TRSTMH

Screening diabetes mellitus patients for pulmonary tuberculosis: a multi-site study in Indonesia, Peru, Romania and South Africa.

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Screening diabetes mellitus patients for pulmonary tuberculosis: a multi-site study in Indonesia, Peru, Romania and South Africa.

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Abstract

Background: Diabetes Mellitus (DM) patients are 3-times more likely to develop tuberculosis (TB) ~~disease~~ than the general population. ~~WHO promotes~~ A~~a~~ctive TB screening in people with DM ~~as~~ is part of a bi-directional approach. The aim of this study was to conduct pragmatic active TB screening among DM patients in four countries to inform policy.

Methods: DM patients were recruited in Indonesia (n=809), Peru (n=600), Romania (n=603), and South Africa (n=51). TB cases were diagnosed using an algorithm including clinical symptoms and chest x-ray. Presumptive TB patients were examined with sputum smear and culture.

Results: 171 (8.3%) individuals reported ever having had TB (South Africa 26%; Indonesia 12%; Peru 7%; Romania 4%), 15 of whom were already on TB treatment. Overall, 14 (0.73%, 95% CI 0.40 – 1.23%) TB cases were identified from screening. Poor glucose control, smoking, lower body mass index, education and socio-economic status were ~~all~~ associated with newly diagnosed/current TB. Thirteen of the 14 TB cases diagnosed from this screening would have been picked up from a symptom-based approach.

Conclusions: These data support the WHO recommendation for routine symptom-based screening for TB in known DM patients in high TB-burden countries. DM patients with any symptoms consistent with TB should be investigated and diagnostic tools should be easily accessible.

Key words: Diabetes mellitus, Screening, Tuberculosis

Introduction

Tuberculosis (TB) remains a major global public health threat with more than 10 million TB cases and 1.3 million deaths every year.[1] Globally the number of people living with diabetes mellitus (DM) is estimated to grow from 425 million to 629 million by the year 2045.[2] People with DM have an estimated three times greater risk of developing active TB compared to non-DM patients.[3-6] Moreover, patients with concurrent TB and DM have poorer outcomes and more treatment failure.[7, 8] In 2013, it was estimated that approximately 15% of adult TB cases globally were attributable to DM – corresponding to about one million cases of DM-associated TB per year.[9] Low- and middle-income countries (LMIC), which are experiencing the greatest increase in number of people with DM and tend to have ongoing high TB burdens, will increasingly be affected the most.[5, 9-11]

Enhancing joint activities for TB and DM control is recommended by the World Health Organization (WHO)[12] and the International Union against TB and Lung Disease.[13] Specifically, one-off active screening is recommended for newly diagnosed DM patients, while symptom-based passive screening is recommended for people with DM already in care. Detailed and up-to-date clinical and epidemiological data, however, remain unknown in many countries and it is not clear how best to operationalise bi-directional screening and co-management of TB and DM within existing health systems.[6, 9, 10] The present study was part of the TANDEM multi-national research programme exploring the interface between TB and DM in four countries – Indonesia, Romania, Peru and South Africa.[14] The aim of this study was to determine the yield from a single active screening process for TB in known DM patients, in the four countries, compare a universal x-ray based algorithm with the yield from a symptom-based approach and explore possible factors associated with the diagnosis of TB to assist TB screening algorithms.

Methods

Study design and settings

This cross-sectional study was conducted in four field sites in Indonesia, Peru, Romania and South Africa. In Indonesia, 9.5% of TB cases in 2010 were estimated to be attributable to DM, and in

2030 this is expected to increase to 14.4% (a relative increase of 50%).[5] A similar increase in TB-DM comorbidity is also expected in South Africa, Peru and Romania[9,15-18] (Supplementary Table S2). In Indonesia, DM patients were recruited from 25 community health centres (CHCs) and from the outpatient endocrinology clinic in a tertiary hospital in Bandung. Recruitment in Peru was conducted in the outpatient diabetes clinic at one tertiary hospital in Lima. Patients in Romania were recruited from two secondary level hospitals in Craiova. In South Africa, patients were recruited at three community health care clinics in Capetown (Supplementary file). We aimed to recruit approximately 2000 DM patients. We anticipated that approximately 1-2% (n=20-40) of DM cases overall would be diagnosed with TB disease.

