ratio 1.11:1) across all programmes. However, there were significant variations between programs, with a male to female ratio ranging from 1.1:1 (UK and NL) to 9.8:1 (IT). The majority of individuals were young adults aged 18-44 (72.4%), with about 10.8% aged 0-17 and 9.2% older than 45 years. Whilst the pattern was similar across programmes there were again some notable variations with more children and adolescents in Sweden (38.7%) and more young adults in Italy (86.6%).

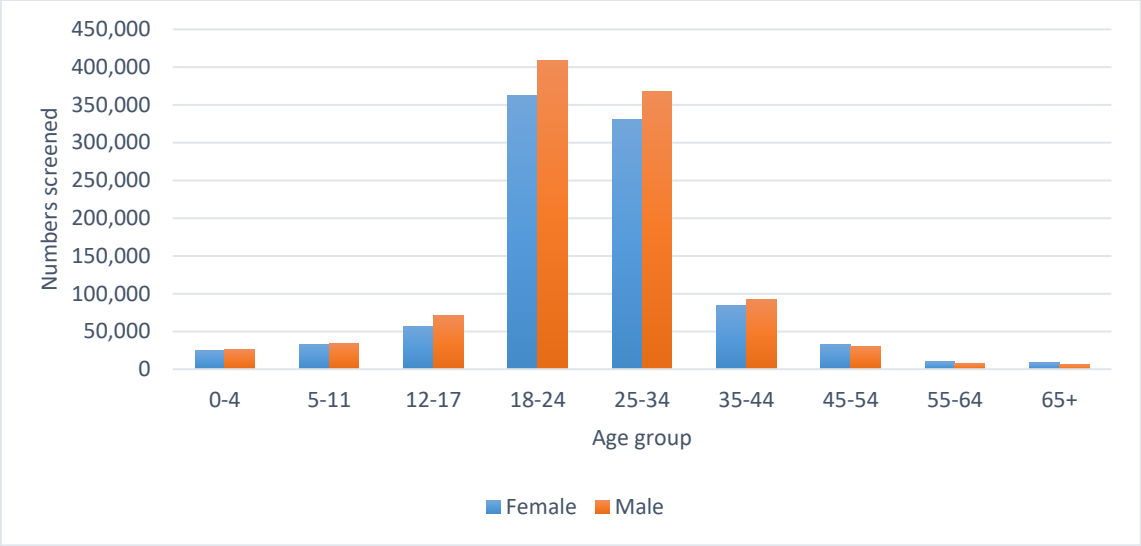

Figure 3. Age and sex breakdown of individuals screened for active TB in all screening countries combined.

The most common countries of birth or nationalities were from Asia (78%), particularly from South (46.8%) and East Asia (18.7%) as well as from Africa (18%) with smaller proportions from other world regions, including Europe (3%), mostly Eastern Europe (2.5%). The pattern of distribution across world regions was similar for Sweden, the Netherlands and the UK, but in Italy there were significantly more migrants from Africa (83.6%) and less from Asia (16.3%) (Figure 4).

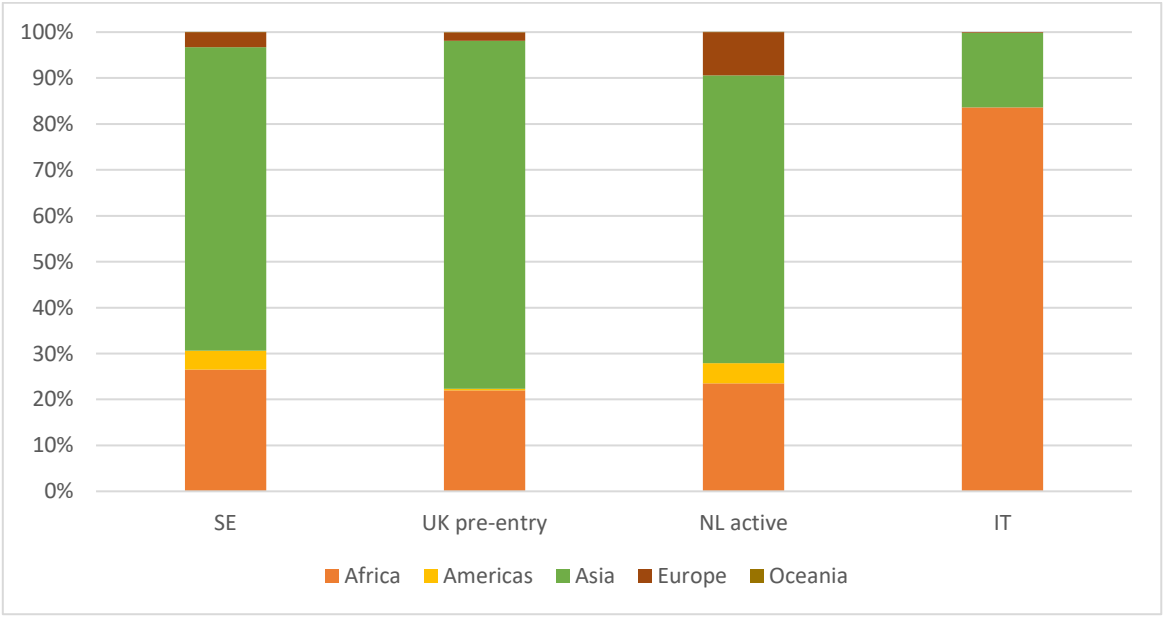

Figure 4. Percentage of word region of origin of persons screened, by screening country.

3.1.2 Chest X-ray findings and yield of active TB

Across all programmes and years, there were a total of 2,047 TB cases recorded during 2,331,785 screening episodes (1,536 confirmed and 511 probable cases). CXR results by screening country is shown in Figure 5, and correlation between CXR finding in final TB diagnosis across all countries in Figure 6.

