Effectiveness of pre-entry active tuberculosis and post-entry latent tuberculosis infection in new-entrants to the UK: a restrospective, population-based cohort study.

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Abstract

Background Evaluating interventions that may lead to a reduction in people diagnosed with tuberculosis (TB) in high-income low incidence countries is key to accelerate progress towards elimination. We assessed the effectiveness of pre-entry active TB and post-entry latent TB infection (LTBI) screening to reduce TB incidence and the effect of primary care access on TB incidence in new-entrant migrants to the UK.

Methods We performed a population-based cohort study of migrants from 66 countries, who were negative for active TB at pre-entry screening between January 1, 2011 and December 31, 2014 and were eligible for LTBI screening. We used record linkage to track their first contact with primary care, uptake of LTBI screening and development of active TB in England, Wales or Northern Ireland. To assess the effectiveness of the pre-entry screening programme we identified a control group of migrants not screened for active TB using the specific code for new-entrants registering in primary care within the NHS patient registration data system. Our primary outcome was development of active TB notified to the National Enhanced Surveillance System (ETS).

Findings Our cohort comprised 224234 migrants screened for active TB before entry to the UK, and a control group of 118738 migrants not screened for active TB. 1771 incident active TB cases were identified in the entire cohort of migrants who registered in primary care (n=222728), giving an incidence rate of 174 (95% CI 166-182) per 100000 person-years. In migrants not screened for LTBI (n=220277) those not screened for active TB (n=117691) were more likely to develop TB than those screened for active TB (n=102586) (IRR 1·49, 1·33-1·67; p <0·0001). 2451(1·1%) of the 222728 migrants registered in primary care were screened for LTBI, of whom 421 (17·18%) tested positive and 1961 (80·01%) tested negative; none developed active TB within the observed time period. Accounting for 17938 (8%) migrants who migrated to Scotland and Northern Ireland, 103990 (50·4%) of the 224234 migrants screened for active TB registered in primary care. Migrants settling in the least deprived areas had a decreased risk of developing TB (IRR 0·74, 0·62-0·89; p=0·002), and time from UK arrival to GP registration ≥ one year was strongly associated with increased risk of developing TB (IRR 2·96, 95% CI 2·59-3·38; p <0·0001).

Interpretation Pre-entry TB screening, early primary care registration and LTBI screening are strongly and independently associated with lower TB incidence in new-entrant migrants.

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Research in context

Evidence before this study

We searched PudMed and Web of Science for articles in English, Spanish or French on the effectiveness of screening for active TB and latent TB infection (LTBI) in migrants, and migrants' healthcare access and migrant's health in high-income countries published until

September 30 2018. We used the terms “TB screening” or “pre-entry TB screening”, “LTBI screening”, “migrant health” and “healthcare access”. We identified two recent systematic reviews on active TB and LTBI screening, and one article synthesising a series of literature reviews on migration and health. The available literature suggests that screening for active TB is efficient when targeted to migrants from higher TB incidence countries. The effectiveness of LTBI is limited by the large pool of migrants with LTBI, and targeted LTBI programmes must ensure high screening uptake and treatment completion to have the greatest individual and public health benefit. None of these studies assessed the effectiveness of active TB and LTBI screening on health outcomes in migrants. There is few evidence on migrants’ health status and outcomes, although some surveys done in European countries contain some information about the health of migrants, it is out of date.

Added value of this study

We followed a large cohort of migrants from 66 high TB incidence countries and, by documenting the length of time from UK arrival to their first contact with primary care, we were able to assess healthcare access. We identified groups of migrants within our cohort that were exposed or not exposed to two major interventions for TB control in the UK; pre-entry TB screening for active TB and post-entry screening for LTBI. We estimated the incidence of TB in each group, and could therefore, for the first time, not only assess the effectiveness of these two interventions on an important health outcome in migrants, but also measure the effect that migrants’ healthcare access may have on TB incidence in the UK.