Study procedures

Known DM patients aged above 18 years were recruited from December 2013 to June 2016. Those who had gestational or steroid-induced diabetes were ineligible. Following written informed consent, research doctors conducted an in-person interview and examination. Data collected included socio-demographic characteristics (age, gender, ethnicity, education, employment, residence, household members), socio-economic factors (sellable and non-sellable assets), behavioural characteristics (smoking and alcohol consumption), ~~and~~ diabetes characteristics (DM history, medication, complications and management) and comorbidities. Anthropometric data (weight, height, mid-upper arm circumference (MUAC), waist, and hip circumference) were measured by research nurses using calibrated digital scales and a Standard Operating Procedure. Non-fasting venous blood was taken for laboratory haemoglobin (Hb), and glycated haemoglobin (HbA1c), unless a recent (<3 months) HbA1c measurement was available. HIV status was determined for any patients who had probable or definite TB.

TB screening

Patients were asked whether they had a history of TB or were currently taking TB medication. Questions about TB symptoms included cough, sputum production, fever, dyspnoea, weight loss, and chest discomfort. They were examined for the presence of a Bacillus Calmette-Guerin (BCG) scar and all underwent a chest x-ray that was read by a radiologist independent of the study.[19,20]

Those who had a chest x-ray result suggestive of TB *or* symptoms of cough for two or more weeks were asked to give two sputum samples (morning-spot) for acid-fast bacilli (AFB) smear and *M. tuberculosis* culture testing in certified local laboratories in each site. Xpert© MTB/RIF testing (Cepheid, Sunnyvale, CA) was also performed on patients who were suspected to have drug-resistant TB, or at the respiratory clinician's discretion. In Romania, DM patients were only asked to provide sputum if they had a chest x-ray result suggestive of TB *as well as* a cough of two or more weeks; those who had a suggestive chest x-ray were followed passively for 6 months for the development of TB, through searching endocrinology and TB clinic records.

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Patients with and without a past history of TB were classified into four categories:

1) Definite TB: on anti-TB medication, or *M. tuberculosis culture* or Xpert MTB/RIF positive.
2) Probable TB: TB symptoms, chest x-ray suggestive of TB and sputum smear positive but culture negative.
3) Possible TB: TB symptoms and/or chest x-ray suggestive of TB, but smear and culture negative.
4) No TB: no evidence of TB after symptom review and investigations.

Data analysis

A central, anonymized database was developed using REDCap 6.9.1.[21] Data collection was standardised and monitored and reviewed locally and centrally. Weight and height were classified according to the Asia Pacific Criteria of Body Mass Index (BMI)[22] for Indonesian patients, and according to the WHO[23] for the other sites. Central obesity was according to the International Diabetes Federation[24] (Supplementary Table S3). Waist-to-Hip ratio (WHR) was measured as the waist circumference divided by the hip circumference.[23] Laboratory HbA1c was categorised into four groups for analysis: <6.5%; 6.5-8.0%; 8.1-10%; ≥10%.[25,26] Anaemia was classified as <12.0 d/l for females and <13.0 d/l for males.[27] Principal Component Analysis[28] was performed to build a socio-economic status index based on asset ownership by patients that included non-sellable (possession of a bank account, type of sanitation facility, household water source) and sellable assets (e.g. stove, refrigerator, washing machine, television).

Categorical variables were presented with their frequencies and continuous variables were summarized using median and interquartile ranges (IQR). Proportions with TB prior to screening and from the screening process itself at each site were calculated. Univariable analysis was undertaken to assess possible risk factors for patients classified as newly diagnosed TB or currently on treatment and reported as crude odds ratios and 95% confidence intervals. All factors with a p-value of <0.15 on the univariable analysis as well as variables considered potentially important (age, sex, BCG) were included in a multivariable analysis by logistic regression, with country entered as a fixed effect and robust standard errors calculated using country as a cluster variable. All statistical analyses were performed using STATA 12.1.[29]

Results

General patient characteristics

A total of 2063 DM patients were included in Indonesia (n=809), Peru (n=600), Romania (n=603), and South Africa (n=51). All patients in Peru and South Africa had type 2 DM, compared to 98% in Indonesia and 87% in Romania. Almost half (48%) of patients had had DM for six or more years. The overall median age was 59 years, 62% were female, 33% had an education of primary school or less, and 28% had socio-economic status classified as Q1-poorest or Q2-poor. The median overall HbA1c was 8.7% and ranged from 7.7 in Peru to 10.4 in South Africa. More than a third of patients (33%) had an HbA1c of >10%; this proportion was higher in Romania (42%) and South Africa (62%) (Table 1). Of participants with a known HIV status, six were HIV positive (Indonesia 2; Peru 1; Romania 1; South Africa 2).

