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Tuberculosis screening in Portuguese healthcare workers using the tuberculin skin test and the interferon-γ release assay

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ABSTRACT: The prevalence of latent tuberculosis (TB) infection (LTBI) and the incidence of active tuberculosis in healthcare workers (HCWs) in a Portuguese hospital were examined.

This cross-sectional study comprises 4,735 hospital workers screened between May 2005 and September 2008. Tuberculin skin test (TST) and interferon-γ release assay (IGRA) were used simultaneously in 1,219 HCWs (25.7%). Radiographs were taken in symptomatic HCWs or in test-positive HCWs. The tests were repeated annually or bi-annually depending on risk assessment.

IGRA was positive in 32.6% and TST in 74.2% of the HCWs. Years spent in healthcare were a risk factor for a positive IGRA, but not for a positive TST. Repeated bacillus Calmette–Guérin vaccination increased the probability of TST+/IGRA- discordance (35.4% *versus* 54.4%, respectively). In those tested three times with TST during the study period (n=59), the mean diameter of TST increased from 5 to 7 to 10 mm. Within 3 yrs, 31 HCWs were diagnosed with active TB (annual incidence rate 191 out of 100,000 people). In eight HCWs with active TB, TST and IGRA were performed at the time of diagnosis and each test was positive.

TB burden in HCWs in Portugal is high. With IGRA, the number of radiographs needed to exclude active TB could have been reduced by about half without missing a case of active TB. Therefore IGRA should be introduced into TB screening programmes.

KEYWORDS: Healthcare workers, interferon-γ release assay, Portugal, tuberculin skin test, tuberculosis

Screening healthcare workers (HCWs) for latent tuberculosis infection (LTBI) and active tuberculosis (TB) is fundamental in infection control programmes in hospitals [1]. In Portugal, screening of HCWs for TB has been performed only in the context of contact tracing through the public health department, while occupational medicine has been nonexistent in most Portuguese hospitals. Since 2005, Hospital S. João, in Northern Portugal (Porto), has been building up an Occupational Health Division for the hospital staff, which screens HCWs for TB on a regular basis, depending on risk assessment following Centers for Disease Control and Prevention guidelines [1].

For about a century, the tuberculin skin test (TST) has been used to detect LTBI. However, the TST has known limitations, including cross-reactivity with bacillus Calmette–Guérin (BCG) and non-tubercular mycobacteria (NTM) infections [2]. Advances in molecular biology have led to the development of new *in vitro* assays that measure interferon (IFN)-γ released by sensitised T cells after stimulation with *Mycobacterium tuberculosis* antigens. These tests are more specific than the TST because they use antigens not shared by any of the BCG vaccine strains nor by the more common species of NTM (*e.g. Mycobacterium avium*) [3]. Besides a higher specificity and an at-least equal sensitivity as the TST, interferon-γ release assays (IGRAs) correlate better with surrogate measures of exposure to *M. tuberculosis* [4–6] and have a higher predictive value for LTBI progression to active TB in close contact in low-incidence settings [7].

So far, only a few systematic investigations of LTBI in HCWs using the IGRA have been published [8–14]. Therefore, we studied the prevalence of LTBI and active TB in Portuguese HCWs and compared IGRA and TST performance.

MATERIALS AND METHODS

Study setting and study subjects

The population of this cross-sectional study comprises all workers of the Hospital S. João who participated in TB screening from May 2005