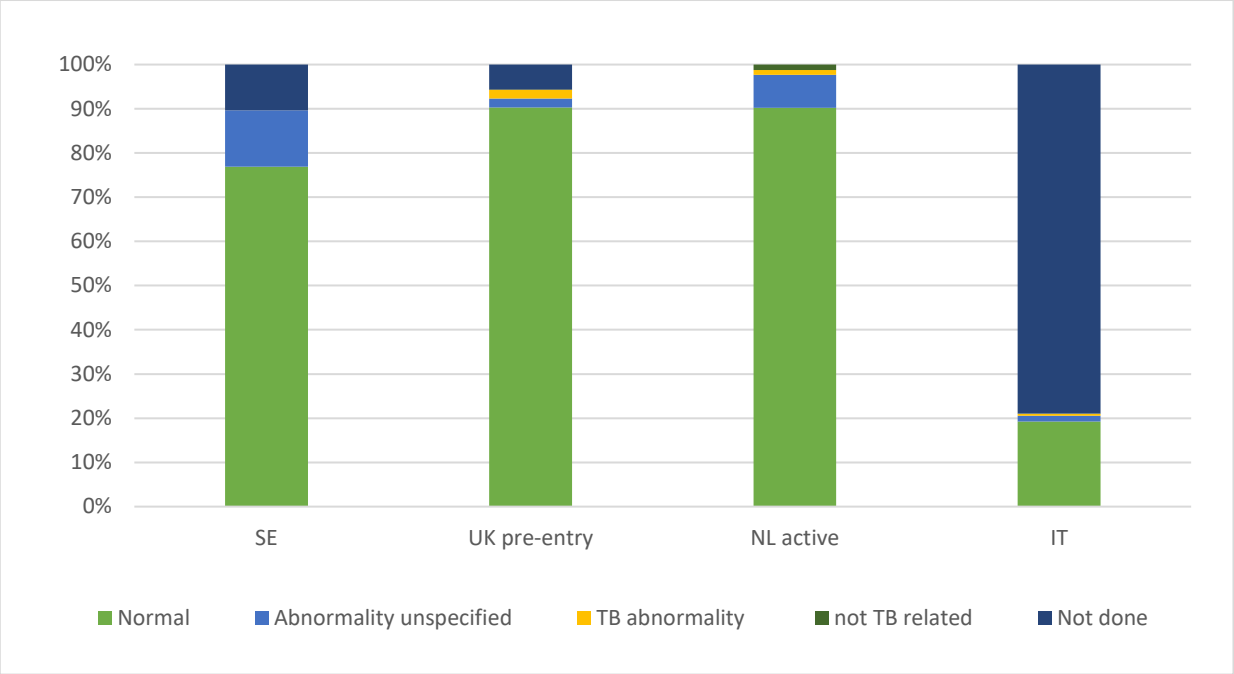

Figure 5. Percentages with different chest X-ray results, by screening country.

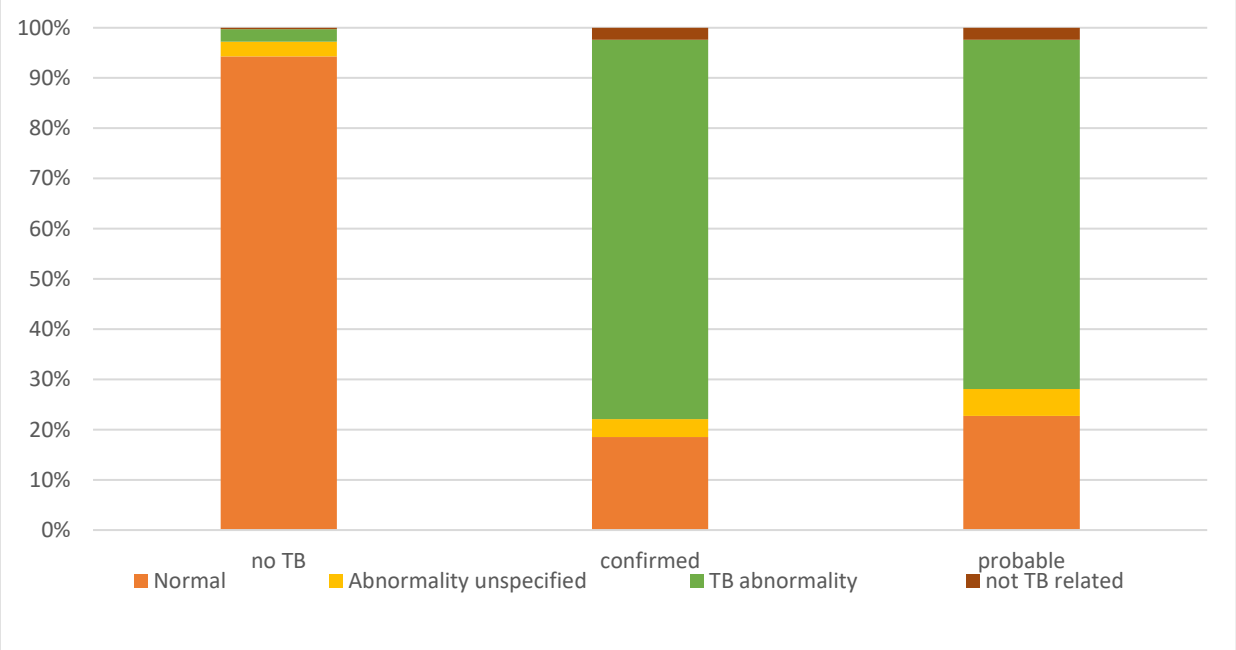

Figure 6. Percentages of different chest X-ray results by final diagnosis, all countries combined.

Overall yield per 100,000 varied between programmes and was 804.4 (569.4-1,135.3) in Italy, 217 (200.6-234.8) in the Netherlands, 201.1 (111.4-362.68) in Sweden, and 68.9 (CI 65.4-72.7) in UK (table 2). All confirmed cases had at least one positive mycobacterial culture result.

