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Prevalence and factors associated with tuberculosis infection in India

Sriram Selvaraju [a], Banurekha Velayutham [a,*], Raghuram Rao [b], Kiran Rade [c], Kannan Thiruvengadam [a], Smita Asthana [d], Rakesh Balachandar [e], Sampada Dipak Bangar [f], Avi Kumar Bansal [g], Jyothi Bhat [h], Vishal Chopra [i], Dasarathi Das [j], Shantha Dutta [k], Kangjam Rekha Devi [l], Gaurav Raj Dwivedi [m], Arshad Kalliath [n], Avula Laxmaiah [o], Major Madhukar [p], Amarendra Mahapatra [j], Suman Sundar Mohanty [q], Chethana Rangaraju [r], Jyotirmayee Turuk [j], Pradeep Aravindan Menon [a], Rajendran Krishnan [a], Manjula Singh [s], Krithikaa Sekar [a,1], Aby Robinson [a,1], Alka Turuk [s,1], Nivethitha N. Krishnan [a,1], Nivetha Srinivasan [a,1], Catherine Rexy [a], M. Suresh [a], Luke Elizabeth Hanna [a], Avijit H Choudhury [c], Malik Parmar [c], Ranjani Ramachandran [c], Nishant Kumar [b], Rajendra Panduranga Joshi [b], Somashekar Narasimhaiah [r], Padmapriyadarsini Chandrasekaran [a], A.M. Khan [g,s], Samiran Panda [s], Balram Bhargava [s], on behalf of the National TB Prevalence Survey Group [2]

[a] *ICMR - National Institute for Research in Tuberculosis, Chennai, India*
[b] *Central TB Division, New Delhi, India*
[c] *WHO Country Office, New Delhi, India*
[d] *ICMR - National Institute of Cancer Prevention and Research, Noida, India*
[e] *ICMR - National Institute for Occupational Health, Ahmedabad, India*
[f] *ICMR - National AIDS Research Institute, Pune, India*
[g] *ICMR - National JALMA Institute for Leprosy and Other Mycobacterial Diseases, Agra, India*
[h] *ICMR - National Institute of Research in Tribal Health, Jabalpur, India*
[i] *Government Medical College, Patiala, India*
[j] *ICMR - Regional Medical Research Centre, Bhubaneswar, India*
[k] *ICMR - National Institute of Cholera and Enteric Diseases, Kolkata, India*
[l] *ICMR - Regional Medical Research Centre, Dibrugarh, India*
[m] *ICMR - Regional Medical Research Centre, Gorakhpur, India*
[n] *State TB Cell, Kerala, India*
[o] *ICMR - National Institute of Nutrition, Hyderabad, India*
[p] *ICMR - Rajendra Memorial Research Institute of Medical Sciences, Patna, India*
[q] *ICMR - National Institute for Implementation Research on Non-Communicable Diseases, Jodhpur, India*
[r] *National Tuberculosis Institute, Bangalore, India*
[s] *Indian Council of Medical Research, New Delhi, India*

* Correspondence to: ICMR-National Institute for Research in Tuberculosis, No: 1, Mayor Sathyamoorthy road, Chetpet, Chennai 600031, India.
E-mail address: banurekha.vv@icmr.gov.in (B. Velayutham).

[1] Contributed Equally

[2] Rushikesh Andhalkar, K. Naga Bhushanam, Anshuman Choudhary, Ezhilarasan Ilayaperumal, Alok Kumar, Shreejaa Varrier, Vimith C Wilson, Ashwini Yadav, Ganesh Yadav, Vikas Dhikav, AR Nirmala, Vijay Kumar Shukla, Pranav Patel, Avijit Basu, Anindya Mitra, Rajesh Bhaskar, Asha Frederick, Vinod Kumar Garg, Santosh Gupta, Prasanta Kumar Hota, S.K. Jha, Padmaja Jogewar, Ashwini Khanna, Rajesh Kumar, Sunil Kumar, B.K.Mishra, Varsha Rai, A. Rajesham, Talluri Ramesh, Rajesh Raju, Barun Santra, Aparup Das, Debjit Chakraborty, Rajni Kant, Kanwar Narain, Krishna Pandey, Sanghamitra Pati, Hemalatha Rajkumar, Seema Sahay, Shalini Singh

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ABSTRACT

Background: The risk of tuberculosis (TB) disease is higher in individuals with TB infection. In a TB endemic country like India, it is essential to understand the current burden of TB infection at the population level. The objective of the present analysis is to estimate the prevalence of TB infection in India and to explore the factors associated with TB infection.

Methods: Individuals aged ≥ 15 years in the recently completed National TB prevalence survey in India who were tested for TB infection by QuantiFERON-TB Gold Plus (QFT-Plus) assay were considered for this sub-analysis. TB infection was defined as positive by QFT-Plus (value > 0.35 IU/ml). The estimates for prevalence, prevalence ratio (PR) and adjusted risk ratio (aRR) estimates with 95% confidence intervals (CIs) were calculated.

Results: Of the 16864 individuals analysed, the prevalence of TB infection was 22.6% (95% CI:19.4 –25.8). Factors more likely to be associated with TB infection include age > 30 years (aRR:1.49;95% CI:1.29–1.73), being male (aRR:1.26; 95%CI: 1.18–1.34), residing in urban location (aRR:1.58; 95%CI: 1.03–2.43) and past history of TB (aRR:1.49; 95%CI: 1.26–1.76).

Conclusion: About one fourth (22.6%) of the individuals were infected with TB in India. Individuals aged > 30 years, males, residing in urban location, and those with past history of TB were more likely to have TB infection. Targeted interventions for prevention of TB and close monitoring are essential to reduce the burden of TB in India.

