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Prevalence of tuberculosis infection in healthcare workers of the public hospital network in Medellín, Colombia: a Bayesian approach

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SUMMARY

A latent tuberculosis infection (LTBI) prevalence survey was conducted using tuberculin skin test (TST) and Quantiferon test (QFT) in 1218 healthcare workers (HCWs) in Medellín, Colombia. In order to improve the prevalence estimates, a latent class model was built using a Bayesian approach with informative priors on the sensitivity and specificity of the TST. The proportion of concordant results (TST+,QFT+) was 41% and the discordant results contributed 27%. The marginal estimate of the prevalence P(LTBI+) was 62·1% [95% credible interval (CrI) 53·0–68·2]. The probability of LTBI+ given positive results for both tests was 99·6% (95% CrI 98·1–99·9). Sensitivity was 88·5 for TST and 74·3 for QFT, and specificity was 87·8 for TST and 97·6 for QFT. A high LTBI prevalence was found in HCWs with time-accumulated exposure in hospitals that lack control plans. In a context of intermediate tuberculosis (TB) incidence it is recommended to use only one test (either QFT or TST) in prevalence surveys or as pre-employment tests. Results will be useful to help implement TB infection control plans in hospitals where HCWs may be repeatedly exposed to unnoticed TB patients, and to inform the design of TB control policies.

Key words: Latent class model, occupational exposure, sensitivity, specificity.

INTRODUCTION

Several studies indicate that healthcare workers (HCWs), especially those who care for patients with pulmonary tuberculosis (TB) have a higher frequency of latent tuberculosis infection (LTBI) and active TB [1]. In the early twentieth century, for example, HCWs had a higher reported incidence of TB disease than the general population [2]. The sustained reduction in the frequency of TB in industrialized countries decreased the interest in studying the risks workers have of becoming infected and getting sick. However, this interest increased in the 1990s when several outbreaks of TB in hospitals were described along with the importance of repeated, inadvertent exposures to patients without a TB diagnosis, and attention was again drawn to the increased risk of infection (LTBI) and disease in HCWs [2]. A recent systematic review indicated that the incidence of active TB in Latin American HCWs is 91 [interquartile range (IQR) 81–723] per 100 000, higher than the

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rate the authors use for comparison with the general population of those countries (82×100 000, IQR 28–223) [1].

LTBI is a complex condition difficult to diagnose, characterized by the presence of the immune response to infection by *M. tuberculosis* without clinical evidence of active TB. With respect to diagnostic methods of LTBI, the WHO recommends the tuberculin skin test (TST) or interferon-γ release assay (IGRA) [3]. The latter is expensive and little studied in Colombia, but is being increasingly used because of its advantages compared to the TST; i.e. requires only a single visit, has comparable sensitivity and improved specificity in people with previous immunization with bacillus Calmette-Guérin (BCG), such as the case of the population of Colombian HCWs [4]. In Colombia, the performance of TST and IGRA has not been assessed in HCWs and the occupational risk of TB for HCWs remains mainly unaddressed in practice. Furthermore, there are no national or local guidelines to monitor HCWs and there is a lack of local knowledge on this subject in Colombia. In general, high-income countries include the diagnosis and treatment of LTBI in their plans to eliminate TB, have TB control plans in their hospitals and allocate resources for the regular monitoring of HCWs. This situation is very different in countries of intermediate and high incidence of TB, such as Colombia, where the control programme is centred on the passive detection and treatment of TB cases and lacks information on the prevalence of LTBI in HCWs and the political will to systematize and consolidate hospital TB control plans.

In Medellín, Colombia, the incidence of TB (all forms) in 2013 was 63·8 cases/100 000 inhabitants, but rates above 100/100 000 have been recorded in some areas of the city (*comunas*) [5]. The delay in the diagnosis of pulmonary TB is problematic for the city (it may increase the repeated exposure of HCWs with *M. tuberculosis*) given that the median between the onset of symptoms and the start of treatment was 61 days in 2014 (IQR 32–105) [6].

