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Early View

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Drivers determining TB disease screening yield in four European screening programmes: a comparative analysis

Dominik Zenner, Daniella Brals, Joanna Nederby-Öhd, Dee Menezes, Robert Aldridge, Sarah Anderson, Gerard de Vries, Connie Erkens, Valentina Marchese, Alberto Matteeli, Morris Muzyamba, Job van Rest, Ineke Spruijt, John Were, Giovanni Battista Migliori, Knut Lönnroth, Frank Cobelens, Ibrahim Abubakar

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Drivers determining TB disease screening yield in four European screening programmes: a comparative analysis.

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Abstract

Introduction

The WHO End-TB Strategy emphasises screening for early diagnosis of tuberculosis (TB) in high-risk groups, including migrants. We analysed key drivers of TB yield differences in four large migrant TB screening programmes to inform TB control planning and feasibility of a European approach.

Methods

We pooled individual TB screening episode data from Italy, the Netherlands, Sweden, and the UK and analysed predictors and interactions for TB case yield using multivariable logistic regression models.

Results

Between 2005-2018 in 2,302,260 screening episodes among 2,107,016 migrants to four countries; the programmes identified 1,658 TB cases (yield 72.0 per 100,000; 95% confidence interval, CI68.6-75.6). In logistic regression analysis, we found associations between TB screening yield and age (>55 years odds ratio, OR2.91, CI2.24-3.78), being an asylum seeker (OR3.19, CI1.03-9.83) or on a settlement visa (OR1.78, CI1.57-2.01), close TB contact (OR12.25, 11.73-12.79), and higher TB incidence in the country of origin (CoO). We demonstrated interactions between migrant typology and age, as well as CoO. For asylum seekers, the elevated TB risk remained similar above CoO incidence thresholds of 100 per 100,000.

Conclusions

Key determinants of TB yield included close contact, increasing age, incidence in CoO and specific migrant groups including asylum seekers and refugees. For most migrants such as UK students and workers, TB yield significantly increased with levels of incidence in CoO. The high, CoO-independent TB risk in asylum seekers above a 100 per 100,000 threshold could reflect higher transmission and reactivation risk of migration routes; with implications for selecting populations for TB screening.

Introduction

With 1.6 million annual fatalities, tuberculosis (TB) is a leading cause of death from any infectious agent globally[1]. A combination of biological and well-recognised socioeconomic risk factors makes TB a complex disease to control, necessitating the use of a wide range of TB control mechanisms. The multipronged approach is reflected in the WHO End-TB Strategy (2016–2035) [2] and the Sustainable Development Goals (SDGs), aiming to decrease incidence, deaths and catastrophic costs through adoption of wide-ranging measures [3]. This includes screening of migrants from high incidence countries among other groups, which is considered key to achieving TB elimination in low-incidence countries[4–6]. In 2020, progress to reach the End-TB Strategy targets was disrupted by the COVID-19 pandemic. Disrupted TB services [7,8], affecting all parts of national TB control programmes led to decreases in TB notifications, with an expected significant and observed increase of TB mortality over the next few years [1,9]. The "path to recovery" will require emphasis on early diagnosis [10] and thereby increase the relevance of screening.

Screening programmes for TB disease have a long history including the radiographic screening in the early 20th century, mostly stopped as a population-wide approach with decreasing incidence and (cost-)effectiveness [11]. Nonetheless, this approach continues to be used for specific risk groups, including people from TB high-risk countries migrating to low TB incidence countries [12,13].

Our recent study, which described four migrant screening programmes in Europe using the same database, showed that in addition to considerable programme-level variation there was individual-level variation in TB screening yield, driven by age, TB incidence in the country of birth, and migrant group [14]. Whilst individual risk factors have been previously described, more granular analysis is needed to understand the relative importance of these variables, and how they interact to determine TB yield. Risk variations might apply to all in a similar fashion or differently to different population groups. In addition, the interplay between programmatic and

individual variables is poorly understood. Such knowledge will enable better understanding and decision making about whether and how much programmes can or should be harmonised or not, considering country differences in their populations or policy preferences. In addition, no previous studies are available reporting on merged large individual datasets from different European countries and this therefore potentially represents a pilot study to improve European TB screening surveillance.

Therefore, in our European Commission-funded study, coordinated with European Centres of Disease Prevention and Control (ECDC), we analysed key drivers behind similarities and differences in TB yield between different migrant screening programmes and determined the relative importance of these factors, including demographic characteristics, specific programme features and year of screening as well as the role of interaction between these characteristics.

Methods

We compared individual-level data from four European TB screening programmes pooled in a multi-country database. The often Chest X-Ray based screening programmes, have been previously described [15,16]. The database contains data from the national data registry on new immigrants in the Netherlands [17], the Swedish Migration Authority and electronic medical records in the Stockholm Region health services in Sweden [18], from specific district screening projects in Italy and the UK new entrant screening programme [19], with screening records from 2005 to 2018 [15]. We also conducted surveys and semi-structured interviews to obtain contextual and programme-level information to assist in data interpretation [14].

Following explorative analysis with simple cross-tabulations and graphics (data not shown), we performed univariable and multivariable logistic regression analyses to determine the effect of individual (e.g., demographic) and programme-level exposure variables on TB yield. We defined yield (primary outcome) as prevalent cases, notified within 151 days of screening over the total

screened population using a modified version of the EU TB case definition and consistent with the Dutch definition of prevalent cases and included stratification into possible, probable, and confirmed cases (annex) [16]. Recent self-reported (via screening questionnaire) household-type TB contact was included in the analysis, where available. We also analysed the effect of exposure variables on a range of secondary outcomes, including patients with any lesions compatible with TB on chest x-ray (CXR positivity) and patients with a positive TB culture result.

