Screening for tuberculosis among high-risk groups attending London Emergency Departments: a prospective observational study

Rishi K. Gupta[1], Swaib A Lule[1], Maria Krutikov[1], Lara Gosce[1], Nathan Green[2], Jo Southern[3], Ambreen Imran[4], Robert W Aldridge[5], Heinke Kunst[6], Marc Lipman[4,7], William Lynn[8], Helen Burgess[9], Asif Rahman[10], Dee Menezes[5], Ananna Rahman[6], Simon Tiberi[6,11], Peter J White[2,12], Ibrahim Abubakar[1]

Affiliations:

1. Institute for Global Health, University College London, London, UK
2. MRC Centre for Global Infectious Disease Analysis and NIHR Health Protection Research Unit in Modelling and Health Economics, Imperial College London, London, UK
3. TB Unit, Public Health England, Colindale, London, UK
4. Royal Free London NHS Foundation Trust, London, UK
5. Centre for Public Health Data Science, Institute of Health Informatics, University College London, London, UK
6. Blizard Institute, Queen Mary University of London, London, UK
7. UCL-TB and UCL Respiratory, University College London, London, UK
8. London North West University NHS Trust, London, UK
9. West Middlesex University Hospital, Chelsea and Westminster NHS Foundation Trust, London, UK
10. Imperial College London NHS Trust, London, UK
11. Division of Infection, Barts Health NHS Trust, London, UK
12. Modelling and Economics Unit, National Infection Service, Public Health England, London, UK

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Corresponding Author: i.abubakar@ucl.ac.uk

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To the editor

Most tuberculosis (TB) cases in low-incidence settings are thought to be due to reactivation of latent TB infection (LTBI) in high-risk populations.[1-3] Assessment of patients at Emergency Departments (EDs) is a potential opportunity to achieve early TB diagnosis, and interrupt transmission. An earlier study in London found that 39% of patients diagnosed with TB had attended an ED in the preceding six months.[4] Of these, 76% had a chest radiograph performed, of which 86% and 40% were abnormal in cases of pulmonary and extra-pulmonary TB, respectively. Attendances at EDs provides opportunity to identify individuals with LTBI, who may be at risk for progression to active disease and unlikely to engage with healthcare services via other routes.

Between July 2013 - May 2017, we recruited individuals over the age of 16 years, who were recent entrants from, or prolonged travellers to, high TB incidence countries, or people with a history of homelessness, imprisonment, or problem drug use attending EDs at seven London hospitals. We investigated the yield of interferon-gamma release assay (IGRA) and TB disease screening among eligible ED attendees, regardless of their reason for ED attendance. Participants were tested with either the QuantiFERON Gold-in-Tube (Qiagen, Hilden, Germany), or QuantiFERON-TB Plus. A subset of participants were screened for TB disease; symptomatic individuals (≥2 week history of cough or fever, accompanied by haemoptysis, drenching night sweats, or unexplained weight loss) were tested with chest radiograph, sputum Xpert MTB/RIF and subsequent referral for further evaluation and management.[5] Those screened with IGRA were followed-up through data linkage to national TB surveillance notifications to identify subsequent active TB notification.[6] This study was approved by the Stanmore National Health Service (NHS) Research Ethics Committee (14/LO/2160) and registered on ClinicalTrials.gov (NCT02512484; full study protocol available at the institutional website.[7, 8]

Descriptive analyses were performed to assess the yield of screening and incidence rates of TB disease among those tested by IGRA. Logistic regression models were used to examine factors associated with IGRA positivity. The final multivariable model included *a priori* variables (age, sex, presence of social risk factors, history of TB contact, ethnicity and country of birth), and variables found to be significant in univariable analyses ($p<0.2$).

A total of 1,407 participants were recruited to the IGRA screening study, of whom 241 (17.1%) had a history of substance use disorders, homelessness or imprisonment, while the remainder were migrants from high TB burden countries. Of the 1,407 participants, 642 (45.6%) were female, and the majority (1,010; 70.8%) were over 35 years of age (median 45 years). Among those recruited due to recent migration from, or travel to, a high TB incidence country, most participants (736/1,166; 63.1%) were South Asian, while the largest ethnic group among those with social risk factors was white (100/241; 41.5%). Almost one fifth (258/1,407; 18.2%) of participants reported previous contact with a TB case. Diabetes was common, affecting 239/1,407 (17.0%). Of the 1407 participants, 109 (7.7%) were not

registered to a general practitioner (GP) practice; this was more common among those with social risk factors (35/241; 14.5%) when compared with the migrant group (74/1,166; 6.3%).