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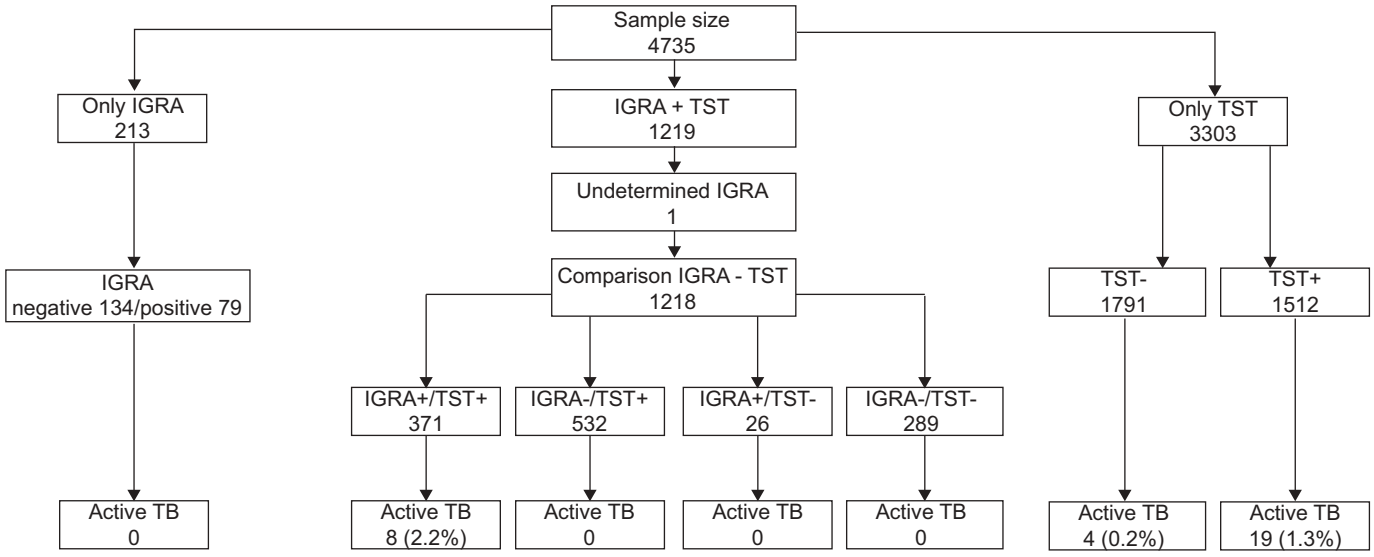

FIGURE 1. Study population. IGRA: interferon-γ release assay; TST: tuberculin skin test; TB: tuberculosis.

until September 2008. HCWs in infection and TB wards are considered to be at high risk, workers with regular patient contact in other wards are considered to be at medium risk and workers with no regular patient contact or no contact with biological material are considered to be at low risk [1]. Upon commencement of employment, all workers are examined. HCWs considered at high risk are evaluated annually. All others are evaluated every other year or after known exposure to patients with active TB.

Screening was initially performed using TST only. Since January 2007, TST and IGRA have been performed simultaneously. TST was performed when the diameter of a previous TST was <15 mm or when no previous TST result was known. A chest radiograph was performed when TST was ⩾10 mm or in HCWs with TB symptoms.

BCG vaccination was assessed through the individual vaccination register or by scars. Following the national vaccination plan, BCG vaccination for newborns is mandatory in Portugal and, until January 2000, was repeated if TST was <5 mm [15]. Therefore, every HCW has been vaccinated at least once.

TST was performed by trained personnel following standard procedures. In brief, 0.1 mL (2 TU) of purified protein derivate (RT23; Statens Serum Institute, Copenhagen, Denmark) was injected intradermally at the volar side of the forearm and the transverse diameter of the induration was read 72–96 h later. A diameter ⩾10 mm was considered positive.

Before TST application, an interview was performed and blood for the IGRA was drawn. As IGRA, the QuantiFERON-TB® Gold In-Tube Assay (Cellestis Limited, Carnegie, Australia) was administrated, following the manufacturer's protocol. Observers were blinded to the results of the TST and *vice versa*.

Statistical analysis

Chi-squared tests were used for categorical data. Adjusted OR and 95% CI were calculated for putative predictive variables using conditional logistic regression. Model building was performed backwards using the chance criteria for variable selection [16].

All persons gave their informed consent prior to their inclusion in the study.

RESULTS

The study population comprised 4,735 HCWs. In 213 HCWs (4.5%), only IGRA results were available because the TST was contraindicated, refused, or the second appointment for TST reading was missed (fig. 1). The characteristics of those 1,219 HCWs (25.7%) tested simultaneously with TST and IGRA are given in table 1.

TST was positive in 74.2% and IGRA in 32.6% of the HCWs. The probability of a positive IGRA increased with the induration diameter of the TST (table 2), with age and with years spent as an HCW (table 3). The OR for TST ⩾10 mm in HCWs with three or more additional BCG vaccinations after birth was 2.0 (95% CI 1.29–3.02). The variable ''years since the last vaccination'' did not influence TST results. A positive IGRA was less likely when only ⩽10 yrs had passed since the last vaccination (OR 0.2; 95% CI 0.09–0.52). No association with profession or risk assessment was observed in either test.

