THE LANCET
Infectious Diseases

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Abubakar I, Drobniewski F, Southern J, et al, on behalf of the PREDICT Study Team. Prognostic value of interferon-γ release assays and tuberculin skin test in predicting the development of active tuberculosis (UK PREDICT TB): a prospective cohort study. *Lancet Infect Dis* 2018; published online August 30. http://dx.doi.org/10.1016/S1473-3099(18)30355-4

Supplementary appendices

S1: Further details of recruitment

S2: Case definitions for active TB

S3: Statistical model and additional details of sample size calculation

S4: Detailed test results

4a: Results for each test
4b: Cross tabulations of test results with TST^{5}
4c: Cross tabulations of test results with TST^{10}
4d: Cross tabulations of test results with TST^{15}

S5: Sensitivity analyses

5a: Excluding those with assumed BCG status
5b: Using all available data (not excluding participants with some missing test information)
5c: Stratified by migrants versus contacts
5d: Restricting the analysis to one year follow up

S1: Further details of recruitment

Participants aged 16 years and over were recruited from 54 different NHS centres and community settings located in London, Leicester and Birmingham. Participants were recruited from healthcare, work and community settings including places of worship, schools/colleges and workplaces if they were: (a) close contacts of cases of active TB or (b) migrants arriving in the last 5 years from high incidence countries defined as exceeding 40 per 100,000 and operationalised by focussing on those from sub-Saharan Africa or Asia. Eligible persons were identified by study TB specialists or Practice Nurses and written informed consent obtained following provision of information sheets (translated as appropriate). GPs of all participants were informed of their patients' participation by letter.

At the time of the study, treatment of LTBI was recommended only for individuals aged under 35 years. We therefore prioritised the recruitment of patients aged >35 years (not eligible for chemoprophylaxis) in order to estimate and compare the ability of TST and IGRA tests to predict natural progression to active disease. Individuals aged 16-34 were also eligible, as they may not be offered, or may not accept, chemoprophylaxis.

Recruitment of contacts

In the UK, individuals who have been in contact with a patient with active TB are invited to attend a TB clinic to be screened for active disease and latent infection. Contacts of all active TB (pulmonary and extra-pulmonary) patients, attending participating TB clinics for screening were invited to take part in the PREDICT study. Contacts included all individuals with a cumulative duration of exposure of greater than eight hours to the relevant index case in a confined space during the period of infectiousness (prior to initiation of treatment).

Additionally, in some situations contacts of active cases were recruited through mass screening events organised as part of the public health response to a case of active TB. For example, clinical teams may attend workplaces or colleges where an exposure has taken place, to facilitate screening of large numbers of contacts.

Recruitment of migrants

Migrants to the UK from high incidence countries were identified through primary care and through community events.

For recruitment through primary care, study flyers and the contact details of the coordinating centre were displayed in GP surgeries so that interested people could contact the study team. At the appointment, as with all recruitment meetings, a research nurse went through the full patient information leaflet before taking written informed consent to undertake study procedures. We also utilised the PCT-held Flag4 data (records held by the local primary care group about international migrants who register with an NHS GP) to invite newly registered patients, recently arrived from the countries of interest, to take part in the study.

Migrants were also recruited from community settings on non-NHS premises, such as places of worship and community centres.

In addition to recruiting participants who had recently come to the UK, individuals born in high incidence countries who entered the UK more than five years ago, but who had spent more than one year (cumulative) in the past five years in a high incidence country as per the study's defined list, were also eligible to participate.

S2: Case definitions for active TB

Individuals were considered to have progressed to active TB if they had culture confirmed TB or were clinically diagnosed with radiological or histological evidence of TB and a clinician had decided to treat the individual with a full course of anti-TB disease treatment, the definition used for the TB register. In addition, participants were considered to have progressed to TB only if:

- The participant had no evidence of active TB at the time of enrolment determined through the review of clinical records.
- The clinical diagnosis of active TB was at least 21 days after recruitment/enrolment to the PREDICT study, based on the date of diagnosis (or treatment start date if date of diagnosis was not available). The study steering committee discussed and agreed 21 days in view of the delays before first appointment and likely higher chance of early progression that will be excluded with a longer time window.

In the absence of laboratory confirmation of TB, awareness by the clinician of a prior positive IGRA/TST result should not influence the clinical diagnosis of active TB. Any case that was subsequently denotified (i.e. where the clinician reported that the patient did not have TB) was not considered a progression.

If a participant self-reported a diagnosis of active TB in the follow-up phone call at 12 or 24 months, the national dataset of clinical reports and local hospital records were searched to confirm the diagnosis.

