Diabetes mellitus and latent tuberculosis infection: cross-sectional study within a large UK cohort

Supplementary information

Supplementary methods

The study protocol is available at: http://www.nets.nihr.ac.uk/projects/hta/086801.

Recruitment

Individuals aged ≥16 years were invited to take part in the study through two strategies targeting high-risk groups between January 2011 and July 2015. Firstly, contacts of active TB cases ("contacts") were invited to participate when attending appointments for TB screening (contacts are screened for active TB and LTBI as part of the routine public health response to active TB cases in the UK). Secondly, recent entrants to the UK were recruited through the registers of participating general practitioners and mass recruitment events in community settings such as places of worship. Recent entrants were eligible to participate if they entered the UK from a high incidence country (≥40 per 100,000 based on WHO data (12)) within the last five years and/or made frequent visits to a high incidence country (at least one year cumulatively spent in a high incidence country over the previous five years). Some recent entrants were also recruited through the same process as contacts, after referral following entry screening. Participants were recruited primarily in London, but also in Birmingham and Leicester. Participants with evidence of active TB at baseline were excluded.

Before recruitment, potential participants were asked screening questions to identify symptoms of possible TB (night sweats, unintended weight loss, or persistent cough). Individuals reporting a recent history of any of these were not recruited and were advised to contact their GP.

Exposure, outcome and covariates

Questionnaire completion was assisted by study nurses and translators were provided if necessary.

The main exposure of interest was a self-reported history of DM. Data were also collected on the method of DM control used (categorised as monitoring and/or diet only, oral hypoglycaemic medications, or insulin). Other self-reported covariates investigated were sex, age, country of birth (UK or elsewhere), ethnicity (classified according to standard practice in the UK's Enhanced Tuberculosis Surveillance system), previous BCG vaccination (confirmed by sight of scar), previous TB diagnosis, previous contact with a TB patient (for contacts, this means contacts prior to the one resulting in recruitment to the study), HIV status, other immunosuppression, smoking status (never or ever smoker), social risk factors, and type of participant (contact or new entrant). Body mass index (BMI) was calculated as weight(kg)/height(m)^2, with weight and height being either self-reported or measured by study nurses.

Participants were considered to have "other immunosuppression" if they reported a history of using anti-TNF-α or other immunosuppressive drugs, solid organ transplant, haematological malignancy, jejuno-ileal bypass, chronic renal failure or haemodialysis, or gastrectomy. Social risk factors considered were current or past homelessness, imprisonment or problem drug use; participants were classified as having either no social risk factors or any social risk factor.

The outcome of interest was LTBI, defined as having a positive result for either or both of the two commercially available IGRAs, Quantiferon-TB Gold In-Tube (QFT-GIT – Qiagen) and TSpot.*TB* (Oxford Immunotec, Abingdon, UK). Each IGRA result was recorded as positive, negative or indeterminate according to the manufacturer's instructions (TSpot.*TB* can additionally generate borderline positive and borderline negative results, which were treated

as positive and negative, respectively). Participants usually received both IGRAs; however in some cases, notably community recruitment events, only the QFT-GIT was administered. Those who were negative on both assays, or negative on one and indeterminate on the other, were considered not to have LTBI. Participants with no valid IGRA results were excluded from this analysis.

Sample size

The sample size for the current cross-sectional analysis was determined by the number of participants recruited to PREDICT. Given that data were available for 756 diabetic and 8401 non-diabetic participants, we estimated that we would have 98% power to detect a difference in the prevalence of a positive IGRA of 50% from a baseline prevalence of 10%, with 95% confidence.

Statistical analysis

Binomial regression with a log link was used to estimate crude and adjusted prevalence ratios (PRs and aPRs) and 95% CIs for the relationship between DM and LTBI (16). The outcome (LTBI) was common in the PREDICT cohort (approximately 28%), reflecting the targeted high-risk population, so odds ratios generated by logistic regression would not approximate the prevalence ratio (16). For multivariable modelling, age and sex were treated as *a priori* confounders. Other covariates for adjustment were identified from a causal diagram of the relationships between potential confounders and outcomes using directed acyclic graphs, interpreted using dagitty.net (17) (Figure S1). P values were derived from likelihood ratio tests. We assessed potential interactions between DM and age (4) and DM and ethnicity (18), as observed for active TB (4, 18). All analyses used a complete-case approach.