TB characteristics

A total of 171 (8.3%; 95% CI 7.1-9.6%) patients had been previously diagnosed with TB (South Africa 25.5% [95% CI 14.3-39.6%]; Indonesia 12.0% [95% CI 9.8-14.4%]; Peru 6.7% [95% CI 4.8-9.0%]; Romania 3.5% [95% CI 2.2-5.3%]), 15 (all in Indonesia) of whom were on TB treatment at the time of recruitment. Just over half of the patients reported having any symptoms that may be in keeping with TB (54%) (Table 2). Despite some between-country variability, the most

frequent symptom reported was weight loss (33.8%) followed by breathlessness (16.8%). Cough of more than two weeks was reported by 10.2% of patients. Of those with a chest x-ray result (n=1917), 61 patients (all in Indonesia) had an x-ray suggestive of active TB, and 33 had possible active TB (Table 2). Six patients (Indonesia n=5; Peru n=1) had an AFB positive result and 11 patients (Indonesia n=10; South Africa n=1) had a culture positive result. Of the 38 patients (Indonesia n=6; South Africa n=32) who had an Xpert test performed, 4 were positive, none were rifampicin resistant. Fourteen patients were positive on any TB test (Indonesia n=12; Peru n=1; South Africa n=1) (Tables 2 & 3). The clinical symptoms and diagnostic results for these 14 patients are described in Table 4. Indonesia had the highest proportion of patients with definite TB or on anti-TB medication (n=25, 3.1%; 95% CI 2.0-4.6%) and the highest proportion of possible TB (n=76, 9.5%; 95% CI 7.5-11.7%) (Table 3). In Peru there was one case of definite TB (0.2%; 95% CI 0.0-1.0%) and one case of possible TB (0.2%; 95% CI 0.0-1.0%). In Romania there were three cases of possible TB (0.6%; 95% CI 0.1-1.7%) but none had a cough of any duration. In South Africa, there was one case of definite TB (2.0%; 95% CI 0.05-10.4%) and five cases of possible TB (9.8%; 95% CI 3.2-21.4%) (Table 3).

Factors associated with newly diagnosed TB or patients currently on treatment

Multivariable analysis including patients newly diagnosed with TB or currently on TB treatment (n=28) showed that being aged ≥60 years (AOR 0.69; 95% CI 0.55-0.85), increased BMI (18-24.9 kg/m^2: AOR 0.19 (95% CI 0.18-0.20), 25-29.9 kg/m^2: AOR 0.09 (95% CI 0.07-0.11), ≥30 kg/m^2: 0.11 (95% CI 0.03-0.36)), DM duration between 6-15 years (AOR 0.66; 95% CI 0.61-0.72), increased education (Secondary school: AOR 0.75 (95% CI 0.67-0.83), High school: AOR 0.25 (95% CI 0.11-0.58), Post high school: AOR 0.27 (95% CI 0.21-0.34)), and higher socio-economic status, (Middle-income: AOR 0.37 (95% CI 0.22-0.63), Upper-middle-rich: AOR 0.34 (95%CI 0.25-0.45)) were all associated with a reduced odds of TB. Being female (AOR 2.67; 95% CI 1.63-4.37), ~~i~~ncreased HbA1c (8.1-10%: AOR 1.21 (95% CI 1.14-1.28), >10%: 2.60 (95% CI 2.15-3.15)) and smoking (AOR 2.15; 95% CI 1.21-3.81) were ~~both~~ associated with a higher risk of TB (Table 5). When each risk factor was considered as a possible guide to restrict the number needed to investigate (Supplementary Table S4), none performed better than symptoms. For example, 13 of the 14

newly diagnosed TB cases were found amongst the 54% of DM patients who had at least one TB symptom, while 50% of DM patients had a BMI<27 kg/m^2 and 12 of the 14 TB cases were found within this group.

Discussion

In this study, the yield of new diagnoses from an active screening process, including universal chest x-ray, was very low, even in the highest burden country (Indonesia, yield 1.5%). However, a reasonably large proportion of DM patients had been diagnosed with TB in the past. The majority of DM patients in our cohorts were type 2 DM and aged over 50 years. Most had poor glycaemic control. While living in a high incidence country, poor glucose control, lower education and socio-economic status, smoking, and those with a low BMI may place DM patients at higher risk of TB, symptoms alone as a guide to investigation would have reduced the number investigated by half, and picked up 13 of 14 cases diagnosed. These findings support the WHO guidelines for doctors of known DM patients in high TB burden countries to have a symptom-based approach to the diagnosis of TB disease.

