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Supplementary appendix

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Supplementary Appendix

Effectiveness of nationwide programmatic latent tuberculosis infection testing and treatment in migrants in England.

List of investigators:

Luis C. Berrocal-Almanza, PhD

Ross J. Harris, PhD

Simon M. Collin, PhD

Morris C. Muzyamba, PhD

Olivia Conroy, MSc

Adil Mirza, MSc

Anne-Marie O'Connell, MSc

Lynn Altass, MSc

Sarah Anderson, MD

Lucy Thomas, MD

Colin Campbell, MD

Dominik Zenner, MD

Nick Phin, MD

Onn Min Kon, MD

E. Grace Smith, FRCPath

Ajit Lalvani DM,

Methods

Author contributions

Luis C. Berrocal-Almanza and Ajit Lalvani conceived and designed the study. The data was gathered, processed and cleaned by Morris C. Muzyamba and Olivia Conroy. Adil Mirza, Anne-Marie O'Connell and Luis C. Berrocal-Almanza did the record linkage. Luis C. Berrocal-Almanza, Ross J. Harris and Simon M. Collin analysed the data. Luis C. Berrocal-Almanza wrote the first draft of the manuscript. All authors substantially contributed to discussion of content and reviewed and edited the manuscript before submission. All authors were involved in

the decision and agreed to publish the paper. This research is sponsored by NIHR grant Health Protection Research Unit in Respiratory Infections.

Evaluation design and participants

In England, the LTBI testing and treatment programme is offered to migrants born in one of the 70 selected high incidence countries (≥150/100000 or sub-Saharan Africa).[1] The number of evaluation participants according to country of origin and Enhanced Tuberculosis Surveillance system region is shown in supplementary table S1.[2]

Data sources

The evaluation cohort was created by probabilistic record linkage of three databases. The pre-entry screening for active TB database held at the UK Health Security Agency (UKHSA) records sociodemographic information including first and last name, and the date of pre-entry screening of all individuals from 101 countries who were screened for active TB as part of their visa application process; this database does not record date of UK entry or primary care registration; the National Health Service (NHS) Patient Registration Data System (PRDS) is held in a central repository by NHS digital,[3] it holds sociodemographic information of all patients registered in primary care in England and Wales including first and last name; this database does not provide date of primary care registration to the public, although this information can be retrieved for individuals born or who lived abroad using the special "flag4" code within the PRDS.[4] The Index of Multiple Deprivation 2015 is the official measure of relative deprivation for lower-layer super output areas, based on the 2011 census in England.[5] It ranks every small area in England from the most to least deprived. It uses deprivation deciles calculated by ranking the 32844 small areas in England from the most to the least deprived and dividing them into 10 equal groups.[5] It is constructed by combining the following seven domains of deprivation: income, employment, education, skills and training, health and disability, crime, barriers to housing and services, and living environment.[5]

Record linkage

We used a validated probabilistic linkage method[6] to create a cohort of all foreign-born individuals that registered in primary care in England from January 1, 2011, to December 31, 2018 by linking three different datasets: the pre-entry active TB screening programme which holds records of all individuals from 101 high-burden countries (>40 cases per 100000 population) who applied for visas for greater than six-months to enter the UK;[7] records extracted from the National Health Service (NHS) Patient Registration Data System, which holds information on all patients registered with primary care in England and Wales;[3] and the 'Flag 4' code within the NHS Patient Registration Data System which indicates that someone who has registered for the first time with an NHS general practitioner in England and Wales was born outside the UK, or if the individual's previous address was outside the UK.[4] This cohort was first linked probabilistically to the database of the national LTBI programme to assess LTBI testing and treatment uptake, and later to the Enhanced Tuberculosis Surveillance system to identify subsequent development of any form of active TB in England, Wales, or Northern Ireland between January 1, 2014, and November 30, 2019, without any restrictions on geographical location or country of birth. The variables used for probabilistic record linkage were first and last name, date of birth, sex and NHS number. A matching

threshold was calculated and one author (LCBA) performed a manual review of records with a matching score of 10 above and below the matching threshold.

Statistical analysis

Survival analysis

For the survival analysis, univariate models were first fitted for each covariate, we then assessed effect interactions and modifications between the main outcomes and all covariates, after which, a multivariate model was fitted including all covariates and significant effect modifications. The proportionality of hazards assumption was assessed using Schoenfeld and scaled Schoenfeld residuals, and by including interactions of the predictors and time as time-variant covariates in the regression models. The best-fitting multivariate models, determined by a likelihood ratio test, were used to estimate adjusted survival functions. For the analysis stratified by time of follow-up, 6 months was used as the first time point because it had the lowest log likelihood compared to 7-12 months.

In a separate multivariate model, we explored area-level variation using a three-level mixed-effects parametric survival-time model with CCG and general practice level random intercepts; for this analysis, we assumed a Log Normal conditional distribution of the response given the random effects based on its lowest Akaike's information criterion when compared with Weibull and Log Logistic distributions.

We did sensitivity analyses to account for the imputation method using complete case analysis, and for treatment completion using only participants with confirmed date of treatment completion.

Multiple imputation

We used a multiple imputation by chained equations (MICE) model to impute missing values, while accounting for the uncertainty in missing information.[8] The creation and analysis of 5 imputed datasets is described in this section.

The country of origin for some individuals who had programmatic LTBI testing was not captured from the data returned to the UKHSA for programme monitoring and evaluation. These individuals were kept in the study because all other data was consistent with them having LTBI testing as part of the programme and their region of origin was imputed. The WHO estimated TB incidence in country of origin was imputed as a continuous variable using a truncated regression and transformed as categorical ordinal variable after imputation. The percentage of missing information and the models used to impute each variable is shown in supplementary table S2. All variables used in the estimation of main effects were part of the imputation model, including the effect modification of pre-entry screening and year of arrival in England or primary care registration. The predictor variables and the imputed variables were included in the model iteratively with 10 iterations per missing variable per imputation, the burn-in period was 10 and the seed set at 53421.

We initially performed a complete case analysis using Cox proportional-hazards models, followed by the creation and analysis of 5 imputations. The imputation model was assessed after estimation using the average relative variance increase (RVI), the largest fraction of missing information (FMI) and the Monte Carlo error (MCE) estimate. We used trace plots to assess model converge. The results of the complete case analysis did not differ from those of the data with multiple imputations.

Results and sensitivity analysis

Effectiveness of the LTBI testing and treatment programme

The complete case analysis of the multivariate Cox proportional-hazards models assessing the overall effect of LTBI testing and treatment on time to TB diagnosis is shown in (supplementary table S3). This model included LTBI testing and treatment as time-variant covariate and a significant effect modifications between pre-entry active TB screening and cohort year which estimates from the complete case analysis are shown in the multiplicative scale in (supplementary table S3) and in the additive scale in (supplementary table S4 and supplementary figure S1). The results of the complete case analysis were consistent with those of the analysis with the imputed dataset.

We performed a sensitivity analysis excluding TB cases diagnosed within 60 and 90 days of primary care registration or LTBI testing; 82 TB cases in the group without LTBI testing were diagnosed within 60 days of primary care registration and 66 TB cases in the group with LTBI testing were diagnosed within 60 days of LTBI testing. The unadjusted Kaplan Meier curves (supplementary figure S2 a and b) show that the early effect of increased risk of TB diagnosis in individuals who received an IGRA test persist even after excluding this TB cases. The curves also confirm that the increased risk disappears as time accrues because the curves converge, indicating that the hazard of TB diagnosis is not proportional i.e. the hazard ratio (HR) changes over time. The overall effectiveness of the LTBI testing and treatment programme was lower but still significantly associated with lower risk (hazard) of TB diagnosis (HR 0·82; 95% CI 0·69 - 0·99) and (HR 0·81; 95% CI 0·68 - 0·96) for 60 and 90 days respectively (supplementary tables S5 and S6). The stratified analysis also confirmed that, even if the TB cases diagnosed within 60 and 90 days of primary care registration or LTBI testing are considered prevalent and excluded from the analysis, the intervention has an early effect being associated with higher risk of TB diagnosis during the first 6 months of follow-up (HR 11·14; 95% CI 8·11 - 15·3) and (HR 15·72; 95% CI 10·3 - 23·9), after which time it is associated with a significantly lower risk (HR 0·55; 95% CI 0·38 - 0·77) and (HR 0·56; 95% CI 0·39 - 0·79) for 60 and 90 days respectively (supplementary tables S5 and S6).

We explored the influence of area level variation using a three-level mixed-effects parametric survival-time model with CCG and general practice level random intercepts; for this analysis, we assumed a Log Normal conditional distribution of the response given the random effects. The results of these analysis shown in supplementary table 5 demonstrate that all main effects remained significant despite a significant area level variation at the CCG and general practice level. The parametric model used is an accelerated failure time model, for this type of models the parameter estimates are interpreted as effects on the time scale, which can either accelerate or decelerate survival time. The effect measure used for this type of models is the Time Ratio (TR); if the TR is >1 it means that the factor accelerates survival time or leads to longer survival, in this case longer TB free survival; if the TR is <1 it

means the factor decelerates survival time or leads to shorter survival, shorter TB free survival. The overall effect of LTBI testing and treatment in this model only showed the association between the intervention and shorter TB free survival (TR 0·40 95%CI 0·31-0·52) this is because this model did not include the time-varying effect of the intervention. However, the stratified analysis by follow-up period showed that initially the intervention is associated with shorter TB free survival before six months of follow-up (TR 0·48 95%CI 0·42-0·56), after this time it is associated with longer TB free survival (TR 1·75 95%CI 1·15-2·67) supplementary table S7.