There are different categories and levels for potential predictors of TB yield, including individual risk (e.g., patient demography), higher-level programmatic or country interventions, timebound factors, and predictors on the screening pathway.

Variables were deemed fit for inclusion in the multivariable model if they had a p-value<0.2 in univariate analysis and/or had a priori biological plausibility for outcome association. The logistic regression model was built manually by including new variables in a stepwise fashion, assessing the explanatory power of each new variable for TB yield through a likelihood ratio test (LRT) and the change of effect estimates in the model. The relationship between these factors was explored first by mapping (e.g., through direct acyclical graph) and cross-tabulation. We tested violations of assumptions of independence of variables formally through correlation coefficients, and the Variance Inflation Factor (VIF). If collinearity was detected, only the variable considered most informative and with higher biological plausibility was retained for further analysis.

New variables were kept in the model if they significantly added to the explanatory power of the model (LRT p<0.05), changed effect estimates and/or there was a priori biological plausibility, such as age and sex. We tested continuous variables for linear association (χ2 test for trend) and treated them as categorical if they were not linear.

We have previously demonstrated significant variation at individual (largely demographic, risk factor dependent) and screening programme level [14] and we sought to fit a hierarchical

multilevel regression model to explore the effect of individual predictors, as well as the effect of programme-level predictors on TB yield. The collinearity of key programme-level indicators, such as the partial collinearity between migrant typology with screening programmes precluded hierarchical analysis of the full dataset. We therefore performed logistic regression analysis instead, using robust standard error estimation, adjusted for clustering at the TB screening programme.

Through restriction of records to asylum seekers, we performed a subgroup analysis with screening records in three of the four programmes in a hierarchical multilevel model, adjusting for the higher level of the programme variable with individuals as the unit of analysis, nested in the higher level of the screening programme.

Variables with a biological plausibility of effect modification were tested by assessing interaction terms using an LRT. We used the STATA *lincom* command for post-estimation of effect differences in the models. MS Excel for Mac version 16.46 (Microsoft Corporation, Redmond, Washington, USA) was used for figures and tables. All statistical analysis was carried out with STATA 16.1 (Statacorp, Texas, USA).

Results

We included 2,302,260 screening episode records between 2005 and 2018 for 2,107,016 migrants to four European countries; of these 3,978 episodes were reported from Italy, 286,140 from the Netherlands, 5,471 from Sweden, and the remaining 2,006,671 from the UK. In total, the programmes detected 1,658 persons with TB (Italy 26, Netherlands 238, Sweden 11, and UK 1383 [14].

In our logistic regression model, older age in adults, migrant typology, greater TB incidence in the country of origin (CoO), being a contact of a TB case, and the screening years 2010-12 and

2013-15 were significantly associated with a higher TB yield in both univariate and multivariate regression analysis, adjusted for clustering at the programme level (main model, table 1). Asylum seekers and individuals who came on settlement, and family visas, as well as immigrants to the Netherlands, had a significantly higher TB yield compared with UK-bound migrants on student or worker visas. TB yield also varied significantly over time with lower yields in early and more recent years.

We found significant interaction between TB incidence in the CoO and migrant typology ($p<0.001$, annex table 5). Within most migrant categories such as UK students and workers, TB yield significantly increased by incidence category, albeit at different levels. TB yield among asylum seekers was higher than for any other migrant category, but where their CoO had an incidence of above 100 per 100,000, TB yield did not increase further. We also found significant interactions between TB yield determined by being a TB contact and CoO ($p<0.003$) and age and migrant typology (annex tables 1 and 2).

We replicated the model with two secondary outcomes. Restricting the analysis to culture-confirmed TB cases (n=1278, 77.1% of all cases, annex table 3), leads to different effect estimates, most notably for migrant typology but with an overall direction of effect similar compared with the main model.

We also replicated the model analysing TB-related abnormalities on Chest-X-Rays (CXRs). These are used as a first screening step in many of the programmes leading to a selection of individuals for further tests with higher specificity (e.g., sputum culture). The multivariable analysis showed a similar effect for most variables, but a smaller effect of incidence in CoO and migrant typology, and a larger effect of age on CXR abnormality, compared with the main model (annex table 4).

Finally, we performed an analysis on asylum seekers only among the three programmes where data was available, to allow adjustment for programme level and in-depth analysis of asylum

seeker characteristics associated with TB yield. There were 132,372 screened asylum seekers recorded in total (3,978 from Italy, 122,923 from the Netherlands, 5,471 from Sweden). Within this group, there were 174 TB cases (26 from Italy, 137 from the Netherlands and 11 from Sweden, giving yields of 131.1 per 100,000 (95% confidence interval, CI 113.3-152.5) overall and 653.6 (CI 445.4-958.2), 111.5 (CI 94.3-131.8), and 201.1 (CI 111.4-362.7) for Italy, the Netherlands, and Sweden, respectively. In total, 123 (70.7%) of the 174 TB cases were culture confirmed; 18 (69.2%) of those detected in Italy, 98 (71.5%) in the Netherlands and 7 (63.6%) in Sweden.