Age group was treated as a categorical variable (16-25, 26-35, 36-45 and >45 years) as this produced the best fit in univariate analysis (based on likelihood ratio tests comparing models using either continuous age or a linear term for age group). BMI was also treated as a categorical variable, classified as <18.5kg/m^2, 18.5-25kg/m^2 and ≥25kg/m^2 (underweight, normal weight and overweight, respectively).

We conducted five sensitivity analyses. Firstly, we adjusted for age as a continuous variable using fractional polynomials (19). Secondly, we repeated the primary analysis using Poisson regression with robust standard errors instead of log-binomial regression (20), as there is debate about which of these methods is more appropriate for modelling epidemiological associations when the outcome is common (21-23) (p values here were derived from Wald tests, as likelihood ratio tests cannot be used with robust standard errors). Thirdly, we restricted the analysis to contacts of active TB cases. In these participants, any LTBI is likely to be a result of recent infection, whereas recent entrants to the UK may have been infected many years ago in their country of origin. Fourthly, we included only participants who had concordant results for the two IGRAs. Finally, we repeated the primary analysis additionally adjusting for country of birth.

Supplementary results

713 participants were excluded from the analysis due to missing data on DM and/or LTBI status (Figure S1). Those who were included in the analysis were more likely to be male, aged 26-45 years and new entrants than those who were excluded (Table S1). There were also differences in ethnicity, with a higher percentage of participants of Pakistani, Bangladeshi and Mixed ethnicity, and a lower percentage of individuals of Indian ethnicity, in the group included in the analysis compared to those who were excluded.

Table S1: Comparison of participants who were included in the analysis and those who were excluded due to missing data on diabetes and / or IGRA status

		Included [n (%)]	Excluded [n (%)]	p
Total		9157	713	
Sex (n = 9797)	Male	4555 (50.0)	317 (45.9)	0.039
	Female	4552 (50.0)	373 (54.1)	
Age group (years) (n = 9846)	16-25	2257 (24.7)	176 (25.4)	0.009
	26-35	3145 (34.4)	208 (30.0)	
	36-45	1419 (15.5)	97 (14.0)	
	>45	2331 (25.5)	213 (30.7)	
Country of birth (n = 9820)	Non-UK	7664 (83.9)	567 (82.3)	0.26
	UK	1467 (16.1)	122 (17.7)	
Ethnicity (n = 9618)	Indian	3759 (42.1)	328 (48.0)	<0.001
	White	1112 (12.5)	85 (12.4)	
	Black African	1090 (12.2)	94 (13.7)	
	Mixed	873 (9.8)	57 (8.3)	
	Pakistani	878 (9.8)	51 (7.5)	
	Bangladeshi	695 (7.8)	23 (3.4)	
	Black Caribbean	220 (2.5)	27 (4.0)	
	Black Other / Chinese / Other	307 (3.4)	19 (2.8)	
Type of participant (n = 9870)	Contact	4670 (51.0)	429 (60.2)	<0.001
	New entrant	4487 (49.0)	284 (39.8)	
Previous BCG vaccination (n = 8312)	No	1418 (18.3)	98 (17.7)	0.74
	Yes	6341 (81.7)	455 (82.3)	
Previous TB diagnosis (n = 9682)	No	8689 (96.4)	638 (95.2)	0.11
	Yes	323 (3.6)	32 (4.8)	
Previous contact with TB case (n = 9487)	No	7679 (86.9)	576 (88.1)	0.40
	Yes	1154 (13.1)	78 (11.9)	
HIV positive (n = 9183)	No	8487 (99.4)	641 (9.5)	0.65
	Yes	52 (0.6)	3 (0.5)	
Other immunosuppression[a] (n = 9828)	No	8908 (97.4)	662 (97.6)	0.65
	Yes	242 (2.6)	16 (2.4)	
Smoking (n = 9802)	No	7390 (81.0)	558 (82.4)	0.36
	Yes	1735 (19.0)	119 (17.6)	
BMI (kg/m^2)	<18.5	430 (5.0)	29 (4.7)	0.32

(n = 9204)	18.5 – 25	4224 (49.2)	285 (46.3)	
	≥25	3935 (45.8)	301 (48.9)	
Any social risk factor[b] (n = 9870)	No	8735 (95.4)	688 (96.5)	0.17
	Yes	422 (4.6)	25 (3.5)	

[a] Other immunosuppressive factors considered were: history of using anti-TNF-α or other immunosuppressive drugs, solid organ transplant, haematological malignancy, jejunoilealbypass, chronic renal failure or haemodialysis, gastrectomy.

