INT J TUBERC LUNG DIS 13(4):446–453

Analysis of discordance between the tuberculin skin test and the interferon-gamma release assay

A. Machado Jr,*† K. Emodi,‡ I. Takenami,* B. C. Finkmoore,‡ T. Barbosa,§ J. Carvalho,* L. Cavalcanti,* G. Santos,* M. Tavares,* M. Mota,* F. Barreto,* M. G. Reis,*¶ S. Arruda,*# L. W. Riley‡

*** Escola Bahiana de Medicina e Saúde Pública, Salvador, Bahia, † Hospital Especializado Octávio Mangabeira, Salvador, Bahia, Brazil; ‡ School of Public Health, University of California, Berkeley, California, USA; § Laboratório Integrado de Microbiologia e Imunorregulação, Salvador, Bahia, ¶ Laboratório de Patologia e Biologia Molecular, # Laboratório Avançado de Saúde Pública, Centro de Pesquisas Gonçalo Moniz, Salvador, Bahia, Brazil**

SUMMARY

OBJECTIVE: To analyze factors associated with discordance between tuberculin skin test (TST) and interferon-gamma release assay (IGRA) results among household contacts of pulmonary tuberculosis (PTB) patients.

DESIGN: TST (purified protein derivative) and IGRA (QuantiFERON®-TB Gold) were performed on household contacts of PTB patients diagnosed between 2006 and 2007 in Salvador, Brazil. Discordant test groups were compared with the TST−/IGRA− group.

RESULTS: Of 261 household contacts satisfactorily tested by TST, 145 (55.6%) had positive TST results; of 298 satisfactorily tested by IGRA, 127 (43.1%) had positive results. The test agreement was 0.76 ($\kappa = 0.53$, 95%CI 0.43–0.63). Sixty-one (24%) were discordant: 44 (72%) with TST+/IGRA− and 17 (28%) with TST−/IGRA+ results. Compared to the TST−/IGRA− group, the TST+/IGRA− and TST+/IGRA+ groups were significantly more likely to have a chest X-ray showing old lung scars (OR = 6.8, 95%CI 1.3–35.0; OR = 7.4, 95%CI 2.2–24.4, respectively). The TST−/IGRA+ group was exposed to their index cases for significantly longer than the TST−/IGRA− group (OR = 7.2, 95%CI 1.7–29.3).

CONCLUSION: The TST+/IGRA− and TST+/IGRA+ groups shared more similar characteristics with each other than with the TST−/IGRA− group. In a setting endemic for TB, TST results appear to be more suitable in the decision to treat latent TB infection.

KEY WORDS: latent tuberculosis infection; interferon-gamma release assay; tuberculin skin test; household contacts

BRAZIL has the highest number of reported tuberculosis (TB) cases in South America, with an incidence ranging from 50 to 80 cases per 100 000 population between 1996 and 2006.[1,2] Close and prolonged contact with pulmonary TB (PTB) patients increases the risk of infection.[3,4] In Brazil, severe cases of TB are often hospitalized; these represent about 14% of PTB disease in the country.[2] Data about the prevalence of latent TB infection (LTBI) in household contacts of such hospitalized TB patients are limited.

Until recently, the tuberculin skin test (TST) with an intradermal injection of purified protein derivative (PPD) was the only test widely used to detect LTBI. Although simple and inexpensive, the TST lacks specificity for *Mycobacterium tuberculosis* infection.[5,6] Previous exposure to non-tuberculous mycobacteria and bacille Calmette-Guérin (BCG) vaccination can influence TST results.[5,7] Patients must also return 48–72 h later to have the test results read. Despite these limitations, the TST remains the test most commonly used to initiate preventive treatment.[8,9]

Interferon-gamma release assays (IGRAs) are based on interferon-gamma (IFN-γ) secretion by lymphocytes exposed to *M. tuberculosis*-specific antigens encoded by the region of difference 1 (RD1)—early secreted antigenic target 6 (ESAT-6) and culture filtrate protein 10 (CFP-10).[10,11] Recently, a commercial test kit, QuantiFERON®-TB Gold (Cellestis, Carnegie, VIC, Australia) containing these two proteins, was approved for use in LTBI diagnosis in the United States.[11]

A recent meta-analysis that compared TST and IGRA showed that IGRA has a high specificity and that it is unaffected by BCG vaccination.[6] Most studies have shown agreement between TST and IGRA to range from 60% to 80%.[5,12] A substantial proportion of the test results are therefore discordant. When an individual has a positive TST result and a negative IGRA result, the discordance is often attributed to BCG vaccination. There is little evidence to support the influence of BCG on test discordance. In countries that have routine contact tracing programs, assessment

Correspondence to: Almério Machado Jr, Escola Bahiana de Medicina e Saúde Pública, Salvador, Bahia, Brazil 40080002. Tel: (+55) 71 3336 0513. Fax: (+55) 71 3245 0822. e-mail: almeriojr@yahoo.com.br
Article submitted 25 July 2008. Final version accepted 29 October 2008.

of LTBI is important because the decision to initiate LTBI treatment of contacts depends on the accuracy of these tests. Because TST-positive test results are used in the decision to initiate LTBI treatment, it is not clear what should be done for those who also test negative on IGRA. No studies comparing TST and IGRA in high-risk populations report systematic analyses of discordant test results.