In the simple multivariable logistic regression model restricted to asylum seekers (table 2), the differences between the screening programmes became more apparent. Asylum seekers were almost three and more than five times as likely to be diagnosed with TB in Sweden and Italy respectively, compared with the Netherlands after adjustment for other factors. Notably, the difference in TB yields by incidence in CoO among asylum seekers was only significant in lower incidence categories (OR 5.07, CI 3.12 -8.23, $p<0.001$ comparing <50 and 50-100 per 100,000) but not in higher categories (OR 0.97, CI 0.53-1.78, $p=0.91$ comparing 200-300 and >300 per 100,000). A similar observation can be made for age groups with significant differences in categories between the youngest but not older age groups. We tested but did not detect significant interactions in this restricted model.

A hierarchical model with two levels (random intercept/fixed slope), adjusting for the screening programme as the higher level (table 3), showed a better fit of the data than the simple logistic regression model (LRT $p<0.001$), and effects were different for sex (males now have significantly larger risk) with similar effects for age, incidence in the CoO, and time period of screening.

			Univariable analysis			Multivariable Analysis			
	population	**TB cases**	**OR**	**95% Confidence interval**		**aOR**	**95% Confidence interval**		**P- value**
Sex									0.30
Female	955,531	751	reference category						
Male	1,058,396	790	0.95	0.86	1.05	1.08	0.96	1.23	
Age group									<0.01
<18 years old	248,422	100	0.52	0.42	0.63	0.36	0.22	0.57	
18-34 years old	1,485,035	1,157	reference category						
35-54 years old	251,796	197	1.00	0.86	1.17	0.89	0.81	0.98	
55+ years old	140,810	125	1.14	0.95	1.37	2.91	2.24	3.78	
Migrant typology									<0.01
UK Students and workers	1,056,195	572	reference category						
NL immigrants	163,116	101	1.14	0.93	1.41	0.79	0.30	2.07	
Asylum seekers (IT, NL, SW)	132,198	174	2.43	2.05	2.88	3.19	1.03	9.83	
UK settlements and family	576,485	624	2.00	1.78	2.24	1.78	1.57	2.01	
UK working holiday and others	112,558	81	1.33	1.05	1.68	1.06	0.88	1.27	
Incidence in country of origin									<0.01
Less than 50	146,946	39	reference category						
Between 50 and 100	504,131	122	0.91	0.64	1.31	2.12	0.88	5.06	
Between 100 and 200	460,651	397	3.25	2.34	4.51	7.52	5.82	9.71	
Between 200 and 300	808,274	692	3.23	2.34	4.45	6.68	5.56	8.02	
More than 300	251,040	348	5.22	3.75	7.27	19.78	15.86	24.67	
Contact of TB case									<0.01
no	1,917,818	1287	reference category						

yes	2,986	43	21.46	15.80	29.14	12.25	11.73	12.79	
unknown	379,798	328	1.29	1.14	1.45	1.49	0.58	3.86	
Time period of screening									<0.01
Before 2010	370,604	262	reference category						
2010-2012	336,007	309	1.30	1.10	1.53	1.27	0.97	1.67	
2013-2015	717,099	669	1.32	1.14	1.52	1.55	1.49	1.60	
2016-2018	876,892	418	0.67	0.58	0.79	0.77	0.54	1.11	

Table 1: logistic regression model assessing predictors for TB at the time of screening (prevalent TB or yield). Standard errors were adjusted for clustering at the programme level. TB contacts are either family or other close (household type) contacts. Incidence in country of origin refers to 2019 WHO estimates. P-values are calculated using the likelihood ratio test comparing to restricted models with less predictors. OR: Odds Ratios, aOR: adjusted Odds Ratios

			Univariate analysis			Multivariate Analysis			
	population	**TB cases**	**OR**	**95% Confidence interval**		**aOR**	**95% Confidence interval**		P-**value**
Programme									<0.001
Netherlands	122,786	137	reference category						
Sweden	5,460	11	1.81	0.98	3.34	2.86	1.38	5.91	
Italy	3,952	26	5.90	3.87	8.98	5.25	3.05	9.05	
Sex									0.007
female	47,409	40	reference category						
male	84,677	134	1.88	1.32	2.67	1.70	1.18	2.44	
Age group									0.149
<18 years old	43,843	39	0.52	0.36	0.75	0.65	0.44	0.96	
18-34 years old	60,955	104	reference category						
35-54 years old	22,985	26	0.66	0.43	1.02	0.99	0.63	1.53	
55+ years old	3,815	4	0.61	0.23	1.67	0.95	0.35	2.61	
Incidence in country of origin									<0.001
Less than 50	58,810	25	reference category						
Between 50 and 100	27,859	48	4.05	2.50	6.57	5.12	3.13	8.36	
Between 100 and 200	17,440	52	7.01	4.35	11.30	6.12	3.71	10.10	
Between 200 and 300	11,872	34	6.74	4.02	11.30	5.54	3.20	9.59	
More than 300	5,077	15	6.95	3.66	13.19	7.52	3.91	14.47	
Time period of screening									<0.001
2010-2012	19,392	41	reference category						
2013-2015	81,138	99	0.58	0.40	0.83	0.55	0.38	0.81	
2016 and beyond	31,668	34	0.51	0.32	0.80	0.16	0.09	0.29	