A 5-year study by the National Epidemiological Surveillance System describes an increase in the reported active TB cases in HCWs for Colombia for 2010 and 2011 [7]. Antioquia – the province where Medellín is located, contributes 16% ($n = 84/532$) of the total TB cases in the country. The public hospital network of Medellín (ESE Metrosalud) has nine hospitals and one administrative centre with a total of 1532 HCWs (official census at beginning of the study). Although these institutions supervise most of the treatments for TB patients in the city and are usually the first point of contact between the respiratory patient and the health services, they lack institutional TB control plans: poor ventilation conditions, lack of resources for isolates and absence of periodic training of HCWs to prevent TB exposition and infection.

With the foregoing in mind, a prevalence survey of LTBI was conducted using TST and IGRA [QuantiFERON®-TB Gold In-Tube test (QFT); Cellestis-Qiagen, Australia] simultaneously in a population of HCWs (vaccinated with BCG at birth) from 10 institutions of the public hospital network of Medellín. Because both tests are imperfect due to the lack of a gold standard for the diagnosis of LTBI, we built a latent class model (LCM), which considers that the results of the prevalence survey are influenced by a latent common variable (true state of LTBI), which can not be measured directly [8]. The fitting of the LCM model was made using a Bayesian approach.

The LCM estimated the improved prevalence of LTBI in HCWs using TST and QFT results, and the sensitivity and specificity of both tests. This information will allow us to assess the usefulness of both tests to monitor HCWs in a context of limited resources and help design the policies to control nosocomial transmission of *M. tuberculosis* in Colombia.

METHODS

Study design and participants

A LTBI prevalence survey was conducted in a cohort of 1218 HCWs from nine hospitals and the administrative centre of the public hospital network in the city of Medellín, Colombia, between 2013 and 2015.

We set out to study the totality of HCWs (clinical, administrative and support personnel). Of 1532 registered employees, 1218 voluntarily agreed to participate (Fig. 1). We report on the results of 1004 HCWs who received both the TST and QFT. The HCWs from one hospital and the administrative centre ($n = 214$) were not included in the analysis because they received only the QFT due to the world shortage of TST, including Tubersol® (PPD; Sanofi Pasteur Ltd, Canada) [9, 10], which affected the availability of the test in Colombia for 6 months.

We used TST and QFT simultaneously. Both tests are markers of exposure to *M. tuberculosis* and measure the body's immune response: TST produces a skin

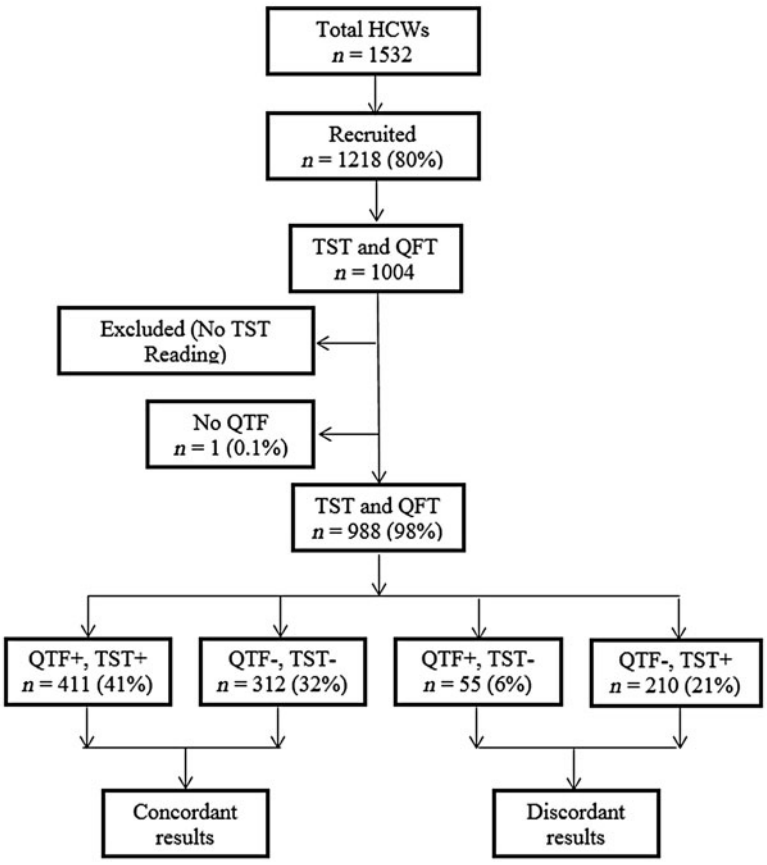

Fig. 1. Flow chart of study subjects. Prevalence of latent tuberculosis infection in healthcare workers (HCWs) of the public hospital network in Medellín, Colombia, 2013–2015.