Implications of all the available evidence

Independently to pre-entry active TB and post-entry LTBI screening, early primary care registration is associated with lower TB incidence in new-entrant migrants. Thus, removing barriers and facilitating early access to health services for new migrants is likely to reduce TB

in this population. The pre-entry and LTBI screening programmes are likely to be responsible for the reduction in TB incidence in the UK. However, the LTBI programme will only succeed by securing early access to health services, because its effectiveness may be compromised by low attendance to primary care. The pre-entry screening programme provides an opportunity to actively deliver health promotion to inform its participants about the LTBI screening and primary care registration upon UK arrival. Likewise, the compulsory payment of an immigration health surcharge must be coupled with information on entitlements and the importance of primary care registration as entry point to the health system in the UK.

Introduction

Tuberculosis (TB) is a continuing public health problem, but in several high-income countries, TB rates are at pre-elimination levels (<10 cases per million), suggesting that elimination may be possible through combining a number of interventions.[1] In the UK, similar to other low-incidence countries, TB epidemiology is characterised by the majority of cases occurring in people from high-incidence countries often as a result of progression of latent TB infection (LTBI).[1, 2]

In 2017 the UK had the lowest number of cases 5567 and the lowest TB incidence rate since 1990 (8·4 per 100000 population).[3] The improvement of TB control in the UK, over the last years included the implementation of a number of interventions, such as the roll out of a pre-entry TB screening programme for visa applicants from high TB incidence countries and, within the Collaborative Tuberculosis Strategy for England 2015-2020, a new programme for voluntary LTBI screening and treatment for all new-entrant migrants from high-incidence countries.[4-7]

Migrants from countries with high TB burden have a higher risk of developing TB in the initial years after arrival to the UK.[2, 4] Although the strongest risk factor for progression from LTBI to TB is time since infection,[8] in migrants additional factors may be important such as the stress produced by the migration and adaptation process, the presence of comorbidities and their living and work environment.[9] Moreover, migrants may face barriers to access health services,[10, 11] and this is of particular importance because LTBI screening is provided through primary care services.[12] The major challenge for the LTBI programme is to ensure that it reaches all individuals at risk of LTBI reactivation early after their arrival to the UK. The population level effectiveness of LTBI and pre-entry screening interventions, and the effect of improving healthcare access, on reducing the TB burden in new-entrant migrants to the UK, and their larger effects on the UK TB epidemiology are still uncertain.

In this comprehensive, large cohort study we followed migrants who tested negative for active TB at pre-entry screening, and tracked their journey within the National Health Service (NHS) and TB control programme starting from first contact with primary care, uptake of LTBI screening and development of active TB. Our goal was to assess the effectiveness of pre-entry and LTBI screening to reduce TB incidence and the effect of primary care access on TB incidence in new-entrant migrants to the UK.

Methods

Study design and participants

We performed a population-based cohort study of all migrants from 66 countries who screened negative for active TB pre-entry between January 1, 2011 and December 31, 2014, and who fulfilled the eligibility criteria for the national LTBI screening programme of being aged 16 to 35 years, born in a high-incidence country (≥150/100000 or sub-Saharan Africa) and arriving in England within the last five years (appendix).

Control groups were migrants from the same countries who registered in primary care but did not have pre-entry screening, these groups included migrants screened and not screened for LTBI and were identified by the flag-4 code within the NHS Patient Registration Data System (PRDS). The flag-4 code indicates that someone who registered with a NHS general practitioner (GP) in England and Wales was previously living overseas.[13, 14] It is generated if an individual who registers for the first time with a GP, was either born outside the UK, or if the individual's previous address was outside the UK.[13, 14]

Record linkage

We used deterministic record linkage[15] to identify migrants' primary care registrations up to June 30 2017 by linking to the PRDS, which holds records of all patients registered with primary care in England and Wales, to create a cohort of migrants registered and not registered in primary care (figure 1).

The control group of migrants not screened for active TB was identified by extracting from the PRDS 586579 flag-4 registrations of individuals aged 16 to 35 years, recorded between January 1, 2011 and December 31, 2014 in the Clinical Commissioning Groups (CCGs) areas where the LTBI programme has been rolled out in London, North of England and Midlands (figure