Table 2: Logistic regression model restricted to asylum seekers assessing determining factors for prevalent TB at the time of screening (yield). Standard errors were adjusted for clustering at the programme level. Incidence in country of origin refers to 2019 WHO estimates. P-values are calculated using the likelihood ratio test comparing to restricted models with less predictors. OR: Odds Ratios, aOR: adjusted Odds Ratios

	adjusted OR	p Value (Wald)	95% Confidence interval		p Value (LRT)
Sex					<0.01
Female	reference category				
Male	1.72	<0.01	1.20	2.47	
Age group					<0.01
<18 years old	0.66	0.04	0.45	0.98	
18-34 years old	reference category				
35-54 years old	1.00	0.99	0.64	1.56	
55+ years old	1.02	0.98	0.37	2.78	
Incidence in country of origin					
Less than 50	reference category				<0.01
Between 50 and 100	5.76	<0.01	3.53	9.40	
Between 100 and 200	6.71	<0.01	4.08	11.04	
Between 200 and 300	6.58	<0.01	3.83	11.30	
More than 300	9.14	<0.01	4.78	17.48	
Time period of screening					<0.01
2016	reference category				
2015 and before	2.14	0.44	0.32	14.47	
2017 and after	0.41	0.33	0.07	2.46	
Programme (cluster effect)	3.04		0.43	21.63	<0.01
Time period (random slope)	3.10		0.44	21.58	

Table 3: Restricted (to asylum seekers) multilevel (random slope, random intercept) regression model assessing determining factors for prevalent TB at the time of screening (yield). LRT: Likelihood Ratio Test

Discussion

We analysed relevant exposure factors for TB in a pooled database of four large TB disease screening programmes in Europe and found that age, male sex, screening period, and having been a contact to a TB case are important risk factors for TB and demonstrated increasing TB risk with increasing incidence in the country of origin (CoO). Our analyses show that immigrants to the Netherlands and those on UK settlement and dependant visas and particularly asylum seekers are significantly more likely to be detected with TB compared to UK students and workers.

Our findings compare well to the literature, including the association of TB yield with age, male sex, having had TB contact, increasing TB risk with higher incidence in the CoO [17,20–22] and migrant typology [23] as previously described, mostly in country-specific studies [24–26]. In addition, our large sample allowed us to show significant interactions between different key factors often used to determine eligibility for TB screening programmes.

In our cross-country comparison, we demonstrate that migrant typology is a significant risk factor, particularly being an asylum seeker. However, from a threshold of 100 per 100,000 further CoO incidence increases do not significantly change TB risk in this group. This was confirmed by sub-analysis restricted for incidence in the CoO. Although the higher TB risk among asylum seekers has been described in country-specific studies, there TB risk often increases alongside CoO incidence [24].

CoO-independent risk among asylum seekers is likely related to unknown or unmeasured co-factors and could relate to specific circumstances asylum seekers face during their journeys or on arrival, rather than a reflection of background TB incidence in their CoO. Whilst the migration experience in the movement phase varies by route, length of time and socioeconomic circumstances, health hazards particularly along the Mediterranean route are well documented [27–29]. Routes of migration may include long stays in third countries, alongside economic hardship or specific hazards such as imprisonment [28], in turn increasing

TB risk, through reactivation or exposure to high transmission environments, such as overcrowded accommodations or prisons [30]. Lack of access to healthcare during the journey may decrease detection and worsen TB outcomes. Note that lack of healthcare access has likely worsened for migrants during the recent COVID-19 pandemic [31].

Genomic evidence has previously helped to document increased TB risk along migration routes [32], and the migration route may in part explain the high TB detection rate in Italy. The TB risk *en route* raises important considerations [33] well beyond the central Mediterranean route. More in-depth studies are required to describe the TB risk along the route.

The finding that, compared to other migrant typologies, TB risk among asylum seekers from high incidence CoOs was less dependent on CoO, is important for determining eligible populations for TB screening programmes.

Some programmes[34] have started apply differential screening criteria to different migrant groups. In the Netherlands, evaluations of national screening data led to adjustments[17], including stopping the screening of immigrants from CoOs <100 per 100,000 and of asylum seekers from CoOs < 50 per 100,000[35]. Practice remains highly variable in Europe[34] due to epidemiological and policy considerations, but possibly also linked to scarcity of evidence how TB risk varies by populations and the migration journey. The increased risks during migration journeys may warrant additional health care provisions for asylum seekers on arrival and screening programmes may benefit from including all asylum seekers from countries with a TB incidence over 100 per 100,000.

TB risk among asylum seekers was less dependent on demographic factors such as age, although it was associated with male sex, which could reflect poorly explained, but well established global prevalence patterns or slightly different migration patterns, with single male migration frequently predating family reunions, and merits further research [36].

We also demonstrated significant differences in yield between different screening programmes, which might be explained by different compositions of the migrant population or by different algorithms and settings. Since the former was at least partly adjusted for in the model, the latter is likely more relevant. Evidence from stakeholder interviews, as well as the country-specific papers [20,24,25,34] from screening programmes demonstrate considerable differences in their scope, timing, target population, algorithm, and setting, which taken together can explain some of the observed variation in screening yield. For example, whilst in the Netherlands' programme, asylum seekers are screened within 24 hours of entry, immigrants are screened up to three months later.

The impact of the screening test [37], setting and algorithm [38] have been previously discussed and these affect TB yield independent of demographic risk factors of the screening cohort. The effects of increasing age [39] and close TB contact on TB risk have previously been documented. We confirmed this in our overall screening cohort.