Introduction

Tuberculosis (TB) is the major cause of mortality and morbidity among the communicable diseases. Globally, an estimated 10 million people develop TB and over a million deaths occur annually [1]. India accounts for about 25% of global TB burden, with an estimated TB incidence of 2.77 million in 2022 [2]. India is committed to end TB by 2025 [3]. In this context, it becomes imperative to address Latent TB infection (LTBI) which is the immune response to stimulation by *Mycobacterium tuberculosis* antigens in the absence of clinically active TB [4]. A mathematical modelling study estimated 1.7 billion with LTBI globally in 2014 [5]. Individuals with TB infection can subsequently break down to TB disease. The lifetime risk of developing TB in healthy individuals is 5–10% which however increases in the presence of co-existing conditions such as HIV, undernutrition, diabetes and habits which include smoking and alcohol use [4,6]. Annual risk of TB infection in India by Tuberculin skin test (TST) surveys has been reported as 1.5% in 2005 [7]. Studies in India have quantified the magnitude of TB infection in high-risk groups for TB which include household contacts, diabetes mellites, rheumatoid arthritis, refugees, health care workers [8–14]. In a TB endemic country like India, it is essential to understand the current burden of TB infection at the population level. A critical component of End TB strategy is treatment of LTBI to prevent active TB disease [15]. The objective of the present analysis is to estimate the prevalence of TB infection among general population in India. The factors associated with TB infection were explored.

Methods

Individuals who were tested for TB infection by Interferon Gamma Release Assay (IGRA) in the National TB prevalence survey in India were included in this sub-group analysis. In brief, the TB prevalence survey which was a cross-sectional study was conducted in 443 clusters across India during the period 2019–2021 to estimate the prevalence of microbiologically confirmed pulmonary TB in those aged ≥ 15 years. Participants willing for the study were interviewed using a semi-structured interview schedule after obtaining informed consent. Data on demographic profile, social habits, co-morbid conditions, health-seeking behaviour, TB treatment, symptoms were collected. Chest x-ray was taken for all survey participants except those bed-ridden or pregnant. Body weight (Kg) and height (cm) was recorded. Point of care blood test for blood sugar and haemoglobin was done. Study participants were eligible for sputum collection if they had symptoms suggestive of TB, if on current TB treatment or with a past history of TB or with abnormal chest x-ray. CBNAAT, liquid culture and smear microscopy was done in the sputum specimen. Chest x-ray reading was done by Medical Officer and by Tele radiologist.

Blood test for IGRA

IGRA testing was planned in 52 clusters which were proportionately distributed based on the total number of clusters in the National TB prevalence survey in each of the 20 State groups. Within each State group, the clusters were randomly selected for IGRA testing. Out of the 52 clusters, we were able to conduct IGRA testing in 26 clusters at the National level due to COVID-19 pandemic, covering atleast one cluster in every state group. The distribution of Districts with clusters tested for TB infection by IGRA across India is illustrated in Fig. 1. The Quantiferon -TB Gold Plus (QFT-Plus) assay was done as per the Manufacturers protocol by trained personnel. The cut-off value was 0.35 IU/ml [16].

Operational definitions

TB Infection – Individuals positive by QFT-Plus assay (value > 0.35 IU/ml) [16].

TB uninfected - Individuals negative by QFT-Plus assay.

TB disease - Bacteriological evidence for TB by two tests (CBNAAT/smear/liquid culture) Or in one test and Chest x-ray abnormality.

Smoker – History of smoking in the past or current.

Alcohol user – History of alcohol use in the past or current.

Diabetes – Self reported or having random blood sugar ≥ 200 mg/dl.

Below Poverty Line (BPL) - Self reported based on availability of BPL card issued by the Government.