Overall, TB was detected slightly more frequently among males compared with females (1029 vs. 908), and most cases were detected in the age groups 18-24 and 25-34 year olds. This pattern is largely similar across programmes. Rates of TB detection, however were much higher in older age groups (Figures 7 and 8)

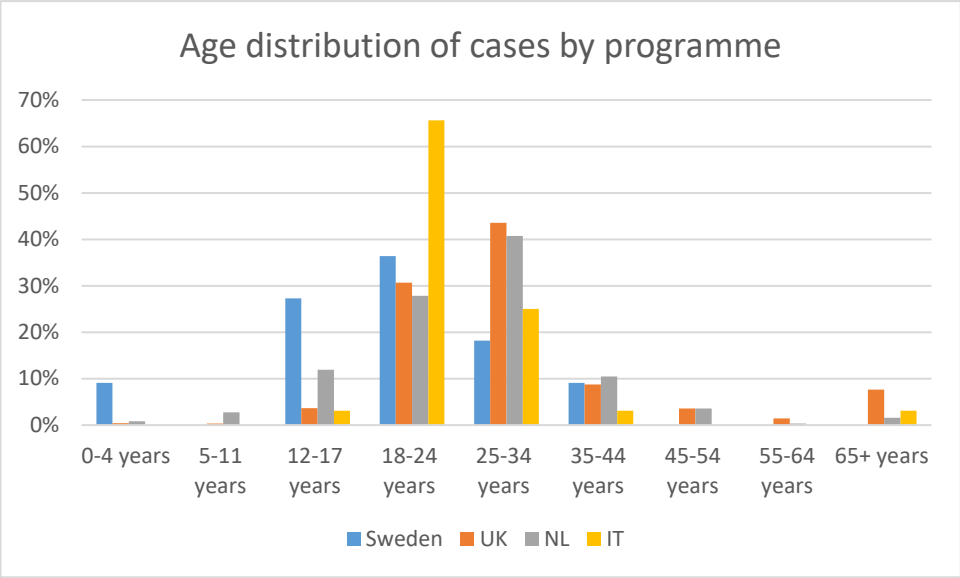

Figure 7. Age distribution of all TB cases by programme.

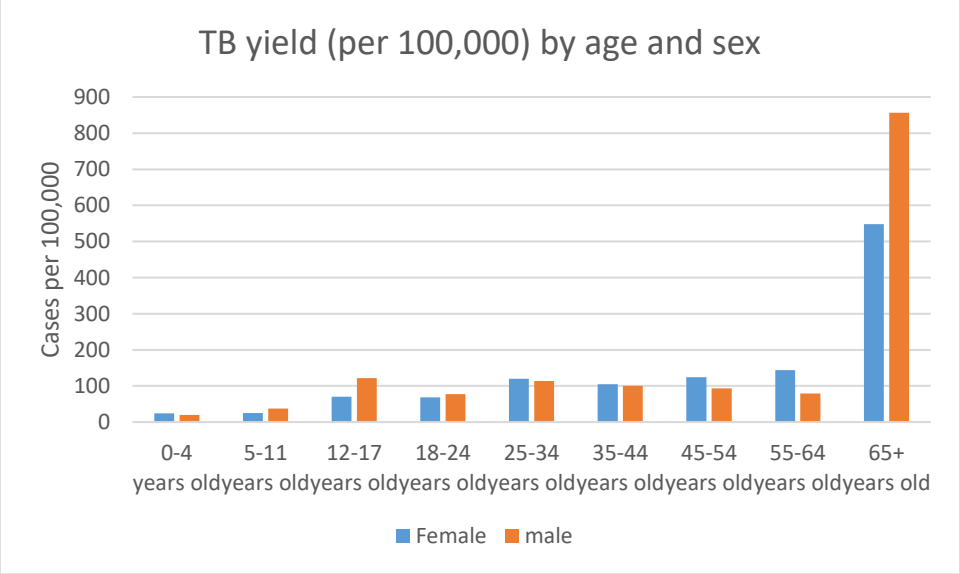

Figure 8. TB yield (per 100,000 pooled data from all programmes) by age and sex.

Yield of active TB by world region of origin and country of screening is shown in Figure 9. The highest yield was in migrants from Africa, followed by migrants from Asia.

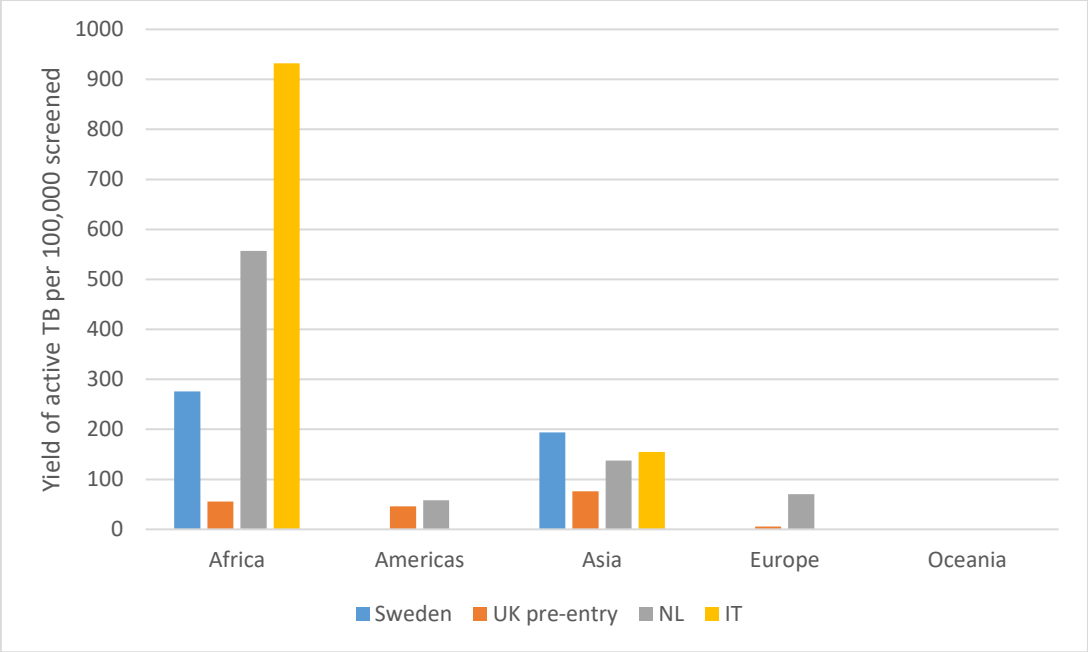

Figure 9. Yield of active TB per 100,000 screened, by world region of origin and country of screening.