There are strengths and limitations in our observational study which utilises data, collected for programmatic reasons and are subject to variable recording quality. Our analysis benefits from the ability to directly compare individual records in different European countries. Harmonisation of variables across programmes may have led to loss of granularity for some variables, such as age, which had to be reclassified as categorical. Migrant programmes are often based on legal frameworks and in the case of the UK are linked to border management, therefore overall data quality was relatively high and misclassification for exposures and outcomes rare. There was some missing data [14] on few exposure variables, likely missing at random, which in complete case analysis slightly decreased sample size but in our large dataset unlikely affected power and conclusions. The fact that the analysis of probable and confirmed cases is highly compatible with analysis of microbiologically confirmed cases further minimises the likelihood of outcome misclassification. Analysis of CXR abnormalities was also compatible with the main results and showed expected differences to the main model, for example an accentuated yield increase with increasing age, likely due to the decreased specificity of the

screening tool since age may increase the likelihood of CXR abnormalities, which on further investigation turn out not to be TB-related.
This first attempt to merge individual data from screening monitoring systems of four different European countries represents also a feasibility study for a future evolution of the ECDC surveillance systems.

In conclusion, our comparative analysis of four large migrant TB screening programmes confirmed the applicability of many previously known TB risk factors and provided more evidence about their effect size and interactions between them, particularly for migrant typology and incidence in the CoO. Traditionally, programmes used relatively simple, often unidimensional eligibility criteria for screening, but some have argued for more complex or even bespoke risk algorithms, particularly in respect of screening for TB infection [40]. A similar argument could be built for TB disease and our research provided more detail on risk interactions which could guide this process. On the other hand, the finding that asylum seekers have an increased TB risk, which was less affected by CoO and age, raises the importance of TB risk during migration journey. This elevated risk in asylum seekers requires urgent research and is an important point of enquiry for practitioners in first reception centres. Widening programme eligibility criteria may make sense for asylum seekers.

Our findings could be used to refine screening policy recommendations, which may take the differential effects of risk factors into consideration to optimise programmes including their effectiveness and cost-effectiveness. Going forward, it will be good to make progress harmonising screening criteria and programmes across Europe through regional TB control recommendations and, eventually, a future upgrade of European TB surveillance systems, to allow close monitoring of screening outcomes at country and regional level.

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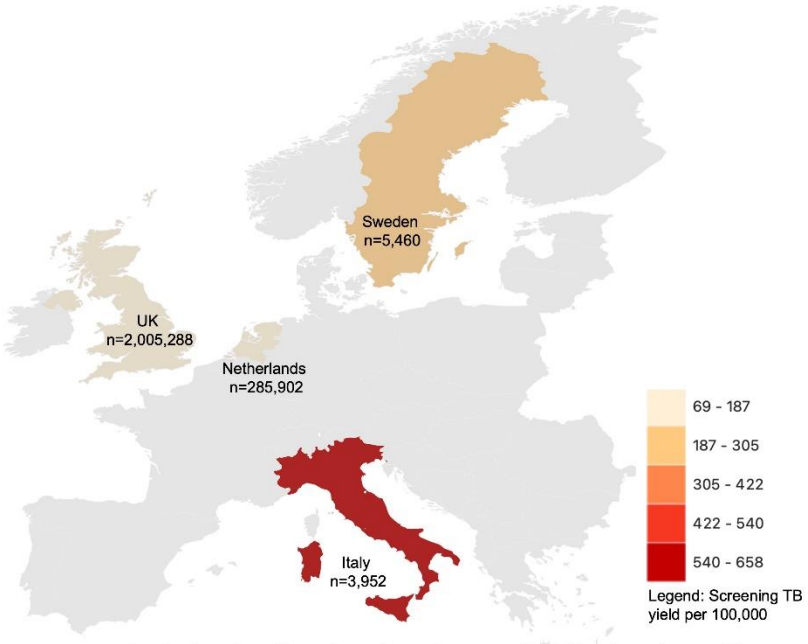

Figure 1: Yield from TB screening (colours) and total number of screens (numbers) performed by screening programmes

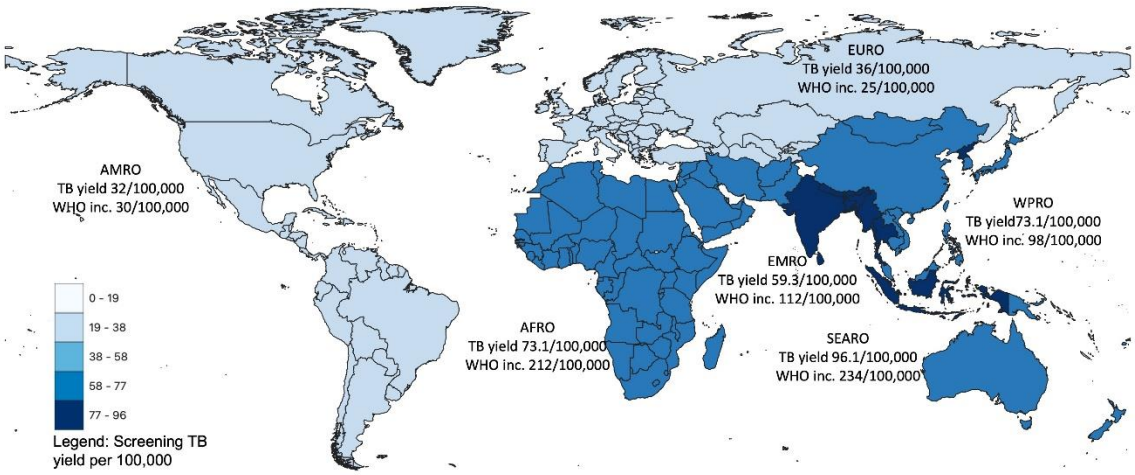

Figure 2: Yield from TB screening and WHO estimated TB incidence rate (2021) in WHO world regions. Colours denote TB yield