Risk of progression to active tuberculosis in IGRA positive migrants

The unadjusted Kaplan Meier curve in supplementary figure S3a indicated that IGRA- positive individuals who did not start LTBI preventative treatment have increased risk of developing TB than IGRA-negative individuals. This result did not vary when the presence of covariates was accounted for in the adjusted survival function shown in supplementary figure S3b.

The complete case analysis of the multivariate Cox proportional-hazards model assessing the risk of progression to active TB according to IGRA status is shown in supplementary table S8. The results of the complete case analysis were consistent with those of the analysis with the imputed dataset.

The association between IGRA status and risk of being diagnosed with TB was lower in the sensitivity analysis when TB cases diagnosed within 60 and 90 days of primary care registration or LTBI testing were excluded (HR 18·6; 95% CI 11·6 - 29·9) and (HR 14·6; 95% CI 8·97 – 23·7) for 60 and 90 days respectively, supplementary tables S9 and S10.

We explored the influence of area level variation using a three-level mixed-effects parametric survival-time model with CCG and general practice level random intercepts; for this analysis, we assumed a Log Normal conditional distribution of the response given the random effects. The results of this analysis shown in supplementary table S11 demonstrate that all main effects remained significant despite a significant area level variation at the CCG level.

Effectiveness of LTBI treatment

The unadjusted Kaplan Meier curve shown in supplementary figure S4a indicated that IGRA-positive individuals who did not start LTBI preventative treatment have increased risk of developing TB than those who started treatment. This result did not vary when the presence of covariates was accounted for in the adjusted survival function supplementary figure S4b.

The complete case analysis of the multivariate Cox proportional-hazards model assessing the risk of progression to active TB according to LTBI treatment status in IGRA-positive individuals is shown in supplementary table S12. The results of the complete case analysis were consistent with those of the analysis with the imputed dataset in the direction of the association; both showed that IGRA-positive individuals who started LTBI treatment had

lower risk of developing active TB than individuals who did not start treatment. However, the effectiveness of LTBI treatment was higher in the complete case analysis (HR 0·12; 95% CI 0·03 to 0·41) than in the analysis with the imputed dataset (HR 0·14; 95% CI 0·06 to 0·32).

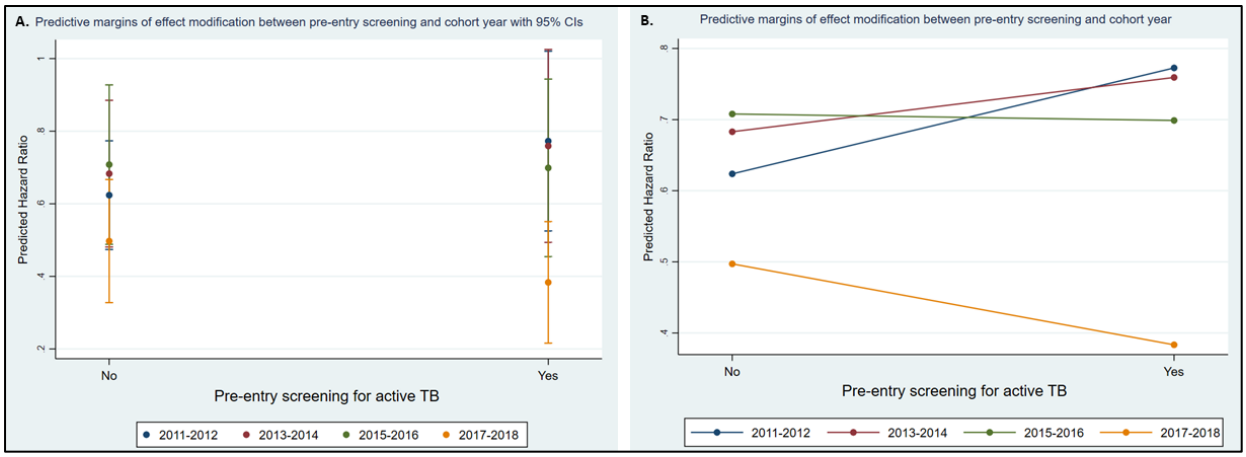
We explored the influence of area level variation using a three-level mixed-effects parametric survival-time model with CCG and general practice level random intercepts; for this analysis, we assumed a Log Normal conditional distribution of the response given the random effects. The results of this analysis shown in supplementary table S13 demonstrate that all main effects remained significant despite a significant area level variation at the CCG level.

Because not all IGRA-positive individuals who started LTBI treatment had a confirmed date of treatment completion, we performed a sensitivity analysis including only individuals with a confirmed date to treatment completion. These results were consistent with those of the complete case analysis and the analysis with the imputed dataset in the direction of the association, however the effectiveness was higher in the complete case (HR 0·13; 95% CI 0·03 to 0·55) and imputed analysis (HR 0·08; 95% CI 0·02 to 0·26) respectively as shown in supplementary tables S14 and S15.

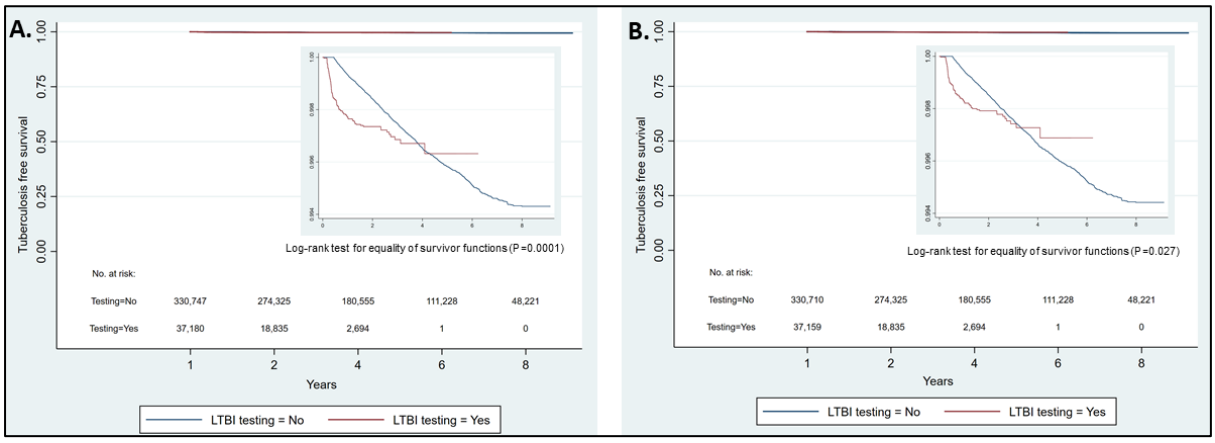
The effectiveness of treatment was lower in the sensitivity analysis when TB cases diagnosed within 60 and 90 days of primary care registration or LTBI testing were excluded. We first performed the analysis using the complete dataset of cases without missing data, this analysis yielded effectiveness of 83% (HR 0·17; 95%CI 0·04-0·77) and 79% (HR 0·21; 95%CI 0·04-0·95) for 60 and 90 days respectively (tables supplementary tables S16 and S17). The parameter estimates of this analysis were used to derive the adjusted numbers needed to treat, these were 33·7 (95%CI 19-48·4) and 34·8 (95%CI 19·8-49·8) for 60 and 90 days respectively (tables supplementary tables S16 and S17). Next, we carried out the analysis with the dataset in which all missing values were imputed, the effectiveness of treatment of 77% (HR 0·23; 95% CI 0·09 - 0·57) and 75% (HR 0·25; 95% CI 0·09 – 0·67) for 60 and 90 days respectively supplementary tables S18 and S19. Thus, although there was variation in treatment effectiveness when these cases were excluded, it did not affect much the adjusted number needed to treat. The reason for this is that the latter value was derived using the parameter estimates of the complete case analysis which results did not varied much from the complete cases analysis when all TB cases were included in the primary analysis. The information on treatment regime, adverse reactions overall and adverse reactions according to treatment regime is shown in supplementary table S20.

Supplementary figures and tables

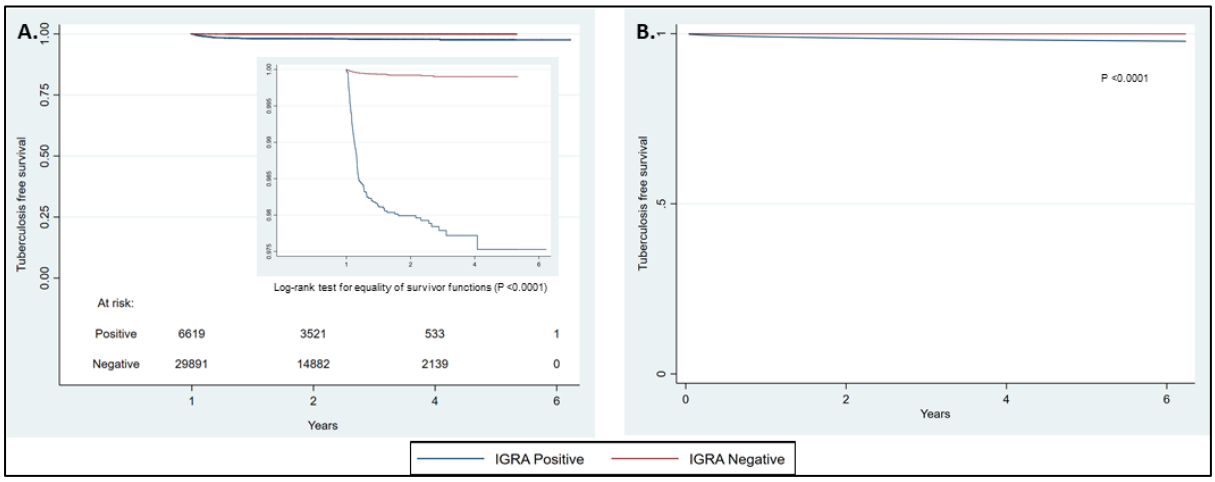
Supplementary figure 1: Marginal effects of effect modification. Plot of marginal effects shown in supplementary table 4 for the effect modification included in the multivariate model 1 of the complete case analysis shown in supplementary table 3. The predictive margins of pre-entry screening by year of arrival in England or primary care registration are shown with and without confidence intervals in A and B respectively.