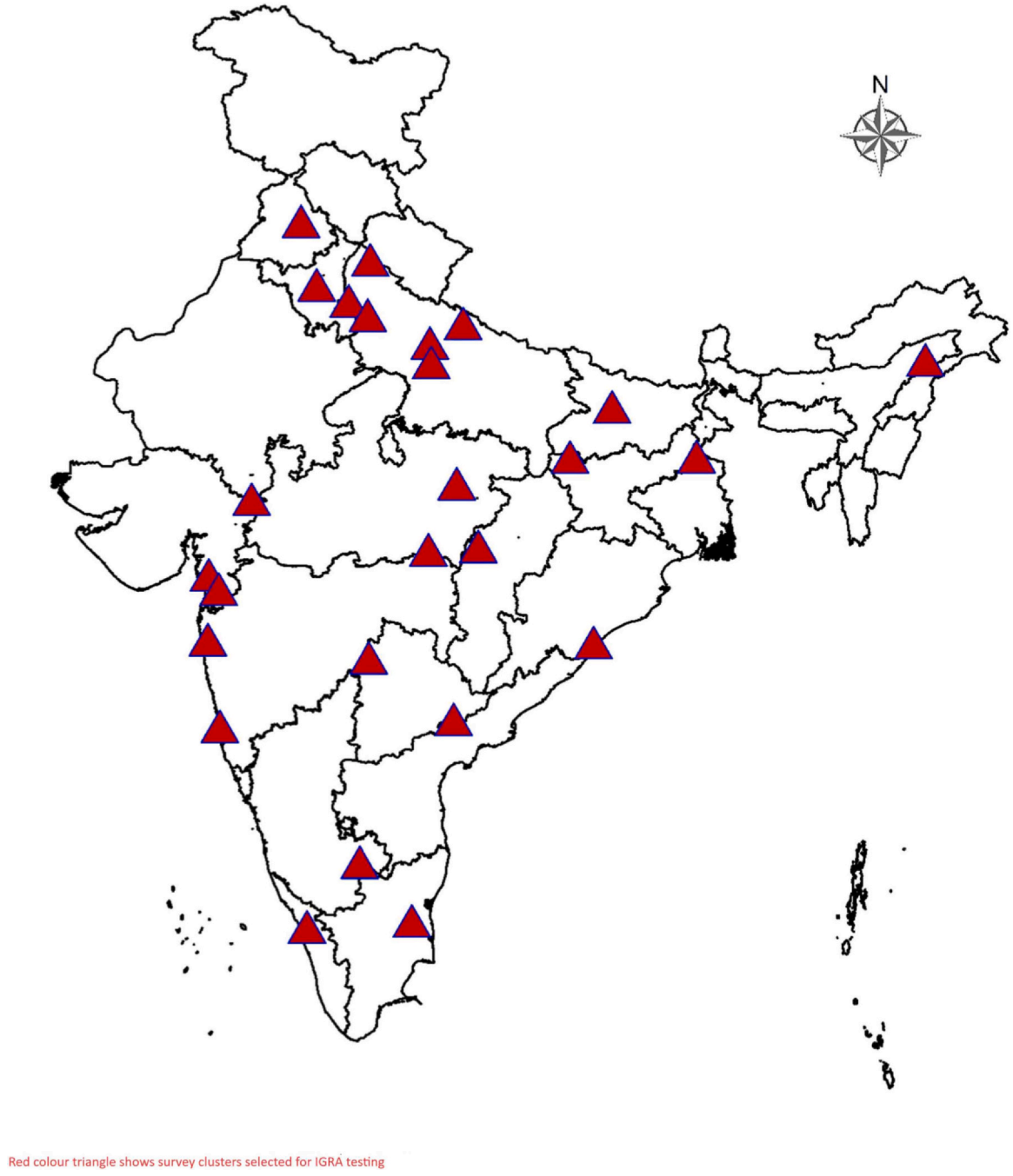

Fig. 1. Distribution of Districts with clusters tested for TB infection by Interferon Gamma Release Assay (IGRA)

Statistical analysis

Data was verified for duplication, outlier and logical validation was done prior to analysis. All the statistical analysis was done using Stata16 (Stata Corporation, College Station, TX, USA). Descriptive analysis for summarizing the characteristics of survey participants is expressed as percentages and rates per 100 with 95% Confidence intervals (CI) using the exact binomial formula. To identify the factors associated with TB infection, a post-hoc analysis was conducted using generalised linear models, binomial and poisson regression along with log link functions. Variables known to be associated with TB infection were chosen based on the data availability, identified by literature review and post-hoc by exploratory data analysis. We calculated the estimates such as prevalence, prevalence ratio (PR) and adjusted risk ratio (aRR) estimates with 95% confidence intervals (CIs) using the Stata *"svy"* commands to adjust for design effect. All the statistical analyses were two-sided, with a type I error set at alpha = 0.05.

Results

There were 20804 individuals eligible in the clusters selected for IGRA of which IGRA testing was done for 16952 (81.5%) [Fig. 2]. The population considered for the present analysis included 16864 (99.5%) of the 16952 tested with IGRA. Those on TB treatment during the survey (n = 27), diagnosed as TB during the survey (n = 51), on TB treatment and diagnosed as TB in the survey (n = 10) were excluded from the analysis.

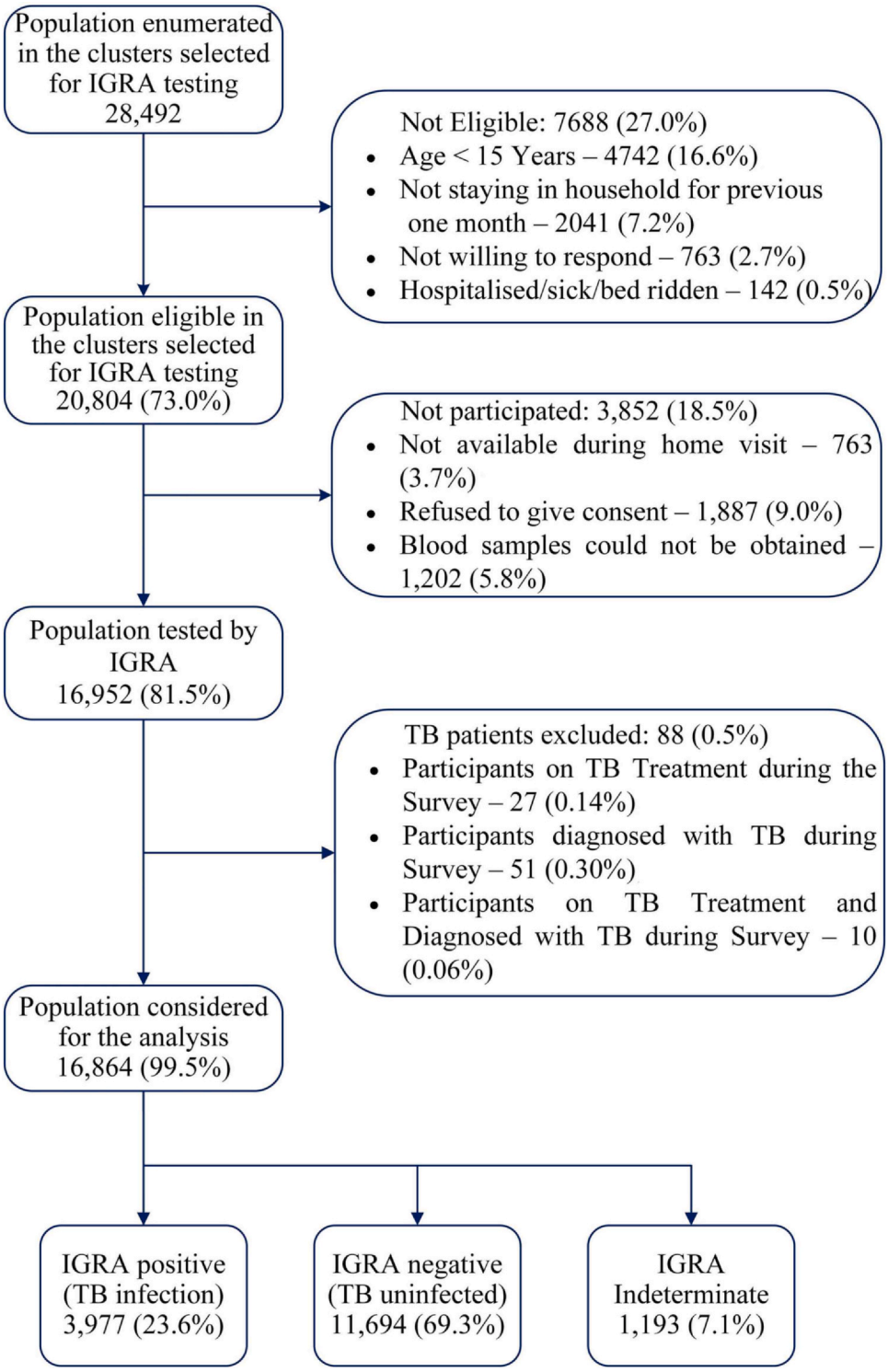

Fig. 2. Flow chart of TB infection status of survey participants tested by Interferon Gamma Release Assay (IGRA)