TST+/IGRA- discordance increased with the number of BCG vaccinations (table 4). TST+/IGRA- discordance was 40.5% when the last vaccination was >15 yrs ago and 56.3% when 1–10 yrs had passed. TST+/IGRA- discordance in nurses was higher than in other professions (table 4) and thay had TST more often repeated during the study period (30.5%) than, for example, physicians (14.7%). Risk assessment was inversely correlated with positive concordant results (low risk 38.7%, high risk 26.7%). Age >60 yrs was associated with increased TST-/IGRA+ discordance (table 4).

In a subgroup of 59 HCWs in whom the TST was repeated three times during the study period (time between the test:

TABLE 1 Study population for comparison interferon-γ release assay with tuberculin skin test

	n	%
Age		
16–29 yrs	443	36.4
30–39 yrs	336	27.6
40–49 yrs	212	17.4
50–59 yrs	199	16.3
⩾60 yrs	28	2.3
Sex		
Female	878	72.1
Male	340	27.9
BCG vaccination		
Only at birth	370	30.4
1 additional	426	35.0
2 additional	301	24.7
⩾3 additional	121	9.9
Years since last BCG		
>15 yrs	920	75.5
>10–15 yrs	227	18.6
1–10 years	71	5.8
Profession		
Administrator	186	15.3
Auxiliaries, cleaning staff	188	15.4
Technicians (radiology, lab, *etc*.)	85	7.0
Nurses	548	45.0
Physicians	211	17.3
Risk assessment		
Low risk	173	14.2
Moderate risk	407	33.4
High risk	638	52.4
Time working in healthcare		
Start of work	208	17.1
<5 yrs	301	27.7
5–<10 yrs	212	17.4
10–<15 yrs	142	11.7
15–<20 yrs	90	7.4
⩾20 yrs	265	21.8

BCG: bacillus Calmette–Guérin.

TABLE 2 Tuberculin skin test (TST) diameter by interferon-γ release assay (IGRA) results

	IGRA					
	Negative		Positive		Total	
	n	Row%	n	Row%	n	Col%
TST						
0–4 mm	133	97.1	4	2.9	137	11.2
5–9 mm	156	87.6	22	12.4	178	14.6
10–15 mm	341	70.6	142	29.4	483	39.7
>15 mm	191	45.5	229	54.5	420	34.5
All	821	67.4	397	32.6	1218	100.0

Row%: % within the TST category; Col%: % of total falling into a certain TST category.

12 months), the median of the induration diameter increased from 5 mm *via* 7 mm to 10 mm (fig. 2).

Active tuberculosis was diagnosed in 31 HCWs (fig. 1) based on positive PCR (n=2) or on culture-confirmed positive smear (n=29). Assuming a dynamic cohort in which every HCW was present for 41 months (May 2005 through September 2008), the annual incidence rate was 191.6 out of 100,000 people. In eight HCWs with active TB, TST and IGRA were performed simultaneously at the time of diagnosis and both tests were positive.

In 16 (51.6%) out of the 31 HCWs with active TB (fig. 1), the diagnosis was initiated by the Occupational Health Division. 13 presented themselves with typical TB symptoms and three were diagnosed based on positive TST and IGRA followed by a suspicious radiograph.

DISCUSSION

This is the largest study to investigate the performance of the TST and the IGRA when screening HCWs, which allowed for the analysis of risk factors for discordant results of the two tests. The annual incidence rate of active TB in Portuguese HCWs (191.6 per 100,000 people) was about six times higher than the one in the general population in Portugal (32 out of 100,000 people) in 2006 [17] and the prevalence of LTBI varied widely depending on the test used. Therefore, the proportion of HCWs needing radiograph might have been reduced from 74.2% with positive TST to 32.6% if only IGRA-positive HCWs undergo radiograph in order to exclude active TB.

So far, little is known about the effect of repeated BCG vaccination on the probability of TST+/IGRA- discordant results [18, 19]. Repeated BCG vaccination increased the probability of positive TSTs not confirmed by IGRA. Recent BCG vaccination

