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

Luis C Berrocal-Almanza, Ross Harris, Maeve K Lalor, Morris C Muzyamba, John Were, Anne-Marie O'Connell, Adil Mirza, Onn-Min Kon, Ajit Lalvani, Dominik Zenner**

Summary

Background Evaluating interventions that might lead to a reduction in tuberculosis in high-income countries with a low incidence of the disease is key to accelerate progress towards its elimination. In such countries, migrants are known to contribute a large proportion of tuberculosis cases to the burden. We assessed the effectiveness of screening for active tuberculosis before entry to the UK and for latent tuberculosis infection (LTBI) post-entry for reduction of tuberculosis in new-entrant migrants to the UK. Additionally, we investigated the effect of access to primary care on tuberculosis incidence in this population.

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

Findings Our cohort comprised 224 234 migrants who were screened for active tuberculosis before entry to the UK and a control group of 118 738 migrants who were not. 103 990 (50%) migrants who were screened for active tuberculosis registered in primary care; all individuals in the control group were registered in primary care. 1828 tuberculosis cases were identified during the cohort time, of which 31 were prevalent. There were 26 incident active tuberculosis cases in migrants with no evidence of primary care registration, and 1771 cases in the entire cohort of migrants who registered in primary care (n=222 728), giving an incidence rate of 174 (95% CI 166–182) per 100 000 person-years. 672 (1%) of 103 990 migrants who were screened for active tuberculosis went on to develop tuberculosis compared with 1099 (1%) of 118 738 not screened for active tuberculosis (incidence rate ratio [IRR] 1·49, 95% CI 1·33–1·67; p<0·0001). 2451 (1%) of the 222 728 migrants registered in primary care were screened for LTBI, of whom 421 (17%) tested positive and 1961 (80%) tested negative; none developed active tuberculosis within the observed time period. Migrants settling in the least deprived areas had a decreased risk of developing tuberculosis (IRR 0·74, 95% CI 0·62–0·89; p=0·002), and time from UK arrival to primary care registration of 1 year or longer was associated with increased risk of active tuberculosis (2·96, 2·59–3·38; p<0·0001).

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

Funding National Institute for Health Research (NIHR) Health Protection Research Unit in Respiratory Infections and NIHR Imperial Biomedical Research Centre.

Lancet Infect Dis 2019; 19: 1191–01

Published Online August 27, 2019 http://dx.doi.org/10.1016/S1473-3099(19)30260-9

See Comment page 1151

*Contributed equally

National Institute for Health Research Health Protection Research Unit in Respiratory Infections (L C Berrocal-Almanza PhD, Prof O-M Kon MD, Prof A Lalvani DM, D Zenner MD) **and Tuberculosis Research Centre, Respiratory Medicine** (O-M Kon, A Lalvani)**, National Heart and Lung Institute, Imperial College London, London, UK; Statistics, Modelling and Economics Department** (R Harris MSc)**, Tuberculosis Unit, TARGET** (M K Lalor PhD, M C Muzyamba PhD, J Were MPH, A Mirza MSc, D Zenner)**, and Data and Analytical Sciences Department** (A-M O'Connell MSc)**, National Infection Service, Public Health England, London, UK; Institute for Global Health, University College London, London, UK** (M K Lalor)**; and St Mary's Hospital, Imperial NHS Healthcare, London, UK** (Prof O-M Kon)

Correspondence to: Prof Ajit Lalvani, National Institute for Health Research Health Protection Research Unit in Respiratory Infections, Medical School Building, Imperial College London, St Mary's Campus, London W2 1PG, UK **a.lalvani@imperial.ac.uk**

Introduction

Tuberculosis is an ongoing public health problem, but in several high-income countries, the incidence of tuberculosis is at pre-elimination levels (fewer than ten cases per 1 million population), suggesting that elimination might be possible through combining several interventions.[1] In the UK, similar to other low-incidence countries, the epidemiology of tuberculosis is characterised by most cases occurring in people from high-incidence countries, often as a result of progression of latent tuberculosis infection (LTBI).[1,2]

In 2017, the UK had the lowest number of cases (n=5567) and the lowest incidence (8·4 per 100 000 population) of tuberculosis since 1990 (when there were 5010 tuberculosis cases in England, with an incidence of 10·5 per 100 000 population).[3] Improvements in tuberculosis control in the UK during the past 6 years included the implementation of several interventions, such as the

Research in context

Evidence before this study

We searched PudMed and Web of Science for articles in English, Spanish, or French about the effectiveness of screening for active tuberculosis and latent tuberculosis infection (LTBI) in migrants, and migrants' health care access and health, in high-income countries published from January, 1990, up until Sept 30, 2018. We used the search terms "TB screening" or "pre-entry TB screening", "LTBI screening", "migrant health", and "healthcare access". We identified two recent systematic reviews on screening for active tuberculosis and LTBI and one article synthesising a series of literature reviews on migration and health. The available literature suggests that screening for active tuberculosis is efficient when targeted to migrants from countries with a high incidence of tuberculosis. The effectiveness of LTBI screening is limited by the large pool of migrants with LTBI, and targeted programmes must ensure high LTBI screening uptake and treatment completion to have the greatest individual and public health benefit. Little evidence is available on migrants' health status and outcomes; although some surveys done in European countries between 1994 and 2009 contain some information about the health of migrants, these are outdated.

Added value of this study

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

Implications of all the available evidence

Independently to pre-entry active tuberculosis and post-entry LTBI screening, early primary care registration is associated with a reduced incidence of tuberculosis in new-entrant migrants to the UK. Therefore, removal of barriers and facilitation of early access to health services for new migrants is likely to reduce the incidence of tuberculosis in this population. The pre-entry active tuberculosis and post-entry LTBI screening programmes are likely to be responsible for the reduction in tuberculosis incidence in the UK. However, the effectiveness of the LTBI screening programme could be compromised by low attendance to primary care. The pre-entry screening programme provides an opportunity to inform its participants about the availability of LTBI screening and primary care on arrival to the UK. Similarly, the compulsory payment of an immigration health surcharge as part of the visa application process must be coupled with information about entitlements and the importance of primary care registration as the entry point to the UK health system.

rollout of a pre-entry tuberculosis screening programme for visa applicants from countries with a high tuberculosis incidence 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 a high tuberculosis burden have an increased risk of developing tuberculosis in the initial years after arrival to the UK.[2,4] Although the strongest risk factor for progression from LTBI to active tuberculosis is short time since infection,[8] in migrants additional factors might also be important, such as the stress created by the migration and adaptation process, the presence of comorbidities, and their living and work environment.[9] Moreover, migrants can face barriers to access health care services,[10,11] which 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 pre-entry screening for active tuberculosis and post-entry screening for LTBI, and the effect of improving health care access, on reducing the tuberculosis burden in new-entrant migrants to the UK, and their larger effects on the UK tuberculosis epidemiology, are still uncertain.