1). At the time of linkage on 30 September 2017, the LTBI programme had been rolled out in 56 CCGs.[2] After exclusion of 436149 individuals born in the UK or who were from countries not eligible for LTBI screening, we probabilistically linked this cohort of 150430 records to the cohort of 224234 migrants screened for active TB. The exclusion of 31692 records, common to both cohorts from the former, revealed a population of 118738 migrants that registered with primary care but were not screened for active TB (Figure 1). These two cohorts were probabilistically linked to the database of the national LTBI programme to assess LTBI screening uptake, and to generate four comparison groups: 1404 screened for active TB and LTBI, 102586 screened for active but not LTBI, 1047 not screened for active TB but screened for LTBI, and 117691 not screened for active TB or LTBI (Figure 1). Under programmatic conditions a migrant is diagnosed as LTBI positive using a single interferon gamma release assay (IGRA) blood test according to the manufactures cut-off for positivity.[12]

The pre-entry active TB screening programme was initially done in 15 pilot countries from 2005 onwards and then rolled out to 101 high TB burden countries (>40/100000) between May 2012 and March 2014.[4] However, our cohort started in January 2011. Therefore, we used the country of origin and its starting date of pre-entry screening, to stratify the cohort into two groups; migrants from countries with and without an active pre-entry screening programme (appendix), because the migrants not screened for active TB could be from countries that did not have an active pre-entry screening programme at their time of UK arrival.

A validated probabilistic linkage method[16] was used to identify cases of all forms of active TB by linking the records of all cohorts to the Enhanced Tuberculosis Surveillance (ETS) system to identify subsequent development of any form of active TB in England, Wales or Northern Ireland between January 1, 2011 and August 31, 2017 without geographical or country of birth

restrictions. A detail description of data sources and all variables used in the analysis is provided in the appendix. Cases notified within 90 days of the issue of a TB clearance certificate were assumed to be prevalent (not incident) cases missed by pre-entry screening and were excluded from incidence rate analyses.[4] Cohort time started upon entry to UK, determined as the date the certificate of clearance was issued plus 30 days of average visa processing time, and ended by death, becoming an active incident case or the end of cohort time 31 August 2017.

Because the PRDS only records GP registrations in England and Wales, there was no data to identify primary care registrations in Scotland and Northern Ireland. Therefore, to calculate the total percentage of primary care registrations, after linkage to the database of the national LTBI programme and to ETS, we randomly excluded 8% of records, as validated previously[4], from the group of migrants not registered in primary care (figure 1); according to the data for long-term international migration to the UK, these percentage of migrants would have entered to Scotland and Northern Ireland between January 1, 2011 and December 31, 2014.[17]

All databases were stored, processed and analysed at Public Health England (PHE). Under the UK Health and Social Care Act 2012, PHE has authority to hold and analyse national surveillance data for public health and research purposes. By taking part in the pre-entry and LTBI screening programmes, migrants consented for their data to be used by PHE and the NHS for research, monitoring and evaluation. The migrants' pathway and each intervention is shown in (figure 2).

Outcomes

Our primary outcome measure was new cases of active TB notified to the ETS either bacteriologically or clinically diagnosed, in keeping with its case definition.[18, 19] The secondary outcomes were primary care registration and LTBI screening uptake.

Statistical analysis

We used multiple imputation by chained equations (MICE) [20] to produce imputed values for the following variables when they were missing; visa category, deprivation index, time from UK arrival to primary care registration and follow-up time; 100 imputed data sets were created and analysed according to Rubin's rules.[21] This approach accounts for the uncertainty in imputed values and obtain unbiased estimates if the missing at random assumption holds: namely that an unbiased prediction for the missing variable can be obtained, conditional on its specified relationship with observed covariates.[21] The MICE method uses sequential regressions that specify a separate imputation model appropriate for each variable with missing data and uses the other complete variables as predictors.[20, 22]

To identify risk factors for the primary outcome active TB cases and the secondary outcome LTBI screening uptake, each imputed dataset was analysed separately using univariate and multivariate Poisson and logistic regression models respectively, and the results were combined into a single multiple-imputation result.[21] We used univariate and multivariate logistic regression to assess the factors associated with the secondary outcome primary care registration. The results are presented as odds ratios (OR), incidence per 100000 person-years and incidence rate ratios (IRR), with 95% CIs and two-sided p values. Baseline characteristics of study participants are presented as total counts and percentages. We did a sensitivity analysis to account for the imputation method using complete case analysis, and for emigration out of the UK in the IRR estimates by using only the person-year contributions of migrants that

remained in the UK until the end of follow-up according to visa category. A detailed description of the multiple imputation method and the sensitivity analysis is provided in the appendix. Stata version 15 was used for all statistical analysis.