[b] Social risk factors considered were: current or past homelessness, imprisonment or problem drug use.

Participants who were included in the complete case analysis were similar to those with incomplete data in terms of IGRA positivity, reported DM prevalence, age group, sex and BMI category. However, there was evidence that those included were less likely to be immunosuppressed than those who were excluded. There were also some differences in the ethnic composition of the two groups, with greater representation of people of Indian and Pakistani ethnicity, and less representation of those of Black Caribbean ethnicity, in the complete case analysis (Table S2).

Table S2: Comparison of participants included in and excluded from the complete case analysis.

		Included in complete case analysis [n (%)]	Excluded from complete case analysis [n (%)]	p
Total	9157	8336 (91.0)	821 (9.0)	
IGRA positive (n = 9157)	No	6027 (72.3)	596 (72.6)	
	Yes	2309 (27.7)	225 (27.4)	0.86
Diabetes (n = 9157)	No	7659 (91.9)	742 (90.4)	
	Yes	677 (8.1)	79 (9.6)	0.14
Sex (n = 9107)	Male	4178 (50.1)	377 (48.9)	
	Female	4158 (49.9)	394 (51.1)	0.52
Age group (years) (n = 9152)	16-25	2054 (24.6)	203 (24.9)	
	26-35	2878 (34.5)	267 (32.7)	
	36-45	1304 (15.6)	115 (14.1)	
	>45	2100 (25.2)	231 (28.3)	0.20
Ethnicity (n = 8934)	Indian	3523 (42.3)	236 (39.5)	
	White	1024 (12.3)	88 (14.7)	
	Black African	1019 (12.2)	71 (11.9)	
	Mixed	816 (9.8)	57 (9.5)	
	Pakistani	832 (10.0)	46 (7.7)	
	Bangladeshi	646 (7.8)	49 (8.2)	
	Black Caribbean	194 (2.3)	26 (4.4)	
	Black Other / Chinese / Other	282 (3.4)	25 (4.2)	0.02
Other immunosuppression[a] (n = 9150)	No	8132 (97.6)	776 (95.3)	
	Yes	204 (2.4)	38 (4.7)	<0.001
BMI (kg/m^2) (n = 8589)	<18.5	421 (5.1)	9 (3.6)	
	18.5 – 25	4107 (49.3)	117 (46.3)	
	≥25	3808 (45.7)	127 (50.2)	0.27

Full results from the multivariable model are shown in Table S3.

Table S3: Adjusted prevalence ratios for the association of diabetes mellitus and other baseline characteristics with latent tuberculosis infection from multivariate log binomial model (n = 8336)

		Prevalence ratio (95% CI)	**p**
Diabetes	No	Referent	
	Yes	1.15 (1.02-1.30)	0.025
Sex	Male	Referent	
	Female	0.80 (0.74-0.85)	<0.001
Age group (years)	16-25	Referent	
	26-35	1.27 (1.15-1.41)	
	36-45	1.47 (1.31-1.65)	
	>45	1.32 (1.17-1.48)	<0.001
Ethnicity	Indian	Referent	
	White	0.81 (0.71-0.92)	
	Black African	1.40 (1.27-1.54)	
	Mixed	1.20 (1.07-1.34)	
	Pakistani	1.15 (1.02-1.29)	
	Bangladeshi	0.72 (0.61-0.85)	
	Black Caribbean	0.68 (0.50-0.93)	
	Black Other / Chinese / Other	0.97 (0.79-1.19)	<0.001
Other immunosuppression[a]	No	Referent	
	Yes	0.75 (0.57-0.97)	0.02
BMI (kg/m^2)	<18.5	Referent	
	18.5 – 25	0.97 (0.82-1.14)	
	≥25	0.93 (0.79-1.10)	0.52

[a] Other immunosuppressive factors considered were: history of using anti-TNF-α or other immunosuppressive drugs, solid organ transplant, haematological malignancy, jejunoileal bypass, chronic renal failure or haemodialysis, gastrectomy.