3.1.3 Treatment uptake

Treatment uptake was generally high with Italy and the Netherlands reporting the highest proportion of treatment uptake (100 and 99.8% respectively) among those with a probable or confirmed diagnosis of active TB. These figures were 90.9% for Sweden and 72% for the UK. Treatment completion data was only available for the Netherlands, who reported 100% completion among those who commenced treatment.

3.2 Screening for LTBI

Data regarding LTBI screening were included if sex and age group were recorded. A total of 37,770 observations were included in the analysis with 74% of the observations from the UK, 14% from Sweden (SE) , 9% from Italy (IT) and 3% from the Netherlands (NL).

3.2.1 LTBI prevalence

Data from IT were from screened with TST, whereas all others were screened with IGRA. The prevalence of IGRA positivity ranged from 22-25% (UK 22%, NL 24% and SE 25%). Italy had a prevalence of positive TST of 38% (Figure 10).

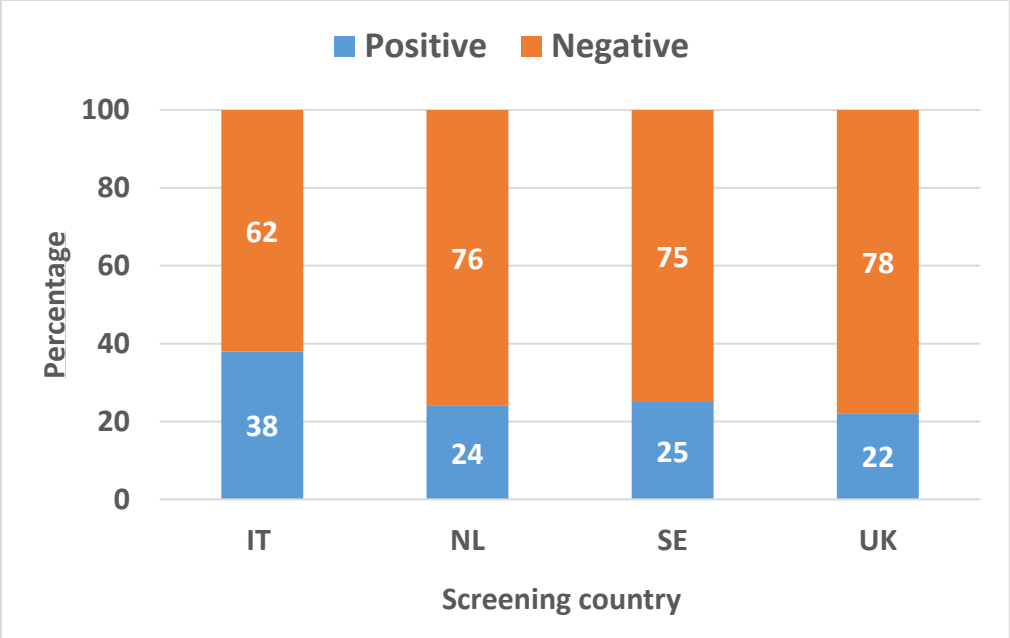

Figure 10. Percentage of positive and negative test of those screened by screening country (TST for Italy and IGRA for all other countries).

A higher percentage of a positive IGRA result was seen with increasing age, ranging from around 4% in the age group 0-11 to around 46% in the age group 55+ (Figure 11). The prevalence of positive TST in the Italian cohort ranged from 5% in the youngest age group while the three age groups spanning 12-34 years all pivoted around 38% and the 35-54 age group had a 51% prevalence.

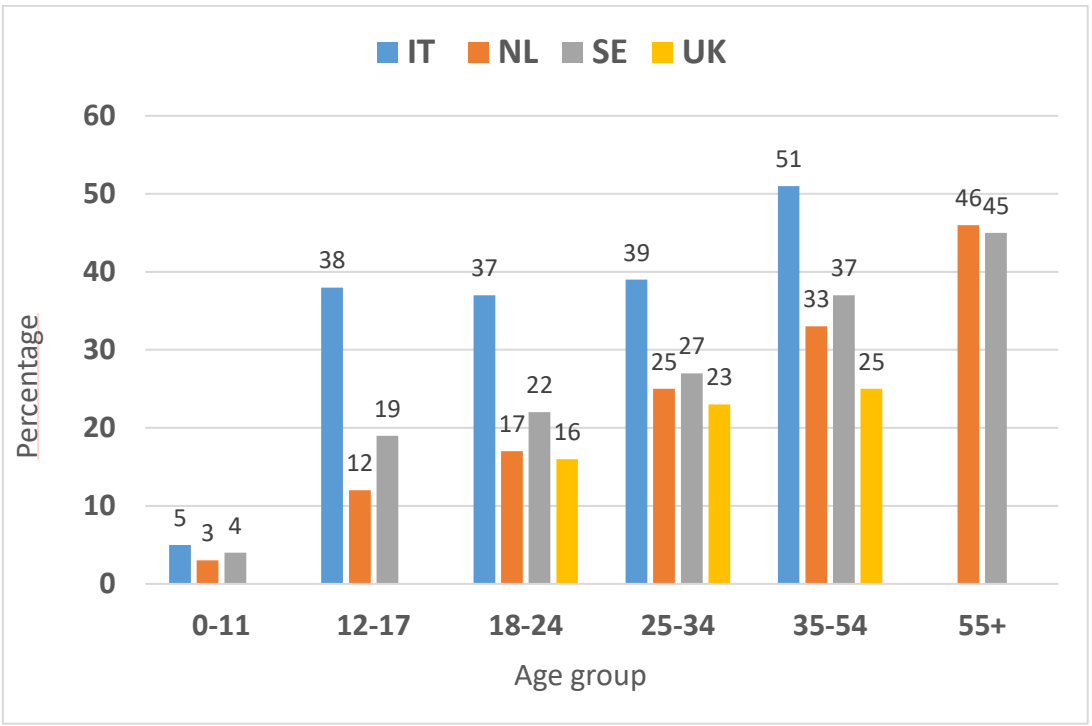

Figure 11. Percentage of positive IGRA/TST of those screened, by age group and by screening country.