S3: Statistical model and additional details of sample size calculation

Poisson regression models were used for analyses of incidence rates accounting for variation in follow-up. For models that compared tests, we followed Pepe (reference 13) fitting models to estimate the relative likelihood ratios for test positive and test negative results to evaluate the relative predictive value of test positive and test negative results. A marginal regression GEE model was fitted, with the two test results as outcomes (with test positive coded as the event) and with test type and progression status as predictors, and an interaction term between test type and progression. The interaction term assessed whether the relationship between progression and test positivity was higher for one test than the other. A similar second model was fitted with test negative as the outcome, such that the interaction term assessed whether the relationship between non-progression and test negativity was stronger for one test than the other. The model accounted for the correlation within individuals between tests using an unstructured correlation matrix and was configured to give population average estimates. The primary analysis fitted models with a binomial error structure and a log link (as described by Pepe), with a Poisson error structure being utilised where there were convergence problems (indicated in table). In a sensitivity analyses we adapted the Poisson model to include follow-up using an offset and obtained identical point estimates to 2 d,p and confidence limits to 1 d.p.. Results We report the binomial model results in the Tables.
Regression models were fitted in STATA V15.0.

The study size (and associated power) was determined by simulating the study and its analysis 1000 times and observing the proportion of simulations yielding significant results across various scenarios. The disease progression of simulated study participants data were created presuming a LTBI prevalence of 30% and 5% of participants with LTBI progressing to active TB in 2 years if untreated, as observed in previous studies [10,23]. Test results were simulated for each participant using sensitivities and specificities of IGRA ranging between 65% and 95%. The simulations indicated that a cohort of 5,000 participants amongst whom 90 incident events would be expected to be observed would have around 85% power to detect significant ($P<0.05$) differences in predictive performance that would arise from differences in sensitivity and specificity of 10% between tests. These

differences correspond to increases in predictive performance (expressed as a ratio of relative rates between test positives) of 30%, which would be clinically useful.

S4. Detailed test results

Table S4a: Results for each test; n (%).

	TST[5]	TST[10]	TST[15]	TSpot.*TB*	QFT-GIT
Positive	3513 (36.6)	2540 (23.0)	1729 (18.0)	1571 (16.4)	1892 (19.7)
Negative	4320 (45.0)	5293 (55.1)	5940 (61.8)	6414 (66.7)	6640 (69.1)
Missing	1777 (18.5)	1777 (18.5)	1941 (20.2)	1625 (16.9)	1078 (11.2)

Table S4b: Cross tabulations of test results with TST[5] ; values are (progressing to TB) total number.

TST[5] positive	**TSpot.TB result**							
QFT-GIT result	**Positive**	**Borderline positive**	**Borderline negative**	**Negative**	**Indeterminate**	**Error**	**Missing**	**Total**
Positive	(39) 745	(2) 52	24	(3) 225	11	16	(3) 40	(47)1,113
Negative	(7)124	(1)49	41	(13) 1,750	(1) 34	27	80	(22)2,105
Indeterminate	18	0	1	(1) 30	2	1	(1) 20	(2)72
Error	6	0	1	9	0	0	0	16
Missing	(2)21	5	0	16	0	3	(4)162	(6)207
Total	(48)914	(3)106	67	(17)2,030	(1)47	47	(8)302	(77)3,513

TST[5] negative	**TSpot.TB result**							
QFT-GIT result	**Positive**	**Borderline positive**	**Borderline negative**	**Negative**	**Indeterminate**	**Error**	**Missing**	**Total**
Positive	(2)170	(2)25	8	222	4	7	14	(4)450
Negative	(2)56	(7)34	29	2,966	54	89	145	(9)3,373
Indeterminate	0	(1)0	0	33	1	1	19	(1)54
Error	3	0	1	30	0	1	0	35
Missing	20	4	4	121	1	0	(1)258	(1)408
Total	(4)249	(10)63	42	3,372	60	98	(1)436	(15)4,320

TST[5] missing	**TSpot.TB result**							
QFT-GIT result	**Positive**	**Borderline positive**	**Borderline negative**	**Negative**	**Indeterminate**	**Error**	**Missing**	**Total**
Positive	(1)174	10	6	46	(1)3	27	63	329
Negative	26	10	7	(2)795	8	84	232	1,162
Indeterminate	5	0	3	10	2	0	17	37
Error	2	0	0	8	0	3	1	14
Missing	11	1	1	27	1	1	(1)193	235
Total	(1)218	21	17	(2)886	(1)14	115	(1)506	(5)1,777

Table S4c: Cross tabulations of test results with TST[10]; values are (progressing to TB) total number.