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

Methods

Study design and participants

We did a population-based, retrospective cohort study in migrants from 66 countries who tested negative for active tuberculosis before entry to the UK between Jan 1, 2011, and Dec 31, 2014, and who fulfilled the eligibility criteria for the national LTBI screening programme. These criteria were age 16–35 years, born in a high-incidence country (≥150 cases per 100 000 population or from any country in

sub-Saharan Africa), and arriving in England within the previous 5 years (appendix p 1). Participants were excluded if the first or last name was missing.

The control group were migrants aged 16–35 years from countries with a high incidence of tuberculosis (or any country in sub-Saharan Africa) who registered in primary care between Jan 1, 2011, and Dec 31, 2014, but did not undergo pre-entry screening for active tuberculosis. This group included migrants who were screened or not screened for LTBI in the Clinical Commissioning Group areas in London, the north of England, and the Midlands where the screening programme for LTBI has been rolled out. At the time of data linkage on Sept 30, 2017, the LTBI programme had been rolled out to 56 of 211 Clinical Commissioning Group areas.[2]

Procedures

We used deterministic record linkage[13] to identify individuals in the cohort that underwent active tuberculosis screening who did and did not register in primary care up to June 30, 2017, by linking to the NHS Patient Registration Data System, which holds records of all patients registered with primary care in England and Wales.

To identify the control group, we used the Flag 4 code in the NHS Patient Registration Data System. The Flag 4 code indicates that someone who has registered with an NHS general practitioner (GP) in England and Wales was previously living overseas.[14,15] It is generated if an individual who registers for the first time with a GP was born outside the UK, or if the individual's previous address was outside the UK.[14,15] After exclusion of records for individuals who were born in the UK or from countries not eligible for LTBI screening, we probabilistically linked the records to the cohort of migrants who were screened for active tuberculosis. The exclusion of records common to both cohorts from the control group revealed a population of migrants who were registered with primary care but did not undergo pre-entry screening. Next, to identify and stratify migrants according to the presence of an active pre-entry screening programme in their country of origin, we used an individual's country of origin and the country's starting date of pre-entry screening (appendix p 1). This step was necessary because our study was started in January, 2011, but the pre-entry active tuberculosis screening programme was initially done in only 15 countries from 2005 onwards, and then rolled out to 101 countries with a high tuberculosis burden (>40 cases per 100 000 population) between May, 2012, and March, 2014.[4]

The control group of migrants not screened for active tuberculosis and all individuals who underwent pre-entry screening for active tuberculosis were probabilistically linked to the database of the national LTBI programme to assess LTBI screening uptake and generate four groups: individuals screened for both active tuberculosis and LTBI, individuals screened for active tuberculosis but not LTBI, those not screened for active tuberculosis but screened for LTBI, and those not screened for either. Under programmatic conditions, an individual is diagnosed as positive for LTBI using a single interferon-γ release assay blood test according to the manufacturers' cut-off for positivity.[12]

A validated probabilistic linkage method[16] in which the records of all cohorts were linked to the Enhanced Tuberculosis Surveillance system was used to identify subsequent development of any form of active tuberculosis in England, Wales, or Northern Ireland between Jan 1, 2011, and Aug 31, 2017, without any restrictions on geographical location or country of birth. A detailed description of data sources and all variables used in the analysis is provided in the appendix p 2. Cases notified within 90 days of the issue of a tuberculosis 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 the UK, determined as the date the certificate of clearance was issued plus 30 days

See **Online** for appendix

For the **NHS Patient Registration Data System** see https://digital.nhs.uk/services/nhais/primary-care-registration

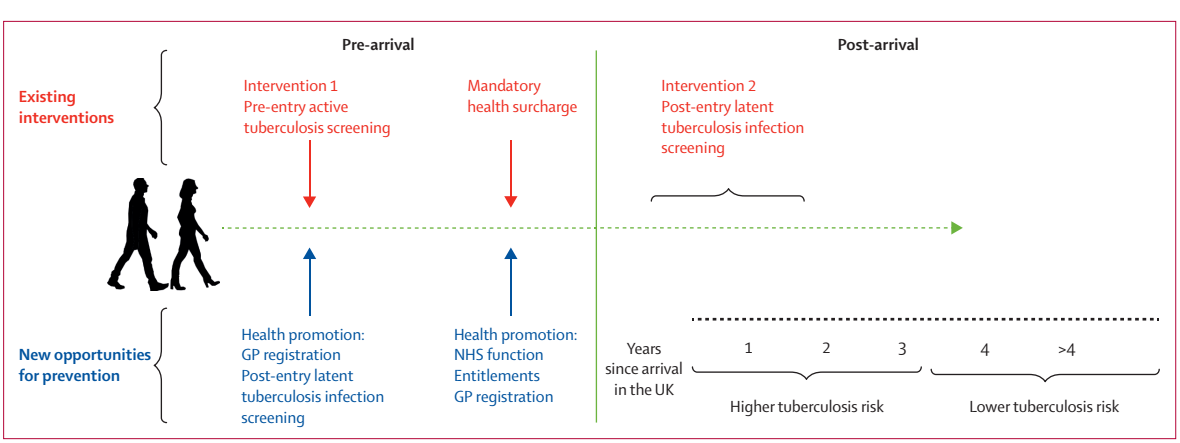

Figure 1: **Migrants' pathway, interventions, and missed opportunities for prevention**
During the pre-arrival stage, red arrows indicate mandatory steps and blue arrows represent missed opportunities for health promotion and prevention. GP=general practitioner.