A systematic review[30] found four studies prior to 2009 that used chest x-ray and bacteriological confirmation to screen for TB. These studies from Hungary, India (n=2) and South Korea found between 2 and 6% of DM patients had prevalent pulmonary TB and the yield was highest in the highest TB burden countries. In Mexico, Castellanos-Joya et al,[31] conducted screening in 783 DM patients from a large registry: 27 (3.4%) had already been diagnosed with TB and 11 (1.4%) were newly diagnosed and bacteriologically confirmed. Zhao et al[32] screened previously diagnosed DM patients in the community in China with chest x-ray followed by sputum smear and culture examination: 54 (1.3%) of 4085 DM patients had previously been diagnosed with TB, 14 (0.3%) TB cases were identified from screening. In Botswana, Majumder et al[33] screened 672 DM patients for TB in Soweto, conducting Xpert® tests on those who had symptoms of TB: 67 (10%) ~~of~~ patients had a past history of TB, 27 (4%) had symptoms and none were diagnosed with TB from screening. Berkowitz et al[34] screened 440 DM patients in a clinic in Cape Town using symptom screening alongside microbiological examination of sputum using smear, culture and

GeneXpert in all who were able to provide a sample: 13 (3%) microbiologically confirmed TB cases were identified, seven of whom were asymptomatic. Mtwangambate et al[35] screened 693 DM patients at one hospital in Tanzania for cough, followed by detailed symptom screening and sputum collection for smear and culture: 9 (1.3%) patients were diagnosed with TB.

Consistent with our study, lower BMI as a risk for TB in DM patients has been observed elsewhere.[34,36] Poor glycaemic control has also been identified by others to be associated with TB in DM patients in cross-sectional[33] and cohort studies.[37] Lee et al[37] followed 11,260 DM patients in Taiwan as part of a cohort of 123,546 individuals in the community. DM patients with poor glycaemic control had twice the risk of TB compared to both DM patients with good glycaemic control and non-DM participants. Berkowitz et al[34], in Cape Town found a strongly significant association with HIV status (adjusted OR 11.3; 95% CI 3.3 to 39.4). HIV positivity was too low to assess in our study population.

With respect to regular active symptom-based screening, Lin et al[38] screened for TB, on the basis of symptoms, in DM clinics in five hospitals across eastern China. Approximately 75% of DM patients attending the clinics were symptom screened and from 11,330, seven were found to have TB already and 48 patients were newly diagnosed with TB (21 were bacteriologically confirmed). The India Diabetes Mellitus-Tuberculosis Study Group[39] introduced routine symptom-based screening for TB amongst DM patients in six Indian tertiary care facilities. Uptake reached approximately 50% of patient clinic visits and 254 TB cases were identified (114 were bacteriologically confirmed through sputum smear) from nearly 10,000 patient visits, although only 18 were attributable to the screening.

Our study had several limitations. While data completeness was generally high, for some investigations there were a reasonable number of patients who were not tested. For example, 37% of patients in Peru did not have an HbA1c result and 16% of patients in Romania did not have a chest x-ray. The number of patients from South Africa was very small because the site was earmarked primarily for intense immune-bioprofiling on a small number of patients. For

Romania, the indications for sputum examination were different from the other sites. We followed Romanian patients passively, for 6 months to confirm that they did not develop TB and we note that less than 5% of patients with a positive sputum smear and culture are expected to have a normal chest x-ray.[40] Finally, it is possible that some patients had a mis-diagnosis of TB in the past and variables that are time dependent may have had a different result around the time of a prior diagnosis, potentially biasing our results, although we restricted our multi-variable analysis to include only current TB cases. Lastly, this study was of DM patients presenting at a health clinic or hospital and therefore is not generalizable to people with DM in the general population.

Even in high TB burden countries, the yield from a single screen in known DM patients is likely to be low, using chest x-ray and microbiological confirmation, and almost all newly diagnosed TB cases are likely to be picked up through a symptom-based approach. Doctors should have a high index of suspicion of TB in DM patients who present with symptoms and signs consistent with TB disease. Challenges such as the need to travel to other facilities for diagnostic testing could be addressed by provision of a one-stop service for diagnosis (chest x-ray and sputum examination) in high TB burden settings.[35, 41] Where available, tests for *M. tuberculosis* infection could be used and preventive treatment considered.[42] Furthermore, a chronic disease approach is recommended, whereby chest x-ray can be used to screen for diseases such as heart failure when done on patients suspected of having TB. Further studies are required in newly diagnosed DM patients to confirm whether the guideline for one-off active screening is optimal.

Authors' contributions

BA, CUG, NMP, HMD, RR, GW, JAC, DAJM, RvC, and PH conceived the study and designed the study protocol; BA, SMM, CUG, NMP, KR, RCK, CZ, ALR, STM, LK, SL, RR, MI, and GW carried out study implementation; BA, SMM, FP, and JAC analysed and interpreted the data; BA and SMM drafted the manuscript; JAC, DAJM, RvC, and PH critically revised the manuscript. All authors reviewed and approved a final draft of the manuscript. BA, SMM and PH are guarantors of the paper.