Results

There were 485793 screening episodes for the pre-entry programme between January 1 2011 and December 31 2014 (Figure 1). After exclusion of duplicates and applicants not eligible for LTBI screening and treatment, 224234 records were deterministically and probabilistically linked to the PRDS and ETS respectively, the baseline characteristics of the study participants are depicted in (Table 1).

A total of 1828 TB cases were identified during the cohort time, of which 31 were prevalent. There were 26 incident cases in migrants with no evidence of primary care registration, and 1771 incident cases in those registered in primary care; of these 672 were screened and 1099 not screened for active TB. This includes all forms of TB; pulmonary and extra pulmonary among migrants registered in primary care, giving an incidence rate of 174 (95% CI 166-182) per 100000 person-years in a total follow-up time of 1015121 person-years with median follow-up of 4·5 years per person (IQR 2·06). In the intervention groups the incidence rate was 139 (95% CI 129-150) and 206 (95% CI 194-218) per 100 000 person-years in migrants screened and not screened for active TB respectively (Figure 1). In migrants not screened for LTBI, those not screened for active TB were more likely to develop TB than migrants screened for active TB (Table 2). A further analysis stratified according to the presence of an operational pre-entry programme in the country of origin showed that, after adjustments, migrants from

countries without an operational programme had a higher risk of developing incident TB (2·39, 2·06-2·77; p <0·0001) (appendix). None of the migrants screened for LTBI developed active TB within the observed time period. The majority of TB cases occurred within the first three years of arrival. The multivariate analysis of risk factors associated with incident TB in the 222728 migrants registered in primary care adjusting for age, sex, visa category, region of origin and estimated TB incidence in country of origin, showed that migrants settling in the least deprived areas had a decreased risk of developing TB, while time from UK arrival to GP registration of equal or more than one year was strongly associated with increased risk of all forms of TB (Table 2). None of the databases used recorded the length of stay of each study participant in the UK after arrival, and any change in the length of stay would affect the time at risk of being diagnosed with active TB. Therefore, we performed a sensitivity analysis which showed that our results were stable when emigration was taken into account (appendix).

The results of the linkage to PRDS showed that, accounting for 17938 (8%) migrants who migrated to Scotland and Northern Ireland, only 103 990 migrants (50·4%) registered with a GP after arrival to the UK. A multivariate analysis of factors associated with primary care registration showed that being male, having a work or family reunion visa category, being from the South East Asia, Eastern Mediterranean and Western Pacific WHO regions, along with not having a chest radiography done were associated with a decreased probability to register with primary care (Table 3). In contrast, migrants in the settlements and dependents visa category and those with abnormal chest radiography were more likely to register (Table 3).

A total of 2451 (1·1%) of the 222728 migrants in the cohort registered in primary care were screened for LTBI; of which 421 (17·2%) were positive and 1961 (80·01%) were negative,

with a median follow-up time from the date of screening of 0·63 years ± IQR 0·67 per person (appendix). In a subsequent multivariate analysis, the age group 16-25 years, having a settlements and dependents or family reunion visa category, and being from the South East Asia and Eastern Mediterranean regions were more likely to be screened for LTBI (Table 4). Conversely, being male, from the Western Pacific region, from a country with estimated TB incidence of more than 350 cases per 100000 population, from the least and middle deprived group and being from a country without an operational pre-entry screening programme were all factors associated with being less likely to be screened (Table 4).

Discussion

We provide direct evidence of a positive association between the pre-entry and LTBI screening programmes and lower TB incidence in new-entrant migrants. Our study also demonstrates low levels of primary care registration among migrants from high TB incidence countries and a significant association between delayed access to primary care and the risk of developing active TB. We show that improving migrants' primary care access would likely improve TB control in the UK.