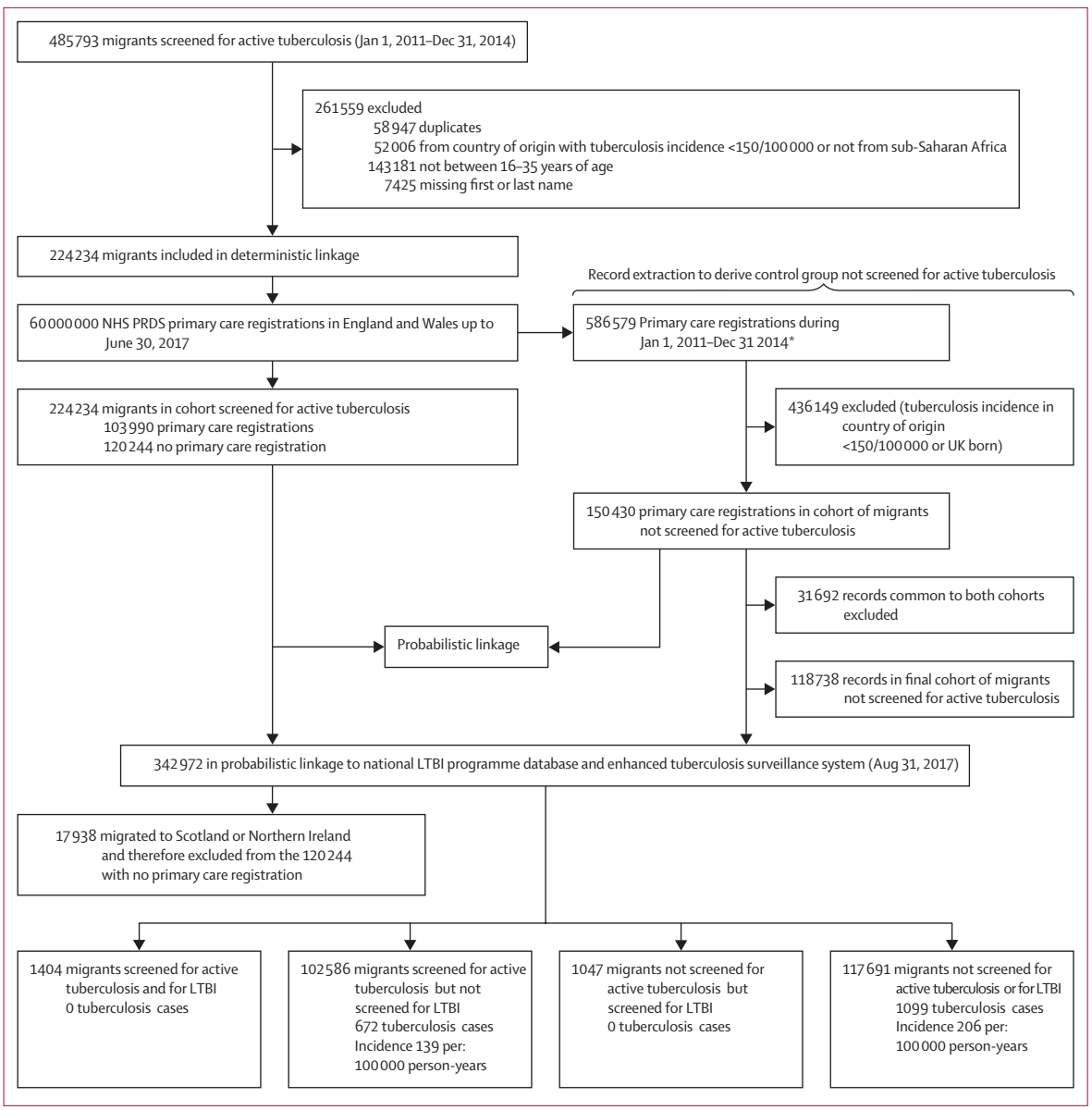

Figure 2: **Study design and participants**
LTBI=latent tuberculosis infection. NHS=National Health Service. PRDS=Patient Registration Data System. *Individuals born or lived abroad, aged between 16 and 35 years, and living in London, the north of England, or the Midlands.

of average visa processing time, and ended at death, development of active tuberculosis, or the end of the study (Aug 31, 2017), whichever occurred first.

Because the Patient Registration Data System only records primary care registrations in England and Wales, no data were available to identify primary care registrations in Scotland and Northern Ireland. Therefore, to calculate the total proportion of new-entry migrants who registered in primary care, after linkage to the database of the national LTBI programme and to the Enhanced Tuberculosis Surveillance system, we randomly excluded 8% of records, as validated previously,[4] from the group of migrants not registered in primary care; according to the data for long-term international migration to the UK, this percentage of migrants would have entered Scotland and Northern Ireland between Jan 1, 2011, and Dec 31, 2014.[17]

For each participant, we extracted baseline data on age, sex, type of visa (students, settlements and dependents, work, family reunion, or other), WHO region of country of origin, deprivation index (appendix p 3), and time from arrival in the UK to primary care registration (<1 year or ≥1 year; appendix p 3). All databases were stored, processed, and analysed at Public Health England (Colindale, London, UK). Under the UK Health and

Social Care Act 2012, Public Health England 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 Public Health England and the NHS for research, monitoring, and evaluation. The migrants' pathway (ie, all the processes from being screened for active tuberculosis before UK entry through to primary care registration and post-entry LTBI screening) is shown in figure 1.

Outcomes

The primary outcome measure was new cases of active tuberculosis notified to the Enhanced Tuberculosis Surveillance system, either bacteriologically or clinically diagnosed, in keeping with its case definition.[18,19] The secondary outcomes were primary care registration and uptake of LTBI screening, both at any point during follow-up.