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Conflict of interest

The authors declare that no competing interests exist.

Ethical approval

Ethical approval was received from the Observational/Interventions Research Ethics Committee, London School of Hygiene and Tropical Medicine (LSHTM ethics ref: 6449) and Institutional Review Boards in Indonesia, Romania, Peru and South Africa.

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Table

Table 1: General and diabetes characteristics of diabetes patients (total and stratified by country)

Characteristics	Total n (%) n=2063	Indonesia n (%) n=809	Peru n (%) n=600	Romania n (%) n=603	South Africa n (%) n=51
Sex, Female	1286 (62.3)	511 (63.2)	427 (71.2)	321 (53.2)	27 (52.9)
Age; Median (IQR)	59 (52-66)	59 (53-65)	60 (52-67)	59 (51-66)	53 (44-60)
Education					
<Primary school	675 (32.9)	249 (30.8)	304 (50.7)	84 (14.2)	38 (74.5)
Secondary school	474 (23.1)	153 (18.9)	112 (18.7)	201 (33.9)	8 (15.7)
High school	644 (31.4)	229 (28.3)	164 (27.4)	247 (41.6)	4 (7.8)
Post high school	259 (12.6)	178 (22.0)	19 (3.2)	61 (10.3)	1 (2.0)
Not available	11	0	1	10	0
Socio-economic status					
Q1: poorest	232 (11.4)	106 (13.3)	82 (13.7)	43 (7.3)	1 (2.0)
Q2: poor	331 (16.2)	117 (14.7)	121 (20.2)	93 (15.7)	0 (0.0)
Q3: middle income	377 (18.5)	124 (15.5)	126 (21.0)	119 (20.1)	8 (16.0)
Q4: upper middle income	466 (22.8)	182 (22.8)	123 (20.5)	148 (25.0)	13 (26.0)
Q5: richest	634 (31.1)	269 (33.7)	147 (24.5)	190 (32.0)	28 (56.0)
Not available	23	11	1	10	1
Smoking status					
Current	265 (12.9)	117 (14.5)	34 (5.7)	93 (15.4)	21 (41.2)
Past	640 (31.1)	235 (29.0)	222 (37.0)	172 (28.6)	11 (21.6)
Never	1155 (56.1)	457 (56.5)	343 (57.3)	336 (55.9)	19 (37.3)
Not available	3	0	1	2	0
Alcohol consumption	658 (31.9)	14 (1.7)	288 (48.0)	338 (56.1)	18 (35.3)
BMI category[a]					
Underweight	47 (2.3)	29 (3.6)	4 (0.7)	14 (2.3)	0 (0.0)
Normal	512 (24.9)	203 (25.1)	186 (31.1)	111 (18.6)	12 (23.5)
Overweight	572 (27.8)	152 (18.8)	210 (35.1)	188 (31.5)	22 (43.1)
Obese	924 (45.0)	425 (52.5)	198 (33.1)	284 (47.6)	17 (33.3)
Not available	8	0	2	6	0
BMI; Median (IQR)	27.0 (23.8-30.8)	25.3 (22.5-28.1)	27.4 (24.2-31.2)	29.6 (25.9-33.6)	28.7 (25.2-32.1)
Central Obesity					
Females	1080/1282 (84.2)	352/511 (68.9)	409/427 (95.8)	292/317 (92.1)	27/27 (100.0)
Males	474/770 (65.6)	110/298 (36.9)	131/173 (75.7)	217/275 (78.9)	16/24 (66.7)
Duration of DM					
<1 year	392 (19.0)	144 (17.8)	126 (21.0)	122 (20.3)	0 (0.0)
1-5 years	674 (32.7)	311 (38.4)	237 (39.6)	110 (18.3)	16 (32.0)
6-15 years	694 (33.7)	286 (35.4)	139 (23.2)	249 (41.4)	20 (40.0)
≥15 years	299 (14.5)	68 (8.4)	97 (16.2)	120 (20.0)	14 (28.0)
Not available	4	0	1	2	1
DM medication[b]					
No medication	181 (8.8)	65 (8.0)	87 (14.5)	29 (4.8)	0 (0.0)
Insulin	785 (38.1)	230 (28.4)	120 (20.0)	406 (67.3)	29 (56.9)
Metformin	1281 (62.1)	445 (55.0)	392 (65.3)	398 (66.0)	46 (90.2)
Other oral DM drugs	717 (34.8)	365 (45.1)	91 (15.2)	248 (41.1)	13 (25.5)
HbA1c					
<6.5%	299 (16.5)	143 (17.7)	112 (29.5)	43 (7.3)	1 (2.7)
6.5-8.0%	436 (24.1)	234 (29.0)	95 (25.0)	103 (17.5)	4 (10.8)
8.1-10%	487 (26.9)	204 (25.3)	78 (20.5)	196 (33.3)	9 (24.3)
≥10%	589 (32.5)	225 (27.9(	95 (25.0)	246 (41.8)	23 (62.2)
Not available	252	3	220	15	14
HbA1c; Median (IQR)[c]	8.7 (7.0-10.7)	8.3 (6.8-10.3)	7.7 (6.2-10.0)	9.5 (8.1-11.3)	10.4 (9.0-12.0)
Comorbidities					
Infarct (CAD, angina, MI)	325 (15.8)	140 (17.3)	46 (7.7)	133 (22.10	6 (11.8)
Heart failure	15 (0.7)	14 (1.7)	1 (0.2)	0 (0.0)	0 (0.0)
Cerebrovascular disease	6 (0.3)	0 (0.0)	3 (0.5)	0 (0.0)	3 (5.9)
Peripheral vascular disease	28 (1.4)	21 (2.6)	0 (0.0)	6 (1.0)	1 (2.0)
Kidney disease	31 (1.5)	21 (2.6)	7 (1.2)	3 (0.5)	0 (0.0)
Eye problems[d]	1038 (50.3)	279 (34.5)	464 (77.3)	258 (42.8)	37 (72.6)
COPD (including asthma)	9 (0.4)	7 (0.9)	2 (0.3)	0 (0.0)	0 (0.0)
Cancer	22 (1.1)	19 (2.4)	2 (0.3)	1 (0.2)	0 (0.0)