Systematic screening for active TB in migrants has emerged as a potential strategy to improve early TB diagnosis and outcomes, but there is dearth of data to prove its effectiveness as a public health intervention.[1, 9, 23, 24] Notably, we provide novel evidence from a study including a non-intervention comparison group, that the pre-entry screening programme is also effective at reducing the number of incident TB cases after arrival to the UK. We speculate that this intervention may also have a TB awareness raising effect among its participants; in our study, migrants from countries with no operational programme were less likely to be screened for

LTBI and had the highest risk to develop TB. It is likely that the majority of migrants in the non-intervention group were screened upon UK arrival as part of the previous system.[4, 9] In this scenario, our results indicate that pre-entry screening reduces incident TB when compared to upon arrival chest X-rays, thus this is another advantage to its suggested higher yield.[25]

The epidemiology of TB in England supports the notion that LTBI treatment could be of great benefit for recent immigrants from countries with high TB burden. [2, 26-28] In our cohort, none of the participants that were screened for LTBI developed active TB within the observed time period, potentially indicating the benefit of this intervention to reduce the number of incident TB cases. However, our results indicate that the effectiveness of this intervention might be affected by low attendance to primary care, as only half of the eligible new-entrant migrants registered in primary care. Since primary care is most often the first contact of immigrants with the NHS,[14] the LTBI programme will only succeed by securing early access to health services within the first year of UK arrival.

Primary care is the first contact point with health services, and GPs in the UK are gatekeepers for the NHS and provide integrated care addressing diverse healthcare needs in a family and community context.[29] The beneficial effect of primary care on health outcomes, may be accounted for by a combination of mechanisms that include a greater focus on prevention, and the early management of health problems.[29] In our study, half of the participants did not register in a primary care facility and there was an association between the type of visa and the probability of registration. We recently found that migrants may lack clarity about legality and rights to access health care, have competing priorities or fear the consequences of their immigration status.[30] It is also likely that this is a young cohort that tends to be relatively healthy upon arrival. However, it has been shown that this healthy migrant effect wanes with

length of residence in the host country, possibly due to the acquisition of unhealthy lifestyle habits and the new living and working conditions.[31] Consistent with this observation, our data show that deprivation index is an independent predictor of disease occurrence with migrants settling in the most deprived areas being more likely to develop TB, and the majority of cases occur within two to three years of arrival. Thus, early primary care access represents an important opportunity to offer preventive interventions for TB such as LTBI screening and treatment, and for other comorbidities that render this population at higher risk of TB.

Access to healthcare services regardless of migration or financial status is a key intervention for TB elimination,[1] and one of the founding principles of the NHS is to provide universal and equitable healthcare according to need.[32] However, migrants are affected by barriers to access health services, and the introduction of new reforms, such as removing the right of migrants without an indefinite leave to remain to access free NHS care, and demanding NHS frontline staff to identify and charge patients in hospital care, are likely to increase their exclusion from primary and hospital care.[10, 11, 32] Our results highlight the adverse consequences that such reforms may have on migrants' and public health. We found a strong association between length of time to primary care registration and the risk of developing active TB, and other studies identified challenges for accessing healthcare as a main barrier for TB diagnosis and treatment uptake[33] Although the health of migrants is of rising interest worldwide, there is a lack of evidence on migrants' health status and outcomes, due to the challenge of gathering reliable information.[34, 35] Our study followed a large cohort of migrants from 66 countries and included key sociodemographic variables such as country of origin, visa category, age, sex, and deprivation index in the settlement area; all factors that might influence their health status.[34]

Our study has some limitations. We followed a well-defined cohort of migrants but cannot ascertain that all study participants remained in the UK until the end of follow-up. However, we performed a sensitivity analysis to account for emigration according to visa category and our results were consistent. Our study did not include data on undocumented migrants, thus our results may underestimate the reported associations, due to potential under-ascertainment of cases in that population which likely face more barriers to access health services than regular migrants; there could also be under-ascertainment in the number of TB cases due to emigration. Likewise, our analysis did not account for the presence of important comorbidities such as HIV that may increase the risk to develop active TB. In addition, though our results may be affected by missing information, we accounted for the uncertainty and potential bias introduced by missing values in some variables as far as possible using a multiple imputation model. Our data on LTBI screening have some caveats, because we cannot ascertain treatment uptake and completion as this data was not available, and the average follow-up time after LTBI screening was less than one year. The size of the LTBI screened population in our cohort is small, but the percentage of positive for LTBI is the same to the prevalence in the national cohort.[2] We cannot rule out the presence of confounders because this is not a randomised trial, however, we adjusted for the most important known factors such as age, sex, TB incidence in country of origin and deprivation index.