Baseline characteristics

Of the 16864 analysed, 6546 (38.8%) were aged 15–34 years, 6255 (37.0%) aged 35–54 years and 4063 (24.0%) aged ≥ 55 years (Table 1). There were 9661 (57.3%) females, 11831 (70.2%) were located in the rural area, 7664 (45.4%) were employed and 9734 (57.7%) were below poverty line (BPL). Smokers constituted 1395 (8.3%) and 1644 (9.7%) reported alcohol use. There were 1005 (6.0%) individuals with diabetes, 951 (5.6%) who were hypertensive while HIV status was unknown for 16047 (95.2%). Body mass index (BMI) of < 18.5 kg/m^2 and ≥ 23 kg/m^2 was observed in 3782 (22.4%) and 6532 (38.7%) respectively. There were 391 (2.3%) individuals with past history of TB (Table 1).

Prevalence of TB infection

Of the 16864, QFT-G assay was positive in 3977 (23.6%), negative in 11694 (69.3%) and indeterminate in 1193 (7.1%) [Fig. 2]. The crude prevalence of TB infection was 23.6% (95% CI:22.9 –24.2) and

Table 1
Baseline characteristics of individuals tested by Interferon Gamma Release Assay (IGRA) for TB infection in the survey.

Characteristics		Total (N = 16864) n (%)
Age group (years)	15–24	3279 (19.4)
	25–34	3267 (19.4)
	35–44	3287 (19.5)
	45–54	2968 (17.6)
	55–64	2440 (14.5)
	≥ 65	1623 (9.6)
Gender	Female	9661 (57.3)
	Male	7202 (42.7)
	Transgender	1 (0)
Geographicallocation	Rural	11831 (70.2)
	Urban	5033 (29.8)
Occupation status	Unemployed	1622 (9.6)
	Housewife/Student	7578 (44.9)
	Employed	7664 (45.4)
Below Poverty Line(BPL) status	Non-BPL	7130 (42.3)
	BPL	9734 (57.7)
Smoker	Never	15469 (91.7)
	Current/Past	1395 (8.3)
Alcohol use	Never	15220 (90.3)
	Current/Past	1644 (9.7)
Diabetes	No	15801 (93.7)
	Yes	1005 (6.0)
	Unknown	58 (0.3)
Hypertension	No	15913 (94.4)
	Yes	951 (5.6)
HIV status	Negative	816 (4.8)
	Positive	1 (0)
	Unknown	16047 (95.2)
Body Mass Index(Kg/m^2)	≥ 23.00	6532 (38.7)
	18.50–22.99	6550 (38.8)
	16.50–18.49	2501 (14.8)
	< 16.50	1281 (7.6)
Past history of TB	No	16473 (97.7)
	Yes	391 (2.3)

adjusted prevalence of TB infection was 22.6% (95% CI:19.4 –25.8) (Table 2).

The prevalence of TB infection was 21.7% (95% CI: 18.4 – 25.0) in males and 19.7% (95% CI:16.9 – 22.5) in females (Table 2). The prevalence was 12.8% (95% CI: 9.8–15.8) in the 15–24 years age group, 29.3% (95% CI: 25.9 – 32.8) in the 45–54 years age group and 28.7% (95% CI: 25.7 – 31.7) in those aged ≥ 65 years (Table 2). The prevalence of TB infection was 7.4% (95% CI: 5.6 – 9.6) in West Bengal and 61.2% (95% CI: 57.0 – 65.3) in Delhi (Table 2).

Factors associated with TB infection

The factors associated with TB infection were analysed in 15671 (92.9%) of the 16864 individuals for whom data was available (Table 3). Of the 15671, there were 3977 (25.4%) with TB infection and 11694 (74.6%) TB uninfected. In the multivariate analysis significant factors more likely associated with TB infection include age > 30 years, being male, residing in urban location, and past history of TB (Table 3).

Subclinical TB and TB infection

Of the total 61 diagnosed with TB in the IGRA clusters, 37 (60.7%) were asymptomatic (sub-clinical TB) [Fig. 3]. IGRA testing was done for all the 65 household contacts of the 37 asymptomatic TB patients. Of the 65 tested by IGRA, 18 (27.7%) had TB infection (Fig. 3). There were 24 TB patients with symptoms in the IGRA cluster and 40 of their household contacts had IGRA testing done. Of the 40 household contacts, 11(27.5%) had TB infection.

Discussion

The present analysis has provided an estimate of 226 per 1000 (22.6%) for the burden of TB infection in India for population aged ≥ 15 years. The recent systematic review and meta-analysis concluded 24.8% global prevalence of LTBI based on IGRA [17]. The IGRA based LTBI prevalence for the South East Asia region was reported as 36% (95%CI: 25.3 – 46.7) [17]. A population-based study among 1319 individuals aged ≥ 15 years in Vietnam documented LTBI of 36.8% (95%CI 33.4–40.3) [18]. Population based studies which have reported LTBI based on IGRA include China 24.3% (n = 2169), Saudi Arabia 9.1% (n = 1369) and United States 4.8% (n = 6083) [19–21]. Our findings that about one-fourth of the population has TB infection in India is a matter of concern and needs to be addressed in the context of TB elimination.

Males were more likely to have TB infection as observed in our analysis. Higher TB infection rates among males has been reported in earlier studies [18,19]. This possibly could be attributed to sociological factors [19]. A meta-analysis which included 2.2 million from 56 TB prevalence surveys over 28 countries concluded that TB prevalence is higher among men than women [22]. These findings imply that active case finding to be strengthened in men for detection of TB.

The prevalence of TB infection increased as age advanced in the present analysis. This observation has been reported in previous studies too [18,19]. Similar observation has been reported from an earlier study in household contacts which documented LTBI prevalence of 77% in individuals aged 15–18 years and 85% in persons aged > 45 years [9]. Increased frequency of social contacts and use of public transits leading to increased exposure could be contributing to higher LTBI prevalence with advancing age [9]. These findings suggest that older age groups need to be sensitized about TB, TB case detection be actively undertaken and be considered for intervention with TB preventive therapy.