Abbreviations: BCG: Bacillus Calmette-Guérin; BMI: Body Mass Index; CAD: Coronary artery disease; COPD: Chronic obstructive pulmonary disease; DM: Diabetes Mellitus; HbA1c: Glycated haemoglobin (A1c); IQR: interquartile range; MI: Myocardial infarction

[a] Body Mass Index (kg/m^2) was classified as: Underweight (<18.5); Normal (18.5-22.9 Indonesia; 18.5-24.9 Peru, Romania, South Africa); Overweight (23.0-24.9 Indonesia; 25.0-29.9 Peru, Romania, South Africa); Obese (≥25.0 Indonesia; ≥30 Peru, Romania, South Africa)

[b] The DM medication could be in combination or alone
[c] Data available for 806 Indonesia; 380 Peru; 588 Romania; 37 South Africa
[d] Eye problems include blindness, impaired vision, glaucoma, cataract

Table 2: BCG vaccination, history, symptoms and results of investigations, among diabetes patients (total and stratified by country)

Characteristics	Total n (%) n=2063	Indonesia n (%) n=809	Peru n (%) n=600	Romania n (%) n=603	South Africa n (%) n=51
BCG scar	1645 (79.8)	487 (60.2)	534 (89.0)	595 (98.7)	29 (56.9)
Anaemia[a]	393 (23.7)	174 (22.5)	48 (19.7)	151 (25.4)	20 (40.0)
Number of household members					
1-4	1297 (65.0)	488 (60.3)	330 (55.0)	450 (84.0)	29 (56.9)
5+	699 (35.0)	321 (39.7)	270 (45.0)	86 (16.0)	22 (43.1)
Not available	67	0	0	67	0
Previously diagnosed with TB	171 (8.3)	97 (12.0)	40 (6.7)	21 (3.5)	13 (25.5)
Currently on treatment for TB	15 (0.7)	15 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)
Hospitalised in the last year[b]	402 (19.5)	104 (12.9)	58 (9.7)	230 (38.1)	10 (19.6)
TB symptoms:					
Cough ≥2 weeks	211 (10.2)	97 (12.0)	48 (8.0)	55 (9.1)*	11 (21.6)
Coughing sputum	219 (10.6)	116 (14.3)	49 (8.2)	36 (6.1)	18 (35.3)
Coughing blood	9 (0.4)	3 (0.4)	3 (0.5)	2 (0.3)	1 (5.6)
Breathlessness	346 (16.8)	104 (12.9)	76 (12.7)	152 (25.6)	14 (27.5)
Nightsweats	305 (14.8)	106 (13.1)	62 (10.3)	136 (22.6)	1 (2.0)
Chest pain	252 (12.2)	137 (16.9)	0 (0.0)	108 (18.0)	7 (13.7)
Weight loss	698 (33.8)	212 (26.3)	211 (35.2)	259 (43.7)	16 (31.4)
Any TB symptoms[c]	1104 (53.5)	369 (45.6)	301 (50.2)	402 (66.7)	32 (62.8)
Chest x-ray result					
Normal	1239 (64.6)	395 (49.2)	323 (58.1)	490 (96.8)	31 (60.8)
Abnormal – suggestive active TB	61 (3.2)	61 (7.6)	0 (0.0)	0 (0.0)	0 (0.0)
Abnormal – possible active TB	33 (1.7)	26 (3.2)	1 (0.2)	0 (0.0)	6 (11.8)
Abnormal – not TB	562 (29.3)	309 (38.5)	223 (40.0)	16 (3.2)	14 (27.5)
Abnormal – suggestive inactive TB	22 (1.1)	12 (1.5)	10 (1.8)	0 (0.0)	0 (0.0)
Missing/x-ray not done	146	6	43	97	0
Sputum microbiology[d]	n/N (%)	n/N (%)	n/N (%)	n/N (%)	n/N (%)
AFB positive	6/205 (2.9)	5/112 (4.5)	1/43 (2.3)	0/0	0/50 (0.0)
Culture positive	11/154 (7.1)	10/104 (9.6)	0/0	0/0	1/50 (2.0)
Xpert positive	4/38 (10.5)	3/6 (50.0)	0/0	0/0	1/32 (3.1)
Any test positive	14/206 (6.8)	12/113 (10.6)	1/43 (2.3)	0/0	1/50 (2.0)