Our study supports the hypothesis that the pre-entry and LTBI screening programmes are likely to be responsible, at least in part, for the reduction in TB incidence in the UK as recently suggested, [36] and strongly suggests that promoting early access to health services for new migrants would substantially reduce TB in this population. The pre-entry programme could be actively used for health promotion to inform its participants about the LTBI screening and primary care registration upon UK arrival (figure 2). Likewise, since from April 2015 all non-

EEA nationals must pay an immigration health surcharge,[32] this would be an opportunity to inform about their entitlements and the importance of primary care registration as entry point to the health system (figure 2). Our data on LTBI screening points to a beneficial effect of this intervention and a further evaluation is now required to confirm our findings. We could expect that the careful consideration of these factors will accelerate the progress towards TB elimination in the UK.

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Conflict of interest statement: AL is named inventor on patents pertaining to T cell-based diagnosis, including IGRA technologies. Some of these patents were assigned by the University of Oxford to Oxford Immunotec plc resulting in royalty entitlements for the University of Oxford and AL. All other authors declare no competing interests.

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Table 1 Baseline sociodemographic characteristics of study participants

Overall study cohort (n=342972)	Screened for active TB (n=224234)	Not screened for active TB (n=118738)
Age (years)		
16-25	103418 (46%)	35598 (30%)
26-35	120816 (54%)	83140 (70%)
Sex		
Female	97640 (44%)	55411 (46·7%)
Male	125699 (56%)	63327 (53·3%)
Type of visa		
Students	122459 (54·6%)	63758 (53·7%)
Settlements and dependents	75577 (33·7%)	41502 (35%)
Work	15966 (7·1%)	6641 (5·6%)
Family reunion	3766 (1·6%)	3242 (2·7%)
Other	6404 (2·8%)	3595 (3%)
WHO region		
Africa	42727 (19%)	33367 (28·1%)
Americas	2 (0·00%)	20 (0·02%)
South-East Asia	66960 (29·8%)	67784 (57%)
Europe	68 (0·03%)	698 (0·6%)
Eastern Mediterranean	109497 (48·8)	14024 (11·8%)
Western Pacific	4980 (2·2%)	2845 (2·4%)
WHO estimated TB incidence (per 100000)		
40-149	3317 (1·4%)	4102 (3·4%)
150-349	214492 (95·6%)	107088 (90·2%)
>350	6425 (3%)	7548 (6·4%)
Year of screening		
2011	73274 (32·6%)	..
2012	43507 (19·4%)	..
2013	41803 (18·6%)	..
2014	65650 (29·3%)	..
Chest radiography		
Normal	210002 (93·7%)	..
Abnormal	10333 (4·6%)	..
Not done	3815 (1·7%)	..

Table 2 Univariate and multivariate analysis of factors associated with incident tuberculosis in migrants registered in primary care in England

Migrants registered in primary care (n=222728)	Rate per 100000 person-years (95%CI)*	Univariate IRR (95%CI)	P	Multivariate IRR (95%CI)	P
Age (years)					
16-25	155 (143-169)	0·84 (0·75-0·92)	0·001	0·88 (0·79-0·97)	0·017
26-35	184 (174-195)	1·0		1·0	
Sex					
Female	146 (136-157)	1·0		1·0	
Male	200 (188-212)	1·36 (1·23-1·49)	<0·0001	1·13 (1·00-1·27)	0·034
Type of visa					
Students	184 (173-196)	1·0		1·0	
Settlements and dependents	157 (145-170)	0·81 (0·69-0·94)	0·007	0·89 (0·75-1·05)	0·196
Work	176 (140-222)	0·79 (0·51-1·21)	0·291	0·91 (0·57-1·45)	0·696
Family reunion	376 (298-475)	2·20 (1·61-3·01)	<0·0001	3·27 (1·98-5·39)	<0·0001
Other	74 (47-117)	0·40 (0·18-0·87)	0·023	0·51 (0·23-1·14)	0·102
WHO region					
Africa	137 (122-153)	1·0		1·0	
Americas	0	0		0	
South-East Asia	190 (177-203)	1·38 (1·21-1·58)	<0·0001	1·27 (1·08-1·49)	0·002
Europe	0	0		0	
Eastern Mediterranean	181 (167-196)	1·32 (1·15-1·51)	<0·0001	1·46 (1·24-1·73)	<0·0001
Western pacific	157 (109-228)	1·14 (0·77-1·68)	0·487	1·51 (0·99-2·30)	0·053
WHO estimated TB incidence (per 100000)					
40-149	252 (196-325)	1·0		1·0	
150-349	174 (166-183)	0·69 (0·53-0·89)	0·005	1·35 (0·86-2·10)	0·180
>350	121 (92-160)	0·48 (0·33-0·70)	<0·0001	1·32 (0·77-2·26)	0·307
Deprivation index					
1-3 deciles	182 (171-193)	1·0		1·0	
4-6 deciles	182 (168-198)	0·97 (0·87-1·08)	0·637	0·96 (0·86-1·07)	0·408
7-10 deciles	124 (107-144)	0·65 (0·54-0·77)	<0·0001	0·74 (0·62-0·89)	0·002
Time to GP registration					
<1 year	136 (128-144)	1·0		1·0	
≥1 year	436 (402-474)	3·07 (2·69-3·52)	<0·0001	2·96 (2·59-3·38)	<0·0001
Intervention					
Pre-entry (+) LTBI (+)	0	0		0	
Pre-entry (+) LTBI (-)	141 (130-152)	1·0		1·0	
Pre-entry (-) LTBI (-)	205 (193-218)	1·45 (1·32-1·60)	<0·0001	1·49 (1·33-1·67)	<0·0001
Pre-entry (-) LTBI (+)	0	0		0	