Drivers determining TB disease screening yield in four European screening programmes: a comparative analysis - Annex

EU Tuberculosis case definition(1)

Clinical Criteria

Any person with the following two:
— Signs, symptoms and/or radiological findings consistent with active tuberculosis in any site

AND
— A clinician's decision to treat the person with a full course of anti-tuberculosis therapy OR

A case discovered post-mortem with pathological findings consistent with active tuberculosis that would have indicated anti-tuberculosis antibiotic treatment had the patient been diagnosed before dying

Laboratory Criteria

Laboratory criteria for case confirmation

At least one of the following two:

— Isolation of Mycobacterium tuberculosis complex (excluding Mycobacterium bovis-BCG) from a clinical specimen

— Detection of Mycobacterium tuberculosis complex nucleic acid in a clinical specimen AND positive microscopy for acid-fast bacilli or equivalent fluorescent staining bacilli on light microscopy

Laboratory criteria for a probable case

At least one of the following three:
— Microscopy for acid-fast bacilli or equivalent fluorescent staining bacilli on light microscopy — Detection of Mycobacterium tuberculosis complex nucleic acid in a clinical specimen
— Histological appearance of granulomata
Epidemiological Criteria NA

Case Classification

1. Possible case
   Any person meeting the clinical criteria
2. Probable case
   Any person meeting the clinical criteria and the laboratory criteria for a probable case
3. Confirmed case
   Any person meeting the clinical and the laboratory criteria for case confirmation

Antimicrobial resistance

The results of antimicrobial susceptibility tests must be reported according to the methods and criteria agreed between ECDC and Member States as specified by the European Reference Laboratory Network for Tuberculosis and the European Tuberculosis Surveillance Network.

Terms (verbatim definitions)

Migrant: *An umbrella term, not defined under international law, reflecting the common lay understanding of a person who moves away from his or her place of usual residence, whether within a country or across an international border, temporarily or permanently, and for a variety of reasons.* Source: IOM glossary(2)

Asylum-Seeker: *An asylum-seeker is an individual who is seeking international protection. In countries with individualized procedures, an asylum-seeker is someone whose claim has not yet been finally decided on by the country in which he or she has submitted it. Not every asylum- seeker will ultimately be recognized as a refugee, but every refugee is initially an asylum-seeker.* Source: UNHCR Master Glossary of Terms (2006)(3).

Immigration status: *The status of a migrant under the immigration law of the country of destination.* Source IOM glossary(2)

Refugee: *A person who meets the eligibility criteria under the applicable refugee definition, as provided for in international or regional refugee instruments, under UNHCR's mandate, and/or in national legislation.* Source: UNHCR Master Glossary of Terms (2006)(3).

Immigrant: *From the perspective of the country of arrival, a person who moves into a country other than that of his or her nationality or usual residence, so that the country of destination effectively becomes his or her new country of usual residence.* Source: IOM glossary(2)

Additional tables and figures

	Multivariate Analysis			
	aOR	**p Value**	**95% Confidence interval**	
male sex	1.08	0.15	0.97	1.21
age group				
<18 years old	0.36	<0.001	0.29	0.44
18-34 years old	reference group			
35-54 years old	0.89	<0.001	0.76	1.04
55+ years old	2.90	<0.001	2.37	3.55
Migrant typology				
UK Students and workers	reference group			
NL immigrants	1.14	0.26	0.91	1.42
Asylum seekers	4.62	<0.001	3.83	5.58
UK settlements and family	1.77	<0.001	1.56	2.01
UK working holiday and others	1.05	0.68	0.82	1.36
TB contact/ Incidence in country of origin				
No TB contact/ Incidence less than 50	reference group			
No TB contact/ Incidence between 50 and 100	2.07	<0.001	1.41	3.03
No TB contact/ Incidence between 100 and 200	7.50	<0.001	5.28	10.66
No TB contact/ Incidence between 200 and 300	6.55	<0.001	4.59	9.35
No TB contact/ Incidence more than 300	20.24	<0.001	14.18	28.88
TB contact/ Incidence less than 50	1.00			
TB contact/ Incidence between 50 and 100	382.24	<0.001	114.13	1280.18
TB contact/ Incidence between 100 and 200	92.64	<0.001	40.53	211.74
TB contact/ Incidence between 200 and 300	96.52	<0.001	53.81	173.13
TB contact/ Incidence more than 300	152.09	<0.001	76.18	303.63
time period of screening				
before 2010	reference group			
2010-2012	1.28	0.00	1.08	1.52
2013-2015	1.57	<0.001	1.34	1.85
2016 and beyond	0.77	0.00	0.65	0.92