Abbreviations: AFB: Acid Fast Bacilli; BCG: Bacillus Calmette Guerin; Hb: haemoglobin; IQR: Interquartile range
[a] Proportions were of those with data available: 772 Indonesia; 244 Peru; 595 Romania; 50 South Africa
[b] Hospitalisation could be for any reason – not exclusively for TB
[c] Any of: productive cough, weight loss, breathlessness, night sweats, body temperature >38^{O}C
[d] Categories are not mutually exclusive
* of these 55, no microbiological testing was done at the time of cough. Assessment of hospital records revealed none of these patients were diagnosed with TB in the following six months.

Table 3: Final tuberculosis (TB) case definitions, total and stratified by country

TB case definition categories	Total n=1911		Indonesia n=803		Peru n=557		Romania n=500		South Africa n=51	
	Cases	Proportion % (95% CI*)	Cases	Proportion % (95% CI*)	Cases	Proportion % (95% CI*)	Cases	Proportion % (95% CI*)	Cases	Proportion % (95% CI*)
Definite TB[a]	13	0.7 (0.4-1.2)	11	1.4 (0.7-2.4)	1	0.2 (0.0-1.0)	0	0.0 (0.0-0.7)	1	2.0 (0.05-10.4)
Definite TB[a] or on anti-TB medication	27	1.4 (0.9-2.0)	25	3.1 (2.0-4.6)	1	0.2 (0.0-1.0)	0	0.0 (0.0-0.7)	1	2.0 (0.05-10.4)
Probable TB[b]	1	0.05 (0.001-0.3)	1	0.1 (0.003-0.7)	0	0.0 (0.0-0.7)	0	0.0 (0.0-0.7)	0	0.0 (0.0-7.0)
Possible TB	85	4.4 (3.6-5.5)	76	9.5 (7.5-11.7)	1	0.2 (0.0-1.0)	3	0.6 (0.1-1.7)	5	9.8 (3.3-21.4)

Denominator = total recruited minus those with missing x-rays

*Exact binomial confidence intervals (CI)

[a] Definite TB: culture or Xpert positive

[b] The patient with Probable TB had been diagnosed with TB <6 months and was on TB treatment but still had a positive AFB result

Table 4: Characteristics of patients with definite or probable tuberculosis (TB) diagnosed through screening

Patient	Age	Sex	Country	Symptoms	Chest x-ray	AFB	Culture	X-pert	TB definition
1	66	M	Indonesia	Breathless	Suggestive active TB	Neg	Pos	NA	Definite
2	57	M	Indonesia	No	Suggestive active TB	Pos	Pos	Pos	Definite
3	54	M	Indonesia	Cough 2+ weeks; cough sputum; breathless	Suggestive active TB	Neg	Neg	Pos	Definite
4	53	M	Indonesia	Cough 2+ weeks; cough sputum; breathless; night sweats; weight loss; chest pain	Suggestive active TB	Pos	Pos	Pos	Definite
5	52	M	Indonesia	Weight loss	Suggestive active TB	Neg	Pos	NA	Definite
6	54	M	Indonesia	Cough 2+ weeks; cough sputum; cough blood; breathless; weight loss; chest pain	Suggestive active TB	Pos	Pos	NA	Definite
7	39	F	Indonesia	Cough 2+ weeks; cough sputum; breathless; weight loss; chest pain	Suggestive active TB	Neg	Pos	NA	Definite
8	63	F	Indonesia	Cough 2+ weeks; night sweats	Abnormal, not TB	Neg	Pos	NA	Definite
9	47	M	Indonesia	Weight loss	Suggestive active TB	Neg	Pos	NA	Definite
10	72	F	Indonesia	Cough 2+ weeks; cough sputum; breathless; night sweats; weight loss; chest pain	Suggestive active TB	Pos	Pos	NA	Definite
11	44	M	Indonesia	Breathless; night sweats; weight loss.	Suggestive active TB	Neg	Pos	NA	Definite
12	69	F	Peru	Cough 2+ weeks; cough sputum; breathless; weight loss	Normal	Neg	Pos	NA	Definite
13	48	M	Sth Africa	Cough 2+ weeks; cough sputum; breathless; chest pain	Possible active TB	Neg	Pos	Pos	Definite
14	53	F	Indonesia	Cough 2+ weeks; cough sputum; breathless; night sweats; weight loss; chest pain	Suggestive active TB	Pos	NA	NA	Probable*