We focused on household contacts of index cases of TB in Salvador, Brazil, because they represent a uniform group (similar age and ethnic distribution, low prevalence of human immunodeficiency virus [HIV] infection, high BCG coverage) at high risk for LTBI who are prime candidates for treatment. To date, only a small number of studies have examined the prevalence of LTBI among close contacts of index TB cases by comparing TST and IGRA.[13,14] Analysis of household contacts of these index cases thus provided an opportunity to evaluate factors associated with discordant results of the two tests.

METHODS

Setting

We conducted a cross-sectional study from November 2006 to October 2007 at the Hospital Especializado Octávio Mangabeira (HEOM) in Salvador, Bahia, Brazil, a 217-bed public chest disease hospital. Salvador is the capital of Bahia, with a population of 2 714 018 in 2006,[15] and has one of the highest TB incidence rates in Brazil.[2]

Study participants

The study was approved by the respective human subjects committees of Oswaldo Cruz Foundation in Salvador, Brazil, and the University of California at Berkeley, USA. Informed consent was obtained from all study subjects who agreed to participate in the study. There were no payments for transport or reimbursement for study participation.

Index cases

Index cases were defined as hospitalized patients with symptoms consistent with TB and one or more of the following characteristics: 1) chest radiography (CXR) suggestive of TB opacities, 2) sputum samples that contained acid-fast bacilli on microscopy, 3) individuals who responded to anti-tuberculosis drugs. CXR was classified as 1) cavitary disease, when cavitary densities were observed surrounded by pulmonary infiltration; 2) without cavity, when pulmonary infiltration but no cavity was observed; or 3) normal, when no pulmonary lesion was seen. Sputum was analyzed using the Ziehl-Neelsen staining method and classified as negative, 1+, 2+, or 3+.[16]

Household contacts

Contacts who resided in the same household and spent at least 100 h with the index case during the latter's symptomatic period were considered household contacts and were invited to participate in the study.[17]

Data collection

Household contacts who enrolled underwent TST, blood tests and CXR and were interviewed by members of the study team (AM, KE, IT). A standardized questionnaire was used to collect interview data. Study participants were asked about their current use of medications and diabetes status. Study participants were not directly asked about their HIV status nor were the data sought from clinic charts. All of the household contacts were directly examined for BCG scar by a chest physician on the research team (AM).

Laboratory tests

CXRs were reviewed by a chest physician on the research team (AM). TST was performed by trained nursing staff at HEOM with 0.1 ml of PPD RT23 (2 tuberculin unit [TU], Statens Serum Institute, Copenhagen, Denmark). The reaction was read 72 h later (AM). The cut-off point for a positive reaction was ⩾10 mm induration because this is the cut-off used in the decision to initiate LTBI treatment in Brazil.[9]

The IGRA used was a whole blood assay, the QuantiFERON®-TB Gold In-Tube kit, performed according to the manufacturer's recommendations at the immunology laboratory at Gonçalo Moniz Research Centre.[18] A positive test was defined as IFN-γ blood concentration ⩾ 0.35 international units (IU)/ml. Samples with indeterminate IGRA results were re-processed. Samples with two indeterminate IGRA results were excluded from analysis.

Statistics

The data were analyzed using STATA 10.0 Intercooled (Stata Corp, College Station, TX, USA). Agree-

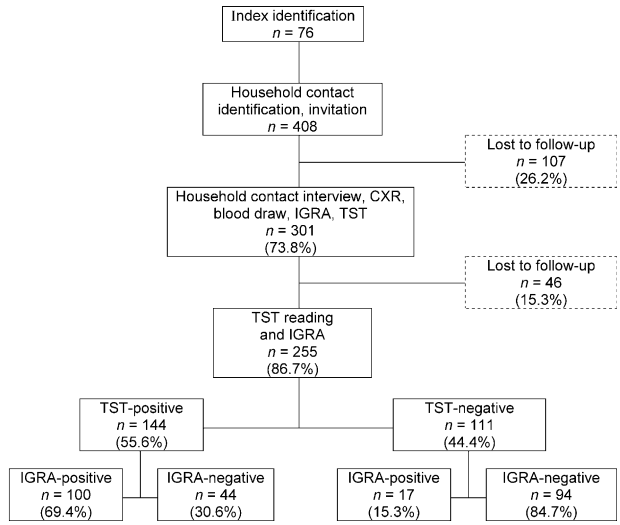

Figure Flowchart of recruitment into study. CXR = chest X-ray; IGRA = interferon-gamma release assay; TST = tuberculin skin test.