Statistical analysis

We used multiple imputation by chained equations[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 datasets were created and analysed according to Rubin's rules.[21] This approach accounts for the uncertainty in imputed values and allows unbiased estimates to be obtained if the missing-at-random assumption holds—namely, that an unbiased prediction for the missing variable can be obtained, conditional on its specified association with observed covariates.[21] The multiple imputation by chained equations 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 of active tuberculosis, each imputed dataset was analysed separately using univariate and multivariate Poisson regression models. We used logistic regression models for the secondary outcome of LTBI screening uptake. The results of these analyses were combined into one multiple-imputation result.[21] We used univariate and multivariate logistic regression to assess the factors associated with the secondary outcome of primary care registration. The multivariate analyses accounted for differences in age, sex, visa category, region of origin, and estimated tuberculosis incidence in country of origin. The results are presented as odds ratios (ORs), incidence per 100 000 person-years, or incidence rate ratios (IRRs), with 95% CIs and two-sided p values. The baseline characteristics of the 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 using only the person-year contributions of migrants who remained in the UK until the end of follow-up according to visa category. A detailed description of the multiple imputation method and sensitivity analyses is provided in the appendix p 3. Stata version 15·1 was used for all statistical analyses.

	Screened for active tuberculosis (n=224 234)	Not screened for active tuberculosis (n=118 738)
Age group		
16–25 years	103 418 (46%)	35 598 (30%)
26–35 years	120 816 (54%)	83 140 (70%)
Sex		
Female	97 640 (44%)	55 411 (47%)
Male	125 699 (56%)	63 327 (53%)
Type of visa		
Students	122 459 (55%)	63 758 (54%)
Settlements and dependents	75 577 (34%)	41 502 (35%)
Work	15 966 (7%)	6641 (6%)
Family reunion	3766 (2%)	3242 (3%)
Other	6404 (3%)	3595 (3%)
WHO region		
Africa	42 727 (19%)	33 367 (28%)
Americas	2 (<1%)	20 (<1%)
South-East Asia	66 960 (30%)	67 784 (57%)
Europe	68 (<1%)	698 (<1%)
Eastern Mediterranean	109 497 (49%)	14 024 (12%)
Western Pacific	4980 (2%)	2845 (2%)
WHO estimated tuberculosis incidence (cases per 100 000)		
40–149	3317 (1%)	4102 (3%)
150–349	214 492 (96%)	107 088 (90%)
>350	6425 (3%)	7548 (6%)
Year of screening		
2011	73 274 (33%)	NA
2012	43 507 (19%)	NA
2013	41 803 (19%)	NA
2014	65 650 (29%)	NA
Chest radiography		
Normal	210 002 (94%)	NA
Abnormal	10 333 (5%)	NA
Not done	3815 (2%)	NA

NA=not applicable.

Table 1: **Baseline sociodemographic characteristics of all study participants (n=342 972)**

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had the final responsibility for the decision to submit for publication.

Results

There were 485 793 screening episodes (one per migrant) for active tuberculosis infection in the pre-entry

	Incidence per 100 000 person-years (95% CI)*	Univariate IRR (95% CI)	p value	Multivariate IRR (95% CI)	p value
Age group					
16–25 years	155 (143–169)	0·84 (0·75–0·92)	0·001	0·88 (0·79–0·97)	0·01
26–35 years	184 (174–195)	1·0 (ref)	..	1·0 (ref)	..
Sex					
Female	146 (136–157)	1·0 (ref)	..	1·0 (ref)	..
Male	200 (188–212)	1·36 (1·23–1·49)	<0·0001	1·13 (1·00–1·27)	0·03
Type of visa					
Students	184 (173–196)	1·0 (ref)	..	1·0 (ref)	..
Settlements and dependents	157 (145–170)	0·81 (0·69–0·94)	0·007	0·89 (0·75–1·05)	0·19
Work	176 (140–222)	0·79 (0·51–1·21)	0·29	0·91 (0·57–1·45)	0·69
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)	0·02	0·51 (0·23–1·14)	0·10
WHO region					
Africa	137 (122–153)	1·0 (ref)	..	1·0 (ref)	..
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)	0·48	1·51 (0·99–2·30)	0·05
WHO estimated tuberculosis incidence (cases per 100 000)					
40–149	252 (196–325)	1·0 (ref)	..	1·0 (ref)	..
150–349	174 (166–183)	0·69 (0·53–0·89)	0·005	1·35 (0·86–2·10)	0·18
>350	121 (92–160)	0·48 (0·33–0·70)	<0·0001	1·32 (0·77–2·26)	0·30
Deprivation index					
1–3 deciles (most deprived)	182 (171–193)	1·0 (ref)	..	1·0 (ref)	..
4–6 deciles	182 (168–198)	0·97 (0·87–1·08)	0·63	0·96 (0·86–1·07)	0·40
7–10 deciles (least deprived)	124 (107–144)	0·65 (0·54–0·77)	<0·0001	0·74 (0·62–0·89)	0·002
Time from arrival in the UK to primary care registration					
<1 year	136 (128–144)	1·0 (ref)	..	1·0 (ref)	..
≥1 year	436 (402–474)	3·07 (2·69–3·52)	<0·0001	2·96 (2·59–3·38)	<0·0001
Intervention					
Pre-entry screen and LTBI screen	0	0	..	0	..
Pre-entry screen but no LTBI screen	141 (130–152)	1·0 (ref)	..	1·0 (ref)	..
No pre-entry screen or LTBI screen	205 (193–218)	1·45 (1·32–1·60)	<0·0001	1·49 (1·33–1·67)	<0·0001
LTBI screen but no pre-entry screen	0	0	..	0	..

IRR=incidence rate ratio. LTBI=latent tuberculosis infection. *Incidence rate per 100 000 person-years and 95% CI were derived from one imputation because the multiple imputation by chained equations method does not provide a combined result from all imputations for incidence rates.

Table 2: **Univariate and multivariate analysis of factors associated with incident active tuberculosis in migrants registered in primary care in England (n=222 728)**

programme between Jan 1, 2011, and Dec 31, 2014 (figure 2). After exclusion of duplicates and applicants not eligible for LTBI screening and treatment, records for 224 234 migrants screened for active tuberculosis were deterministically and probabilistically linked to the Patient Registration Data System and Enhanced Tuberculosis Surveillance system, respectively. After exclusion of the 17 938 (8%) individuals who migrated to Scotland and Northern Ireland, 103 990 (50%) registered in primary care after arrival to the UK. Additionally, we identified a control group of 118 738 migrants who were not screened for active tuberculosis and had registered in primary care. The baseline characteristics of the study participants are shown in table 1.