Annex table 1: logistic regression model assessing predictors for TB at the time of screening (prevalent TB or yield) fitting interaction terms between TB contact and country of origin. LR Test p<0.003 (comparing this model to one without interaction terms)

	aOR	p Value	95% CI	
male sex	1.07	0.22	0.96	1.19
Age/Migrant type				
NL Immigrants/<18 years	0.39	0.06	0.15	1.06
NL Immigrants/18-35 years	1.16	0.22	0.91	1.48
NL Immigrants/35-54 years	0.64	0.17	0.34	1.20
NL Immigrants/55+ years	2.83	0.14	0.70	11.40
Asylum seekers/<18 years	2.31	<0.001	1.66	3.22
Asylum seekers/18-35 years	4.52	<0.001	3.62	5.64
Asylum seekers/35-54 years	3.49	<0.001	2.33	5.24
Asylum seekers/55+ years	3.14	0.02	1.17	8.45
UK settlement& family/<18 years	0.49	<0.001	0.36	0.66
UK settlement& family/18-35 years	1.51	<0.001	1.31	1.75
UK settlement& family/35-54 years	1.98	<0.001	1.61	2.43
UK settlement& family/55+ years	6.40	<0.001	5.13	7.97
UK student & work/<18 years	0.36	0.00	0.18	0.72
UK student & work/18-35 years	reference group			
UK student & work/35-54 years	0.51	<0.001	0.35	0.74
UK student & work/55+ years	0.89	0.87	0.22	3.56
UK Working Holiday & other/<18 years	0.13	0.04	0.02	0.94
UK Working Holiday & other/18-35 years	1.19	0.25	0.89	1.60
UK Working Holiday & other/35-54 years	0.92	0.78	0.53	1.61
UK Working Holiday & other/55+ years	1.45	0.37	0.65	3.25
Incidence in country of origin				
Less than 50	reference group			
Between 50 and 100	2.03	<0.001	1.39	2.98
Between 100 and 200	7.30	<0.001	5.13	10.38
Between 200 and 300	6.36	<0.001	4.46	9.08
More than 300	19.04	<0.001	13.34	27.18
Contact with TB case	11.99	<0.001	8.66	16.60
time period of screening				
before 2010	reference group			
2010-2012	1.30	0.00	1.10	1.54
2013-2015	1.59	<0.001	1.35	1.87
2016 and beyond	0.78	0.01	0.66	0.94

Annex table 2: logistic regression model assessing predictors for TB at the time of screening (prevalent TB or yield) fitting interaction terms between age and migrant typology. LR Test p<0.001 (comparing this model to one without interaction terms)

	Univariate analysis				Multivariate Analysis				
	OR	p Value (Wald)	95% CI		aOR	p Value (Wald)	95% CI		LR Test
male sex	0.92	0.15	0.82	1.03	1.08	0.24	0.95	1.23	0.15
age group									
<18 years old	2.55	<0.001	1.97	3.32	3.85	<0.001	2.60	5.71	
18-34 years old	reference category								<0.001
35-54 years old	2.35	<0.001	1.74	3.18	3.12	<0.001	2.02	4.82	
55+ years old	3.26	<0.001	2.38	4.47	12.07	<0.001	6.48	22.46	
Migrant typology									
UK Students and workers	reference category								<0.001
NL immigrants	0.43	<0.001	0.33	0.55	0.24	<0.001	0.16	0.37	
Asylum seekers (IT, NL, SE)	1.04	0.68	0.86	1.27	1.12	0.73	0.59	2.12	
UK settlements and family	0.48	<0.001	0.42	0.54	0.56	<0.001	0.47	0.66	
UK working holiday and others	0.45	<0.001	0.33	0.61	0.44	<0.001	0.43	0.45	
Incidence in country of origin									
Less than 50	reference category								<0.001
Between 50 and 100	0.83	0.40	0.55	1.27	1.64	0.30	0.64	4.21	
Between 100 and 200	3.61	<0.001	2.47	5.27	7.79	<0.001	5.57	10.91	
Between 200 and 300	3.50	<0.001	2.41	5.08	7.02	<0.001	5.18	9.51	
More than 300	4.58	<0.001	3.11	6.74	15.58	<0.001	12.42	19.54	
tbcontact2									
no	reference category								
yes	20.40	<0.001	14.32	29.06	11.66	<0.001	11.62	11.70	<0.001
unknown	1.22	0.01	1.06	1.40	2.13	0.01	1.24	3.66	
time period of screening									
before 2010	reference category								<0.001
2010-2012	1.94	<0.001	1.58	2.38	1.94	<0.001	1.53	2.46	
2013-2015	1.70	<0.001	1.41	2.05	2.35	<0.001	2.30	2.39	
2016 and beyond	1.14	0.17	0.94	1.38	1.49	0.04	1.01	2.20	

Annex table 3: logistic regression model assessing predictors for culture-confirmed TB at the time of screening. Standard errors were adjusted for clustering at the programme level. TB Contacts are either family or other close (household type) contacts. Incidence in country of origin refers to 2019 WHO estimates. P-values are calculated using the likelihood ratio test comparing to restricted models with less predictors. OR: Odds Ratios, aOR: adjusted Odds Ratios, CI: confidence intervals.