TST[10] positive	**TSpot.TB result**							
QFT-GIT result	**Positive**	**Borderline positive**	**Borderline negative**	**Negative**	**Indeterminate**	**Error**	**Missing**	**Total**
Positive	(39)705	(1)45	20	(2)181	10	12	(3)37	(45)1,010
Negative	(7)90	(1)33	30	(9)1,085	(1)22	16	52	(18)1,328
Indeterminate	17	0	1	(1)14	1	1	(1)17	(2)51
Error	6	0	1	4	0	0	0	(4)11
Missing	(2)7	3	0	8	0	3	(2)119	140
Total	(48)825	(2)81	52	(12)1,292	(1)33	32	(6)225	(69)2,540

TST[10] negative	**TSpot.TB result**							
QFT-GIT result	**Positive**	**Borderline positive**	**Borderline negative**	**Negative**	**Indeterminate**	**Error**	**Missing**	**Total**
Positive	(2)210	(1)32	12	(3)266	5	11	17	(6)553
Negative	(2)90	50	40	(11)3,631	66	100	173	(13)4,150
Indeterminate	1	0	0	(1)49	2	1	22	(1)75
Error	3	0	1	35	0	1	0	40
Missing	34	6	4	129	1	0	(3)301	(3)475
Total	(4)338	(1)88	57	(15)4,110	74	113	(3)513	(23)5,293

TST[10]missing	**TSpot.TB result**							
QFT-GIT result	**Positive**	**Borderline positive**	**Borderline negative**	**Negative**	**Indeterminate**	**Error**	**Missing**	**Total**
Positive	(1)174	10	6	46	(1)3	27	63	(2)329
Negative	26	10	7	(2)795	8	84	232	(2)1,162
Indeterminate	5	0	3	10	2	0	17	37
Error	2	0	0	8	0	3	1	14
Missing	11	1	1	27	1	1	(1)193	(1)235
Total	(1)218	21	17	(2)886	(1)14	115	(1)506	(5)1,777

Table S4d: Cross tabulations of test results with TST[15]; values are (progressing to TB) total number.

TST[15] positive	**TSpot.TB result**							
QFT-GIT result	**Positive**	**Borderline positive**	**Borderline negative**	**Negative**	**Indeterminate**	**Error**	**Missing**	**Total**
Positive	(36)585	35	12	(2)112	6	8	(3)27	(41)785
Negative	(6)68	(1)21	19	(7)636	(1)16	8	32	(15)800
Indeterminate	14	0	0	10	1	0	(1)11	(1)36
Error	6	0	1	0	0	0	0	7
Missing	(2)12	2	0	5	0	2	(1)80	(3)101
Total	(44)685	(1)58	32	(9)763	(1)23	18	(5)150	(60)1,729

TST[15] negative	**TSpot.TB result**							
QFT-GIT result	**Positive**	**Borderline positive**	**Borderline negative**	**Negative**	**Indeterminate**	**Error**	**Missing**	**Total**
Positive	(5)317	(1)39	20	(3)325	8	15	25	(9)749
Negative	(3)111	60	50	(13)3,976	71	107	188	(16)4,563
Indeterminate	4	0	1	(2)52	2	2	28	(2)89
Error	3	0	1	38	0	1	0	43
Missing	29	7	4	131	1	1	(4)323	(4)496
Total	(8)464	(1)106	76	(18)4,522	82	126	(4)564	(31)5,940

TST[15] missing	**TSpot.TB result**							
QFT-GIT result	**Positive**	**Borderline positive**	**Borderline negative**	**Negative**	**Indeterminate**	**Error**	**Missing**	**Total**
Positive	(1)187	(1)13	6	56	(1)4	27	65	(3)358
Negative	27	12	8	(2)899	9	85	237	(2)1,277
Indeterminate	5	0	3	11	2	0	17	38
Error	2	0	0	9	0	3	1	15
Missing	11	1	1	28	1	1	(1)210	(1)253
Total	(1)232	(1)26	18	(2)1,003	(1)16	116	(1)530	(6)1,941

S5: Results of sensitivity analyses

5a Excluding those with assumed BCG status
5b Using all available data (not excluding participants with some missing test information)
5c Stratified by migrants versus contacts
5d Restricting the analysis to one year follow up

Table S5a Sensitivity analysis—IR and IRR when excluding those with assumed BCG status, and using the lower or upper threshold for those with unknown (not recorded or assumed BCG status).