A total of 1828 cases of active tuberculosis were identified during the cohort time (ie, from Jan 1, 2011, to the date of record linkage to the enhanced TB surveillance system on Aug 31, 2017), of which 31 were prevalent. There were 26 incident cases in 120 244 migrants with no evidence of primary care registration, and 1771 incident cases in 222 728 migrants who registered in primary care; of these, 672 were screened and 1099 were not screened for active tuberculosis. This number of incident cases includes all forms of tuberculosis in migrants registered

	Primary care registration (n=103 990)	No primary care registration (n=120 244)	Univariate OR (95% CI)	p value	Multivariate OR (95% CI)	p value
Age group						
16–25 years	46 931 (45%)	56 487 (47%)	0·92 (0·91–0·94)	<0·0001	0·92 (0·90–0·94)	<0·0001
26–35 years	57 059 (55%)	63 757 (53%)	1·0 (ref)	..	1·0 (ref)	..
Sex						
Female	55 940 (54%)	41 700 (35%)	1·0 (ref)	..	1·0 (ref)	..
Male	48 019 (46%)	77 680 (65%)	0·46 (0·45–0·46)	<0·0001	0·54 (0·53–0·55)	<0·0001
Type of visa						
Students	49 938 (48%)	72 521 (60%)	1·0 (ref)	..	1·0 (ref)	..
Settlements and dependents	45 660 (44%)	29 917 (25%)	2·21 (2·17–2·26)	<0·0001	1·85 (1·81–1·89)	<0·0001
Work	4103 (4%)	11 863 (10%)	0·50 (0·48–0·52)	<0·0001	0·55 (0·53–0·57)	<0·0001
Family reunion	1578 (2%)	2188 (2%)	1·04 (0·98–1·11)	0·16	0·62 (0·57–0·67)	<0·0001
Other	2707 (3%)	3697 (3%)	1·07 (1·02–1·13)	0·01	0·71 (0·67–0·75)	<0·0001
WHO region						
Africa	24 934 (24%)	17 793 (15%)	1·0 (ref)	..	1·0 (ref)	..
Americas	0	2 (<1%)	0	..	0	..
South-East Asia	24 596 (24%)	42 364 (35%)	0·41 (0·40–0·42)	<0·0001	0·40 (0·39–0·41)	<0·0001
Europe	29 (<1%)	39 (<1%)	0·54 (0·33–0·90)	0·01	0·66 (0·39–1·13)	0·13
Eastern Mediterranean	52 279 (50%)	57 218 (48%)	0·64 (0·63–0·66)	<0·0001	0·57 (0·56–0·59)	<0·0001
Western Pacific	2152 (2%)	2828 (2%)	0·54 (0·50–0·57)	<0·0001	0·51 (0·47–0·54)	<0·0001
WHO estimated tuberculosis incidence (cases per 100 000)						
40–149	1809 (2%)	1508 (1%)	1·0 (ref)	..	1·0 (ref)	..
150–349	98 371 (95%)	116 121 (97%)	0·70 (0·65–0·75)	<0·0001	0·86 (0·78–0·92)	<0·0001
>350	3810 (4%)	2615 (2%)	1·22 (1·11–1·33)	<0·0001	1·13 (1·02–1·21)	0·01
Year of screening						
2011	32 588 (31%)	32 588 (31%)	1·0 (ref)	..	1·0 (ref)	..
2012	20 371 (20%)	20 371 (20%)	1·10 (1·07–1·13)	<0·0001	0·97 (0·95–1·00)	0·09
2013	21 212 (20%)	21 212 (20%)	1·29 (1·25–1·32)	<0·0001	1·03 (1·00–1·06)	0·02
2014	29 819 (29%)	29 819 (29%)	1·04 (1·01–1·06)	<0·0001	0·86 (0·84–0·89)	<0·0001
Chest radiography						
Normal	98 267 (95%)	111 735 (93%)	1·0 (ref)	..	1·0 (ref)	..
Abnormal	5015 (5%)	5318 (4%)	1·07 (1·02–1·11)	0·001	1·14 (1·10–1·20)	<0·0001
Not done	690 (1%)	3125 (3%)	0·25 (0·23–0·27)	<0·0001	0·27 (0·24–0·29)	<0·0001

OR=odds ratio.

Table 3: **Univariate and multivariate analysis of factors associated with primary care registration in England and Wales in migrants screened for active tuberculosis (n=224 234)**

in primary care, giving an incidence rate of 174 (95% CI 166–182) per 100 000 person-years in a total follow-up time of 1 015 121 person-years with median follow-up of 4·5 years (IQR 3·3–5·8) per person. In the intervention group, the incidence rate was 139 (95% CI 129–150) per 100 000 person-years in migrants screened for active tuberculosis and 206 (194–218) per 100 000 person-years in migrants not screened for active tuberculosis, giving an incidence rate ratio (IRR) of 1·49 (95% CI 1·33–1·67; p<0·0001).

In migrants not screened for LTBI, those not screened for active tuberculosis were more likely to develop tuberculosis than migrants screened for active tuberculosis (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 tuberculosis (IRR 2·39 [95% CI 2·06–2·77], p<0·0001; appendix p 4). None of the migrants screened for LTBI developed active tuberculosis within the observed time period (table 2). Most tuberculosis cases occurred within the first 3 years of arrival into the UK (data not shown).