	Univariate analysis				Multivariate Analysis				
	OR	**p Value (Wald)**	**95% CI**		**aOR**	**p Value (Wald)**	**95% CI**		**LR Test**
male sex	0.90	<0.001	0.89	0.92	0.92	0.29	0.79	1.08	<0.001
age group									
<18 years old	1.17	<0.001	1.14	1.20	1.38	<0.001	1.23	1.55	
18-34 years old	reference category								<0.001
35-54 years old	2.23	<0.001	2.17	2.30	2.46	<0.001	1.98	3.05	
55+ years old	9.86	<0.001	9.51	10.21	10.66	<0.001	6.96	16.33	
Migrant typology									
UK Students and workers	reference category								<0.001
NL immigrants	1.58	<0.001	1.54	1.61	1.00	0.85	0.96	1.05	
Asylum seekers	1.21	<0.001	1.18	1.24	0.86	<0.001	0.80	0.93	
UK settlements and family	0.57	<0.001	0.57	0.58	0.80	0.03	0.65	0.97	
UK working holiday and others	1.07	<0.001	1.04	1.10	1.01	0.83	0.95	1.06	
Incidence in country of origin									
Less than 50	reference category								<0.001
Between 50 and 100	0.34	<0.001	0.33	0.35	0.62	0.39	0.21	1.84	
Between 100 and 200	0.89	<0.001	0.87	0.91	1.38	<0.001	1.19	1.59	
Between 200 and 300	0.71	<0.001	0.69	0.73	1.11	0.55	0.78	1.58	
More than 300	1.41	<0.001	1.37	1.45	1.91	<0.001	1.58	2.31	
tbcontact2									
no	reference category								
yes	4.98	<0.001	4.53	5.47	3.98	<0.001	3.33	4.76	<0.001
unknown	1.99	<0.001	1.96	2.02	2.26	<0.001	2.14	2.38	
time period of screening									
before 2010	reference category								<0.001
2010-2012	0.92	<0.001	0.90	0.94	0.72	0.01	0.56	0.92	
2013-2015	0.80	<0.001	0.79	0.81	0.58	<0.001	0.55	0.61	
2016 and beyond	0.64	<0.001	0.63	0.65	0.56	<0.001	0.49	0.63	

Annex table 4: logistic regression model assessing predictors for TB-related CXR abnormality at the time of screening. Standard errors were adjusted for clustering at the programme level. TB Contacts are either family or other close (household type) contacts. Incidence in country of origin refers to 2019 WHO estimates. P-values are calculated using the likelihood ratio test comparing to restricted models with less predictors. OR: Odds Ratios, aOR: adjusted Odds Ratios, CI: confidence intervals.

	aOR	p Value (Wald)	95% Confidence interval	
male sex	1.05	0.39	0.94	1.17
age group				
<18 years old	0.35	<0.01	0.28	0.43
18-34 years old	reference category			
35-54 years old	0.88	0.10	0.75	1.02
55+ years old	2.85	<0.01	2.32	3.49
Migrant type/ Incidence in country of origin				
NL immigrants/ Incidence less than 50	0.45	0.17	0.14	1.39
NL immigrants/ incidence between 50 and 100	0.69	0.48	0.25	1.92
NL immigrants/ incidence between 100 and 200	1.61	0.33	0.62	4.19
NL immigrants/ incidence between 200 and 300	4.98	<0.01	1.81	13.69
NL immigrants/ incidence more than 300	6.20	<0.01	2.49	15.47
Asylum seekers/ Incidence less than 50	1.14	0.79	0.44	2.94
Asylum seekers/ incidence between 50 and 100	5.76	<0.01	2.32	14.29
Asylum seekers/ incidence between 100 and 200	9.33	<0.01	3.78	23.07
Asylum seekers/ incidence between 200 and 300	9.98	<0.01	3.96	25.17
Asylum seekers/ incidence more than 300	9.64	<0.01	3.54	26.25
UK settlement& family/ Incidence less than 50	1.00*			
UK settlement& family/ incidence between 50 and 100	1.37	0.52	0.53	3.57
UK settlement& family/ incidence between 100 and 200	5.76	<0.01	2.54	13.03
UK settlement& family/ incidence between 200 and 300	4.27	<0.01	1.90	9.61
UK settlement& family/ incidence more than 300	17.42	<0.01	7.67	39.59
UK student & work/ Incidence less than 50	reference category			
UK student & work/ incidence between 50 and 100	0.50	0.12	0.21	1.20
UK student & work/ incidence between 100 and 200	3.48	<0.01	1.54	7.88
UK student & work/ incidence between 200 and 300	2.82	0.01	1.25	6.38
UK student & work/ incidence more than 300	6.67	<0.01	2.90	15.34
UK Working Holiday/ Incidence less than 50	1.00*			
UK Working Holiday/ incidence between 50 and 100	0.89	0.85	0.27	2.93
UK Working Holiday/ incidence between 100 and 200	0.68	0.52	0.21	2.23
UK Working Holiday/ incidence between 200 and 300	3.45	0.01	1.41	8.44
UK Working Holiday/ incidence more than 300	14.95	<0.01	6.26	35.71
Contact of TB case				
no	reference category			

yes	12.15	<0.01	8.76	16.84
unknown	1.49	0.02	1.06	2.08
time period of screening				
before 2010	reference group			
2010-2012	1.27	0.01	1.08	1.51
2013-2015	1.53	<0.01	1.29	1.80
2016 and beyond	0.77	0.01	0.64	0.92

Annex Table 5: logistic regression model assessing determining factors for prevalent TB at the time of screening (yield) with interaction terms for migrant typology and country of origin; standard errors adjusted for clustering at the programme level. Interaction terms are presented as TB yield in each stratum. NL: The Netherlands, UK: United Kingdom, *perfectly predicts failure (small cell volume)

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