The percentage of a positive test of those screened increased with TB incidence in the country of origin (Figure 12). (For the UK the analysis could not be performed due to high rates of missing data concerning country of birth or origin).

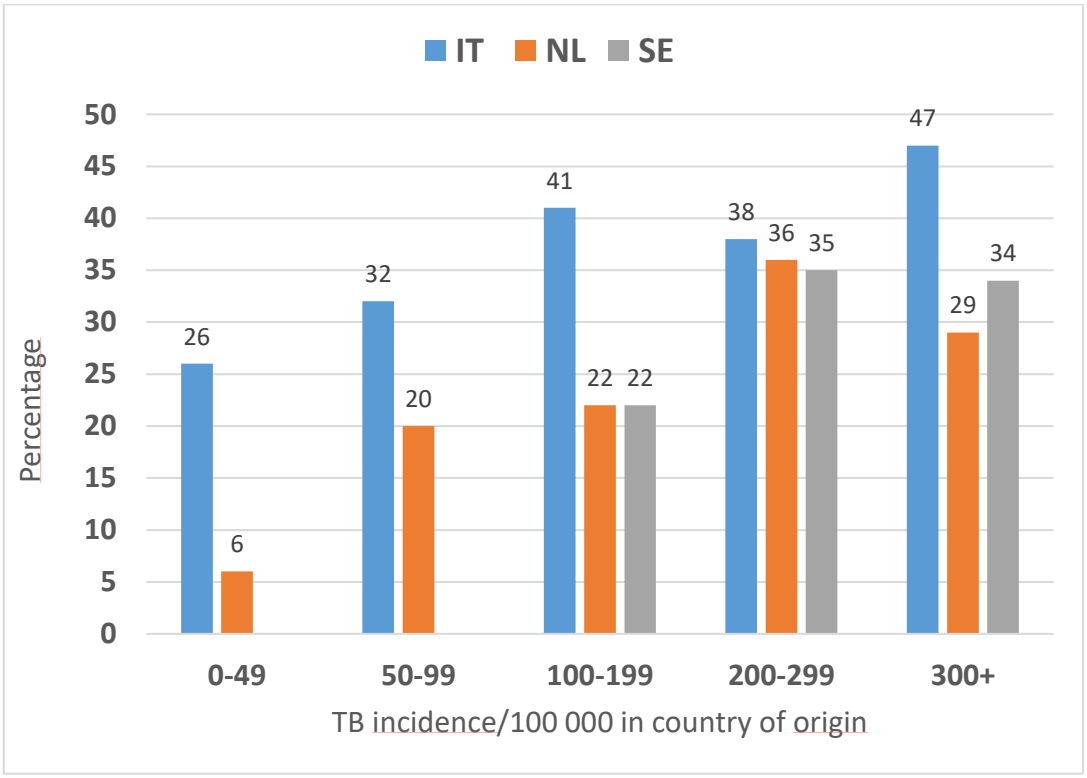

Figure 12. Percentage with positive IGRA/TST, by country of origin categorized according to TB incidence/100 000 in country of origin and by screening country.

3.2.2 Care cascade for persons screened positive for LTBI

Across all countries of screening, 38% of those screened positive for LTBI started treatment and 29% completed treatment. Of those that started treatment 76% completed treatment (Figure 13).

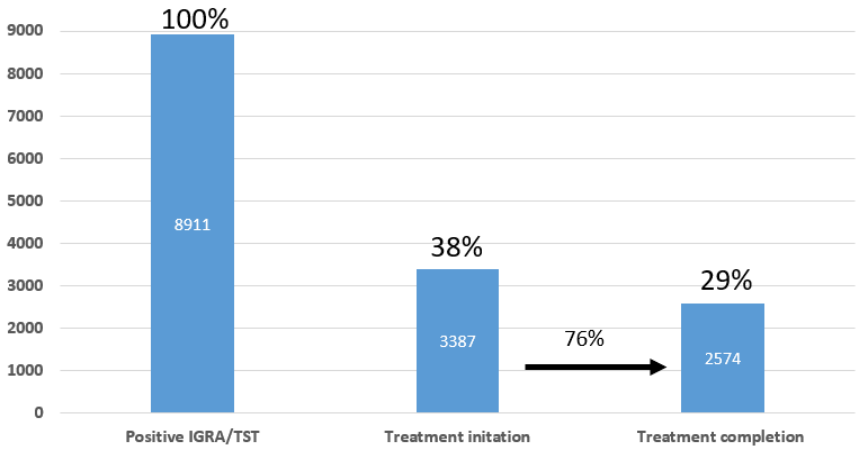

Figure 13. LTBI care-cascade from a positive screening test to completed treatment, all countries combined.

The cascade-of-care differed between countries (Figure 14). Sweden (26%) and Italy (29%) had the lowest treatment initiation of those with a positive IGRA/TST compared to the Netherlands (68%) and the UK (95%). For the UK, only part of the different regions' data in England could be included due to missing data, and there is an assumed reporting bias favoring data associated with high treatment initiation.