The multivariate analysis of risk factors associated with incident tuberculosis in the 222 728 migrants registered in primary care, adjusting for age, sex, visa category, region of origin, and estimated tuberculosis incidence in country of origin, showed that migrants settling in the least deprived areas had a decreased risk of developing tuberculosis (IRR 0·74, 95% CI 0·62–0·89; p=0·002),

	Univariate OR (95% CI)	p value	Multivariate OR (95% CI)	p value
Age group†				
16–25 years	1·39 (1·28–1·51)	<0·0001	1·41 (1·30–1·53)	<0·0001
26–35 years	1·0 (ref)	..	1·0 (ref)	..
Sex				
Female	1·0 (ref)	..	1·0 (ref)	..
Male	0·64 (0·59–0·70)	<0·0001	0·77 (0·70–0·85)	<0·0001
Type of visa				
Students	1·0 (ref)	..	1·0 (ref)	..
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)	0·05	1·24 (0·85–1·79)	0·24
Family reunion	1·44 (1·03–2·00)	0·02	1·69 (1·10–2·60)	0·01
Other	1·11 (0·78–1·59)	0·52	1·54 (1·07–2·22)	0·01
WHO region				
Africa	1·0 (ref)	..	1·0 (ref)	..
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)	0·01	0·48 (0·29–0·80)	0·005
WHO estimated tuberculosis incidence (cases per 100 000)				
40–149	1·0 (ref)	..	1·0 (ref)	..
150–349	1·15 (0·89–1·49)	0·27	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 (least deprived)	1·0 (ref)	..	1·0 (ref)	..
4–6 deciles	0·64 (0·58–0·70)	<0·0001	0·71 (0·65–0·78)	<0·0001
7–10 deciles (most deprived)	0·22 (0·18–0·27)	<0·0001	0·27 (0·21–0·33)	<0·0001
Time from arrival in the UK to primary care registration				
<1 year	1·0 (ref)	..	1·0 (ref)	..
≥1 year	0·93 (0·78–1·11)	0·44	0·90 (0·76–1·07)	0·24
Cohort				
Screened for active tuberculosis	1·0 (ref)	..	1·0 (ref)	..
Not screened for active tuberculosis	0·65 (0·60–0·70)	<0·0001	0·95 (0·87–1·05)	0·37
From country with pre-entry screening programme	0·76 (0·70–0·83)	<0·0001	1·03 (0·94–1·14)	0·44
From country without pre-entry screening programme	0·38 (0·32–0·44)	<0·0001	0·63 (0·53–0·74)	<0·0001

OR=odds ratio. *Frequency distributions are not shown because the table contains variables with imputed values and the multiple imputation by chained equations method does not provide a combined result for descriptive statistics. †Includes 103 990 migrants screened for active tuberculosis and registered in primary care and the control group of 118 738 migrants registered in primary care but not screened for active tuberculosis.

Table 4: **Univariate and multivariate analysis of factors associated with latent tuberculosis infection screening in migrants registered with primary care in England (n=222 728)***

and time from UK arrival to primary care registration of 1 year or longer was associated with an increased risk of all forms of tuberculosis (pulmonary and extrapulmonary; IRR 2·96, 95% CI 2·59-3·38; p <0·0001; table 2). Having a family reunion visa type and being from the South East Asian and Eastern Mediterranean WHO regions were also associated with an increased risk of developing tuberculosis.

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 tuberculosis. Therefore, we did a sensitivity analysis, which showed that our results were stable when emigration was taken into account (appendix p 5).

A multivariate analysis of factors associated with primary care registration showed that being male, being aged 16–25 years, having a work or family reunion visa category, being from the South-East Asia, Eastern Mediterranean, or Western Pacific WHO regions, and being from a country with 150–349 tuberculosis cases per 100 000, along with not having a chest radiography done, were associated with a decreased probability of registering with primary care (table 3). By contrast, migrants in the settlements and dependents visa category, those with abnormal chest radiography, and those from a country with more than 350 tubersulosis cases per 100 000 were more likely to register with primary care (table 3).

2451 (1%) of the 222 728 migrants who registered in primary care were screened for LTBI, of whom 421 (17%) were positive and 1961 (80%) were negative, with a median follow-up time from the date of screening of 0·63 years (IQR 0·3–1·0) per person (appendix p 6). In a multivariate analysis, individuals in the age group 16–25 years, those with a settlements and dependents or family reunion visa category, and those from the WHO 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 an estimated tuberculosis incidence of more than 350 cases per 100 000 population, from the middle and least deprived group, and from a country without an operational pre-entry screening programme were all factors associated with reduced likelihood of being screened for LTBI (table 4).

Discussion

In this study, we provide direct evidence of a positive association between the pre-entry active tuberculosis and post-entry LTBI screening programmes and a reduced incidence of tuberculosis in new-entrant migrants to the UK. Our study also demonstrates low levels of primary care registration in migrants from countries with a high incidence of tuberculosis and a significant association between delayed access to primary care and the risk of developing active tuberculosis. These results may suggest that improving migrants' access to primary care would probably improve tuberculosis control in the UK.

Systematic screening for active tuberculosis in migrants has emerged as a potential strategy to improve early tuberculosis diagnosis and outcomes, but data proving its effectiveness as a public health intervention are scarce.[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 tuberculosis cases after arrival to the UK. We speculate that this intervention

might also help to raise tuberculosis awareness among its participants; in our study, migrants from countries with no operational programme were less likely to be screened for LTBI than those from countries with screening programmes and had the highest risk of developing tuberculosis. Most of the migrants in the non-intervention group were probably screened upon arrival in the UK as part of the previous system (chest radiographs upon arrival).[4,9] In this scenario, our results indicate that pre-entry screening reduces incident tuberculosis compared with chest radiographs done upon arrival; thus, this is another advantage to the suggested higher yield of pre-entry screening.[25]

The epidemiology of tuberculosis in England supports the notion that treatment for LTBI could be of great benefit for recent immigrants from countries with a high tuberculosis burden.[2,24,26,27] In our cohort, none of the participants who were screened for LTBI developed active tuberculosis within the observed time period, potentially indicating the benefit of this intervention to reduce the number of incident tuberculosis cases. However, our results indicate that the effectiveness of this intervention might be affected by low attendance to primary care, since only about 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 health care needs in a family and community context.[28] The beneficial effect of primary care on health outcomes might be accounted for by a combination of mechanisms that include an increased focus on prevention and the early management of health problems.[28] 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 primary care registration. In a previous study,[29] we found that migrants might lack clarity about immigration status and their rights to access health care, have competing priorities (eg, working), or fear the consequences of their immigration status.[29] Additionally, the population in our study probably comprise a young cohort that tends to be relatively healthy upon arrival. However, it has been shown that this so-called healthy migrant effect wanes with duration of residence in the host country, possibly due to the acquisition of unhealthy lifestyle habits and the new living and working conditions.[30] 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 tuberculosis, and most cases occur within 2–3 years of arrival. Thus, early primary care access represents an important opportunity to offer preventive interventions for tuberculosis, such as LTBI screening and treatment, and for other comorbidities that render this population at higher risk of tuberculosis.