Table 1 Characteristics of 76 pulmonary tuberculosis patients and their households

Characteristic	*n* (%)
Age, years	
0–14	2 (3)
⩾15	74 (97)
Male sex	44 (58)
History of tuberculosis*	16 (23)
CXR†	
Cavities	42 (63)
No cavities	24 (36)
Normal	1 (2)
Sputum density of index	
1+	31 (41)
2+	14 (18)
3+	26 (34)
Negative	2 (3)
Not available‡	3 (4)
Household size	
Median number of members per household	4.0
Median number of people per room	1.2
Median household dimension, m^2§	60
Median number of rooms per household	4.0
Type of building	
Finished walls and tile roof	75 (99)
Wood frame with zinc roof, unfinished sides	1 (<1)
Household amenities	
Running water inside the house	75 (99)
Electricity	76 (100)
Toilet inside the house	74 (98)
Formal garbage collection service	73 (96)

* Data not available for five index cases.
† CXR not available for nine index cases.
‡ Two patients were aged <5 years and samples could not be obtained; one patient did not yield a sputum sample.
§ Forty-six households reported the dimensions of their household.
CXR = chest radiograph.

ment between the TST and IGRA results was assessed by the kappa statistic (κ). The discordant groups (TST+/IGRA−; TST−/IGRA+) and the concordant positive group (TST+/IGRA+) were each compared with the reference group (TST−/IGRA−). Multivariate logistic regression models were created in STATA (Stata Corp). The models were adjusted for clustering by household with a robust variance estimator, which also corrects for multiple testing of variables.

Table 2 Characteristics of 301 household contacts of 76 pulmonary tuberculosis patients

Characteristic	*n* (%)
Age, years	
0–14	83 (28)
⩾15	218 (72)
Female sex	181 (60)
BCG scar*	
Present	228 (76)
Absent	72 (24)
Household contact CXR†	
Normal	253 (89)
Old scar	31 (11)
Relationship to index case	
Sibling	51 (17)
Daughter/son	49 (16)
Parent	39 (13)
Uncle/aunt	30 (10)
Spouse	25 (8)
Other	81 (27)
Contact sleeps in same room as index case	82 (28)

* Data not available for one contact.
† CXR not available for nine index cases, representing 17 household contacts.
BCG = bacille Calmette-Guérin; CXR = chest radiograph.

RESULTS

Index cases

Between 30 October 2006 and 30 August 2007, 76 hospitalized patients with active TB, representing 76 distinct households, were recruited into this study as index cases (Figure, Table 1).

Household contacts

Of the 408 eligible household contacts identified by index cases, 301 (74%) were enrolled in this study (Tables 2 and 3). BCG scar was present in 228 (76%). The median age was 22.0 years (interquartile range [IQR] 12–37) among those with BCG scar and 33.5 years (IQR 24.3–52.8) in those without ($P < 0.01$). During the initial evaluation of the household contacts, active TB was diagnosed in two (0.7%) of 301 individuals, as evidenced by their clinical presenta-

Table 3 Median values of principal characteristics of household contacts: the positive concordant (TST+/IGRA+) group and the discordant groups (TST+/IGRA− and TST−/IGRA+) compared to the reference group (TST−/IGRA−)

Characteristic	Reference group TST−/IGRA− (*n* = 94) median (IQR)	TST+/IGRA+ (*n* = 100) median (IQR)	*P* value*	TST+/IGRA− (*n* = 44) median (IQR)	*P* value*	TST−/IGRA+ (*n* = 17) median (IQR)	*P* value*
Age, years	22 (9–36)	30 (15–45)	0.01	21 (13–41)	0.57	37 (20–57)	0.02
Monthly family income, USD	422 (422–533)	422 (422–533)	0.86	422 (422–533)	0.57	422 (422–533)	0.52
Index sputum density	1+ (1–3)	2+ (1–3)	0.94	2+ (1–3)	0.43	1+ (1–3)	0.91
Number of rooms in household	4 (4–5)	4 (3–5)	0.12	4 (4–4)	0.21	4 (3–6)	0.97
Number of people in household	49 (3–6)	4 (3–6)	0.35	4 (3–6)	0.21	4 (3–10)	0.51
Household dimension, m^2†	70 (40–88)	50 (23–72)	0.01	60 (21–68)	0.03	60 (35–81)	0.47
Crowding index‡	0.08 (0.05–0.13)	0.10 (0.06–0.20)	0.02	0.08 (0.05–0.15)	0.45	0.12 (0.06–0.18)	0.14
TST induration diameter, mm	0 (0–4)	16 (14–19)	<0.01	13 (12–16)	<0.01	6 (0–8)	0.01
IFN-γ blood level, IU/ml	0.0 (0.0–0.06)	4.48 (1.63–8.08)	<0.01	0.04 (0.03–0.14)	<0.01	0.75 (0.56–2.21)	<0.01

* *P* values based on the Mann-Whitney test.
† Forty-six households reported household dimensions.
‡ Number of people in the household per m^2.
TST = tuberculin skin test; IGRA = interferon-gamma release assay; IQR = interquartile range.

tion and response to anti-tuberculosis drugs. Of 294 study participants who were asked about diabetes, seven (2%) said they had been previously diagnosed. None of the study participants were on antiretroviral treatment.

TST results

Valid TST results were available for 261 (86.7%) of the 301 household contacts. At a cut-off of ⩾10 mm induration, 145 (55.6%) of 261 household contacts had positive TST results. The remainder did not return to have the test read.