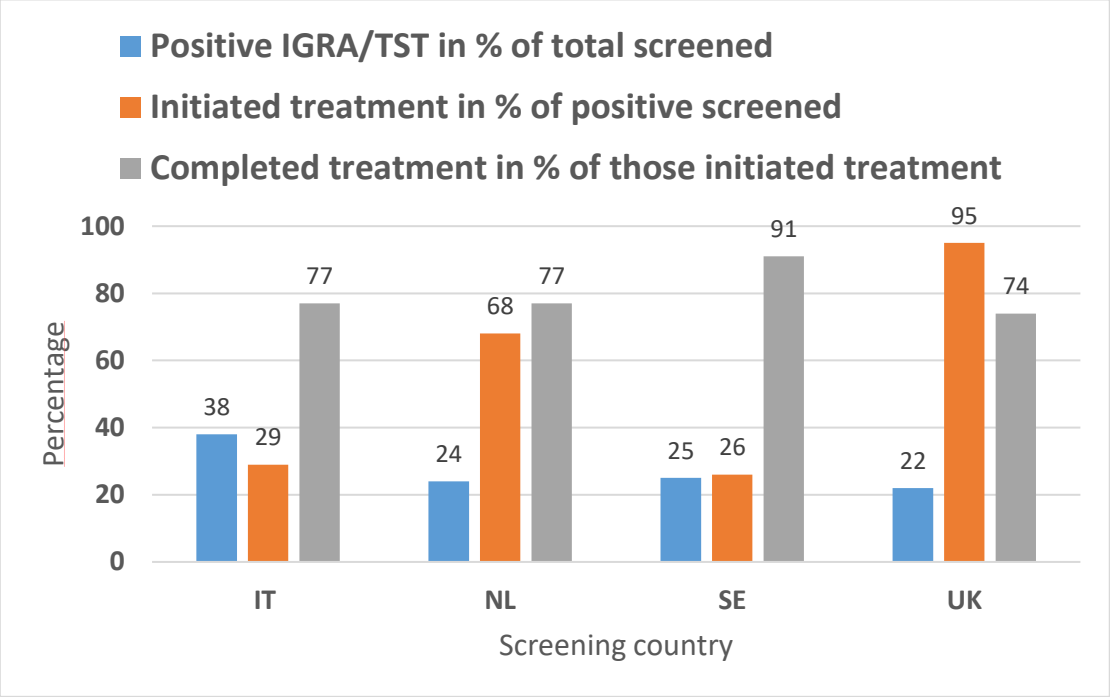

Figure 14. LTBI care cascade from a positive TST/IGRA to treatment initiation and treatment completion, by screening country.

The treatment initiation differed among age groups and screening country (Figure 15). In Sweden, Italy and the Netherlands treatment initiation decreased by age. In the UK the treatment initiation was similar among the age groups. As mentioned earlier, data from England may be biased by a preference to report if treatment was initiated.

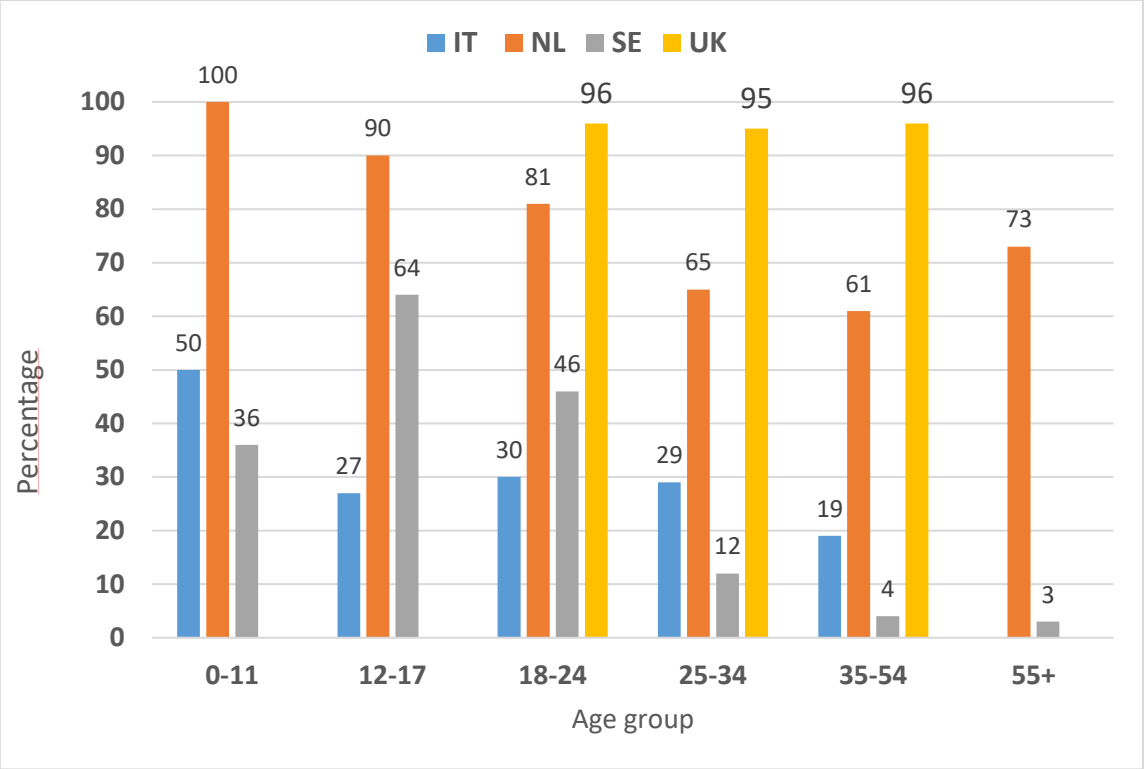

Figure 15. Treatment initiation in percent of those screened positive by TST/IGRA by screening country.

The treatment completion rate was more similar between countries, ranging from 74 to 91%, where the UK had the lowest completion (74%), the Netherlands and Italy both 77% and Sweden 91% completion rate. In the Italian data ongoing treatment cases were included as completed treatment.