	TST[15]		**TST[15] assumed BCG excluded**		**TST[15] BCG unknown lower (6mm) threshold***		**TST[15] BCG unknown higher (15mm) threshold***	
	+	**-**	**+**	**-**	**+**	**-**	**+**	**-**
Progression n/N	52/1,485	25/4,895	44/1,320	23/4,273	53/1,534	25/4,986	53/1,511	25/5,009
(%)	(3.5%)	(0.5%)	(3.3%)	(0.5%)	(3.5%)	(0.5%)	(3.5%)	(0.5%)
Person years at risk	7,620.8	33,397.7	6,444.2	34,574.4	6,950.0	34,530.0	6,996.1	34,483.9
IR (per 1,000 per annum)	11.1	1.6	10.5	1.7	11.0	1.5	11.2	1.5
95% CI	(8.3, 14.6)	(1.0, 2.3)	(7.7, 14.2)	(1.1, 2.5)	(8.2, 14.4)	(1.0, 2.3)	(8.4, 14.6)	(1.0, 2.3)
IRR	7.1		6.4		7.1		7.3	
95% CI	(4.4, 11.4)		(3.8, 10.5)		(4.4, 11.5)		(4.5, 11.7)	

*Using the 6,520 participants now with all test results but excluding participants who were non UK born and initially assumed to be BCG vaccinated.

Table S5b: Sensitivity analysis—IR and IRRs using all available test data (for participants with study time data also)

	TSpot.*TB*		QuantiFERON		TST[5]		TST[10]		TST[15]	
	+	-	+	-	+	-	+	-	+	-
Participants with data for all tests										
Progression n/N (%)	52/1,235 (4.2%)	25/5,145 (0.5%)	47/1,444 (3.3%)	30/4,936 (0.6%)	64/2,957 (2.2%)	13/3,423 (0.4%)	58/2,151 (2.7%)	19/4,229 (0.4%)	52/1,485 (3.5%)	25/4,895 (0.5%)
Person years at risk	3,926.2	16,645.3	4,649.9	15,921.6	9,416.8	11,154.6	6,822.3	13,749.2	4,674.8	15,896.6
IR (per 1,000 per annum)	13.2	1.5	10.1	1.9	6.8	1.2	8.5	1.4	11.1	1.6
95% CI	(9.9, 17.4)	(1.0, 2.2)	(7.4, 13.4)	(1.3, 2.7)	(5.2, 8.7)	(0.6, 2.0)	(6.5, 11.0)	(0.8, 2.2)	(8.3, 14.6)	(1.0, 2.3)
IRR	8.8		5.4		5.8		6.2		7.1	
95% CI	(5.5, 14.2)		(3.4, 8.5)		(3.2, 10.6)		(3.7, 10.3)		(4.4, 11.4)	
Participants with data for each test										
Progression n/N (%)	56/1,566 (3.6%)	29/6,402 (0.5%)	53/1,888 (2.8%)	33/6,624 (0.5%)	77/3,510 (2.2%)	15/4,315 (0.3%)	69/2,540 (2.7%)	23/5,293 (0.4%)	60/1,726 (3.5%)	31/5,935 (0.5%)
Person years at risk	4,633.6	19,506.8	5,605.5	19,541.2	10,831.2	13,365.2	7,826.0	16,370.4	5,285.7	18,372.6
IR (per 1,000 per annum)	12.1	1.5	9.5	1.7	7.1	1.1	8.8	1.4	11.4	1.7
95% CI	(9.1, 15.7)	(1.0, 2.1)	(7.1, 12.4)	(1.2, 2.4)	(5.6, 8.9)	(0.6, 1.9)	(6.9, 11.2)	(0.9, 2.1)	(8.7, 14.6)	(1.1, 2.4)
IRR	8.1		5.6		6.3		6.3		6.7	
95% CI	(5.2, 12.7)		(3.6, 8.6)		(3.6, 11.0)		(3.9, 10.1)		(4.4, 10.4)	

Table S5c: Incidence Rate Ratios for progression to active TB comparing test-positive and test-negative contacts and migrants