Abbreviations: AFB: Acid fast bacilli; NA: Not available; Neg: negative; Pos: positive

*Patient had been diagnosed with TB <6 months and was on TB treatment but still had a positive AFB result

Table 5: Factors associated with newly diagnosed and current TB among diabetes patients (n=28)

Covariate		Crude Odds Ratio (95% CI)	p-value	Adjusted Odds Ratio (95% CI)	p-value
Age at time of recruitment	<40	1.00		1.00	
	40-49	0.97 (0.19-5.09)	0.973	1.50 (0.77-2.94)	0.230
	50-59	0.99 (0.22-4.47)	0.985	1.30 (0.91-1.87)	0.155
	≥60	0.52 (0.11-2.45)	0.410	0.69 (0.55-0.85)	0.001
Sex	Male vs. female	2.27 (1.07-4.83)	0.033	2.67 (1.63-4.37)	<0.001
BMI (kg/m^2)	<18	1.00		1.00	
	18-24.9	0.15 (0.05-0.44)	0.001	0.19 (0.18-0.20)	<0.001
	25-29.9	0.04 (0.01-0.16)	<0.001	0.09 (0.07-0.11)	<0.001
	≥30	0.02 (0.003-0.11)	<0.001	0.11 (0.03-0.36)	<0.001
HbA1c	<6.5%	1.00		1.00	
	6.5-8.0%	1.41 (0.35-5.67)	0.631	1.80 (1.00-3.23)	0.050
	8.1-10%	0.87 (0.19-3.91)	0.853	1.21 (1.14-1.28)	<0.001
	>10%	2.68 (0.77-9.35)	0.121	2.60 (2.15-3.15)	<0.001
Waist to hip ratio	Per 0.1 increase	0.004 (<0.01-0.61)	0.032	0.50 (0.03-7.72)	0.620
DM duration at time of recruitment	Up to 5 years	1.00		1.00	
	6-15 years	0.49 (0.19-1.22)	0.128	0.66 (0.61-0.72)	<0.001
	≥15 years	0.58 (0.17-1.96)	0.378	2.00 (0.45-8.85)	0.362
Taking insulin	Yes vs. no	0.68 (0.30-1.54)	0.358	-	-
Taking metformin	Yes vs. no	0.82 (0.38-1.74)	0.602	-	-
Smoking	Current/past vs. never	2.75 (1.23-6.12)	0.013	2.15 (1.21-3.81)	0.009
Alcohol consumption	Drinks alcohol vs. no drinking	0.17 (0.04-0.74)	0.017	0.97 (0.26-3.66)	0.963
BCG scar	Yes vs. no	0.49 (0.22-1.06)	0.070	1.13 (0.90-1.43)	0.300
Education	<Primary school	1.00		1.00	
	Secondary school	0.69 (0.28-1.70)	0.420	0.75 (0.67-0.83)	<0.001
	High school	0.28 (0.09-0.85)	0.024	0.25 (0.11-0.58)	0.001
	Post high school	0.34 (0.08-1.52)	0.159	0.27 (0.21-0.34)	<0.001
Household members	1-4	1.00			
	>4	0.99 (0.009-0.02)	0.997	-	-
SES	Q1-Q2: poorest-poor	1.00		1.00	
	Q3: middle income	0.37 (0.12-1.13)	0.081	0.37 (0.22-0.63)	<0.001
	Q4-Q5: upper middle-richest	0.26 (0.11-0.61)	0.002	0.34 (0.25-0.45)	<0.001

Abbreviations: BCG: Bacillus Calmette Guerin; BMI: Body mass index; DM: diabetes mellitus; SES: Socio-economic status

Restricted to the total recruited minus those with missing x-rays

Univariate covariates significant at p<0.15 are included in the multivariable model plus age, sex and BCG