*****Incidence rate per 100000 person-years and (95%CI) were derived from one imputation because the MICE method does not provide a combined result from all imputations for incidence rates. The interventions are pre-entry active TB and post-entry LTBI screening, the exposure to one of these interventions or both is indicated by positive (+) and negative (-) symbols.

Table 3: Univariate and multivariate analysis of factors associated with primary care registration in England and Wales

Migrants screened for active TB (n=224234)	Primary care registration (n=103990)	No primary care registration (n=120244)	Univariate OR (95%CI)	P	Multivariate OR (95%CI)	P
Age (years)						
16-25	46931 (45%)	56487 (47%)	0·92 (0·91-0·94)	<0·0001	0·92 (0·90-0·94)	<0·0001
26-35	57059 (55%)	63757 (53%)	1·0		1·0	
Sex						
Female	55940 (54%)	41700 (35%)	1·0		1·0	
Male	48019 (46%)	77680 (65%)	0·46 (0·45-0·46)	<0·0001	0·54 (0·53-0·55)	<0·0001
Type of visa						
Students	49938 (48%)	72521 (60·3%)	1·0		1·0	
Settlements and dependents	45660 (43·9%)	29917 (24·8%)	2·21 (2·17-2·26)	<0·0001	1·85 (1·81-1·89)	<0·0001
Work	4103 (3·9%)	11863 (9·8%)	0·50 (0·48-0·52)	<0·0001	0·55 (0·53-0·57)	<0·0001
Family reunion	1578 (1·5%)	2188 (1·8%)	1·04 (0·98-1·11)	0·168	0·62 (0·57-0·67)	<0·0001
Other	2707 (2·6%)	3697 (3%)	1·07 (1·02-1·13)	0·018	0·71 (0·67-0·75)	<0·0001
WHO region						
Africa	24934 (24%)	17793 (14·8%)	1·0		1·0	
Americas	0	2 (0·00%)	0		0	
South-East Asia	24596 (23·6%)	42364 (35·2%)	0·41 (0·40-0·42)	<0·0001	0·40 (0·39-0·41)	<0·0001
Europe	29 (0·03%)	39 (0·03%)	0·54 (0·33-0·90)	0·019	0·66 (0·39-1·13)	0·133
Eastern Mediterranean	52279 (50·2%)	57218 (47·5%)	0·64 (0·63-0·66)	<0·0001	0·57 (0·56-0·59)	<0·0001
Western pacific	2152 (2%)	2828 (2·3%)	0·54 (0·50-0·57)	<0·0001	0·51 (0·47-0·54)	<0·0001
WHO estimated TB incidence (per 100000)						
40-149	1809 (1·7%)	1508 (1·2%)	1·0		1·0	
150-349	98371 (94·6%)	116121 (96·6%)	0·70 (0·65-0·75)	<0·0001	0·86 (0·78-0·92)	<0·0001
>350	3810 (3·6%)	2615 (2·2%)	1·22 (1·11-1·33)	<0·0001	1·13 (1·02-1·21)	0·012
Year of screening						
2011	32588 (31·4%)	32588 (31·3%)	1·0		1·0	
2012	20371 (19·5%)	20371 (19·5%)	1·10 (1·07-1·13)	<0·0001	0·97 (0·95-1·00)	0·099
2013	21212 (20·4%)	21212 (20·4%)	1·29 (1·25-1·32)	<0·0001	1·03 (1·00-1·06)	0·026
2014	29819 (28·6%)	29819 (28·6%)	1·04 (1·01-1·06)	<0·0001	0·86 (0·84-0·89)	<0·0001
Chest radiography						
Normal	98267 (94·5%)	111735 (93%)	1·0		1·0	
Abnormal	5015 (4·8%)	5318 (4·4%)	1·07 (1·02-1·11)	0·001	1·14 (1·10-1·20)	<0·0001
Not done	690 (0·6%)	3125 (2·6%)	0·25 (0·23-0·27)	<0·0001	0·27 (0·24-0·29)	<0·0001