IGRA results

Valid IGRA results were available for 298 (99%) of the 301 household contacts. Three contacts had duplicate indeterminate IGRA results. Blood samples could not be obtained from three infants and IGRA was not conducted. At a cut-off point of ⩾0.35 IU/ml, 127 (43.1%) of 298 household contacts had positive IGRA results.

Agreement between TST and IGRA results

Data on agreement between the TST and IGRA results were available for 255 (84.7%) of the 301 household contacts. Of these, 100 (39.2%) had concordant positive results (TST+/IGRA+) and 94 (36.8%) had concordant negative results (TST−/IGRA−). At a cut-off point of ⩾10 mm induration for a positive TST and ⩾0.35 IU/ml for IGRA, the agreement between tests was 0.76 (κ = 0.53; 95% confidence interval [CI] 0.43–0.63).

Discordant groups

Among the 255 household contacts with valid results by both tests, 61 (24%) had discordant results; 44 (72%) were TST+/IGRA− and 17 (28%) were TST−/IGRA+.

TST+/IGRA−

The median age of individuals with TST+/IGRA− results was 21 years (IQR 13–41) compared to 22 years for those with TST−/IGRA− results (IQR 9–36, P = 0.57; Table 3). The median household dimension was 60 m^2 (IQR 21–68) for individuals with TST+/IGRA− results and 70 m^2 for individuals with TST−/IGRA− results (IQR 40–88, P = 0.03).

Household contacts with TST+/IGRA− results were 6.8 times more likely to have a CXR showing old lung scar than those with TST−/IGRA− results, after adjusting for all other covariates (odds ratio [OR] 6.8, 95%CI 1.3–35, P = 0.02; Table 4). The median

Table 4 Principal covariates associated with discordant test results: the TST+/IGRA− group compared to the reference group (TST−/IGRA−); cut-off: TST ⩾ 10 mm, IGRA ⩾ 0.35 IU/ml

Covariate	TST+/IGRA− *n/N*	Reference group TST−/IGRA− *n/N*	OR (95%CI)	*P* value*	aOR† (95% CI)	*P* value*
Age, years						
⩽10	6/44	24/94	0.5 (0.2–1.2)		0.2 (0.04–1.5)	
>10	38/44	70/94	1.0	0.12	1.0	0.14
Sex						
Male	16/44	39/94	0.8 (0.4–1.7)		1.3 (0.5–3.2)	
Female	28/44	55/94	1.0	0.57	1.0	0.54
BCG scar						
Present	38/44	73/94	1.8 (0.7–4.9)		1.8 (0.6–5.6)	
Absent	6/44	21/94	1.0	0.23	1.0	0.33
Contact CXR						
Old scar	7/44	2/93	8.6 (1.7–43.4)		6.8 (1.3–35.0)	
Normal	37/44	91/93	1.0	0.01	1.0	0.02
Index CXR						
Cavity	26/37	48/80	1.6 (0.7–3.6)		2.2 (0.6–8.5)	
No cavity	11/37	32/80	1.0	0.27	1.0	0.26
Sputum smear of index case						
1+ or 2+	27/44	69/90	1.0		1.0	
3+	14/44	21/90	1.7 (0.8–3.8)	0.20	1.2 (0.4–3.5)	0.73
Sleeps in same room as index case						
Yes	17/43	21/92	2.2 (1.01–4.8)		2.5 (0.9–7.0)	
No	26/43	71/92	1.0	0.05	1.0	0.09
Length of exposure to index						
⩽1 month	24/44	41/93	1.0		1.0	
>1 month	20/44	52/93	0.6 (0.3–1.3)	0.23	0.6 (0.2–2.0)	0.44

* *P* values from two-tailed *t*-test.
† From a multivariate logistic regression in STATA with age ⩽10, sex, BCG scar, index chest X-ray, sputum smear of index case, sleep in the same room of index case and length of exposure to index case included as covariates in the model. CI is based on robust standard errors to adjust for potential clustering by household; adjusted for 48 clusters by household.
TST = tuberculin skin test; IGRA = interferon-gamma release assay; IU = international units; OR = odds ratio; aOR = adjusted OR; CI = confidence interval; BCG = bacille Calmette-Guérin; CXR = chest radiograph.

Table 5 Principal covariates associated with discordant test results: the TST–/IGRA+ group compared to the reference group (TST–/IGRA–); cut-off: TST ⩾ 10 mm, IGRA ⩾ 0.35 IU/ml