Geographical differences in the prevalence of TB infection were observed in the current analysis. This could be attributed to the geographical differences in the prevalence of TB which is mirrored by TB infection. States especially those with high TB infection rates (> 30%) which include Delhi, Telangana, Uttar Pradesh, Punjab, Chandigarh, Karnataka have to identify the possible reasons and plan appropriate targeted interventions. Individuals residing in urban location were more likely to have TB infection in the present analysis. Annual risk of TB infection of 2.2% in the urban compared to 1.3% in the rural areas has been reported in an earlier study from India [7]. This could be attributed to overcrowding, slums, migrant population in urban settings. Advocacy, Communication and Social Mobilisation (ACSM) activities pertaining to TB and active case finding has to be strengthened in urban settings.

Individuals with past history of TB were more likely to have TB infection in this analysis. This is anticipated since prior sensitization with *M.tuberculosis* is likely to be IGRA positive. This enforces that individuals with past history of TB have to be closely evaluated by active case finding periodically and considered for TB preventive strategies.

Body mass index was not associated with TB infection in the present analysis. Undernutrition leads to poor immune response and tests for LTBI are likely to be negative. Undernutrition fuelling the TB burden is well documented and WHO estimated that globally, 1.9 million TB cases are attributed to undernutrition [23]. Cognizant of the burden of undernutrition and TB, the TB programme of India has introduced Direct Benefit Transfer (DBT) for nutritional support to TB patients (Ni-kshay Poshan Yojana) [24]. Individuals with low BMI in the community have to be counselled for appropriate nutritional intake, periodically screened for TB for early case detection and if required offered TB preventive strategies which warrants further evaluation.

We observed that smoking and or alcohol use not to be associated with TB infection. Nevertheless, it has been reported that alcohol use disorders and smoking attribute 0.74 and 0.73 million TB cases respectively worldwide [23]. TB programme of India offers counselling, linkage to de-addition centres and tobacco cessation services including social support systems to TB patients with smoking and alcohol use [24]. ACSM activities for community sensitization on the adverse effects of smoking and alcohol use needs to be strengthened along with providing relevant information on interventions available for quitting.

Diabetes is a potential risk factor for TB and WHO has estimated 0.37 million TB cases to be attributed to diabetes [23]. In the present analysis we did not observe diabetes mellites to be associated with TB infection or disease. HIV being a potent risk factor for TB could not be analysed since status of HIV was unknown in 95.2% of the population in our study.

Table 2
Prevalence of TB infection by gender,age group and state groups.

Characteristics		Total N	TB infection n	Crude TBI % (95%CI)	Adjusted* TBI % (95%CI)
	Overall	16864	3977	23.6 (22.9–24.2)	22.6 (19.4–25.8)
Gender	Female	9661	2018	20.9 (20.1–21.7)	19.7 (16.9–22.5)
	Male	7202	1958	27.2 (26.2–28.2)	21.7 (18.4–25.0)
	Transgender	1	1	NA	NA
Agegroup	15–24	3279	437	13.3 (12.2–14.5)	12.8 (9.8–15.8)
	25–34	3267	663	20.3 (18.9–21.7)	21.2 (17.1–25.2)
	35–44	3287	848	25.8 (24.3–27.3)	26.0 (22.7–29.3)
	45–54	2968	841	28.3 (26.7–30.0)	29.3 (25.9–32.8)
	55–64	2440	711	29.1 (27.3–31.0)	28.5 (25.1–32.0)
	≥ 65	1623	477	29.4 (27.2–31.7)	28.7 (25.7–31.7)
Stategroup	AP	734	165	22.5 (19.5–25.7)	NA
	BR	724	199	27.5 (24.3–30.9)	NA
	CG	722	137	19.0 (16.2–22.0)	NA
	DL	554	339	61.2 (57.0–65.3)	NA
	GJ,DN,DD	1274	240	18.8 (16.7–21.1)	NA
	HP,UK,JK	645	101	15.7 (12.9–18.7)	NA
	HR	589	63	10.7 (8.3–13.5)	NA
	JH	712	159	22.3 (19.3–25.6)	NA
	KA	733	227	31.0 (27.6–34.5)	NA
	KL,LD	675	122	18.1 (15.2–21.2)	NA
	MH,GA	908	235	25.9 (23.1–28.9)	NA
	MP	1401	252	18.0 (16.0–20.1)	NA
	NE	739	114	15.4 (12.9–18.2)	NA
	OD	650	169	26.0 (22.7–29.6)	NA
	PB,CH	689	214	31.1 (27.6–34.7)	NA
	RJ	675	62	9.2 (7.1–11.6)	NA
	TN,PY,AN	725	137	18.9 (16.1–21.9)	NA
	TS	739	275	37.2 (33.7–40.8)	NA
	UP	2261	714	31.6 (29.7–33.5)	NA
	WB	715	53	7.4 (5.6–9.6)	NA

TBI – TB infection; CI – Confidence Interval; NA – Not applicable
AP - Andhra Pradesh; AN – Andaman & Nicobar; NE – Assam, Tripura, Meghalaya, Manipur, Nagaland, Arunachal Pradesh, Mizoram, Sikkim; BR – Bihar; CG – Chhattisgarh; CH-Chandigarh, DL – Delhi; DN - Dadar & Nagar Haveli; DD – Daman & Diu; GJ – Gujarat; GA – Goa; HR – Haryana; HP - Himachal Pradesh; JH – Jharkhand; JK – Jammu & Kashmir; KA – Karnataka; KL – Kerala; LD – Lakshadweep; MP - Madhya Pradesh; MH – Maharashtra; OD – Odisha; PB – Punjab; PY – Pondicherry; UK – Uttarakhand; RJ – Rajasthan; TN - Tamil Nadu; TS – Telangana; UP - Uttar Pradesh; WB - West Bengal
* Adjustment for clustering (design effect)

Table 3
Factors associated with TB infection in the individuals tested by Interferon Gamma Release Assay (IGRA).