Table S4 summarises the adjusted prevalence ratios by participant ethnicity.

Table S4: Estimated prevalence ratios for the association of diabetes mellitus with latent tuberculosis infection by ethnicity, adjusted for age group, sex, BMI category and immunosuppression.

Ethnicity	**Prevalence ratio (95% CI)**	**p**
Indian	1.00 (0.85-1.18)	0.96
White	0.58 (0.23-1.46)	0.25
Black African	1.48 (1.16-1.90)	0.002
Mixed	1.37 (0.95-1.98)	0.09
Pakistani	1.41 (1.01-1.99)	0.05
Bangladeshi	1.53 (0.91-2.57)	0.11
Black Caribbean	1.26 (0.57-2.78)	0.57
Black other, Chinese or Other	1.78 (0.97-3.26)	0.06

Table S5 summarises the results of sensitivity analyses.

Table S5: Adjusted prevalence ratios for the association between diabetes mellitus and latent tuberculosis infection from multivariate log binomial model, in sensitivity analyses. All estimates are adjusted for sex, age group, ethnicity, other immunosuppression and BMI.

Sensitivity analysis	**n**	**Prevalence ratio (95% CI)**	**p**
Adjusted for age using fractional polynomials	8336	1.15 (1.01-1.30)	0.04
Poisson regression with robust standard errors	8336	1.15 (1.01-1.30)	0.03
Restricted to participants with concordant IGRA results	6300	1.16 (0.97-1.40)	0.11
Restricted to contacts	4238	1.29 (1.09-1.52)	0.002
Further adjusted for country of birth	8322	1.14 (1.00-1.28)	0.04

Figure S1: Causal diagram summarising the relationship between diabetes mellitus, latent tuberculosis infection and relevant covariates. Direct relationships between covariates and LTBI are shown by solid black lines, between covariates and DM by dashed black lines, other relationships by grey lines.