IGRA results were available for 1232 participants, of which 34 (2.4%) were indeterminate. A total of 256/1,198 (21.4%) participants with valid available were IGRA positive. The prevalence of IGRA positivity was 24% among migrants and 19% among those with social risk factors (Table 1). In a multivariable logistic regression model, only male sex (odds ratio (OR) 1.38; 95% confidence interval (CI) 1.01-1.87; p=0.041), age >35 years (OR 1.67; 95% CI 1.12-2.55; p=0.012) and non-UK country of birth (OR 6.32; 95% CI 2.99-15.6; p<0.001) were independently associated with IGRA-positivity.

Participants screened by IGRA were followed up for a median of 381 days (IQR 303-605), via linkage to national TB surveillance records until 31/12/2017. Of the 256 with a positive IGRA, five were notified with TB disease during follow-up, giving a TB incidence rate among those with a positive IGRA of 1476.4/100,000 person-years (95% confidence interval (529.4-3173.2). All five TB cases had extra-pulmonary disease (lymph node (notified 5 days after recruitment), spinal (35 days), disseminated (52 days), genito-urinary (162 days) and intra-abdominal (412 days)), and none reported recent TB contact at study recruitment. Median quantitative interferon-gamma responses to *Mycobacterium tuberculosis* antigens were 6.02IU/mL (range 0.62 to >10) among the five progressors to TB disease, compared to 2.57IU/mL (0.35 to >10) among non-progressors. No TB cases were notified among participants who had negative or indeterminate IGRAs.

Of the 513 participants screened in the active TB study, only 14 (2.7%) were symptomatic and 13 had a chest radiograph, with eight providing an adequate sputum sample for Xpert MTB/RIF testing. None of these patients were diagnosed with TB during the study.

Previous studies have retrospectively reviewed ED presentations among notified TB cases in low-incidence settings,[4, 9-12] and examined the yield of TB screening in high-incidence countries.[13, 14]. A study in the US also investigated the yield of LTBI screening among risk groups attending EDs using the tuberculin skin test (TST) [15]. Notably, nearly half of the participants in the US study did not return to have the TST read. Our study has demonstrated the feasibility of prospective IGRA testing among high-risk groups attending EDs in London. Valid IGRA results were available for 85% of participants, which is comparable to other IGRA evaluations.[16, 17] Linkage to national TB surveillance records provided a previously validated mechanism to identify participants screened by IGRA who subsequently progressed to TB disease [6], with median follow-up longer than one year.

Major study limitations were that patients with positive IGRA results were not routinely linked to TB services for evaluation for TB disease and consideration of LTBI treatment since LTBI screening among risk groups attending EDs was not part of national policy at the time. Thus, we are unable to estimate the proportions of IGRA-positive participants who would have started and completed therapy if referred to TB services following detection. This remains a key knowledge gap, since effectiveness (and cost-

effectiveness) of screening is dependent upon completion of LTBI treatment for these individuals, to reduce risk of TB disease. In addition, although the vast majority of participants in the study were registered with general practitioners, it is unclear how engaged they were with these services; limiting our ability to assess precisely how well ED screening could complement the primary care screening programme. Data was not available on individuals who attended EDs and screened for eligibility but not recruited to the study.

In the TB disease screening study arm, proactive screening for pulmonary TB disease used a symptom screen followed by chest radiograph and sputum testing. Consequently, pulmonary TB cases without typical symptoms and extra-pulmonary cases may have been missed. Moreover, our sample size of 513 participants screened for TB symptoms may have been too small to detect active cases; we therefore could not evaluate risk factors for active TB or cost-effectiveness of TB disease screening.

In summary, our study suggests that ED IGRA screening among TB risk groups could be implemented to identify individuals at risk of TB who may be difficult to engage via other screening approaches. Such screening must be supported by a dedicated protocol that detects individuals at higher risk of TB for screening, and resources to facilitate onward referral of those with a positive IGRA to local TB services. In contrast, this study suggests that resource-intensive, symptom-based active TB screening in EDs is unlikely to be worthwhile as the yield is likely to be too low to justify the resource. However, other high-throughput screening models such as automated, routine chest X-rays review in EDs may be evaluated in future research.

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Data sharing

The authors agree to share the data on reasonable request.