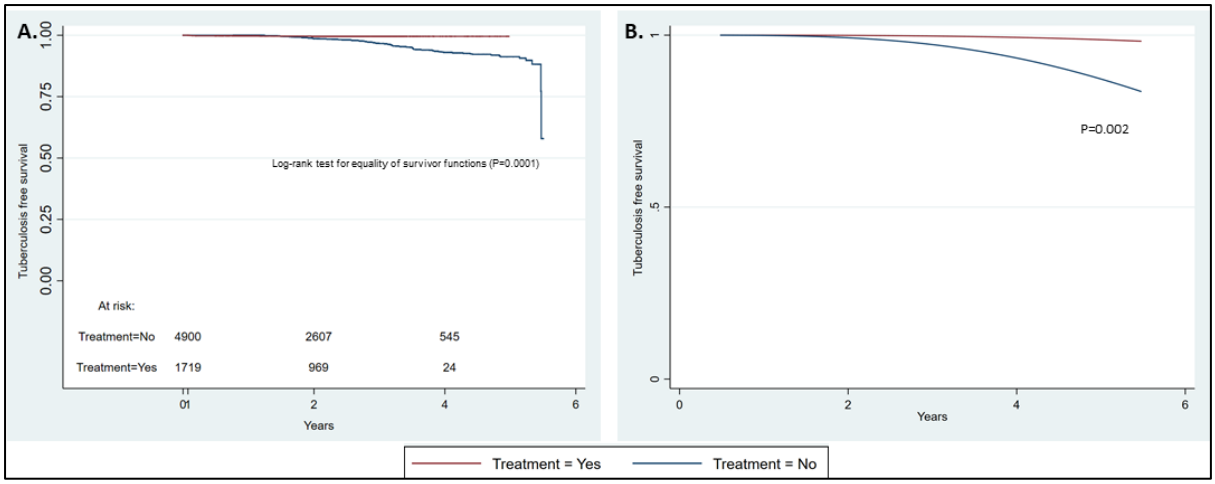
Supplementary figure 2. Unadjusted Kaplan Meier curve comparing TB-free survival between migrants tested and not tested for LTBI. TB-free survival is on the vertical axis and time since starting follow-up is on the horizontal axis. The curve was derived using all study participants excluding those who developed TB within 60 (a) and 90 (b) days of primary care registration or LTBI testing TB and those diagnosed 21 days after starting treatment n=367928 in (a) and 367870 in (b). The inset shows the same data on an enlarged y axis.



Supplementary figure 3: Survival functions for risk of progression according to IGRA status. Unadjusted (A) and adjusted (B) survival functions comparing TB-free survival between IGRA-positive and IGRA-negative individuals that did not start treatment. TB-free survival is on the vertical axis and time since starting follow-up is on the horizontal axis. The adjusted survival function depicted in B was derived after fitting a parametric regression model including all variables shown in supplementary table 6 setting each covariate to its mean value. n= 36510 in A and n=19968 in B.



Supplementary figure 4: Survival functions for risk of progression according to treatment status. Unadjusted (A) and adjusted (B) survival functions comparing TB-free survival between IGRA-positive individuals who did and did not start treatment. TB-free survival is on the vertical axis and time since starting follow-up is on the horizontal axis. The adjusted survival function depicted in B was derived after fitting a parametric regression model including all variables shown in supplementary table 8 setting each covariate to its mean value. n= 6619 in A and n=3804 in B.



256 **Supplementary table S1. Country and region of origin of evaluation participants.**

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Country of origin	WHO tuberculosis incidence (cases per 100000)	All participants (n= 368097)	Intervention Group (n=37268)	Control group (n=330829)
Africa				
Angola	150-349	1534	30	1504
Benin	40-149	222	5	217
Botswana	>350	417	14	403
Burkina Faso	40-149	65	3	62
Burundi	150-349	177	5	172
Cape Verde	150-349	415	11	404
Cameroon	150-349	2213	67	2146
Central African Republic	>350	11	1	10
Chad	150-349	56	3	53
Comoros Islands	40-149	10	0	10
Congo	>350	1383	51	1332
Democratic Republic of Congo	>350	367	42	325
Djibouti	>350	59	3	56
Equatorial Guinea	150-349	156	6	150
Eritrea	40-149	7054	603	6451
Ethiopia	150-349	2548	160	2388
Gabon	>350	84	1	83
Gambia	150-349	1402	91	1311
Ghana	40-149	13073	581	12492
Guinea	150-349	613	25	588
Guinea-Bissau	>350	1199	67	1132
Ivory Coast	150-349	866	13	853
Kenya	150-349	3142	140	3002
Lesotho	>350	21	2	19
Liberia	150-349	188	6	182
Madagascar	150-349	127	1	126
Malawi	150-349	295	15	280
Mali	40-149	2161	64	2097
Mauritania	150-349	54	1	53
Mauritius	40-149	1982	35	1947
Mozambique	>350	262	11	251
Namibia	>350	275	13	262
Niger	150-349	36	2	34
Nigeria	150-349	21322	959	20363
Rwanda	40-149	287	6	281
Sao Tome and Principe	40-149	413	15	398
Senegal	150-349	765	32	733
Seychelles	40-149	131	0	131
Sierra Leone	150-349	1281	35	1246
Somalia	150-349	4419	262	4157
South Africa	>350	12311	208	12103
Sudan	150-349	5511	434	5077
Eswatini	150-349	67	4	63
Tanzania	150-349	1029	36	993
Togo	40-149	133	3	130
Uganda	150-349	1666	94	1572
Zambia	>350	460	22	438
Zimbabwe	>350	2703	117	2586
Americas				
Haiti	150-349	78	1	77
Europe				
Moldova	150-349	10,381	305	9996
East and South East Asia				
Cambodia	>350	246	8	238
East Timor	>350	566	29	537
Indonesia	150-349	4361	129	4232
Kiribati	>350	1	0	1
North Korea	>350	7	0	7
South Korea	150-349	4738	7	4731
Lao People's Democratic Republic	150-349	98	6	93
Marshall Islands	>350	2	0	2

Mongolia	150-349	615	17	598
Myanmar	>350	998	49	949
Papua New Guinea	150-349	45	0	45
Philippines	150-349	8114	221	7893
Thailand	150-349	6595	135	6460
Tuvalu	150-349	2	0	2
Viet Nam	150-349	5	5	0
South Asia				
Afghanistan	150-349	6998	790	6208
Bangladesh	150-349	22909	2506	20403
Bhutan	150-349	57	3	54
India	150-349	121,564	8302	113262
Nepal	150-349	5619	422	5197
Pakistan	150-349	64,404	4302	60,102
Sri Lanka	150-349	7	7	0

Supplementary table S2. Percentage of missing information, variables and models used for multiple imputation.

Variable	Observed n (%)	Missing n (%)	Model
Age group	367880 (99·94)	217 (0·06)	Logistic regression
Sex	367402 (99·81)	695 (0·19)	Logistic regression
ETS region of origin	353388 (96·01)	14709 (3·99)	Augmented multinomial logistic regression
WHO estimated TB incidence in country of origin	353388 (96·01)	14709 (3·99)	Truncated regression
UKHSA estimated TB incidence in CCG area of residence	352881 (95·87)	15216 (4·13)	Ordered logistic regression
Deprivation index	359713 (97·73)	8384 (2·27)	Ordered logistic regression
Year of arrival in England or primary care registration	353388 (96·01)	14709 (3·99)	Augmented ordered logistic regression

Supplementary table S3. Hazard ratios from univariate and multivariate Cox regression models predicting the time to TB diagnosis. ‡ Effect modification is shown in the multiplicative scale using pre-entry active TB screening (yes) as the baseline group n=332579. ¶ Models 2-6 include the same covariates as model 1 and the time-variant effect of LTBI testing and treatment. # Rate per one person-year (95%CI). ETS: Enhanced Tuberculosis Surveillance system, CCG: Clinical Commissioning Group, LTBI: Latent TB infection.