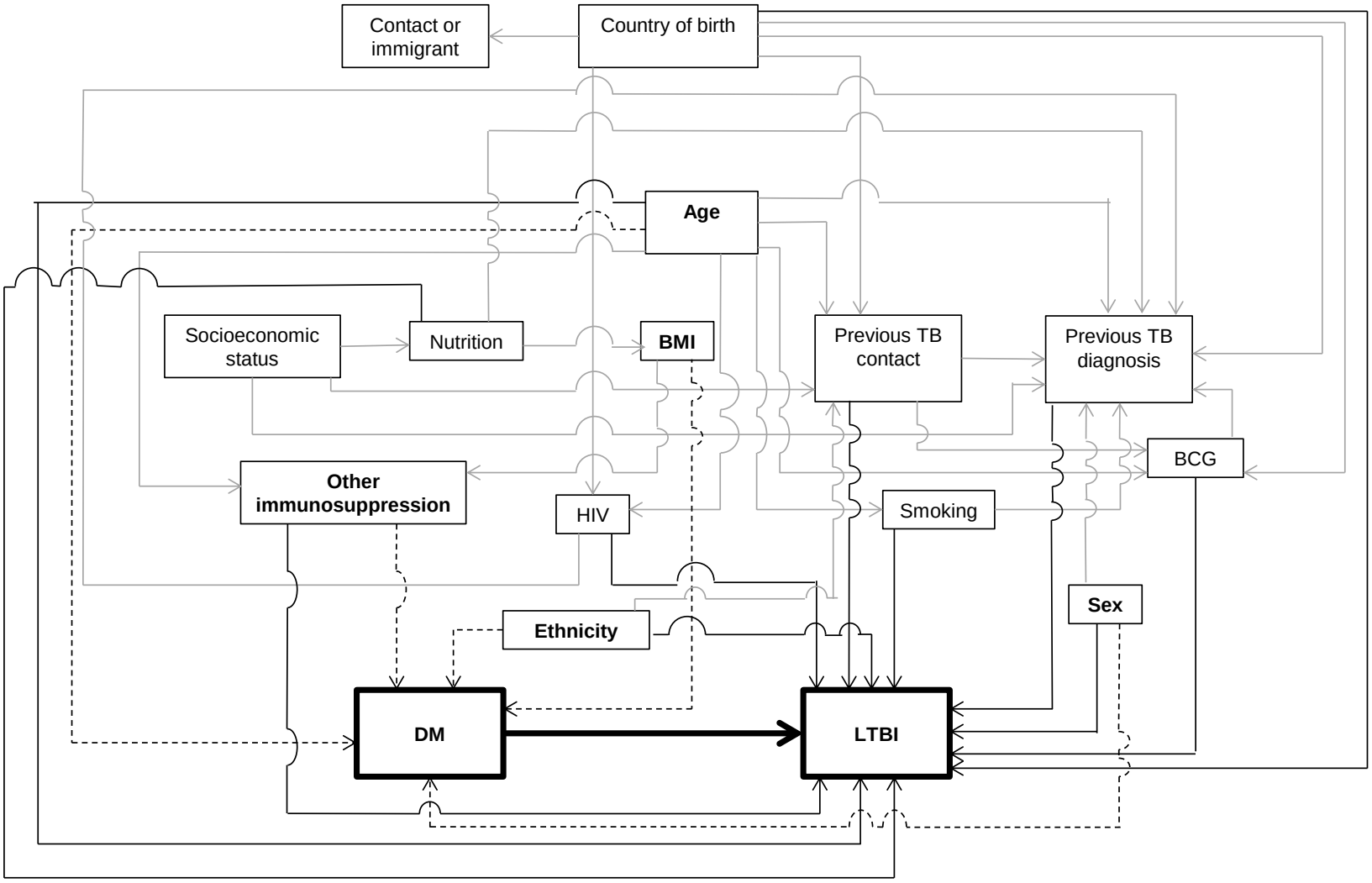
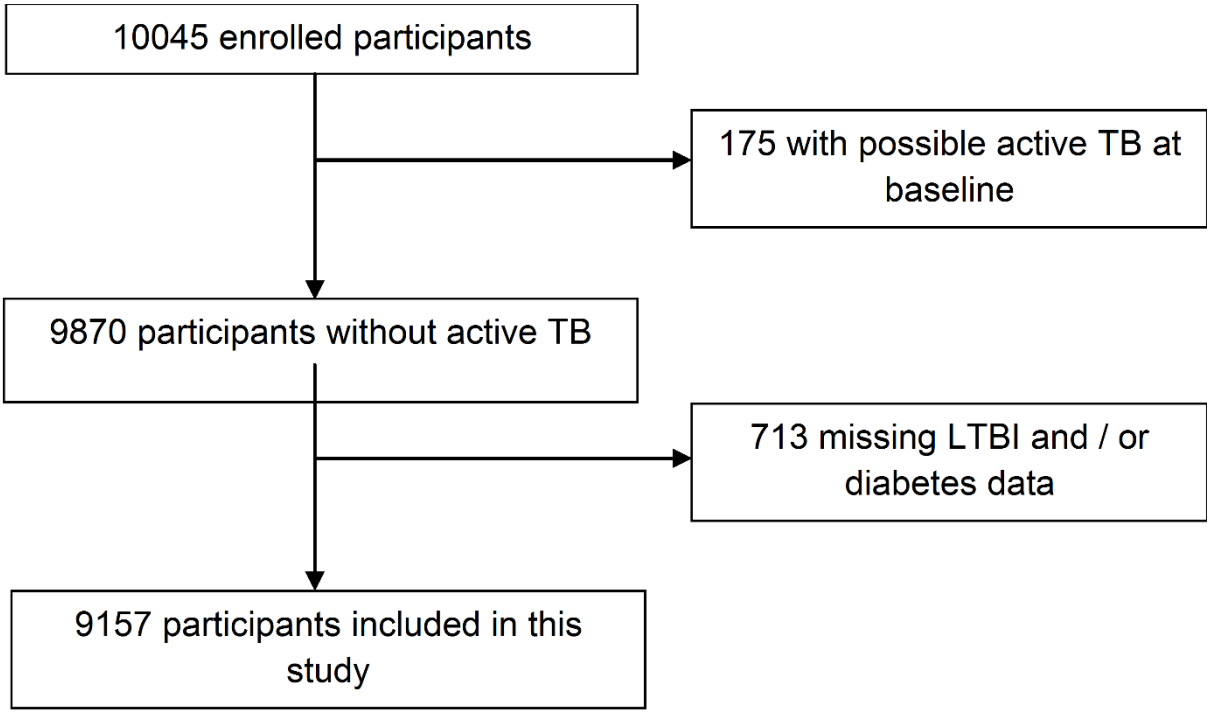