Contributors

RKG wrote the first draft of the manuscript. RKG, MK and SAL were responsible to the critical review of the draft. RKG, LG and NG performed the analysis with oversight from PJW and IA. IA conceived and designed the study, with support from JS, RWA and AR. IA and JS led recruitment of participants with all site principal investigators (including ML, HK, WL, HB AR and RD). AI, NG, DV and AR contributed to participant recruitment and follow-up. All other authors contributed to study design, analysis or interpretation. All authors have seen and agreed on the final submitted version of the manuscript.

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Competing interests

All authors have completed the Unified Competing interest form (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Transparency declaration

The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported and that no important aspects of the study have been omitted.

Table 1: Table showing risk factors for latent tuberculosis infection (LTBI) in multivariable logistic regression model (n=1,027). Variables were included in the model if considered of clinical importance *a priori*, or if significant in univariate analysis (p<0.2). Percentages reflect row percentages. IGRA = interferon-gamma release assay; OR = odds ratio; CI = confidence interval

	IGRA result		Univariable				Multivariable		
Characteristic	Negative, N = 942[1]	Positive, N = 256[1]	N	OR[2]	95% CI[2]	p-value	OR[2]	95% CI[2]	p-value
Age (years)			1,193			<0.001			0.012
<=35	286 (87%)	41 (13%)		—	—		—	—	
>35	652 (75%)	214 (25%)		2.29	1.61, 3.33		1.67	1.12, 2.55	
Missing	4	1							
Sex			1,193			0.062			0.041
Female	446 (81%)	104 (19%)		—	—		—	—	
Male	493 (77%)	150 (23%)		1.30	0.99, 1.73		1.38	1.01, 1.87	
Missing	3	2							
Ethnicity			1,188			0.007			0.2
White	165 (87%)	24 (13%)		—	—		—	—	
South Asian	534 (77%)	162 (23%)		2.09	1.34, 3.38		1.56	0.89, 2.89	
Black African Or Caribbean	52 (73%)	19 (27%)		2.51	1.27, 4.95		2.13	0.96, 4.75	
Other	184 (79%)	48 (21%)		1.79	1.06, 3.10		1.29	0.68, 2.51	
Missing	7	3							
Country of Birth			1,190			<0.001			<0.001
UK	180 (93%)	13 (6.7%)		—	—		—	—	
Non-UK	755 (76%)	242 (24%)		4.44	2.58, 8.33		6.32	2.99, 15.6	
Missing	7	1							
TB contact	161 (75%)	53 (25%)	1,160			0.175			0.2

	IGRA result		Univariable				Multivariable		
Characteristic	Negative, N = 942[1]	Positive, N = 256[1]	N	OR[2]	95% CI[2]	p-value	OR[2]	95% CI[2]	p-value
Missing	29	9							
No				—	—		—	—	
Yes				1.28	0.89, 1.80		1.28	0.87, 1.85	
Diabetes	147 (74%)	53 (26%)	1,191			0.064			0.4
Missing	7	0							
No				—	—		—	—	
Yes				1.40	0.98, 1.98		1.16	0.79, 1.68	
Any social risk factor*	153 (81%)	37 (19%)	1,198			0.483			0.5
No				—	—		—	—	
Yes				0.87	0.58, 1.27		1.20	0.70, 2.01	
BMI (kg/m2)			1,165			0.032			0.5
<=25	398 (82%)	90 (18%)		—	—		—	—	
>25	517 (76%)	160 (24%)		1.37	1.03, 1.83		1.10	0.81, 1.51	
Missing	27	6							
Travel (last 3 years)**	809 (78%)	234 (22%)	1,177			0.012			0.4
Missing	17	4							
No				—	—		—	—	
Yes				1.86	1.14, 3.22		1.35	0.67, 2.91	
Registered with a GP	871 (78%)	240 (22%)	1,198			0.474			
No				—	—				
Yes				1.22	0.72, 2.21				

[1]Statistics presented: n (%); Median (IQR)

[2]OR = Odds Ratio, CI = Confidence Interval

*Includes history of homelessness, imprisonment or harmful drug use.

	IGRA result		Univariable				Multivariable		
Characteristic	Negative, N = 942[1]	Positive, N = 256[1]	N	OR[2]	95% CI[2]	p-value	OR[2]	95% CI[2]	p-value

**Indicates any travel to a high TB incidence country in the last 3 years.

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