3.3 Cost-effectiveness analysis of LTBI screening

The total costs of the different components are reported per country in table 4. The lowest screening cost was estimated for the UK (England) with 33 euros per screened person. In England, IGRA testing was included as part of an integrated primary care visit and with no extra interpreter cost. Costs were defined in a negotiated framework contract. The highest screening cost was estimated for the Netherlands where TB/LTBI screening was delivered as a stand-alone activity. Netherlands also had the highest IGRA price of all countries (91 euros) and a higher interpreter costs compared to Italy and Sweden. Cost of LTBI treatment for those completing the cascade also varied considerably. It was 4 times higher in Sweden and the Netherlands compared to Italy.

Table 4. LTBI screening and treatment costs in different countries.

Site	Screening costs (all are screened)		Cost (€) per person treated for LTBI (for those completing cascade)
	Cost per person screened (€)	Note	
England	33	Integrated into primary care, low IGRA cost. Negotiated framework contract.	484
Sweden (age group 12-17)	142	Integrated in general health examination for asylum seekers	898
Netherlands (asylum seekers)	193	Stand-alone TB screening	802
Italy	50	Only including reimbursed costs	182

The results of the cost-effectiveness analyses are shown in figure 16. The ICER for all age groups in England were under 30 000 pounds/QALY (33 000 euros/QALY), the threshold recommended by NICE guidelines for cost effectiveness. There is a lack of specific ICER recommendations for cost effectiveness in Italy. However, applying UK threshold for Italy the results show a borderline cost-effective result with the lowest ICER among the age group 18-34 (24 000 euros/QALY). In Sweden, where the recommended ICER threshold for cost effectiveness is around 50 000 euros/QALY, screening was moderately cost effective for the young age group (less than 18) while it was not cost effective for older groups. In the Netherlands, where threshold values of €20,000 to €80,000 per QALY are commonly used, the results show high ICERs for all age groups.

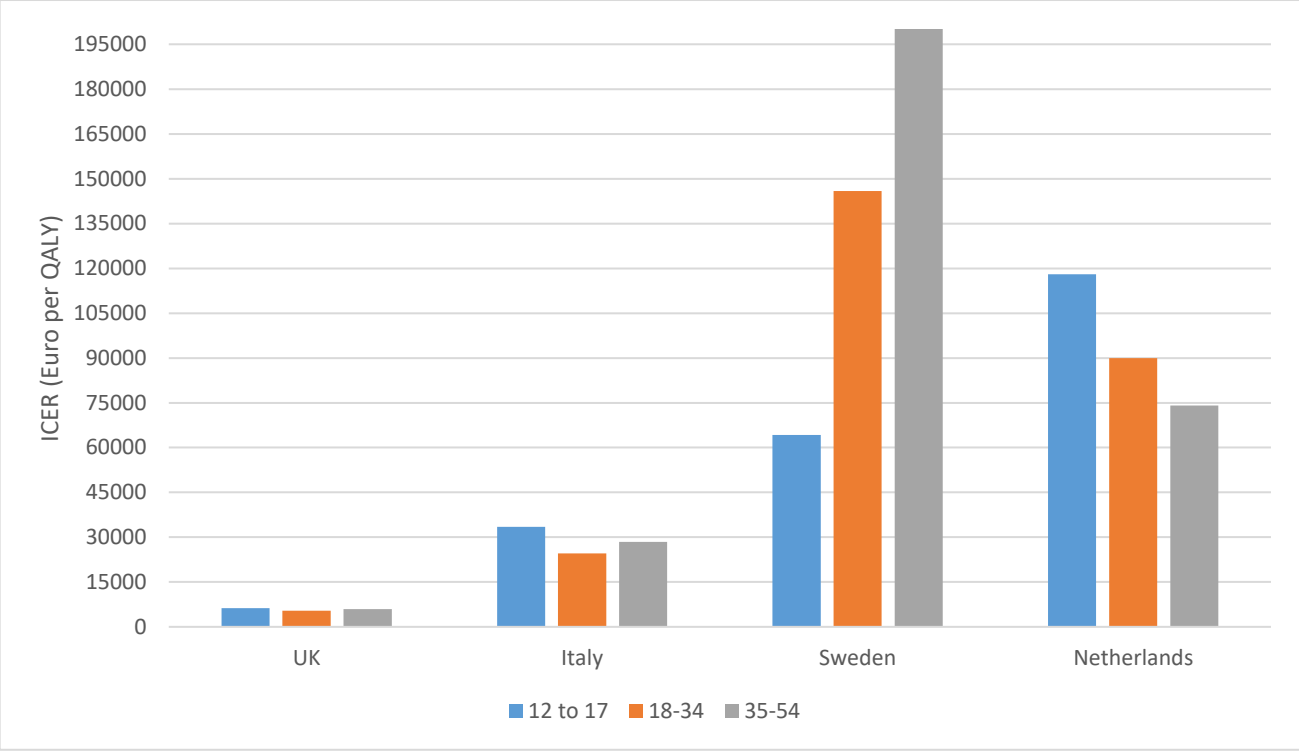

Figure 16. Incremental cost effectiveness ratios (ICER) of LTBI screening and treatment, by screening country and by age group (Euros/QALY)

4 Discussion

4.1 Screening for active TB

Our analysis confirmed that TB yield varies largely predictably according to previously known factors, including migrant typology and country of birth or nationality. This supports a tailored approach to screening with country incidence thresholds and bespoke screening for those migrants at particular risk of TB, including asylum seekers. However, it is worth noting that the four active TB screening programmes significantly varied in their population, screening algorithm, and consequently outcomes, leading to very different estimates of effect. It is therefore not advisable to directly compare individual outcomes in these screening programmes, without adjusting for programme-level confounders. In addition, programmes have not been static. Numerous large changes have occurred during the investigation period, and this could partly explain significant variations in outcomes over time.

A considerable effort has gone into cleaning and harmonising the data, improving and ultimately allowing a comparison between very different screening and data collection systems. Nevertheless, findings are limited by data availability and on a number of variables there were significant amounts of missing data. This also affects findings on the cascade of care, which where it was possible to determine, demonstrated high uptake of screening and treatment.