Table 4 Univariate and multivariate analysis of factors associated with LTBI screening in migrants registered in primary care in England

Migrants registered in primary care (n=222728) #	Univariate OR (95%CI)	P	Multivariate OR (95%CI)	P
Age (years)				
16-25	1·39 (1·28-1·51)	<0·0001	1·41 (1·30-1·53)	<0·0001
26-35	1·0		1·0	
Sex				
Female	1·0		1·0	
Male	0·64 (0·59-0·70)	<0·0001	0·77 (0·70-0·85)	<0·0001
Type of visa				
Students	1·0		1·0	
Settlements and dependents	2·49 (2·25-2·76)	<0·0001	2·01 (1·79-2·26)	<0·0001
Work	0·70 (0·49-1·00)	0·054	1·24 (0·85-1·79)	0·247
Family reunion	1·44 (1·03-2·00)	0·029	1·69 (1·10-2·60)	0·016
Other	1·11 (0·78-1·59)	0·529	1·54 (1·07-2·22)	0·019
WHO region				
Africa	1·0		1·0	
Americas	0		0	
South-East Asia	1·53 (1·35-1·73)	<0·0001	1·41 (1·23-1·61)	<0·0001
Europe	0			
Eastern Mediterranean	2·94 (2·61-3·31)	<0·0001	2·22 (1·95-2·54)	<0·0001
Western pacific	0·54 (0·33-0·88)	0·015	0·48 (0·29-0·80)	0·005
WHO estimated TB incidence (per 100000)				
40-149	1·0		1·0	
150-349	1·15 (0·89-1·49)	0·278	1·22 (0·87-1·72)	0·238
>350	0·24 (0·15-0·38)	<0·0001	0·46 (0·27-0·76)	0·003
Deprivation index				
1-3 deciles	1·0		1·0	
4-6 deciles	0·64 (0·58-0·70)	<0·0001	0·71 (0·65-0·78)	<0·0001
7-10 deciles	0·22 (0·18-0·27)	<0·0001	0·27 (0·21-0·33)	<0·0001
Time to GP registration				
<1 year	1·0		1·0	
≥1 year	0·93 (0·78-1·11)	0·447	0·90 (0·76-1·07)	0·249
Cohort				
Screened for active TB	1·0		1·0	
Not screened for active TB	0·65 (0·60-0·70)	<0·0001	0·95 (0·87-1·05)	0·375
Not screened for active TB with pre-entry screening programme	0·76 (0·70-0·83)	<0·0001	1·03 (0·94-1·14)	0·449
Not screened for active TB without pre-entry screening programme	0·38 (0·32-0·44)	<0·0001	0·63 (0·53-0·74)	<0·0001

*****Frequency distributions are not shown because the table contains variables with imputed values and the MICE method does not provide a combined result for descriptive statistics. # Includes 103990 migrants screened for

active TB and registered in primary care and the control group of 118738 migrants registered in primary care but not screened for active TB

Figure legends

Figure 1: Study design and participants.

Figure 2: Migrants' pathway, interventions and missed opportunities for prevention. In the pre-arrival stage red arrows indicate mandatory steps, and blue arrows represent missed opportunities for health promotion and prevention.