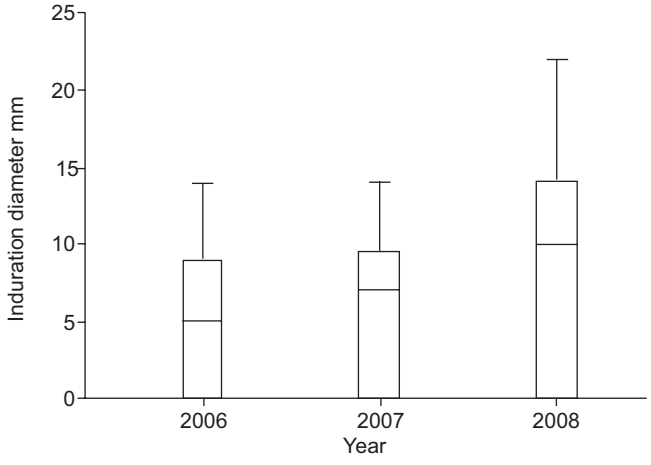

FIGURE 2. Box plot of induration diameter in mm in 59 healthcare workers with three tuberculin skin tests in 2006, 2007 and 2008. Horizontal bars represent medians, boxes represent interquartile range and whiskers represent the data range.

TABLE 3 Proportion of tuberculin skin tests (TST) ⩾ 10 mm and positive interferon-γ release assay (IGRA), and the respective adjusted OR and 95% CI for different putative risk factors

	TST ⩾10mm			IGRA-positive		
	n (%)	OR	95% CI	n (%)	OR	95% CI
Age						
16–29 yrs	212 (47.9)	1		99 (22.3)	1	
30–39 yrs	146 (43.5)	0.9	0.68–1.23	100 (29.8)	1.4	0.97–1.91
40–49 yrs	88 (41.5)	1.0	0.68–1.38	87 (41.0)	1.8	1.26–2.70
50–59 yrs	78 (39.2)	1.1	0.71–1.56	99 (49.7)	2.1	1.40–3.17
⩾60 yrs	8 (28.6)	0.7	0.23–1.68	12 (42.9)	1.4	0.63–3.28
Sex						
Female	391 (44.5)	1		278 (31.7)	1	
Male	141 (41.5)	1.0	0.77–1.31	119 (35.0)	0.9	0.70–1.24
BCG vaccination						
Only at birth	131 (35.4)	1		166 (44.9)	1	
1 additional	186 (43.7)	1.4	1.02–1.82	137 (32.2)	0.8	0.60–1.12
2 additional	149 (49.5)	1.6	1.18–2.24	74 (24.6)	0.8	0.55–1.18
3–10 additional	66 (54.5)	2.0	1.29–3.02	20 (16.5)	0.6	0.34–1.07
Years since last BCG						
>15 yrs	373 (40.5)	1		355 (38.6)	1	
>10–15 yrs	119 (52.4)	1.3	0.91–1.80	36 (15.9)	0.4	0.28–0.67
1–10 yrs	40 (56.3)	1.4	0.84–2.38	6 (8.5)	0.2	0.09–0.52
Profession						
Administrator	76 (40.9)	1		75 (40.3)	1	
Auxiliaries, cleaning staff	65 (34.6)	0.7	0.49–1.13	76 (40.4)	1.5	0.95–2.45
Technicians (radiology, lab, *etc*.)	44 (51.8)	1.4	0.82–2.34	22 (25.9)	0.8	0.43–1.45
Nurses	276 (50.4)	1.3	0.91–1.82	138 (25.2)	0.8	0.52–1.21
Physicians	71 (33.6)	0.7	0.45–1.02	86 (40.8)	1.6	0.98–2.54
Risk assessment						
Low risk	69 (39.9)	1		73 (42.2)	1	
Moderate risk	177 (43.5)	1.2	0.77–1.79	143 (35.1)	0.9	0.59–1.41
High risk	286 (44.8)	1.1	0.77–1.72	181 (28.4)	0.7	0.46–1.07
Time working in healthcare						
Start of work	83 (39.9)	1		43 (20.7)	1	
<5 yrs	142 (47.2)	1.2	0.81–1.72	80 (26.6)	1.7	1.08–2.69
5–<10 yrs	102 (48.1)	1.2	0.81–1.83	58 (27.4)	1.8	1.08–2.86
10–<15 yrs	65 (45.8)	1.1	0.73–1.78	52 (36.6)	2.9	1.34–4.87
15–<20 yrs	36 (40.0)	0.9	0.56–1.58	39 (43.3)	3.0	1.68–5.26
⩾20 yrs	104 (39.2)	1.2	0.79–1.79	125 (47.2)	2.6	1.64–4.13

BCG: bacillus Calmette–Guérin

or repeated BCG vaccination decreased the probability of a negative IGRA. This is most likely due to the fact that TST-negative HCWs are revaccinated, inducing a positive TST without changing the IGRA.