Access to health-care services, irrespective of migration or financial status, is a key intervention for tuberculosis elimination,[1] and one of the founding principles of the NHS is to provide universal and equitable health care according to need.[31] However, migrants are affected by barriers to access health services, and the introduction of new reforms, such as removing the right of migrants without indefinite leave to access free health care, and demanding NHS frontline staff to identify and charge such patients in hospital care are likely to increase their exclusion from primary and hospital care.[10,11,31] Our results highlight the adverse consequences that such reforms could have on both migrants' health and public health. We found a strong association between time to primary care registration and the risk of developing active tuberculosis, and other studies have similarly identified challenges for accessing health care as a main barrier for tuberculosis diagnosis and treatment uptake.[32] Although the health of migrants is of increasing interest worldwide, evidence about migrants' health status and outcomes is generally scarce because of the challenge of gathering reliable information.[33,34] 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 the health status of migrants.[33]

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 did a sensitivity analysis to account for emigration according to visa category, the results of which were consistent with our main analysis. Our study did not include data from undocumented migrants (ie, those who entered the country illegally and visa over-stayers); therefore, our results might underestimate the reported associations, because of potential under-ascertainment of cases in that population, which likely experiences more barriers to accessing health services than migrants who entered the country legally and still have a valid visa. In addition, the number of tuberculosis cases might be underestimated because of emigration. Similarly, our analysis did not account for the presence of important comorbidities, such as HIV, that can increase the risk of developing active tuberculosis. Additionally, although our results might 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: data were not available on treatment uptake or completion, and average follow-up after LTBI screening was less than 1 year. The size of the population that was screened for LTBI in our cohort was small, but the percentage of

individuals who tested positive for LTBI is similar to the prevalence in a national cohort.[2] We cannot rule out the presence of confounders because this study is not a randomised trial; however, we adjusted for the most important known factors, such as age, sex, tuberculosis incidence in country of origin, and deprivation index.[2]

Our study supports the hypothesis that the pre-entry screening programme for active tuberculosis and the post-entry screening programme for LTBI are probably responsible, at least in part, for the reduction in tuberculosis incidence in the UK in the past 6 years, as suggested in a previous study.[35] Furthermore, our results suggest that promoting early access to health services for new migrants entering the UK would substantially reduce the burden of tuberculosis in this population. The pre-entry programme could be actively used for health promotion to inform its participants about the LTBI screening programme and primary care registration upon arrival in the UK. Similarly, given that, since April, 2015, all migrants from countries outside the European Economic Area have had to pay an immigration health surcharge,[31] this occasion when they pay the surcharge would be an opportunity to inform migrants about their entitlements and the importance of primary care registration as the entry point to the UK's health system. Our data on LTBI screening points to a beneficial effect of this intervention, and a further evaluation is now needed to confirm our findings. We expect that careful consideration of these recommendations by policy makers will accelerate the progress towards tuberculosis elimination in the UK.

Contributors

DZ, LCB-A, and AL conceptualised the initial hypothesis and conceived and designed the study. LCB-A and RH analysed the data. LCB-A wrote the first draft of the manuscript. LCB-A, A-MO, and AM did the record linkage. All authors contributed substantially to data acquisition and interpretation, and revision and editing of the manuscript.

Declaration of interests

AL is named inventor on patents pertaining to T-cell-based diagnosis, including interferon-γ release assay technologies. Some of these patents were assigned by the University of Oxford (Oxford, UK) to Oxford Immunotec, resulting in royalty entitlements for the University of Oxford and AL. All other authors declare no competing interests.

Acknowledgments

The research was funded by the National Institute for Health Research Health Protection Research Unit (NIHR HPRU) in Respiratory Infections at Imperial College London (London, UK) in partnership with Public Health England (London, UK). The views expressed are those of the author(s) and not necessarily those of the National Health Service, the NIHR, the Department of Health, or Public Health England. AL was supported by the NIHR Imperial Biomedical Research Centre. We thank Peter Beverly, Claire Puddephatt, and Olivia Conroy, without whose support this study would have not been possible.

References

1 Lonnroth K, Migliori GB, Abubakar I, et al. Towards tuberculosis elimination: an action framework for low-incidence countries. *Eur Respir J* 2015; **45:** 928–52.

2 Public Health England (PHE). Tuberculosis in England 2018. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/774091/TB_Annual_Report_2018_2.pdf (accessed Nov 15, 2018).

3 Public Health England (PHE). Reports of cases of tuberculosis to enhanced tuberculosis surveillance systems: UK, 2000 to 2017. Official statistics. September, 2018. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/741159/PHE_TB_Official_Statistics_2018.pdf (accessed Nov 15, 2018).

4 Aldridge RW, Zenner D, White PJ, et al. Tuberculosis in migrants moving from high-incidence to low-incidence countries: a population-based cohort study of 519 955 migrants screened before entry to England, Wales, and Northern Ireland. *Lancet* 2016; **388:** 2510–18.

5 Pareek M, Watson JP, Ormerod LP, et al. Screening of immigrants in the UK for imported latent tuberculosis: a multicentre cohort study and cost-effectiveness analysis. *Lancet Infect Dis* 2011; **11:** 435–44.

6 Public Health England. Collaborative Tuberculosis Strategy for England 2015–2020. 2015. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/403231/Collaborative_TB_Strategy_for_England_2015_2020_.pdf (accessed Oct 8, 2018).

7 Loutet MG, Burman M, Jayasekera N, et al. National roll-out of latent tuberculosis testing and treatment for new migrants in England: a retrospective evaluation in a high-incidence area. *Eur Respir J* 2018; 51: 1701226.