Characteristics		TB infected **3977** **n (%)**	TB uninfected **11694** **n (%)**	PR**(95% CI)**	p Value	aRR**(95% CI)**	p Value
Age in years	15–30	884 (22.2)	4223 (36.1)	Reference		Reference	
	31–45	1264 (31.8)	3441 (29.4)	1.552 (1.348–1.786)	< 0.001	1.495 (1.291–1.731)	< 0.001
	46–60	1182 (29.7)	2659 (22.7)	1.778 (1.466–2.156)	< 0.001	1.702 (1.408–2.056)	< 0.001
	> 60	647 (16.3)	1371 (11.7)	1.852 (1.485–2.310)	< 0.001	1.702 (1.352–2.142)	< 0.001
Gender	Female	2019 (50.8)	6945 (59.4)	Reference		Reference	
	Male	1958 (49.2)	4749 (40.6)	1.296 (1.208–1.391)	< 0.001	1.261 (1.180–1.347)	< 0.001
Geographical	Rural	2393 (60.2)	8740 (74.7)	Reference		Reference	
Location	Urban	1584 (39.8)	2954 (25.3)	1.624 (1.043–2.528)	0.033	1.589 (1.036–2.437)	0.035
Smoking and	No	3282 (82.5)	10278 (87.9)	Reference		Reference	
or Alcohol use	Yes	695 (17.5)	1416 (12.1)	1.360 (1.228–1.507)	< 0.001	1.044 (0.953–1.145)	0.340
Diabetes	Non-Diabetes	3642 (91.6)	11083 (94.8)	Reference		Reference	
	Diabetes	335 (8.4)	611 (5.2)	1.432 (1.177–1.741)	< 0.001	1.094 (0.940–1.272)	0.235
Body Mass	≥ 18.50	3241 (81.5)	8982 (76.8)	Reference		Reference	
Index (Kg/m2)	16.50–18.49	509 (12.8)	1779 (15.2)	0.839 (0.724–0.973)	0.022	0.949 (0.829–1.088)	0.439
	< 16.50	227 (5.7)	933 (8.0)	0.738 (0.630–0.865)	< 0.001	0.867 (0.742–1.014)	0.072
Past History	No	3818 (96.0)	11504 (98.4)	Reference		Reference	
of TB	Yes	159 (4.0)	190 (1.6)	1.828 (1.537–2.174)	< 0.001	1.492 (1.262–1.764)	< 0.001

PR – prevalence ratio; aRR – adjusted risk ratio; CI – Confidence Interval

Irrespective of subclinical or symptomatic TB in those diagnosed with TB in the survey, 27% of their household contacts had TB infection. An earlier systematic review of 95 studies from low and middle- income countries documented 51.5% (95%CI: 47.1–55.8%) latent TB infection among contacts of TB patients [25]. This underscores the importance of TB preventive therapy (TPT) in contacts of TB patients as recommended by the TB program of India [26]. Individuals with subclinical TB could contribute substantially to the ongoing transmission of *M.tb* [27]. More than half of the TB patients diagnosed in the survey had subclinical TB which is absence of TB symptoms but abnormal chest radiograph and or bacteriological evidence of TB. Though this was a cross-sectional analysis and the number of contacts tested for TB infection is small, the possibility that subclinical TB is transmissible cannot be ruled out. Our observation that transmissibility of subclinical TB is similar to symptomatic TB needs to be explored in future studies.

This analysis has inherent limitations. The numbers may not be sufficient for sub-group analysis of factors associated with TB infection. The findings have to be interpreted considering this limitation. Information on potential factors for TB infection such as contact with TB patient, duration of exposure, biomass fuel use, HIV status and other immunosuppressive conditions was not available. Moreover, information on the time of infection – recent / past could not be elucidated.

Our analysis has shown that in India, about one fourth (22.6%) of the individuals were infected with TB. Geographical variation in the prevalence of TB infection was observed. Those aged > 30 years, being male, residing in urban location, and with past history of TB were more likely to have TB infection. Individuals with TB infection are reservoirs of future TB disease. Recent evidence from modelling study suggest the possibility of self-clearance of *M.tb* infection in 24.4% of individuals within 10 years of infection and 73.1% over a lifetime [28]. Further, the lifetime risk of TB in those retaining the viable infection is 17%. The self-clearance of *M.tb* infection was least in India compared to China and Japan [28]. The target of the END TB Strategy of the World Health Organisation (WHO), is to reduce the incidence of TB by 90% by 2035 while India is committed to eliminate TB by 2025 [1,3]. In the context of TB elimination in India, it is essential to map the population vulnerable to TB infection and provide primordial prevention by means of ACSM activities and improving the awareness on TB prevention. The National TB Elimination Programme (NTEP) in India has been scaling up the implementation of "Guidelines for Programmatic Management of Tuberculosis Preventive Treatment in India, 2021″ by a comprehensive 'cascade of care' approach as a core strategy to deliver TPT services across the country [26]. This guideline is implemented across all the states to systematically reach out and screen all target populations (PLHIV, household contacts, and other groups at risk of developing TB disease) after ruling out TB and provide TPT as a part of the continuum of care. Scaling up of the comprehensive TB prevention strategy is a critical component of the India's National Strategic Plan 2017–25 and would hasten the decline of TB incidence in India. The testing for TB infection by indra-dermal skin test (Cy-TB) offers wider scope of its use under programmatic settings [29]. It is essential to also address determinants of TB disease which include malnutrition, social habits and co-morbid conditions. Targeted interventions which include TB preventive therapy and active screening for early detection of disease in high-risk groups for TB is essential to reduce the burden of TB in India.