	TSpot.TB		QuantiFERON		TST^{5}		TST^{10}		TST^{15}	
	+	-	+	-	+	-	+	-	+	-
Migrants										
Progression n/N	21/587	5/2229	17/651	9/2165	21/1253	5/1563	20/828	6/1988	18/586	8/2230
(%)	(3.6%)	(0.2%)	(2.6%)	(0.4%)	(1.7%)	(0.3%)	(2.4%)	(0.3%)	(3.1%)	(0.4%)
Person years at risk	1,826.0	6,823.5	2,036.0	6,613.4	3,874.5	4,775.0	2,541.6	6,107.9	1,812.4	6,837.0
IR (per 1,000 per annum)	11.5	0.7	8.3	1.4	5.4	1.0	7.9	1.0	9.9	1.2
95% CI	(7.1, 17.6)	(0.2, 1.7)	(4.9, 13.4)	(0.6, 2.6)	(3.4, 8.3)	(0.3, 2.4)	(4.8, 12.2)	(0.4, 2.1)	(5.9, 15.7)	(0.5, 2.3)
IRR	15.7		6.1		5.2		8.0		8.5	
95% CI	(5.9, 41.6)		(2.7, 13.8)		(2.0, 13.7)		(3.2, 19.9)		(3.7, 19.5)	
Contacts										
Progression n/N	31/648	20/2916	30/793	21/2771	43/1704	8/1860	38/1323	13/2241	34/899	17/2665
(%)	(4.8%)	(0.7%)	(3.8%)	(0.8%)	(2.5%)	(0.4%)	(2.9%)	(0.6%)	(3.8%)	(0.6%)
Person years at risk	2,100.1	9,821.8	2,613.8	9,308.2	5,542.3	6,379.6	4,280.7	7,641.2	2,862.4	9,059.6
IR (per 1,000 per annum)	14.8	2.0	11.5	2.3	7.8	1.3	8.9	1.7	11.9	1.9
95% CI	(10.0, 21.0)	(1.2, 3.1)	(7.7, 16.4)	(1.4, 3.4)	(5.6, 10.5)	(0.5, 2.5)	(6.3, 12.2)	(0.9, 2.9)	(8.2, 16.6)	(1.1, 3.0)
IRR	7.2		5.1		6.2		5.2		6.3	
95% CI	(4.1, 12.7)		(2.9, 8.9)		(2.9, 13.2)		(2.8, 9.8)		(3.5, 11.3)	

Table S5d: Results from analysis restricting the duration of follow-up to one or two years

	TSpot.TB		QFT-GIT		TST^{5}		TST^{10}		TST^{15}	
	+	-	+	-	+	-	+	-	+	-
One year follow up										
Progression n/N (%)	41/1235 (3.3%)	18/5145 (0.3%)	36/1444 (2.5%)	23/4936 (0.5%)	50/2957 (1.7%)	9/3423 (0.3%)	46/2151 (2.1%)	13/4229 (0.3%)	42/1485 (2.8%)	17/4895 (0.3%)
Person years at risk	1,204.4	5,125.3	1,418.7	4,911.1	2,918.9	3,410.8	2,115.7	4,214.1	1,453.7	4,876.0
IR (per 1,000 per annum)	34.0	3.5	25.4	4.7	17.1	2.6	21.7	3.1	28.9	3.5
95% Confidence Interval	(24.4, 46.2)	(2.1, 5.6)	(17.8, 35.1)	(3.0, 7.0)	(12.7, 22.6)	(1.2, 5.0)	(15.9, 29.0)	(1.6, 5.3)	(20.8, 39.1)	(2.0, 5.6)
IRR (per 1,000 per annum)	9.7		5.4		6.5		7.0		8.3	
95% Confidence Interval	(5.6, 16.9)		(3.2, 9.1)		(3.2, 13.2)		(3.8, 13.0)		(4.7, 14.6)	
Two years follow up										
Progression n/N (%)	48/1235 (3.9%)	21/5145 (0.4%)	43/1444 (3.0%)	26/4936 (0.5%)	57/2957 (1.9%)	12/3423 (0.4%)	53/2151 (2.5%)	16/4229 (0.4%)	47/1485 (3.2%)	22/4895 (0.4%)
Person years at risk	2,340.6	9,987.7	2,761.4	9,566.9	5,683.5	6,644.8	4,117.0	8,211.3	2,824.0	9,504.3
IR (per 1,000 per annum)	20.5	2.1	15.6	2.7	10.0	1.8	12.9	1.9	16.6	2.3
95% Confidence Interval	(15.1, 27.2)	(1.3, 3.2)	(11.3, 21.0)	(1.8, 4.0)	(7.6, 13.0)	(0.9, 3.2)	(9.6, 16.8)	(1.1, 3.2)	(12.2, 22.1)	(1.5, 3.5)
IRR (per 1,000 per annum)	9.8		5.7		5.6		6.6		7.2	
95% Confidence Interval	(5.8, 16.3)		(3.5, 9.3)		(3.0, 10.3)		(3.8, 11.6)		(4.3, 11.9)	