Covariate	TST–/IGRA+ *n/N*	Reference group TST–/IGRA– *n/N*	OR (95% CI)	*P* value*	aOR† (95%CI)	*P* value*
Age, years						
⩽10	3/17	24/94	0.6 (0.2–2.3)		0.7 (0.1–3.5)	
>10	14/17	70/94	1.0	0.49	1.0	0.67
Sex						
Male	6/17	39/94	0.8 (0.3–2.3)		1.1 (0.4–3.6)	
Female	11/17	55/94	1.0	0.63	1.0	0.82
BCG scar						
Present	13/17	73/94	0.9 (0.3–3.2)		1.8 (0.4–9.1)	
Absent	4/17	21/94	1.0	0.91	1.0	0.47
Contact CXR						
Old scar	3/17	2/93	9.8 (1.5–63.6)		4.4 (0.4–48.7)	
Normal	14/17	91/93	1.0	0.02	1.0	0.22
Index CXR						
Cavity	6/15	48/80	0.4 (0.1–1.4)		0.2 (0.05–0.9)	
No cavity	9/15	32/80	1.0	0.16	1.0	0.04
Sputum smear of index case						
1+ or 2+	13/15	69/90	1.0		1.0	
3+	3/15	21/90	0.8 (0.2–3.28)	0.78	0.8 (0.2–4.4)	0.84
Sleeps in same room as index case						
Yes	4/17	21/92	1.0 (0.3–3.5)		1.1 (0.2–5.5)	
No	13/17	71/92	1.0	0.95	1.0	0.93
Length of exposure to index						
⩽1 month	3/17	41/93	1.0		1.0	
>1 month	14/17	52/93	3.6 (1.0–13.4)	0.06	7.2 (1.7–29.3)	<0.01

**P* values from two-tailed *t*-test.
†From a multivariate logistic regression in STATA with age ⩽10, sex, BCG scar, index CXR, sputum smear of index case, sleep in the same room of index case and length of exposure to index case included as covariates in the model. CI is based on robust standard errors to adjust for potential clustering by household; adjusted for 44 clusters by household.
TST = tuberculin skin test; IGRA = interferon-gamma release assay; OR = odds ratio; CI = confidence interval; aOR = adjusted OR; BCG = bacille Calmette-Guérin; CXR = chest radiograph.

Table 6 Principal covariates associated with positive concordant tests: the TST+/IGRA+ group compared to the reference group (TST–/IGRA–); cut-off: TST ⩾ 10 mm, IGRA ⩾ 0.35 IU/ml

Covariate	TST+/IGRA+ *n/N*	Reference group TST–/IGRA – *n/N*	OR (95% CI)	*P* value*	aOR† (95% CI)	*P* value*
Age, years						
⩽10	11/100	24/94	0.4 (0.2–0.8)		0.3 (0.1–0.7)	
>10	89/100	70/94	1.0	0.01	1.0	0.01
Sex						
Male	41/100	39/94	1.0 (0.5–1.7)		1.2 (0.7–2.4)	
Female	59/100	55/94	1.0	0.95	1.0	0.52
BCG scar						
Present	74/99	73/94	0.9 (0.4–1.7)		1.1 (0.5–2.0)	
Absent	25/99	21/94	1.0	0.64	1.0	0.83
Contact CXR						
Old scar	14/99	2/93	7.5 (1.7–40.0)		7.4 (2.2–24.4)	
Normal	85/99	91/93	1.0	0.01	1.0	<0.01
Index CXR						
Cavity	64/92	48/80	1.5 (0.8–2.9)		1.3 (0.6–2.8)	
No cavity	28/92	32/80	1.0	0.19	1.0	0.51
Sputum smear of index case						
1+ or 2+	43/99	69/90	1.0		1.0	
3+	56/99	21/90	2.5 (1.3–4.7)	<0.01	2.8 (1.3–6.1)	0.01
Sleeps in same room as index case						
Yes	29/100	21/92	1.4 (0.7–2.6)		1.2 (0.5–2.9)	
No	71/100	71/92	1.0	0.33	1.0	0.70
Length of exposure to index						
⩽1 month	42/100	41/93	1.0		1.0	
>1 month	58/100	52/93	1.1 (0.6–1.9)	0.82	1.1 (0.5–2.3)	0.90

**P* values from two-tailed *t*-test.
†From a multivariate logistic regression in STATA with age ⩽10, sex, BCG scar, index CXR, sputum smear of index case, sleep in the same room of index case and length of exposure to index case included as covariates in the model. CI is based on robust standard errors to adjust for potential clustering by household; adjusted for 53 clusters by household.
TST = tuberculin skin test; IGRA = interferon-gamma release assay; OR = odds ratio; CI = confidence interval; aOR = adjusted OR; BCG = bacille Calmette-Guérin; CXR = chest radiograph.

diameter of TST induration was 13 mm (IQR 12–16) among TST+/IGRA− individuals and 16 mm (IQR 14–19) among the positive concordant group, TST+/IGRA+. Using the same covariates included in all logistic regression models in this study, we built a model to compare the TST+/IGRA− group with the TST+/IGRA+; no other risk factors were found.

TST−/IGRA+

The median age of individuals was 37 years (IQR 20–57) for the TST−/IGRA+ group and 22 years (IQR 9–36) for the TST−/IGRA− group ($P = 0.02$; Table 3). Individuals with TST−/IGRA+ results were less likely to be exposed to an index case with a CXR showing evidence of cavitary disease than contacts with negative concordant results (OR 0.2, 95%CI 0.05–0.9, $P = 0.04$). Individuals with TST−/IGRA+ results were 7.2 times more likely to report their length of exposure to the symptomatic index case as >1 month compared to those with concordant negative results (OR 7.2, 95%CI 1.7–29.3, $P < 0.01$; Table 5).