The increase of TST diameter in the small subgroup (n=59) tested three times during the study period most likely indicates a booster effect of serial testing [20] as does the higher rate of TST+/QFT- results in nurses, who also have TST repeated most often. The effect of serial testing with TST on IGRA has still to be elucidated. Preliminary results suggest that IGRA is not substantially influenced when TST is administered 3 days before the IGRA [21].

Working in healthcare is a well-known risk factor for TB [22–24]. As per our data, the probability of a positive IGRA (table 3) increased with years spent in healthcare, while the TST did not reveal such an association. Surprisingly, neither risk assessment [1] nor profession was associated with TST or IGRA. In the two European fingerprint studies [25, 26], the majority of work-related active TB cases occurred when the infection risk was not suspected and preventive measures were not taken. Rotation of the staff is another explanation for the lack of this association. Furthermore, our cross-sectional design might dilute the expected association.

Screening HCWs for LTBI with TST in our populations had shortcomings. The rate of positive TST was high and influenced

TABLE 4 Concordant and discordant tuberculin skin test (TST) ⩾10 mm and interferon-γ release assay (IGRA) results depending on putative risk factors

	TST/IGRA								p-value
	-/-		+/-		-/+		+/+		
	n	%	n	%	n	%	n	%	
Age									
16–29 yrs	132	29.8	212	47.9	10	2.3	89	20.1	
30–39 yrs	90	26.8	146	43.5	6	1.8	94	28.0	
40–49 yrs	37	17.5	88	41.5	2	0.9	85	40.1	
50–59 yrs	22	11.1	78	39.2	5	2.5	94	47.2	
⩾60 yrs	8	28.6	8	28.6	3	10.7	9	32.1	<0.001
Sex									
Female	209	23.8	391	44.5	17	1.9	261	29.7	
Male	80	23.5	141	41.5	9	2.6	110	32.4	0.644
BCG vaccination									
Only at birth	73	19.7	131	35.4	10	2.7	156	42.2	
1 additional	103	24.2	186	43.7	10	2.3	127	29.8	
2 additional	78	25.9	149	49.5	5	1.7	69	22.9	
3–10 additional	35	28.9	66	54.5	1	0.8	19	15.7	<0.001
Years since last BCG									
>15 yrs	192	20.9	373	40.5	24	2.6	331	36.0	
>10–15 yrs	72	31.7	119	52.4	1	0.4	35	15.4	
1–10 years	25	35.2	40	56.3	1	1.4	5	7.0	<0.001
Profession									
Administrator	35	18.8	76	40.9	4	2.2	71	38.2	
Auxiliaries, cleaning staff	47	25.0	65	34.6	4	2.1	72	38.3	
Technicians (radiology, lab, *etc*.)	19	22.4	44	51.8	3	3.5	19	22.4	
Nurses[#]	134	24.5	276	50.4	7	1.3	131	23.9	
Physicians[#]	54	25.6	71	33.6	8	3.8	78	37.0	<0.001
Risk assessment									
Low risk	31	17.9	69	39.9	6	3.5	67	38.7	
Moderate risk	87	21.4	177	43.5	6	1.5	137	33.7	
High risk	171	26.8	286	44.8	14	2.2	167	26.2	0.006
Time working in healthcare									
Start of work	82	39.4	83	39.9	2	1.0	41	19.7	
<5 yrs	79	26.2	142	47.2	10	3.3	70	23.3	
5–<10 yrs	52	24.5	102	48.1	6	2.8	52	24.5	
10–<15 yrs	25	17.6	65	45.8	1	0.7	51	35.9	
15–<20 yrs	15	16.7	36	40.0	1	1.1	38	42.2	
⩾20 yrs	36	13.6	104	39.2	6	2.3	119	44.9	<0.001

BCG: bacillus Calmette–Guérin. [#]: repeated TST during study period: nurses (30.5%) physicians (14.7%), p-value <0.0005.

by repeated BCG vaccination, allowing little discrimination between HCWs at risk of having or of progressing to active TB. Therefore, our data corroborate the conclusion of a Taiwan HCW study [27] that the TST is not useful in contact investigation among BCG-vaccinated HCWs. In the subgroup undergoing TST and IGRA simultaneously, all eight HCWs diagnosed with active TB were positive in both tests. Restricting radiographs to symptomatic or IGRA-positive HCWs would have reduced the number of radiographs by more than half (TST 74.2% *versus* IGRA 32.6%) without decreasing the number of active TB cases detected in our population.

STATEMENT OF INTEREST

None declared.

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