Figure S2: Recruitment of participants to PREDICT and inclusion in the LTBI/diabetes study.



Questionnaire for contacts

Questionnaire- Participants

The UK Prognostic Study of the Interferon Gamma Release Assay for Tuberculosis

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Thank you for your help with this research. The questionnaire will take approximately 10 minutes to complete. If you need any help please feel free to contact: xxx.

Please read each question carefully before you answer it, and try to answer every question. Either tick the appropriate box or write your answer in the space provided in BLOCK CAPITALS.

The information that you give us will be treated in strict medical confidence.

Contact details

a) Name

Title: …… First names (s): …… Surname: …….

b) Identifiers

NHS number: …… Local Patient ID: …….

c) Address/telephone number

Address line one: …….

Address line two: …….

Town: …….

County: …….

Post code: …….

Telephone Number: ……

d) Locality of patient care

Primary Care Trust or Local Health Board (of patient's residence): ……

Local Authority of patient's residence: ……...

Participant's consultant: ……...

Participant's Nurse: ……...

Personal details

a) Gender

☐ Male ☐ Female

b) Age

Date of birth: …… (day/month/year) Age: …… (years)

c) Were you born in the UK?

☐ Yes ☐ No ☐ Not sure

If non UK born please state country of birth: ……

If non UK born please state date of entry to the UK: …… (month/year)

Country of residence prior to arrival in the UK: ……..

d) Current or most recent job?

Health care worker:

☐ *Doctor* ☐ *Nurse*
☐ *Dentist* ☐ *Community care worker*
☐ *Other*

Social/Prison sector worker:

☐ *Social worker* ☐ *Homeless sector worker*
☐ *Prison Detention Officer* ☐ *Probation Officer*
☐ *Other*

Laboratory/pathology:

☐ *Microbiologist* ☐ *Laboratory staff*
☐ *Pathologist* ☐ *PM attendant*
☐ *Other*

Agricultural/animal care worker:

☐ *Works with cattle* ☐ *Works with wild animals*
☐ *Other*

Education:

☐ *Full time Student* ☐ *Lecturer*
☐ *Teacher (inc Nursery)* ☐ *Other*

None:

☐ *Retired* ☐ *Unemployed*
☐ *Child* ☐ *Prisoner*
☐ *House wife/husband* ☐ *Immigration Detainee*
☐ *Asylum seeker* ☐ *Other*

Other: …….. ☐

Not sure ☐

e) Ethnicity

☐ *White* ☐ *Indian*
☐ *Black African* ☐ *Pakistani*
☐ *Black Caribbean* ☐ *Bangladeshi*
☐ *Black Other* ☐ *Chinese*
☐ *Mixed/Other* ☐ *Unknown*

TB history

a) Contact criteria- indicate as appropriate*

Setting	Type	Room	Size of space/distance	Duration (hours)
Household	Sexual/non sexual	Same room?	Within 3 feet? Volume of room?	
Health care	Hospital, nursing home, community, other	Same room/ward or note?	Within 3 feet? Volume of room?	
Education	Secondary, tertiary	Same class?	Within 3 feet? Volume of room?	
Detention	Prison or immigration	Same cell, same wing, same prison?	Within 3 feet? Volume of room?	
Homeless	Residential hostel, night shelter, sofa surfer, rough sleep, day centre	Same room, same wing, same hostel?	Within 3 feet? Volume of room?	
Other congregate living settings	Elderly residential, special needs homes, ,	Same room, same ward, same home?	Within 3 feet? Volume of room?	
Travel	Air-travel, car, bus, train, ship	Sitting in same or next row?	Within 3 feet? Volume of room?	
Workplace/social	Indoor or outdoor type: factory, crack house, restaurant, pub/bar, church, movie, store, garage, construction, office	Same room, open plan?		
Other				

*** To also collect information on sputum and culture result of index case**
Adapted from Shams et al., and UK contact tracing module

When did you last have contact with this person?: ……. (day/month/year) / Not Known

b) Prior to this recent contact, have you previously had contact with anyone else diagnosed with tuberculosis?