Characteristic	No. of events/ Person-years of Follow-up	Rate per 100000 Person-years (95%CI)	Hazard ratio (95% CI)	P value
Model 1				
Age group — no. (%)				
16 – 25 years	763/946151	80 (75-86)	0·89 (0·80-1·00)	0·056
26 – 35 years	644/691631	93 (86-100)	1·00	
Sex — no. (%)				
Female	791/829162	95 (88-102)	1·00	
Male	619/807301	76 (70-82)	0·79 (0·71-0·88)	<0·0001
ETS region of origin — no. (%)				
Africa	377/423383	89 (80-98)	1·00	
Americas, Europe	0/30893	0	0	
East and South East Asia	50/98843	50 (38-66)	0·61 (0·44-0·85)	0·004
South Asia	912/1051897	86 (81-92)	1·12 (0·94-1·34)	0·017
WHO estimated TB incidence in country of origin (cases per 100 000) — no. (%)				
40-149	187/196673	95 (82-109)	1·00	
150-349	1082/1297870	83 (78-88)	0·68 (0·55-0·85)	0·001
>350	70/110474	63 (50-80)	0·70 (0·52-0·93)	0·017

UKHSA estimated TB incidence in CCG area of residence (cases per 100 000) — no. (%)				
≤ 9·2	119/146624	81 (67-97)	1·00	
9·3-31·6	842/970862	86 (81-92)	1·04 (0·85-1·27)	0·686
> 31·6	408/460358	88 (80-97)	1·10 (0·88-1·37)	0·379
Deprivation index — no. (%)				
1–3 deciles (most deprived)	769/821580	93 (87-100)	1·00	
4–6 deciles	482/583210	82 (75-90)	0·92 (0·81-1·03)	0·181
7–10 deciles (least deprived)	122/196726	62 (51-74)	0·71 (0·58-0·86)	0·001
Year of arrival in England or primary care registration — no. (%)				
2011-2012	475/629979	75 (68-82)	1·00	
2013-2014	335/368239	90 (81-101)	1·11 (0·94-1·31)	0·206
2015-2016	368/362067	101 (91-112)	1·13 (0·95-1·34)	0·058
2017-2018	161/244731	65 (56-76)	0·89 (0·72-1·10)	0·294
Pre-entry active TB screening				
Yes	328/374038	87 (78-97)	1·24 (1·00-1·54)	0·048
No	1084/1264195	85 (80-91)	1·00	
Effect modification: pre-entry screening (Yes)/year of arrival in England or primary care registration[‡]				
2011-2012			1·00	
2013-2014			0·97 (0·72-1·31)	0·892
2015-2016			0·89 (0·66-1·19)	0·459
2017-2018			0·47 (0·32-0·70)	<0·001
Time-variant LTBI testing and treatment				
Yes	165/81002	203 (174-237)	0·78 (0·61-1·00)	0·057
No	1247/1557230	80 (75-84)	1·00	
LTBI testing and treatment by follow-up period				
Model 2¶ < 6 months			7·93 (5·71-11·0)	<0·001
Yes	124/26·6	[#]4·65 (3·90-5·54)		
No	110/42·3	[#]2·59 (2·15-3·13)		
Model 3 > 6 months			0·56 (0·36-0·88)	0·013
Yes	42/80969	51·8 (38·3-70·1)		
No	1170/1557198	75·1 (70·9-79·5)		
Model 4 1 year			0.38 (0.19-0.74)	0.004
Yes	18/76490	23·5 (14·8-37·3)		
No	977/1555582	62·8 (58·9-66·8)		
Model 5 2 years			0·48 (0·20-1·17)	0·108
Yes	8/57548	13·9 (6·95-27·8)		
No	698/1474486	47·3 (43·9-50·9)		
Model 6 3 years			0·32 (0·04-2·30)	0·259
Yes	2/30296	6·6 (1·65-26·4)		
No	464/1352527	34·3 (31·3-37·5)		

Supplementary table S4: Predicted marginal effects of the effect modification between pre-entry active TB screening and year of arrival in England or primary care registration. As included in the main effect multivariate model 1 of the complete case analysis shown in supplementary table 3.

Characteristic	Predicted hazard ratio (95% CI)	P value
Pre-entry active TB screening by year of arrival in England or primary care registration		
Pre-entry No# Cohort year 2011-2012	0·61 (0·47-0·76)	<0·0001
Pre-entry No# Cohort year 2013-2014	0·68 (0·48-0·88)	<0·0001
Pre-entry No# Cohort year 2015-2016	0·72 (0·50-0·95)	<0·0001
Pre-entry No# Cohort year 2017-2018	0·55 (0·36-0·73)	<0·0001
Pre-entry Yes# Cohort year 2011-2012	0·76 (0·52-1·01)	<0·0001
Pre-entry Yes# Cohort year 2013-2014	0·75 (0·49-1·01)	<0·0001
Pre-entry Yes# Cohort year 2015-2016	0·68 (0·44-0·92)	<0·0001
Pre-entry Yes# Cohort year 2017-2018	0·36 (0·20-0·52)	<0·0001

Supplementary table S5. Hazard ratios from multivariate Cox regression model predicting the time to TB diagnosis. * The number of events include only participants with no missing information for that characteristic. § The hazard ratio, 95% CI and p value estimates were derived from the total cohort of migrants, excluding those who developed TB within 60 days of primary care registration or LTBI testing and 21 days after starting treatment n= 367948, after imputing the missing values using a multiple imputation by chained equations model. ‡ Effect modification is shown in the multiplicative scale using pre-entry active TB screening (yes) as the baseline group. ¶ Models 2-6 include the same covariates as model 1 and the time-variant effect of LTBI testing and treatment. # Rate per one person-year (95%CI), ETS: Enhanced Tuberculosis Surveillance system, CCG: Clinical Commissioning Group, LTBI: Latent TB infection.

Characteristic	No. of events/ Person-years of Follow-up*	Rate per 100000 Person-years (95%CI)	Hazard ratio (95% CI) §	P value
Model 1				
Age group — no. (%)				
16 – 25 years	715/946137	75 (70-81)	0·86 (0·77-0·96)	0·010
26 – 35 years	583/691616	84 (77-91)	1·00	
Sex — no. (%)				
Female	731/829144	88 (82-94)	1·00	
Male	568/807288	70 (64-76)	0·81 (0·73-0·90)	<0·0001
ETS region of origin — no. (%)				
Africa	349/423375	82 (74-91)	1·00	
Americas, Europe	0/30893	0	0	
East and South East Asia	46/98842	46 (34-62)	0·67 (0·49-0·92)	0·014
South Asia	857/1051881	81 (76-87)	1·18 (0·96-1·44)	0·105
WHO estimated TB incidence in country of origin (cases per 100 000) — no. (%)				
40-149	174/196668	88 (76-102)	1·00	
150-349	1015/1297852	78 (73-83)	0·63 (0·49-0·81)	0·001
>350	63/110472	57 (44-73)	0·62 (0·46-0·83)	0·002
UKHSA estimated TB incidence in CCG area				

of residence (cases per 100 000) — no. (%)				
≤ 9·2	105/146619	71 (59-86)	1·00	
9·3-31·6	782/970844	80 (75-86)	1·03 (0·83-1·28)	0·762
> 31·6	376/460350	81 (73-90)	1·07 (0·85-1·35)	0·549
Deprivation index — no. (%)				
1–3 deciles (most deprived)	711/821566	86 (80-93)	1·00	
4–6 deciles	442/583200	75 (69-83)	0·89 (0·79-1·01)	0·083
7–10 deciles (least deprived)	117/196724	59 (49-71)	0·73 (0·59-0·90)	0·004
Year of arrival in England or primary care registration — no. (%)				
2011-2012	470/629978	74 (68-81)	1·00	
2013-2014	322/368235	87 (78-97)	1·14 (0·97-1·34)	0·097
2015-2016	324/362054	89 (80-99)	1·07 (0·90-1·27)	0·426
2017-2018	136/244724	55 (46-65)	0·64 (0·51-0·81)	<0·0001
Pre-entry active TB screening				
Yes	305/374032	81 (72-91)	1·26 (1·02-1·55)	0·030
No	995/1264170	78 (73-83)	1·00	
Effect modification: pre-entry screening (Yes)/year of arrival in England or primary care registration[‡]				
2011-2012			1·00	
2013-2014			0·93 (0·69-1·24)	0·629
2015-2016			0·82 (0·62-1·10)	0·199
2017-2018			0·43 (0·28-0·63)	<0·0001
Time-variant LTBI testing and treatment				
Yes	102/80990	125 (103-152)	0·82 (0·69-0·97)	0·023
No	1198/1557211	76 (72-81)	1·00	
LTBI testing and treatment by follow-up period				
Model 2¶ < 6 months				
Yes	69/29·7	[#]2·31 (1·83-2·93)	11·14 (8·11-15·3)	<0·0001
No	72/37·3	[#]1·92 (1·53-2·43)	1·00	
Model 3 > 6 months				
Yes	33/80961	40·7 (28·9-57·3)	0·55 (0·38-0·77)	0·001
No	1126/1557174	72·3 (68·2-76·6)	1·00	
Model 4 1 year				
Yes	18/76490	23·5 (14·8-37·3)	0·42 (0·27-0·66)	<0·0001
No	977/1555582	62·8 (58·9-66·8)	1·00	
Model 5 2 years				
Yes	8/57548	13·9 (6·95-27·8)	0·43 (0·22-0·84)	0·014
No	698/1474486	47·3 (43·9-50·9)	1·00	
Model 6 3 years				
Yes	2/30296	6·60 (1·65-26·4)	0·31 (0·07-1·25)	0·100
No	464/1352527	34·3 (31·3-37·5)	1·00	

Supplementary table S6. Hazard ratios from multivariate Cox regression model predicting the time to TB diagnosis. * The number of events include only participants with no missing information for that characteristic. § The hazard ratio, 95% CI and p value estimates were derived from the total cohort of migrants, excluding those who developed TB within 90 days of primary care registration or LTBI testing and 21 days after starting treatment n= 367883, after imputing the missing values using a multiple imputation by chained equations model. ‡ Effect modification is shown in the multiplicative scale using pre-entry active TB screening (yes) as the baseline group. ¶ Models 2-6 include the same covariates as model 1 and the time-variant effect of LTBI testing and treatment. # Rate per one person-year (95%CI), ETS: Enhanced Tuberculosis Surveillance system, CCG: Clinical Commissioning Group, LTBI: Latent TB infection.