CRediT authorship contribution statement

SS,RR,KR,-Conceptualisation, Funding acquisition, Data Collection and Site Coordination, Data analysis, Data Interpretation, reviewing, editing the draft and approval of the final draft, KT,RK- Data Management, Data analysis, Data Interpretation, Writing the first draft, editing and approval of the final draft BV, PC - Conceptualisation,Data analysis, Data Interpretation, Writing the

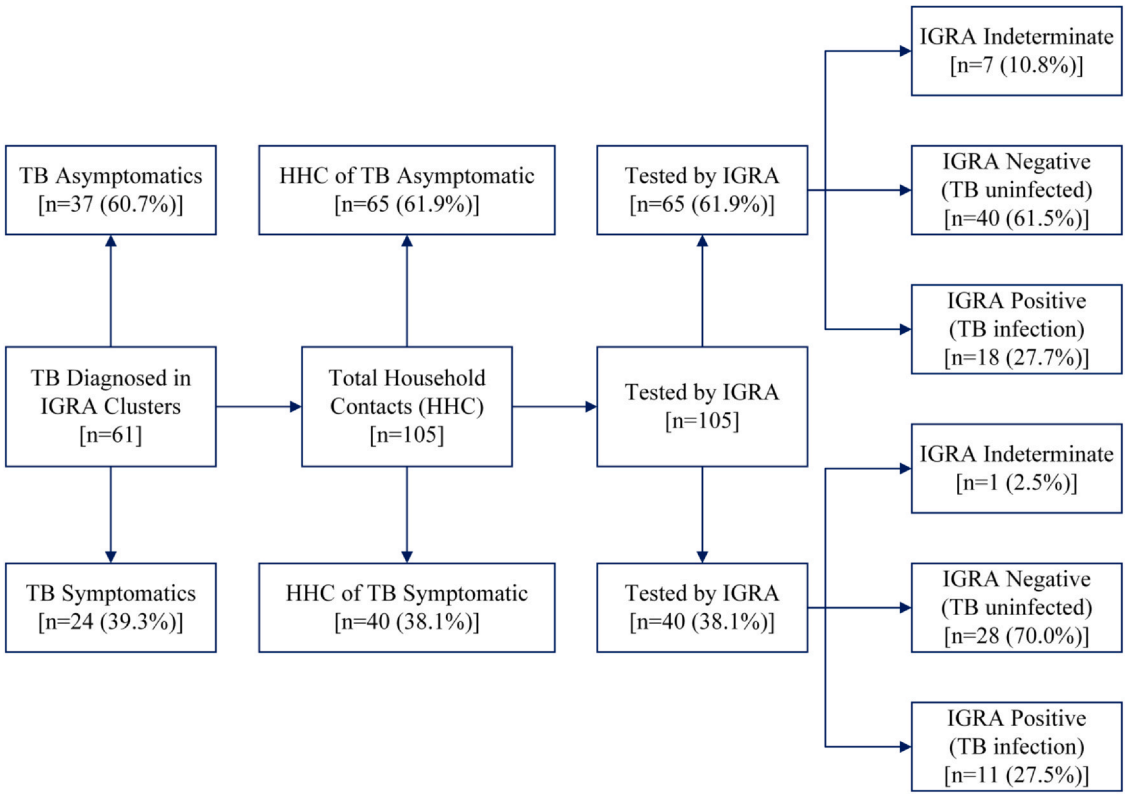

Fig. 3. Subclinical TB and TB infection among the household contacts tested for IGRA in the survey population

first draft, editing and approval of the finaldraft SDB, AKB,JB,DC,VC,DD,KRD,GRD,AK,AL,MM,AM,SSM,CR,JT,PAM,MS,AR,AT, KS,NNK,NS,EI,CR-Data Collection and Site Coordination, RK,AC-Software Design and Data Base Management, Data Collection and Site Coordination, KS,LEH-Lab co-ordination, Data Collection and Site Coordination, reviewing, editing the draft and approval of the final draft, MP, RRC, NK, RPJ, and PC – overall monitoring of the survey, data analysis and drafting the manuscript. All authors and Group authors contributed to the editing, reviewing and approval of the final draft of the manuscript.

Declaration of Competing Interest

The authors have no conflict of interest to declare.

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References

[1] Global tuberculosis report 2022. Geneva: World Health Organization; 2022. Licence: CC BY-NC-SA 3.0 IGO. ⟨https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2022⟩. [Accessed on 26 May 2023].

[2] Mandal S, Rao R, Joshi R. Re-estimating tuberculosis incidence and mortality in India during 2011-2022: a modelling study. Indian J Community Med 2023;48:436–42. https://doi.org/10.4103/ijcm.ijcm_160_23

[3] Central TB Division. Ministry of Health and Family Welfare, New Delhi. National Strategic plan for Tuberculosis elimination, 2017–2025. ⟨https://tbcindia.gov.in/WriteReadData/National%20Strategic%20Plan%202017–25.pdf⟩. [Accessed on 26 May 2023].

[4] WHO consolidated guidelines on tuberculosis. Module 1: prevention – tuberculosis preventive treatment. Geneva: World Health Organization; 2020. Licence: CC BY-NC-SA 3.0 IGO. ⟨https://www.who.int/publications/i/item/9789240001503⟩. [Accessed on 26 May 2023].

[5] Houben RMGJ, Dodd PJ. The global burden of latent tuberculosis infection: a re-estimation using mathematical modelling. PLoS Med 2016;13:e1002152. https://doi.org/10.1371/journal.pmed.1002152

[6] Kiazyk S, Ball TB. Latent tuberculosis infection: an overview. Can Commun Dis Rep 2017;43:62–6. https://doi.org/10.14745/ccdr.v43i34a01

[7] Chadha VK, Kumar P, Jagannatha PS, Vaidyanathan PS, Unnikrishnan KP. Average annual risk of tuberculous infection in India. Int J Tube Lung Dis 2005;9:116–8⟨https://www.ingentaconnect.com/content/iuatld/ijtld/2005/00000009/00000001/art00020;jsessionid=popc7xmzggq0.x-ic-live-01⟩.