Concordant groups

The principal covariates associated with the positive concordant group when compared to the negative concordant group are summarized in Table 6.

DISCUSSION

The prevalence of LTBI in household contacts according to the TST results was 55.6%. This is 2.2 times the estimated prevalence of LTBI among the general Brazilian population.[19] The prevalence found in our study is similar to that found by TST in a point-prevalence study of LTBI in household contacts (52.3%) in Salvador, Brazil.[20] Although the practice of LTBI contact tracing among household contacts is uncommon in countries with high prevalence of TB,[21] our results are consistent with reports from such countries.[14,22]

We found an agreement between tests of 0.76, which is consistent with other studies.[5,6,22,23] It is widely accepted that TST results can be influenced by BCG vaccination. Since the late 1970s, BCG vaccination coverage in Brazil has been universal and is administered in the first month of life.[2,24] BCG scar was observed in 76% of contacts in our study. However, there was no difference in median age between the TST+/IGRA− group and the TST−/IGRA− group; household contacts with TST+/IGRA− did not have a significantly higher odds of having a BCG scar compared to those who tested TST−/IGRA− (OR 1.8, 95%CI 0.6–5.6, $P = 0.333$). This finding suggests that BCG vaccination did not significantly influence TST results in our study population.

Studies that compare TST and IGRA in high-risk populations always identify a subgroup with discordant test results (TST+/IGRA− or TST−/IGRA+). From a clinical management perspective, individuals who have TST+/IGRA− results raise concern. The basis of LTBI treatment in many countries, including Brazil, is a positive TST. In this study, 40 household contacts tested TST+/IGRA−. The question is which test result to believe and use to decide on initiation of treatment. Interestingly, those who tested TST+/IGRA− shared some of the demographic and clinical characteristics observed in those who tested positive by both tests when the two groups were compared with the negative concordant group. After adjusting for all other variables and within-household correlation, the TST+/IGRA− group was significantly more likely to have a CXR showing old lung scar, just like the TST+/IGRA+ group (Table 4). Like the positive concordant group, the TST+/IGRA− group was also more likely to live in smaller households than those who tested negative by both tests. The range of ages in the TST+/IGRA− and the positive concordant group were also similar (15–45 and 13–41 years, respectively), although the median age differed between the two groups (Table 3). No other differences in risk characteristics were found between the TST+/IGRA− and the positive concordant group (data not shown).

On the other hand, the TST−/IGRA+ discordant group was less likely to live with an index case with CXR showing cavitary disease and had higher odds of exposure to the index case >1 month (Table 5). The TST−/IGRA+ group was significantly older (median 37 years) than the TST−/IGRA− group (median 22 years). It should be noted that the mean size of induration of this discordant group was 6 mm compared to 0 mm in the negative concordant group (Table 3). It is possible that older age may have contributed to the weak delayed-type hypersensitivity response, and that a two-step TST might have yielded a positive TST result in this group. However, we also note that the above significant ORs rely on a small sample size ($n = 17$) and hence could represent spurious results.

A similar study was recently conducted in Germany, a country with low incidence of TB.[25] Nienhaus et al. compared TST and IGRA test results in 1033 healthy subjects who were either part of a contact investigation or health workers. At a cut-off point of 10 mm diameter for TST, the discordance was 15.4%, most of which were TST+/IGRA−. BCG vaccination or migration explained 85% of the TST+/IGRA− discordance. Similar to our observation, the TST−/IGRA+ group tended to be older than the TST−/IGRA− group. They concluded that IGRA is suitable for differentiating LTBI from those vaccinated with BCG or migrants in low-incidence areas such as Germany.[25]

In our study, conducted in a city with a high TB incidence, high LTBI prevalence and where BCG is routinely administered, the discordance was greater (24%), and BCG did not account for this discordance.

Thus, it seems that the decision to initiate treatment of LTBI in household contacts in Brazil should continue to rely on a positive TST result until further studies on the disease progression of highly exposed individuals with discordant results are undertaken. A recent study on the disease progression of IGRA− contacts, with either TST+ or TST− results, shows a low risk of progression to active TB disease.[26] However, these results were based on a very different study population with a broader definition of contacts. Because treatment of LTBI is an important part of TB control, recommendations for the initiation of LTBI treatment should not be changed without proper analysis of the diagnostic tests in all populations at risk.

Acknowledgements

The authors thank the director of the Hospital Especializado Octavio Mangabeira and the clinical laboratory at the hospital. This study was supported by a grant from the Fogarty International Center, National Institutes of Health (5U2RTW006885).