There are, however, clear signals that current approaches in tailored screening for active TB are working and our analysis has corroborated some of this evidence and brought further detail. Nevertheless, more granularity is needed to refine screening in the future, and we hope that further analysis of this database and complementary meta data will aid this process.

4.2 Screening for latent TB infection

Similarly to the analysis of screening for active TB, the analysis of the LTBI screening data included in our database demonstrated a number of expected patterns, but also some surprising differences across countries.

LTBI prevalence was rather similar across screening countries (after adjusting for higher sensitivity and lower specificity of TST in Italy vs. IGRA in other sites), both for the whole population of screened individuals and by age group. In all sites, LTBI prevalence increased with age, from less than 5% in persons age less than 10 years to over 40% in those above 55 years. This is fully in line with the previously demonstrated cumulative increase in likelihood of being infected over the lifetime. There was also an expected trend of higher prevalence in persons from countries with higher TB incidence, but only in the lower and higher end of the incidence spectrum. Moreover, there was a tendency of higher prevalence in screening programmes focusing mainly on asylum seekers and refugees, as compared to other migrants.

Our data, after further adjustments for age and type of migrant, can be used to estimate LTBI prevalence by age group and incidence in country of origin in migrants both in the countries that have contributed to this database and for other similar countries in Europe and elsewhere. This is useful both for planning of screening programmes (deciding on screening eligibility and predicting LTBI treatment volumes) as well as for modelling the impact and cost-effectiveness of LTBI screening.

The care-cascade data showed large variation across screening countries. There are apparent reasons for some of the variation. For example, Sweden had the lowest treatment initiation rate among persons screened positive, but only in older age groups. This is because Sweden recommends LTBI treatment for all only in the younger age groups, while for older persons only if there are additional risk factors for progression to active TB. Hence, the treatment uptake falls considerable with age. This attrition is by policy and not an implementation deficiency. In Italy, the delivery model changed over time in order to address observed problems with drop out after a positive screen. When a centralized one-stop screening and treatment model was introduced, the treatment uptake and completion increased considerably (data not shown). Similarly, different delivery models in Netherland had different rates of treatment initiation (data not shown). Treatment completion rates were acceptable across all sites.

The variations across the screening countries that we have identified through analysing the database leads to a number of hypotheses that will be further explored through in-depth analyses of the different screening programmes and the way they have evolved over time. The planned further analysis aims to help countries optimize screening and treatment delivery models that enables easy linkage to care for both the screened migrants and for health care providers. Further analyses will also be done to help develop optimal eligibility criteria for age, country of origin and type of migrant.

4.3 Cost-effectiveness analysis of LTBI screening

Cost effectiveness results varied across screening countries and between age groups. Many factors influenced the results, including the prevalence of LTBI, the LTBI treatment policies, the cascade of care and the unit costs.

When a positive screen leads to treatment, a higher prevalence of LTBI means a higher probability for each screened person to prevent future active TB and thus larger cost savings related to treatment of active TB. Therefore, ICERs are generally lower in age groups with higher prevalence, but only if

persons in these age groups are eligible for treatment when screened positive. This explains the declining ICER with age in Netherland, but the reverse correlation in Sweden.

Another factor that seems to greatly influence cost-effectiveness is the implementation strategy. In the UK (England), where LTBI screening focuses on settled migrants and is integrated in primary care with minimal additional costs related to screening set up including translators use, screening seems to be cost-effective. In the Netherlands, on the other hand, LTBI screening is done on arrival through a specific TB screening program, separated from routine health care services. Interpreters are often needed, and the cost of interpreters is high. Therefore, total marginal costs are considerably higher than in the UK. Another factor limiting the cost effectiveness of LTBI screening in the Netherlands is the high cost of IGRA, compared to the other countries. In Sweden, LTBI treatment is not recommended for people above the age of 35 (in the present cohort restricted also for the age group 20 to 34). Therefore, screening individuals in higher age groups without the intention to treat can explain the high ICERs within these groups, as this investment in screening does not give any investment return in terms of prevention of activation and lower future health care costs. The unit prices of LTBI treatment components are the lowest in Italy, where TST was mainly used for screening, which has a lower cost than IGRA.

The economic analysis has many limitations in term of simplification of disease stages for TB and LTBI, the model structure, the costing approach and the assumptions about epidemiological parameters. However, our analysis has a great advantage over many other cost-effectiveness analyses of LTBI screening through using a real-life cascade of care data from our database.

The analysis has enabled us to identify a number of critical factors that should be considered in the design of LTBI screening programmes. First, it is important to consider which specific high-risk groups within the wider group of migrants should be eligible for screening. As a general principle, screening will be more effective and cost effective when focusing on persons with high LTBI prevalence (based on age, country of origin and type of migrant) and high risk of reactivation. Second, if there is no intention to treat a person screened positive for LTBI, cost-effectiveness will decrease as many persons are screened without direct prevention benefits. Third, once screening eligibility criteria are set, it is essential to design screening and treatment delivery models that optimize access, linkage to care and treatment completion. All elements that improve completion of the screening and treatment cascade improve the cost-effectiveness. Moreover, the delivery model will greatly influence the marginal cost of screening. Integration into general health services while reducing associated costs can greatly improve efficiency and hence the cost-effectiveness ratio. Where possible, negotiating a lower prize for IGRA and other essential medical technologies will also improve cost-effectiveness.

5 Publications resulting from the work described

Nederby Öhd J, Hergens MP, Luksha Y, Buxbaum C, **Shedrawy J, Jonsson J, Bruchfeld J, Lönnroth K**. Assessment of the care cascade of latent tuberculosis screening and treatment of asylum seekers in Stockholm, Sweden 2015-2018 - a record linkage study. Eur Resp J 2020, https://erj.ersjournals.com/content/early/2020/08/18/13993003.02255-2020

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Lönnroth K, Zenner D, Abubakar I. Monitoring migrant LTBI screening - a comparative analysis of data sources for surveillance in selected European countries. Abstract presented at the 47th Union World Conference on Lung Health, 26 - 29 October, 2016, Liverpool, United Kingdom.

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