8 Halliday A, Whitworth H, Kottoor SH, et al. Stratification of latent *Mycobacterium tuberculosis* infection by cellular immune profiling. *J Infect Dis* 2017; **215:** 1480–87.

9 Pareek M, Greenaway C, Noori T, Munoz J, Zenner D. The impact of migration on tuberculosis epidemiology and control in high-income countries: a review. *BMC Med* 2016; **14:** 48.

10 Poduval S, Howard N, Jones L, Murwill P, McKee M, Legido-Quigley H. Experiences among undocumented migrants accessing primary care in the United Kingdom: a qualitative study. *Int J Health Serv* 2015; **45:** 320–33.

11 Stagg HR, Jones J, Bickler G, Abubakar I. Poor uptake of primary healthcare registration among recent entrants to the UK: a retrospective cohort study. *BMJ Open* 2012; **2:** e001453.

12 Public Health England. Latent TB testing and treatment for migrants: a practical guide for commissioners and practitioners. 2015. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/442192/030615_LTBI_testing_and_treatment_for_migrants_1.pdf (accessed Sept 12, 2018).

13 Gill L. Methods for automatic record matching and linkage and their use in national statistics. National satistics methodological series, no. 25. Newport: Office for National Statistics, 2001.

14 The Migration Observatory. Flag 4 records. 2015. https://migrationobservatory.ox.ac.uk/about/data-sources-limitations/flag-4-records/ (accessed Sept 12, 2018).

15 Panchal RK, Browne I, Monk P, Woltmann G, Haldar P. The effectiveness of primary care based risk stratification for targeted latent tuberculosis infection screening in recent immigrants to the UK: a retrospective cohort study. *Thorax* 2014; **69:** 354–62.

16 Aldridge RW, Shaji K, Hayward AC, Abubakar I. Accuracy of probabilistic linkage using the enhanced matching system for public health and epidemiological studies. *PLoS One* 2015; **10:** e0136179.

17 Office for National Statistics. Long-term international migration 2.06, area of destination or origin within the UK. 2016. https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/internationalmigration/datasets/longterminternationalmigrationareaofdestinationororiginwithintheuktable206/current (accessed Nov 5, 2018).

18 Public Health England (PHE). Guidance for epidemiological surveillance to control tuberculosis (TB) and to identify cases for cohort review. 2014. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/360263/Guidance_on_Notifying_Tuberculosis__TB__cases.pdf (accessed Oct 17, 2018).

19 National Institute for Health and Care Excellence (NICE). Tuberculosis prevention, diagnosis, management and service organisation. NICE NG33. January, 2016. https://www.nice.org.uk/guidance/ng33/evidence/full-guideline-80851860868 (accessed Oct 10, 2018).

20 StataCorp. Multiple-imputation reference manual. Stata: Release 15. Statistical Software. College Station, TX: StataCorp LLC, 2017.

21 Rubin DB. Multiple imputation for nonresponse in surveys. New York: John Wiley, 1987.

22 He YL. Missing data analysis using multiple imputation: getting to the heart of the matter. *Circ Cardiovasc Qual Outcomes* 2010; **3:** 98–105.

23 Kranzer K, Afnan-Holmes H, Tomlin K, et al. The benefits to communities and individuals of screening for active tuberculosis disease: a systematic review. *Int J Tuberc Lung Dis* 2013; **17:** 432–46.

24 Greenaway C, Pareek M, Abou Chakra CN, et al. The effectiveness and cost-effectiveness of screening for active tuberculosis among migrants in the EU/EEA: a systematic review. *Euro Surveill* 2018; **23:** 17-00542.

25 Klinkenberg E, Manissero D, Semenza JC, Verver S. Migrant tuberculosis screening in the EU/EEA: yield, coverage and limitations. *Eur Respir J* 2009; **34:** 1180–89.

26 World Health Organization (WHO). Latent tuberculosis infection. Updated and consolidated guidelines for programmatic management. 2018. http://www.who.int/tb/publications/2018/latent-tuberculosis-infection/en/ (accessed Nov 12, 2018).

27 Zenner D, Loutet MG, Harris R, Wilson S, Ormerod LP. Evaluating 17 years of latent tuberculosis infection screening in north-west England: a retrospective cohort study of reactivation. *Eur Respir J* 2017; **50:** 1602505.

28 Starfield B, Shi LY, Macinko J. Contribution of primary care to health systems and health. *Milbank Q* 2005; **83:** 457–502.

29 Berrocal-Almanza LC, Botticello J, Piotrowski H, et al. Engaging with civil society to improve access to LTBI screening for new-entrant migrants in England: a qualitative study. *Int J Tuberc Lung Dis* 2018; **23:** 563–70.

30 Hill TD, Angel JL, Balistreri KS, Herrera AR. Immigrant status and cognitive functioning in late-life: an examination of gender variations in the healthy immigrant effect. *Soc Sci Med* 2012; **75:** 2076–84.

31 Rafighi E, Poduval S, Legido-Quigley H, Howard N. National Health Service principles as experienced by vulnerable London migrants in "austerity Britain": a qualitative study of rights, entitlements, and civil-society advocacy. *Int J Health Policy* 2016; **5:** 589–97.

32 de Vries SG, Cremers AL, Heuvelings CC, et al. Barriers and facilitators to the uptake of tuberculosis diagnostic and treatment services by hard-to-reach populations in countries of low and medium tuberculosis incidence: a systematic review of qualitative literature. *Lancet Infect Dis* 2017; **17:** e128–43.

33 O'Donnell CA, Burns N, Mair FS, et al. Reducing the health care burden for marginalised migrants: the potential role for primary care in Europe. *Health Policy* 2016; **120:** 495–508.

34 Rechel B, Mladovsky P, Ingleby D, Mackenbach JP, McKee M. Migration and health in an increasingly diverse Europe. *Lancet* 2013; **381:** 1235–45.

35 Thomas HL, Harris RJ, Muzyamba MC, et al. Reduction in tuberculosis incidence in the UK from 2011 to 2015: a population-based study. *Thorax* 2018; **73:** 769–75.