References

1 World Health Organization. Global tuberculosis control: surveillance, planning, financing: WHO report 2008. WHO/HTM/TB/2008.393. Geneva, Switzerland: WHO, 2008.
2 Ministério da Saúde, Secretaria de Políticas de Saúde Brazil. DATASUS. Brasilia, Brazil: Ministério da Saúde, 2008. http://tabnet.datasus.gov.br/cgi/deftohtm.exe?idb2006/d0202.def Accessed April 2007. [Portuguese]
3 Cole E C, Cook C E. Characterization of infectious aerosols in health care facilities: an aid to effective engineering controls and preventive strategies. Am J Infect Control 1998; 26: 453–464.
4 Canadian Tuberculosis Committee. Housing conditions that serve as risk factors for tuberculosis infection and disease. An Advisory Committee Statement (ACS). Can Commun Dis Rep 2007; 33 (ACS-9): 1–13.
5 Pai M, Riley L W, Colford J M Jr. Interferon-gamma assays in the immunodiagnosis of tuberculosis: a systematic review. Lancet Infect Dis 2004; 4: 761–776.
6 Menzies D, Pai M, Comstock G. Meta-analysis: new tests for the diagnosis of latent tuberculosis infection: areas of uncertainty and recommendations for research. Ann Intern Med 2007; 146: 340–354.
7 Eum S Y, Lee Y J, Kwak H K, et al. Evaluation of the diagnostic utility of a whole-blood interferon-gamma assay for determining the risk of exposure to *Mycobacterium tuberculosis* in bacille Calmette-Guérin (BCG)-vaccinated individuals. Diagn Microbiol Infect Dis 2008; 61: 181–186.
8 Ministério da Saúde, Secretaria de Políticas de Saúde Brazil. Manual Técnico para o Controle da Tuberculose. In: Básica Secretaria de Políticas de Saúde. Departamento de Atenção Básica, ed. Cadernos de Atenção Básica Série A normas e manuais técnicos. 1st ed. Brasilia, Brazil: Ministério da Saúde, 2002: pp 1–16. [Portuguese]
9 Sociedade Brasileira de Pneumologia e Tisiologia. II Consenso Brasileiro de tuberculose. Diretrizes Brasileiras para tuberculose 2004. Jornal Brasileiro de Pneumologia 2004; 30 (Suppl): S2–S56. [Portuguese]
10 Andersen P, Munk M E, Pollock J M, Doherty T M. Specific immune-based diagnosis of tuberculosis. Lancet 2000; 356: 1099–1104.
11 Centers for Disease Control and Prevention. Guidelines for the investigation of contacts of persons with infectious tuberculosis. Recommendations from the National Tuberculosis Controllers Association and CDC. Guidelines for using the QuantiFERON®-TB Gold test for detecting *Mycobacterium tuberculosis* infection, United States. MMWR 2005: pp 1–57.
12 Pai M, Zwerling A, Menzies D. Systematic review: t-cell-based assays for the diagnosis of latent tuberculosis infection: an update. Ann Int Med 2008; 149: 177.
13 Mantegani P, Piana F, Codecasa L, et al. Comparison of an in-house and a commercial RD1-based ELISpot-IFN-gamma assay for the diagnosis of *Mycobacterium tuberculosis* infection. Clin Med Res 2006; 4: 266–272.
14 Adetifa I M, Lugos M D, Hammond A, et al. Comparison of two interferon gamma release assays in the diagnosis of *Mycobacterium tuberculosis* infection and disease in The Gambia. BMC Infect Dis 2007; 7: 122.
15 Ministerio do Planejamento Orçamento e Gestão. Instituto Brasileiro de Geografia e Estatistica. Populacao. Brasilia, Brazil: Ministerio do Planejamento Orçamento e Gestão, 2008. http://www1.ibge.gov.br/home/estatistica/populacao Accessed May 2008. [Portuguese]
16 International Union Against Tuberculosis and Lung Disease. Sputum examination for tuberculosis by direct microscopy in low-income countries. Technical guide. Paris, France: The Union, 2000. http://www.iuatld.org/pdf/en/guides_publications/microscopy_guide.pdf Accessed April 2008.
17 Behr M A, Hopewell P C, Paz E A, Kawamura L M, Schecter G F, Small P M. Predictive value of contact investigation for identifying recent transmission of *Mycobacterium tuberculosis*. Am J Respir Crit Care Med 1998; 158: 465–469.
18 Cellestis. Package insert for in vitro diagnostic use. QuantiFeron TB Gold (In-Tube Method) for in vitro diagnostic use. Carnegie, VA, Australia: Cellestis, 2007. http://www.cellestis.com/ Accessed March 2008.
19 Dye C, Scheele S, Dolin P, Pathania V, Raviglione M C. Consensus statement. Global burden of tuberculosis: estimated incidence, prevalence and mortality by country. WHO Global Surveillance and Monitoring Project. JAMA 1999; 282: 677–686.
20 Lemos A C, Matos E D, Pedral-Sampaio D B, Netto E M. Risk of tuberculosis among household contacts in Salvador, Bahia. Braz J Infect Dis 2004; 8: 424–430.
21 Morrison J, Pai M, Hopewell P C. Tuberculosis and latent tuberculosis infection in close contacts of people with pulmonary tuberculosis in low-income and middle-income countries: a systematic review and meta-analysis. Lancet Infect Dis 2008; 8: 359–368.
22 Pai M, Gokhale K, Joshi R, 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: 2746–2755.
23 Machado A Jr, Szabo K, Barbosa T, et al. Comparison of whole blood interferon-gamma assay with tuberculin skin testing in household contacts of pulmonary tuberculosis in Salvador, Brazil. Chest 2007; 132: S433.
24 Benevolo-de-Andrade T C, Monteiro-Maia R, Cosgrove C, Castello-Branco L R, Moreau B C G. Rio de Janeiro: an oral vaccine against tuberculosis—review. Mem Inst Oswaldo Cruz 2005; 100: 459–465.
25 Nienhaus A, Schablon A, Diel R. Interferon-gamma release assay for the diagnosis of latent TB infection—analysis of discordant results, when compared to the tuberculin skin test. PLoS ONE 2008; 3: e2665.
26 Diel R, Loddenkemper R, Meywald-Walter K, Niemann S, Nienhaus A. Predictive value of a whole blood IFN-gamma assay for the development of active tuberculosis disease after recent infection with *Mycobacterium tuberculosis*. Am J Respir Crit Care Med 2008; 177: 1164–1170.