[8] Praveen V. Prevalence of LTBI among household contacts of sputum positive TB patients receiving DOTS chemotherapy. Indian J Tube 2020;67:459–65. https://doi.org/10.1016/j.ijtb.2020.07.007

[9] Dolla CK, Padmapriyadarsini C, Thiruvengadam K, Lokhande R, Kinikar A, Paradkar M, et al. Age-specific prevalence of TB infection among household contacts of pulmonary TB: Is it time for TB preventive therapy? Trans R Soc Trop Med Hyg 2019;113:632–40. https://doi.org/10.1093/trstmh/trz049

[10] Narasimhan P, MacIntyre CR, Mathai D, Wood J. High rates of latent TB infection in contacts and the wider community in South India. Trans R Soc Trop Med Hyg 2017;111:55–61. https://doi.org/10.1093/trstmh/trx016

[11] Dabhi PA, Thangakunam B, Gupta R, James P, Thomas N, Naik D, et al. Screening for prevalence of current TB disease and latent TB infection in type 2 diabetes mellitus patients attending a diabetic clinic in an Indian tertiary care hospital. PLoS One 2020;15:e0233385. https://doi.org/10.1371/journal.pone.0233385

[12] Malaviya AN, Aggarwal VK, Rawat R, Baghel S, Thakran R, Zaheer Q, et al. Screening for latent tuberculosis infection among patients with rheumatoid arthritis in the era of biologics and targeted synthetic disease-modifying anti-rheumatic drugs in India, a high-burden TB country: The importance of Mantoux and Quantiferon-TB Gold tests. Int J Rheum Dis 2018;21:1563–71. https://doi.org/10.1111/1756-185X.13261

[13] Dorjee K, Topgyal S, Dorjee C, Tsundue T, Namdol T, Tsewang T, et al. High prevalence of active and latent tuberculosis in children and adolescents in tibetan schools in India: the zero TB kids initiative in Tibetan refugee children. Clin Infect Dis 2019;69:760–8. https://doi.org/10.1093/cid/ciy987

[14] Pai M, Gokhale K, Joshi R, Dogra S, Kalantri S, Mendiratta DK, et al. Mycobacterium tuberculosis infection in health care workers in rural India: comparison of a whole-blood interferon gamma assay with tuberculin skin testing. JAMA 2005;293:2746–55. https://doi.org/10.1001/jama.293.22.2746

[15] World Health Organization. Implementing The End TB Strategy: the Essentials. World Health Organization; 2015⟨https://apps.who.int/iris/handle/10665/206499⟩ Accessed on 26 May 2023.

[16] QuantiFERON® -TB Gold Plus (QFT® -Plus) ELISA Package InsertQIAGEN. QGIT Package [Available from:https://www.quantiferon.com/wp-content/uploads/2020/01/L1083163-R06-QF-TB-Gold-Plus-ELISA-IFU-CE.pdf [Accessed on 30 August 2023].

[17] Cohen A, Mathiasen VD, Schön T, Wejse C. The global prevalence of latent tuberculosis: a systematic review and meta-analysis. Eur Respir J 2019;54:1900655. https://doi.org/10.1183/13993003.00655-2019

[18] Marks GB, Nhung NV, Nguyen TA, Hoa NB, Khoa TH, Son NV, et al. Prevalence of latent tuberculous infection among adults in the general population of Ca Mau, Viet Nam. Int J Tube Lung Dis 2018;22:246–51. https://doi.org/10.5588/ijtld.17.0550

[19] Liu Y, Huang S, Jiang H, Xiong J, Wang Y, Ou M, et al. The prevalence of latent tuberculosis infection in rural Jiangsu, China. Public Health 2017;146:39–45. https://doi.org/10.1016/j.puhe.2017.01.008

[20] Balkhy HH, El Beltagy K, El-Saed A, Aljasir B, Althaqafi A, Alothman AF, et al. Prevalence of latent mycobacterium tuberculosis infection (LTBI) in Saudi Arabia; population based survey. Int J Infect Dis 2017;60:11–6. https://doi.org/10.1016/j.ijid.2017.03.024

[21] Mancuso JD, Diffenderfer JM, Ghassemieh BJ, Horne DJ, Kao TC. The prevalence of latent tuberculosis infection in the United States. Am J Respir Crit Care Med 2016;194:501–9. https://doi.org/10.1164/rccm.201508-1683OC

[22] Horton KC, MacPherson P, Houben RMGJ, White RG, Corbett EL. Sex differences in tuberculosis burden and notifications in low- and middle-income countries: a systematic review and meta-analysis. PLoS Med 2016;13:e1002119. https://doi.org/10.1371/journal.pmed.1002119

[23] Global tuberculosis report 2021. Geneva: World Health Organization; 2021. Licence: CC BY-NC-SA 3.0 IGO. ⟨https://www.who.int/publications/i/item/9789240037021⟩. [Accessed on 26 May 2023].

[24] Central T.B. Division. Ministry of Health and Family Welfare, New Delhi. India TB report, 2023. ⟨https://tbcindia.gov.in/showfile.php?lid=3680⟩. [Accessed on 31 May 2023].

[25] Fox GJ, Barry SE, Britton WJ, Marks GB. Contact investigation for tuberculosis: a systematic review and meta-analysis. Eur Respir J 2013;41(1):140–56. https://doi.org/10.1183/09031936.00070812

[26] Central TB Division. National TB Elimination Programme. Guidelines for Management of Tuberculosis Preventive treatment in India, July 2021. ⟨https://tbcindia.gov.in/WriteReadData/l892s/Guidelines%20for%20Programmatic%20Management%20of%20Tuberculosis%20Preventive%20Treatment%20in%20India.pdf⟩. [Accessed on 26 May 2023].

[27] Kendall EA, Shrestha S, Dowdy DW. The epidemiological importance of subclinical tuberculosis. A Critical Reappraisal. Am J Respir Crit Care Med 2021;203(2):168–74. https://doi.org/10.1164/rccm.202006-2394PP

[28] Emery JC, Richards AS, Dale KD, McQuaid CF, White RG, Denholm JT, et al. Self-clearance of *Mycobacterium tuberculosis* infection: implications for lifetime risk and population at-risk of tuberculosis disease. Proc Biol Sci 2021;288:20201635. https://doi.org/10.1098/rspb.2020.1635

[29] WHO operational handbook on tuberculosis. Module 3: diagnosis. Tests for tuberculosis infection, Geneva: World Health Organisation; 2022. Licence: CC BY-NC-SA 3.0 IGO ⟨https://www.who.int/publications/i/item/9789240058347⟩. [Accessed on 19 September 2023].