Characteristic	No. of events/ Person-years of Follow-up*	Rate per 100000 Person-years (95%CI)	Hazard ratio (95% CI) §	P value
Model 1				
Age group — no. (%)				
16 – 25 years	695/946130	73 (68-79)	0·88 (0·79-0·99)	0·039
26 – 35 years	546/691601	78 (72-85)	1·00	
Sex — no. (%)				
Female	698/829132	84 (78-90)	1·00	
Male	543/807278	67 (61-73)	0·81 (0·72-0·91)	<0·0001
ETS region of origin — no. (%)				
Africa	331/423368	78 (70-87)	1·00	
Americas, Europe	0/30893	0	0	
East and South East Asia	44/98841	44 (33-59)	0·69 (0·50-0·96)	0·029
South Asia	831/1051870	79 (73-84)	1·20 (0·97-1·48)	0·080
WHO estimated TB incidence in country of origin (cases per 100 000) — no. (%)				
40-149	165/196665	83 (72-97)	1·00	
150-349	981/1297837	75 (71-80)	0·63 (0·48-0·83)	0·002
>350	60/110470	60 (42-69)	0·61 (0·44-0·84)	0·003
UKHSA estimated TB incidence in CCG area of residence (cases per 100 000) — no. (%)				
≤ 9·2	102/146618	69 (57-84)	1·00	
9·3-31·6	744/970828	76 (71-82)	1·02 (0·82-1·27)	0·822
> 31·6	362/460345	78 (70-87)	1·07 (0·84-1·36)	0·573
Deprivation index — no. (%)				
1–3 deciles (most deprived)	682/821555	83 (77-89)	1·00	
4–6 deciles	421/583191	72 (65-79)	0·89 (0·78-1·01)	0·084
7–10 deciles (least deprived)	112/196722	56 (47-68)	0·74 (0·59-0·91)	0·006
Year of arrival in England or primary care registration — no. (%)				
2011-2012	468/629978	74 (67-81)	1·00	
2013-2014	315/368232	85 (76-95)	1·11 (0·94-1·31)	0·186
2015-2016	300/362043	82 (74-92)	0·96 (0·80-1·15)	0·709
2017-2018	123/244718	50 (42-59)	0·60 (0·47-0·76)	<0·0001
Pre-entry active TB screening				
Yes	302/374031	80 (72-90)	1·26 (1·02-1·55)	0·029
No	940/1264148	74 (69-79)	1·00	
Effect modification: pre-entry screening (Yes)/year of arrival in England or primary care registration‡				
2011-2012			1·00	
2013-2014			0·92 (0·69-1·24)	0·604
2015-2016			0·82 (0·61-1·10)	0·193

2017-2018			0·43 (0·28-0·65)	<0·0001
Time-variant LTBI testing and treatment				
Yes	81/80986	100 (80-124)	0·81 (0·68-0·96)	0·018
No	1161/1557194	74 (70-78)	1·00	
LTBI testing and treatment by follow-up period				
Model 2¶ < 6 months				
Yes	48/25·2	[#]1·90(1·43-2·52)	15·72 (10·3-23·9)	<0·0001
No	35/19·5	[#]1·78 (1·28-2·49)	1·00	
Model 3 > 6 months				
Yes	33/80961	40·7 (28·9-57·3)	0·56 (0·39-0·79)	0·001
No	1126/1557174	72·3 (68·2-76·6)	1·00	
Model 4 1 year				
Yes	18/76490	23·5 (14·8-37·3)	0·43 (0·27-0·68)	<0·0001
No	977/1555582	62·8 (58·9-66·8)	1·00	
Model 5 2 years				
Yes	8/57548	13·9 (6·95-27·8)	0·44 (0·22-0·86)	0·017
No	698/1474486	47·3 (43·9-50·9)	1·00	
Model 6 3 years				
Yes	2/30296	6·60 (1·65-26·4)	0·31 (0·07-1·27)	0·105
No	464/1352527	34·3 (31·3-37·5)	1·00	

Supplementary table S7. Time ratios from multivariate parametric Log Normal regression model predicting the time to TB diagnosis. ETS: Enhanced Tuberculosis Surveillance system, CCG: Clinical Commissioning Group, LTBI: Latent TB infection. n=332,398, the model includes 55 CCGs and 3,028 primary care practices.

Characteristic	**Time ratio (95% CI)**	**P value**
Model 1		
Age group — no. (%)		
16 – 25 years	1·13 (0·99-1·28)	0·063
26 – 35 years	1·00	
Sex — no. (%)		
Female	1·00	
Male	1·34 (1·17-1·52)	<0·0001
ETS region of origin — no. (%)		
Africa	1·00	
Americas, Europe	0	
East and South East Asia	1·62 (1·13-2·33)	0·008
South Asia	0·97 (0·80-1·19)	0·835
WHO estimated TB incidence in country of origin (cases per 100 000) — no. (%)		
40-149	1·00	
150-349	1·40 (1·09-1·80)	0·007
>350	1·47 (1·05-2·05)	0·022
UKHSA estimated TB incidence in CCG area of residence (cases per 100 000) — no. (%)		
≤ 9·2	1·00	
9·3-31·6	0·96 (0·74-1·25)	0·804
> 31·6	0·96 (0·71-1·29)	0·796
Deprivation index — no. (%)		
1–3 deciles (most deprived)	1·00	

4–6 deciles	1·04 (0·90-1·21)	0·507
7–10 deciles (least deprived)	1·35 (1·07-1·70)	0·010
Year of arrival in England or primary care registration — no. (%)		
2011-2012	1·00	
2013-2014	0·72 (0·59-0·88)	0·001
2015-2016	0·66 (0·54-0·80)	<0·0001
2017-2018	0·91 (0·72-1·16)	0·476
Pre-entry active TB screening		
Yes	0·74 (0·57-0·97)	0·031
No	1·00	
Effect modification: pre-entry screening (Yes)/year of arrival in England or primary care registration‡		
2011-2012	1·00	
2013-2014	1·22 (0·82-1·84)	0·316
2015-2016	1·43 (0·97-2·10)	0·068
2017-2018	2·03 (1·27-3·24)	0·003
LTBI testing and treatment		
Yes	0·44 (0·33-0·58)	<0·0001
No	1·00	
Area level variance		
CCG	0·005 (0·0007-0·463)	
General practice	0·320 (0·209-0·491)	
Model Likelihood-ratio test	<0·0001	
LTBI testing and treatment by follow-up period		
Model 2¶ < 6 months	0·39 (0·32-0·47)	<0·0001
Model 3 > 6 months	1·52 (1·03-2·24)	0·032
Model 4 1 year	1·78 (1·11-2·87)	0·016
Model 5 2 year	1·31 (0·78-2·23)	0·301

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312 **Supplementary table S8. Hazard ratios from multivariate Cox regression model predicting the time to TB**
313 **diagnosis according to IGRA status.** *The number of events include only participants with no missing
314 information for that characteristic. § The hazard ratio, 95% CI and p value estimates were derived from the total
315 cohort of IGRA-positive individuals who did not start LTBI treatment n=19968. Individuals with IGRA results
316 indeterminate or with no results were excluded. ETS: Enhanced Tuberculosis Surveillance system, CCG: Clinical
317 Commissioning Group, LTBI: Latent TB infection

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Characteristic	**No. of events/ Person-years of Follow-up***	**Rate per 100000 Person-years (95%CI)**	**§Hazard ratio (95% CI)**	**P value**
IGRA status				
Positive	128/10684	1190 (1000-1420)	29·1 (14·4-59·0)	<0·0001
Negative	24/64537	37 (24-55)	1·00	
Age group — no. (%)				
16 – 25 years	62/33747	183 (143-235)	1·24 (0·77-1·99)	0·367
26 – 35 years	97/42849	226 (185-276)	1·00	
Sex — no. (%)				
Female	94/33899	277 (226-339)	1·00	
Male	63/41010	153 (120-196)	0·81 (0·51-1·29)	0·386
ETS region of origin — no. (%)				
Africa	24/7598	315 (211-471)	1·00	
Americas, Europe	0/614	0	0	

East and South East Asia	2/1045	191 (478-764)	0·34 (0·04-2·85)	0·321
South Asia	58/35394	163 (126-211)	1·01 (0·47-2·19)	0·964
WHO estimated TB incidence in country of origin (cases per 100000) — no. (%)				
40-149	12/3·856	311 (176-547)	1·00	
150-349	67/39690	168 (132-214)	0·69 (0·26-1·82)	0·463
>350	5/1106	451 (188-1080)	1·62 (0·46-5·65)	0·444
UKHSA estimated TB incidence in CCG area of residence (cases per 100000) — no. (%)				
≤ 9·2	8/5668	141 (70-282)	1·00	
9·3-31·6	61/25554	238 (185-306)	1·38 (0·53-3·59)	0·497
> 31·6	69/37733	182 (144-231)	1·18 (0·44-3·12)	0·734
Deprivation index — no. (%)				
1–3 deciles (most deprived)	91/45531	199 (162-245)	1·00	
4–6 deciles	50/23543	212 (160-280)	1·56 (0·95-2·56)	0·077
7–10 deciles (least deprived)	11/4965	221 (122-400)	0·85 (0·26-2·76)	0·790
Year of arrival in England or primary care registration — no. (%)				
2011-2012	12/4684	256 (145-451)	1·00	
2013-2014	16/6923	231 (141-377)	1·01 (0·47-2·15)	0·969
2015-2016	32/17123	186 (132-264)	0·59 (0·29-1·19)	0·145
2017-2018	24/15921	150 (101-224)	0·35 (0·17-0·73)	0·005

Supplementary table S9. Hazard ratios from multivariate Cox regression model predicting the time to TB diagnosis according to IGRA status. *The number of events include only participants with no missing information for that characteristic. § The hazard ratio, 95% CI and p value estimates were derived from the total cohort of migrants with positive IGRA that did not start LTBI treatment, excluding those who developed TB within 60 days of primary care registration or LTBI testing after imputing the missing values using a multiple imputation by chained equations model n=34740. Migrants with IGRA results indeterminate or with no results were excluded. ETS: Enhanced Tuberculosis Surveillance system, CCG: Clinical Commissioning Group, LTBI: Latent TB infection.