RÉSUMÉ

OBJECTIF : Analyser les facteurs en association avec les discordances entre le test cutané tuberculinique (TCT) et les techniques de libération de l'interféron-gamma (IGRA) chez les sujets au contact dans le ménage avec des patients atteints de tuberculose (TB) pulmonaire.

SCHÉMA : A Salvador au Brésil, nous avons pratiqué le TCT (dérivé protéique purifié) et l'IGRA (QuantiFERON®-TB Gold) chez les sujets au contact dans le ménage avec des patients atteints de TB pulmonaire chez qui le diagnostic avait été porté entre 2006 et 2007. Les groupes de tests discordants ont été comparés au groupe TCT−/IGRA−.

RÉSULTATS : Sur 261 contacts dans le ménage testés de manière satisfaisante par le TCT, les résultats ont été positifs chez 145 sujets (55,6%) ; sur les 298 sujets testés de manière satisfaisante par l'IGRA, les résultats ont été positifs chez 127 sujets (43,1%). Le niveau de concordance entre les tests est de 0,76 ($\kappa = 0{,}53$; IC95% 0,43–0,63). Il y a eu 61 discordances (24%), soit 44 (72%) TCT+/IGRA− et 17 (28%) TCT−/IGRA+. Par comparaison avec le groupe TCT−/IGRA−, le groupe TCT+/IGRA− et le groupe TCT+/IGRA+ sont significativement plus susceptibles d'avoir un cliché thoracique avec présence de vieilles cicatrices pulmonaires (respectivement OR = 6,8 ; IC95% 1,3–35,0 ; et OR = 7,4 ; IC 95% 2,2–24,4). Le groupe TCT−/IGRA+ a été exposé de manière significativement plus prolongée au cas index que le groupe TCT−/IGRA− (OR = 7,2 ; IC95% 1,7–29,3).

CONCLUSION : Les groupes TCT+/IGRA− et TCT+/IGRA+ ont des caractéristiques communes plus semblables entre elles vis-à-vis du groupe TCT−/IGRA−. Dans un contexte endémique de TB, les résultats du TCT apparaissent plus adéquats pour la décision de traiter une infection TB latente.

RESUMEN

OBJETIVO : Analizar los factores asociados con la discordancia entre los resultados de la prueba cutánea de la tuberculina (TST) y las pruebas de liberación de interferón gama (IGRA) en los contactos domiciliarios de pacientes con tuberculosis (TB) pulmonar.

MÉTODO : Se practicó la TST y la IGRA (QuantiFERON®-TB Gold) en los contactos domiciliarios de los pacientes con TB pulmonar diagnosticados entre 2006 y 2007 en Salvador, Brasil. Los grupos discordantes se compararon con el grupo que presentó ambos resultados negativos.

RESULTADOS : De los 261 contactos con una TST satisfactoria, 145 (55,6%) tuvieron resultado positivo ; de los 298 contactos con una IGRA satisfactoria, 127 (43,1%) tuvieron resultado positivo. La prueba de concordancia fue de 0,76 ($\kappa = 0{,}53$; IC95% 0,43–0,63). Sesenta y un (24%) casos fueron discordantes : un primer subgrupo de 44 personas (72%) con TST positiva y IGRA negativa y un segundo subgrupo de 17 (28%) con TST negativa y IGRA positiva. Comparados con el grupo que obtuvo resultados negativos en ambas pruebas, el primer subgrupo y el grupo con ambas pruebas positivas tuvieron una probabilidad significativamente mayor de presentar imágenes de secuelas en la radiografía de tórax (OR = 6,8 ; IC95% 1,3–35,0 ; y OR = 7,4 ; IC95% 2,2–24,4, respectivamente). El segundo subgrupo (TST negativa y IGRA positiva) estuvo expuesto al caso inicial por un período significativamente más largo que el grupo con ambos resultados negativos (OR = 7,2 ; IC95% 1,7–29,3).

CONCLUSIÓN : El grupo con resultado positivo a la TST y negativo a la IGRA y el grupo con ambos resultados positivos compartieron características, más semejantes entre sí, que con el grupo que presentó ambos resultados negativos. En un entorno con TB endémica, los resultados de la TST parecen más adecuados para la decisión de tratar la infección tuberculosa latente.