☐ Yes ☐ No ☐ Not sure

If yes:

☐ Household ☐ Non-household

How many years ago: …….

c) Have you previously received a diagnosis of tuberculosis?

☐ Yes ☐ No ☐ Not sure

If yes, how many years ago: …….

If yes, were you treated with at least 1 month of drug therapy?

☐ Yes ☐ No ☐ Not sure

Medical and Social History

a) Do you have a history of problem drug use?

☐ Yes ☐ No ☐ Not sure

If yes, please select one or more categories:

☐ Current drug use ☐ Drug use in the last 5 years ☐ Drug use more than 5 years ago

b) Are you currently homeless or ever been homeless?

☐ Yes ☐ No ☐ Not sure

If yes, please select one or more categories:

☐ Currently Homeless ☐ Homeless in the last 5 years ☐ Homeless more than 5 years ago

c) Have you ever been in prison?

☐ Yes ☐ No ☐ Not sure

If yes, please select one or more categories:

☐ Currently in prison ☐ In prison in the last 5 years ☐ In prison more than 5 years ago

d) Do you have a history of diabetes?

☐ Yes ☐ No ☐ Not sure

If yes, please state level of control: …….

e) Do you have a history of cancer?

☐ Yes ☐ No ☐ Not sure

If yes, please state type: …….

f) Are you HIV positive?

☐ Yes ☐ No ☐ Not sure

g) Do you have a history of smoking?

☐ Yes ☐ No ☐ Not sure

If yes, please state how many a day and for how long: …….

h) Do you have a history of, or currently use, any of the following?

	Yes	No	Unknown	Type	Amount
Previous Transplant					
Anti-TNF alpha					
Steroids					
Immunosuppressive Drugs					

i) Have you previously received a BCG vaccination?

☐ Yes ☐ No ☐ Not sure

If yes, approximate year of vaccination: …….

j) Have you travelled outside the UK in the last three years (please do not include travel to Western Europe, US, Canada and Australia)?

☐ Yes ☐ No ☐ Not sure

Please list where you travelled to with dates

Place	Date	Duration

k) Have you travelled or lived in any of these places before the three years (please do not include travel to Western Europe, US, Canada and Australia)?

☐ Yes ☐ No ☐ Not sure

EuroQOL

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today

Mobility

I have no problems in walking about	
I have some problems in walking about	
I am confined to bed	

Self-Care

I have no problems with self-care	
I have some problems washing or dressing myself	
I am unable to wash or dress myself	

Usual activities

(e.g. work, study, housework, family or leisure activities)

I have no problems with performing my usual acitivities	
I have some problems with performing my usual activities	
I am unable to perform my usual activities	

Pain or discomfort

I have no pain or discomfort	
I have moderate pain or discomfort	
I have extreme pain or discomfort	

Anxiety or depression

I am not anxious or depressed	
I am moderately anxious or depressed	
I am extremely anxious or depressed	

Thank you for taking the time to fill in this questionnaire. Please return this questionnaire to the research nurse

For Official Use only

Name of Research Nurse:

Please enter study number:

Please enter ID of index case:

For Official Use Only

Weight*:* …….…….. kgs

Height*:* …….…….. metres

Results of laboratory tests

Type of test	Test	Unit	Type
IGRA (*2)	Quantiferon	iu/ml	Numerical
	ELISPOT	Spots	Numerical
Full Blood Count	White Blood Cells (Leukocytes)	No/ml	Numerical
	Red cells	No/ml	Numerical
	Platelets	No/ml	Numerical
	Haemoglobin	mg/ml	Numerical
	Film	Comment	Text
Vitamin D status	25 Hydroxyvitamin D	ng/ml or nmols/L	Numerical
TST	Mantoux test	mm	Numerical