Characteristic	**No. of events/ Person-years of Follow-up***	**Rate per 100000 Person-years (95%CI)**	**Hazard ratio (95% CI) §**	**P value**
IGRA status				
Positive	76/10680	711 (568-890)	18·6 (11·6-29·8)	<0·0001
Negative	17/64536	26·3 (16·3-42·3)	1·00	
Age group — no. (%)				
16 – 25 years	43/33745	127 (94·5-171)	1·20 (0·79-1·81)	0·377
26 – 35 years	53/42846	123 (94·5-161)	1·00	
Sex — no. (%)				
Female	55/33896	162 (124-211)	1·00	
Male	40/41008	97·5 (71·5-132)	0·66 (0·44-0·99)	0·047
ETS region of origin — no. (%)				
Africa	17/7597	223 (139-359)	1·00	
Americas, Europe	0/614	0	0	

East and South East Asia	1/1045	95·6 (134-679)	0·86 (0·11-6·69)	0·886
South Asia	32/35392	90·4 (63·9-127)	0·76 (0·29-1·98)	0·542
WHO estimated TB incidence in country of origin (cases per 100000) — no. (%)				
40-149	12/3856	259 (139-481)	1·00	
150-349	39/39687	98·2 (71·8-134)	0·61 (0·24-1·59)	0·284
>350	1/1106	90·4 (12·7-641)	0·41 (0·08-1·93)	0·252
UKHSA estimated TB incidence in CCG area of residence (cases per 100000) — no. (%)				
≤ 9·2	6/5668	105 (47·5-235)	1·00	
9·3-31·6	31/25552	121 (85·3-172)	1·34 (0·55-3·24)	0·509
> 31·6	46/37731	121 (91·3-162)	0·97 (0·38-2·46)	0·963
Deprivation index — no. (%)				
1–3 deciles (most deprived)	57/45528	125 (96·5-162)	1·00	
4–6 deciles	29/23541	123 (85·6-177)	0·95 (0·60-1·49)	0·835
7–10 deciles (least deprived)	7/4965	140 (67·2-295)	1·24 (0·56-2·77)	0·588
Year of arrival in England or primary care registration — no. (%)				
2011-2012	6/4684	128 (57·5-285)	1·00	
2013-2014	13/6923	187 (109-323)	2·29 (0·91-5·76)	0·076
2015-2016	18/17122	105 (66·2-166)	0·81 (0·35-1·86)	0·623
2017-2018	13/15920	81·6 (47·4-140)	0·22 (0·08-0·60)	0·003

Supplementary table S10. Hazard ratios from multivariate Cox regression model predicting the time to TB diagnosis according to IGRA status. *The number of events include only participants with no missing information for that characteristic. § The hazard ratio, 95% CI and p value estimates were derived from the total cohort of migrants with positive IGRA that did not start LTBI treatment, excluding those who developed TB within 90 days of primary care registration or LTBI testing after imputing the missing values using a multiple imputation by chained equations model n=34724. Migrants with IGRA results indeterminate or with no results were excluded. ETS: Enhanced Tuberculosis Surveillance system, CCG: Clinical Commissioning Group, LTBI: Latent TB infection.

Characteristic	**No. of events/ Person-years of Follow-up***	**Rate per 100000 Person-years (95%CI)**	**Hazard ratio (95% CI) §**	**P value**
IGRA status				
Positive	60/10677	561 (436-723)	14·6 (8·97-23·7)	<0·0001
Negative	14/64535	21·6 (12·8-36·6)	1·00	
Age group — no. (%)				
16 – 25 years	34/33743	100 (72-141)	1·15 (0·73-1·80)	0·526
26 – 35 years	42/42843	98 (72·4-132)	1·00	
Sex — no. (%)				
Female	41/33893	120 (89-164)	1·00	
Male	34/41007	82·9 (59·2-116)	0·70 (0·45-1·09)	0·122
ETS region of origin — no. (%)				
Africa	13/7597	171 (99·3-294)	1·00	
Americas, Europe	0/614	0	0	

East and South East Asia	1/1045	95·6 (13·4-679)	0·99 (0·13-7·31)	1·00
South Asia	28/35391	79·1 (54·6-114)	0·74 (0·27-1·97)	0·514
WHO estimated TB incidence in country of origin (cases per 100000) — no. (%)				
40-149	7/3855	181 (86·5-380)	1·00	
150-349	34/39686	85·6 (61·2-119)	0·70 (0·21-2·29)	0·514
>350	1/1106	90·4 (12·7-641)	0·39 (0·05-3·13)	0·364
UKHSA estimated TB incidence in CCG area of residence (cases per 100000) — no. (%)				
≤ 9·2	5/5668	88·2 (36·7-211)	1·00	
9·3-31·6	22/25550	86·1 (56·7-130)	1·33 (0·51-3·45)	0·555
> 31·6	38/37729	100 (73·2-138)	0·98 (0·35-2·73)	0·978
Deprivation index — no. (%)				
1–3 deciles (most deprived)	45/45525	98·8 (73·8-132)	1·00	
4–6 deciles	25/23540	106 (71·7-157)	1·07 (0·65-1·73)	0·783
7–10 deciles (least deprived)	4/4964	80·5 (30·2-214)	1·32 (0·55-3·15)	0·531
Year of arrival in England or primary care registration — no. (%)				
2011-2012	4/4684	85·3 (32-227)	1·00	
2013-2014	11/6922	158 (87·9-286)	2·34 (0·86-6·36)	0·095
2015-2016	15/17121	87·6 (52·8-145)	0·73 (0·28-1·86)	0·513
2017-2018	12/15919	75·3 (42·8-132)	0·24 (0·08-0·69)	0·008

Supplementary table S11. Time ratios from multivariate parametric Log Normal regression model predicting the time to TB diagnosis according to IGRA status. ETS: Enhanced Tuberculosis Surveillance system, CCG: Clinical Commissioning Group, LTBI: Latent TB infection. n=19968, the model includes 55 CCGs.

Characteristic	**Time ratio (95% CI)**	**P value**
IGRA status		
Positive	0·001 (0·0002-0·008)	<0·0001
Negative	1·00	
Age group — no. (%)		
16 – 25 years	0·74 (0·26-2·14)	0·590
26 – 35 years	1·00	
Sex — no. (%)		
Female	1·00	
Male	1·57 (0·56-4·38)	0·383
ETS region of origin — no. (%)		
Africa	1·00	
Americas, Europe	0	
East and South East Asia	11·05 (0·10-1144)	0·310
South Asia	1·14 (0·21-6·21)	0·877
WHO estimated TB incidence in country of origin (cases per 100 000) — no. (%)		
40-149	1·00	
150-349	1·70 (0·19-15·28)	0·634
>350	0·23 (0·01-4·56)	0·338
UKHSA estimated TB incidence in CCG area of residence (cases per 100 000) — no. (%)		
≤ 9·2	1·00	
9·3-31·6	0·55 (0·03-7·73)	0·660
> 31·6	0·39 (0·02-7·47)	0·534
Deprivation index — no. (%)		
1–3 deciles (most deprived)	1·00	
4–6 deciles	0·43 (0·13-1·44)	0·175
7–10 deciles (least deprived)	1·53 (0·12-18·76)	0·739
Year of arrival in England or primary care registration — no. (%)		

2011-2012	1·00	
2013-2014	1·03 (0·17-6·03)	0·969
2015-2016	2·69 (0·52-13·8)	0·235
2017-2018	6·73 (1·20-37·69)	0·030
Area level variance		
CCG	2·82 (0·79-10·06)	
Model Likelihood-ratio test	0·008	

Supplementary table S12. Hazard ratios from multivariate Cox regression model predicting the time to TB diagnosis according to treatment status. *The number of events include only participants with no missing information for that characteristic. § The hazard ratio, 95% CI and p value estimates were derived from the total cohort IGRA-positive individuals with no missing values n=3,812. ETS: Enhanced Tuberculosis Surveillance system, CCG: Clinical Commissioning Group, LTBI: Latent TB infection

Characteristic	**No. of events/ Person-years of Follow-up***	**Rate per 1000 Person-years (95%CI)**	**Hazard ratio (95% CI) §**	**P value**
Treatment				
Yes	7/3728	187 (89-393)	0·12 (0·03-0·41)	0·001
No	128/11742	1090 (916-1296)	1·00	
Age group — no. (%)				
16 – 25 years	50/4892	1020 (774-1340)	1·23 (0·74-2·05)	0·418
26 – 35 years	83/10218	812 (655-1007)	1·00	
Sex — no. (%)				
Female	80/7747	1032 (829-1280)	1·00	
Male	53/7415	714 (546-935)	0·86 (0·52-1·42)	0·568
ETS region of origin — no. (%)				
Africa	21/2323	903 (589-1380)	1·00	
Americas, Europe	0/68·51	0	0	
East and South East Asia	2/258	772 (193-3080)	0·43 (0·05-3·65)	0·441
South Asia	52/6845	759 (578-996)	0·99 (0·44-2·26)	0·999
WHO estimated TB incidence in country of origin (cases per 100 000) — no. (%)				
40-149	9/988	910 (473-1750)	1·00	
150-349	61/8157	747 (581-961)	0·83 (0·28-2·39)	0·736
>350	5/351	1420 (592-3410)	2·21 (0·60-8·14)	0·231
UKHSA estimated TB incidence in CCG area of residence (cases per 100 000) — no. (%)				
≤ 9·2	8/1176	680 (340-1360)	1·00	
9·3-31·6	54/5461	988 (757-1290)	1·41 (0·54-3·68)	0·474
> 31·6	53/7373	718 (549-940)	0·47 (0·17-1·28)	0·143
Deprivation index — no. (%)				
1–3 deciles (most deprived)	80/9246	865 (694-1070)	1·00	
4–6 deciles	39/4574	852 (622-1160)	1.47 (0.87-2.49)	0.143
7–10 deciles (least deprived)	9/858	1040 (545-2010)	0.55 (0.13-2.35)	0.426
Year of arrival in England or primary care registration — no. (%)				
2011-2012	12/978	1220 (696-2150)	1·00	
2013-2014	15/1438	1042 (628-1730)	1·00 (0·45-2·25)	0·938
2015-2016	29/3844	754 (524-1080)	0·73 (0·34-1·55)	0·416
2017-2018	19/3235	587 (374-920)	1·50 (0·64-3·50)	0·348

Supplementary table S13. Time ratios from multivariate parametric Log Normal regression model predicting the time to TB diagnosis according to treatment status. ETS: Enhanced Tuberculosis Surveillance system, CCG: Clinical Commissioning Group, LTBI: Latent TB infection. n=3812, the model includes 55 CCGs.

Characteristic	Time ratio (95% CI)	P value
Treatment		
Yes	1·78 (1·24-2·56)	0·002
No	1·00	
Age group — no. (%)		
16 – 25 years	0·95 (0·78-1·16)	0·666
26 – 35 years	1·00	
Sex — no. (%)		
Female	1·00	
Male	1·03 (0·85-1·25)	0·715
ETS region of origin — no. (%)		
Africa	1·00	
Americas, Europe	0	
East and South East Asia	1·48 (0·61-3·60)	0·378
South Asia	0·97 (0·70-1·33)	0·851
WHO estimated TB incidence in country of origin (cases per 100 000) — no. (%)		
40-149	1·00	
150-349	0·98 (0·64-1·51)	0·940
>350	0·69 (0·38-1·23)	0·217
UKHSA estimated TB incidence in CCG area of residence (cases per 100 000) — no. (%)		
≤ 9·2	1·00	
9·3-31·6	0·85 (0·54-1·35)	0·514
> 31·6	1·09 (0·65-1·82)	0·732
Deprivation index — no. (%)		
1–3 deciles (most deprived)	1·00	
4–6 deciles	0·92 (0·74-1·16)	0·509
7–10 deciles (least deprived)	1·31 (0·76-2·24)	0·324
Year of arrival in England or primary care registration — no. (%)		
2011-2012	1·00	
2013-2014	1·03 (0·74-1·43)	0·852
2015-2016	1·20 (0·88-1·63)	0·234
2017-2018	1·00 (0·73-1·37)	0·984
Area level variance		
CCG	0·06 (0·01-0·29)	
Model Likelihood-ratio test	0·024	

Supplementary table S14. Hazard ratios from multivariate Cox regression model predicting the time to TB diagnosis according to treatment status in individuals with documented date of treatment completion derived from complete case analysis. § The hazard ratio, 95% CI and p value estimates were derived from the total cohort of IGRA-positive individuals with confirmed date of treatment completion and no missing values n=3400. ETS: Enhanced Tuberculosis Surveillance system, CCG: Clinical Commissioning Group, LTBI: Latent TB infection

Characteristic	Hazard ratio (95% CI) §	P value
Treatment		
Yes	0·13 (0·03-0·55)	0·006
No	1·00	
Age group — no. (%)		
16 – 25 years	1·29 (0·77-2·15)	0·327
26 – 35 years	1·00	
Sex — no. (%)		
Female	1·00	
Male	0·89 (0·53-1·47)	0·656
ETS region of origin — no. (%)		

Africa	1·00	
Americas, Europe	0	
East and South East Asia	0·44 (0·05-3·74)	0·453
South Asia	0·96 (0·42-2·19)	0·932
WHO estimated TB incidence in country of origin (cases per 100 000) — no. (%)		
40-149	1·00	
150-349	0·82 (0·28-2·38)	0·728
>350	2·17 (0·58-7·99)	0·244
UKHSA estimated TB incidence in CCG area of residence (cases per 100 000) — no. (%)		
≤ 9·2	1·00	
9·3-31·6	1·41 (0·54-3·69)	0·473
> 31·6	0·47 (0·17-1·29)	0·147
Deprivation index — no. (%)		
1–3 deciles (most deprived)	1·00	
4–6 deciles	1·51 (0·89-2·56)	0·123
7–10 deciles (least deprived)	0·56 (0·13-2·36)	0·431
Year of arrival in England or primary care registration — no. (%)		
2011-2012	1·00	
2013-2014	1·11 (0·48-2·54)	0·800
2015-2016	0·81 (0·37-1·78)	0·611
2017-2018	1·74 (0·72-4·16)	0·213

Supplementary table S15. Hazard ratios from multivariate Cox regression model predicting the time to TB diagnosis according to treatment status in individuals with documented date of treatment completion. § The hazard ratio, 95% CI and p value estimates were derived from the total cohort of IGRA-positive individuals with confirmed date of treatment completion and imputed data for missing values n=5878. ETS: Enhanced Tuberculosis Surveillance system, CCG: Clinical Commissioning Group, LTBI: Latent TB infection.

Characteristic	**Hazard ratio (95% CI) §**	**P value**
Treatment		
Yes	0·08 (0·02-0·26)	<0·0001
No	1·00	
Age group — no. (%)		
16 – 25 years	1·15 (0·80-1·66)	0·438
26 – 35 years	1·00	
Sex — no. (%)		
Female	1·00	
Male	0·70 (0·49-1·00)	0·051
ETS region of origin — no. (%)		
Africa	1·00	
Americas, Europe	0	
East and South East Asia	0·89 (0·19-4·09)	0·886
South Asia	0·91 (0·45-1·82)	0·777
WHO estimated TB incidence in country of origin (cases per 100 000) — no. (%)		
40-149	1·00	
150-349	0·74 (0·39-1·41)	0·357
>350	0·96 (0·31-3·01)	0·954

UKHSA estimated TB incidence in CCG area of residence (cases per 100 000) — no. (%)		
≤ 9·2	1·00	
9·3-31·6	1·57 (0·72-3·39)	0·247
> 31·6	0·86 (0·40-1·86)	0·709
Deprivation index — no. (%)		
1–3 deciles (most deprived)	1·00	
4–6 deciles	1·02 (0·67-1·54)	0·905
7–10 deciles (least deprived)	1·16 (0·57-2·33)	0·677
Year of arrival in England or primary care registration — no. (%)		
2011-2012	1·00	
2013-2014	1·48 (0·74-2·96)	0·266
2015-2016	0·76 (0·40-1·44)	0·407
2017-2018	0·21 (0·10-0·46)	<0·0001

Supplementary table S16. Hazard ratios from multivariate Cox regression model predicting the time to TB diagnosis according to treatment status. *The number of events include only participants with no missing information for that characteristic. § The hazard ratio, 95% CI and p value estimates were derived from the total cohort IGRA-positive individuals with no missing values excluding those who developed TB within 60 days of primary care registration or LTBI testing and 21 days after starting treatment n=3785. ETS: Enhanced Tuberculosis Surveillance system, CCG: Clinical Commissioning Group, LTBI: Latent TB infection

Characteristic	**No. of events/ Person-years of Follow-up***	**Rate per 1000 Person-years (95%CI)**	**Hazard ratio (95% CI) §**	**P value**
Treatment				
Yes	6/3728	160 (72·3-358)	0·17 (0·04-0·77)	0·021
No	76/11616	654 (522-819)	1·00	
Age group — no. (%)				
16 – 25 years	34/4855	700 (500-980)	2·08 (1·05-4·10)	0·033
26 – 35 years	46/10129	454 (340-606)	1·00	
Sex — no. (%)				
Female	47/7668	612 (460-815)	1·00	
Male	34/7370	461 (329-645)	0·95 (0·49-1·85)	0·898
ETS region of origin — no. (%)				
Africa	14/2305	607 (359-1025)	1·00	
Americas, Europe	0/68·51	0	0	
East and South East Asia	1/255	390 (55-2774)	0	0
South Asia	28/6791	412 (284-597)	0·70 (0·26-1·88)	0·485
WHO estimated TB incidence in country of origin (cases per 100 000) — no. (%)				
40-149	7/982	712 (339-1493)	1·00	
150-349	35/8097	432 (310-601)	0·93 (0·26-3·25)	0·913
>350	1/340	293 (41·3-2084)	1·08 (0·12-9·33)	0·944
UKHSA estimated TB incidence in CCG area of residence (cases per 100 000) — no. (%)				
≤ 9·2	6/1169	513 (230-1142)	1·00	
9·3-31·6	29/5413	535 (372-770)	0·81 (0·26-2·50)	0·722
> 31·6	35/7324	477 (343-665)	0·36 (0·11-1·17)	0·092
Deprivation index — no. (%)				
1–3 deciles (most deprived)	52/9175	566 (431-743)	1·00	
4–6 deciles	21/4536	462 (301-710)	1·33 (0·65-2·70)	0·421

7–10 deciles (least deprived)	5/848	589 (245-1416)	0·53 (0·07-4·03)	0·546
Year of arrival in England or primary care registration — no. (%)				
2011-2012	5/963	519 (216-1247)	1·00	
2013-2014	13/1432	907 (526-1562)	1·96 (0·68-5·64)	0·212
2015-2016	16/3808	420 (257-685)	0·67 (0·22-2·01)	0·483
2017-2018	9/3216	279 (145-537)	0·43 (0·14-1·33)	0·146
	Adjusted number needed to treat at 2 years (95%CI)	Adjusted number needed to treat at 3 years (95%CI)		
	33·7 (19-48·4)	28·6 (9·8-47·4)		

Supplementary table S17. Hazard ratios from multivariate Cox regression model predicting the time to TB diagnosis according to treatment status. *The number of events include only participants with no missing information for that characteristic. § The hazard ratio, 95% CI and p value estimates were derived from the total cohort IGRA-positive individuals with no missing values excluding those who developed TB within 90 days of primary care registration or LTBI testing and 21 days after starting treatment n=3779. ETS: Enhanced Tuberculosis Surveillance system, CCG: Clinical Commissioning Group, LTBI: Latent TB infection

Characteristic	**No. of events/ Person-years of Follow-up***	**Rate per 1000 Person-years (95%CI)**	**Hazard ratio (95% CI) §**	**P value**
Treatment				
Yes	5/3728	134 (55·8-322)	0·21 (0·04-0·95)	0·044
No	60/11571	518 (402-667)	1·00	
Age group — no. (%)				
16 – 25 years	27/4835	558 (382-814)	2·01 (0·96-4·20)	0·063
26 – 35 years	37/10104	366 (265-505)	1·00	
Sex — no. (%)				
Female	36/7638	471 (339-653)	1·00	
Male	28/7355	380 (262-551)	1·08 (0·52-2·24)	0·817
ETS region of origin — no. (%)				
Africa	10/2297	435 (234-808)	1·00	
Americas, Europe	0/68·51	0	0	
East and South East Asia	1/255	390 (550-2774)	0	0
South Asia	24/6780	353 (273-528)	0·59 (0·21-1·63)	0·314
WHO estimated TB incidence in country of origin (cases per 100 000) — no. (%)				
40-149	4/974	410 (154-1093)	1·00	
150-349	30/8086	370 (259-530)	1·54 (0·36-6·52)	0·554
>350	1/340	293 (41·3-2084)	1·80 (0·18-17·5)	0·610
UKHSA estimated TB incidence in CCG area of residence (cases per 100 000) — no. (%)				
≤ 9·2	5/1166	428 (178-1030)	1·00	
9·3-31·6	22/5396	407 (268-619)	0·65 (0·20-2·08)	0·477
> 31·6	28/7304	383 (264-555)	0·28 (0·08-0·94)	0·040
Deprivation index — no. (%)				
1–3 deciles (most deprived)	40/9142	437 (320-596)	1·00	
4–6 deciles	18/4531	397 (250-630)	1·49 (0·70-3·17)	0·294
7–10 deciles (least deprived)	4/844	473 (177-1261)	0	0
Year of arrival in England or primary care registration — no. (%)				
2011-2012	4/960	416 (156-1109)	1·00	
2013-2014	10/1428	700 (376-1301)	2·05 (0·63-6·69)	0·230
2015-2016	13/3798	342 (198-589)	0·81 (0·23-2·83)	0·753

2017-2018	8/3214	248 (124-497)	2·54 (0·66-9·75)	0·172
	Adjusted number needed to treat at 2 years (95%CI)	Adjusted number needed to treat at 3 years (95%CI)		
	34·8 (19·8-49·8)	30·3 (12·7-47·8)		

Supplementary table S18. Hazard ratios from multivariate Cox regression model predicting the time to TB diagnosis according to treatment status. *The number of events include only participants with no missing information for that characteristic. § The hazard ratio, 95% CI and p value estimates were derived from the total cohort of migrants with positive IGRA, excluding those who developed TB within 60 days of primary care registration or LTBI testing and 21 days after starting treatment, after imputing the missing values by multiple imputation by chained equations n=6567. ETS: Enhanced Tuberculosis Surveillance system, CCG: Clinical Commissioning Group, LTBI: Latent TB infection.

Characteristic	**No. of events/ Person-years of Follow-up***	**Rate per 100000 Person-years (95%CI)**	**Hazard ratio (95% CI) §**	**P value**
Treatment				
Yes	6/3728	160 (72·3-358)	0·23 (0·09-0·57)	0·001
No	76/11616	654 (522-819)	1·00	
Age group — no. (%)				
16 – 25 years	34/4855	700 (500-980)	1·61 (1·01-2·57)	0·044
26 – 35 years	46/10129	454 (340-606)	1·00	
Sex — no. (%)				
Female	47/7668	612 (460-815)	1·00	
Male	34/7370	461 (329-645)	0·75 (0·48-1·17)	0·216
ETS region of origin — no. (%)				
Africa	14/2305	607 (359-1025)	1·00	
Americas, Europe	0/68·51	0	0	
East and South East Asia	1/255	390 (55-2774)	1·17 (0·14-9·89)	0·875
South Asia	28/6791	412 (284-597)	0·78 (0·32-1·87)	0·555
WHO estimated TB incidence in country of origin (cases per 100 000) — no. (%)				
40-149	7/982	712 (339-1493)	1·00	
150-349	35/8097	432 (310-601)	0·66 (0·32-1·34)	0·242
>350	1/340	293 (41·3-2084)	0·51 (0·07-3·57)	0·477
UKHSA estimated TB incidence in CCG area of residence (cases per 100 000) — no. (%)				
≤ 9·2	6/1169	513 (230-1142)	1·00	
9·3-31·6	29/5413	535 (372-770)	1·19 (0·48-2·94)	0·697
> 31·6	35/7324	477 (343-665)	0·54 (0·20-1·45)	0·224
Deprivation index — no. (%)				
1–3 deciles (most deprived)	52/9175	566 (431-743)	1·00	
4–6 deciles	21/4536	462 (301-710)	0·98 (0·58-1·65)	0·942
7–10 deciles (least deprived)	5/848	589 (245-1416)	1·08 (0·41-2·86)	0·868
Year of arrival in England or primary care registration — no. (%)				

2011-2012	5/963	519 (216-1247)	1·00	
2013-2014	13/1432	907 (526-1562)	1·99 (0·75-5·33)	0·165
2015-2016	16/3808	420 (257-685)	1·12 (0·45-2·80)	0·794
2017-2018	9/3216	279 (145-537)	1·24 (0·40-3·82)	0·699

Supplementary table S19. Hazard ratios from multivariate Cox regression model predicting the time to TB diagnosis according to treatment status. *The number of events include only participants with no missing information for that characteristic. § The hazard ratio, 95% CI and p value estimates were derived from the total cohort of migrants with positive IGRA, excluding those who developed TB within 90 days of primary care registration or LTBI testing and 21 days after starting treatment, after imputing the missing values by multiple imputation by chained equations n=6550. ETS: Enhanced Tuberculosis Surveillance system, CCG: Clinical Commissioning Group, LTBI: Latent TB infection.

Characteristic	**No. of events/ Person-years of Follow-up***	**Rate per 100000 Person-years (95%CI)**	**Hazard ratio (95% CI) §**	**P value**
Treatment				
Yes	5/3728	134 (55·8-322)	0·25 (0·09-0·67)	0·006
No	60/11571	518 (402-667)	1·00	
Age group — no. (%)				
16 – 25 years	27/4835	558 (382-814)	1·60 (0·96-2·68)	0·070
26 – 35 years	37/10104	366 (265-505)	1·00	
Sex — no. (%)				
Female	36/7638	471 (339-653)	1·00	
Male	28/7355	380 (262-551)	0·80 (0·48-1·32)	0·389
ETS region of origin — no. (%)				
Africa	10/2·297	435 (234-808)	1·00	
Americas, Europe	0/68·51	0	0	
East and South East Asia	1/255	390 (550-2774)	1·53 (0·18-12·3)	0·682
South Asia	24/6780	353 (273-528)	0·81 (0·32-2·05)	0·648
WHO estimated TB incidence in country of origin (cases per 100 000) — no. (%)				
40-149	4/974	410 (154-1093)	1·00	
150-349	30/8086	370 (259-530)	0·76 (0·30-1·92)	0·558
>350	1/340	293 (41·3-2084)	0·49 (0·02-9·27)	0·611
UKHSA estimated TB incidence in CCG area of residence (cases per 100 000) — no. (%)				
≤ 9·2	5/1166	428 (178-1030)	1·00	
9·3-31·6	22/5396	407 (268-619)	1·08 (0·41-2·88)	0·866
> 31·6	28/7304	383 (264-555)	0·50 (0·16-1·51)	0·221
Deprivation index — no. (%)				
1–3 deciles (most deprived)	40/9142	437 (320-596)	1·00	
4–6 deciles	18/4531	397 (250-630)	1·04 (0·58-1·87)	0·879
7–10 deciles (least deprived)	4/844	473 (177-1261)	1·07 (0·35-3·23)	0·901
Year of arrival in England or primary care registration — no. (%)				
2011-2012	4/960	416 (156-1109)	1·00	

2013-2014	10/1428	700 (376-1301)	2·01 (0·66-6·11)	0·214
2015-2016	13/3798	342 (198-589)	1·03 (0·37-2·87)	0·944
2017-2018	8/3214	248 (124-497)	1·30 (0·38-4·42)	0·673

Supplementary table S20. Treatment regime and adverse reactions

Treatment regime	n (%)	Adverse reactions n (rate per 100)	Hepatotoxicity n (rate per 100)
3 months Rifinah	1564 (97·75)	59 (3·77)	5 (0·31)
6 months isoniazid	34 (2·13)	15 (44·11)	6 (17·6)
4 months rifampicin	2 (0·13)	0	0
Total	1600	74 (4·62)	11 (0·68)

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