induration on the site of application which is read in millimetres; QFT quantifies the production of interferon-gamma (IFN-γ) by T cells [11]. The results of both tests are independent, although QFT may vary when performed 72 h after application of TST, and the sources of variability are different for each test [12].

TST

Five tuberculin units (Tubersol PPD) were used with each HCW. The application was made using the Mantoux method [13] by two trained professionals: one in the beginning of the study and a different one towards the end. We trained our personnel extensively to minimize bias. The measurement of induration was performed 72 h after application, and a result $\geqslant 10$ mm was considered positive. If the initial result was <10 mm, a second test was performed within a 1- to 3-week interval to control for the 'booster effect' – an increase in the induration in the absence of a new infection, caused by the recall of waned cell-mediated immunity [14]. The TST was performed immediately after sampling the blood for QFT.

IGRA testing

We used the QFT. Samples from HCWs were obtained by phlebotomy (1 ml blood for each of the three tubes provided by the manufacturer). The tubes were shaken for 5 s and placed in an incubator transport (Cellestis) that guaranteed a temperature of 37 °C until arrival at a certified laboratory. The results were presented according to the manufacturer's instructions with the specific software complement (QFT software v. 2·17, Cellestis). The test was considered positive if the results of IFN-γ production minus those obtained in the null tube were $\geqslant 0{\cdot}35$ IU/ml. The technician performing the QFT was blind to the results of the TST.

The demographic and occupational characteristics of the HCWs were described and the kappa statistic [15] for concordance between TST and QFT was calculated. Frequency histograms were prepared to verify

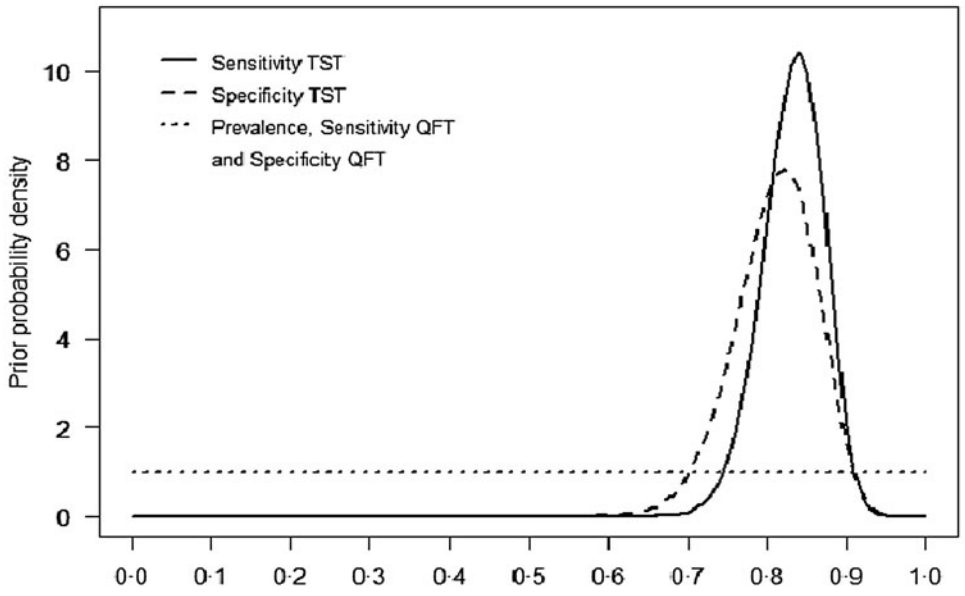

Fig. 2. Prior distributions used for the estimates. Prevalence of latent tuberculosis infection in healthcare workers of the public hospital network in Medellín, Colombia, 2013–2015.

the form of the distribution of the TST results by age and years of employment.

Bayesian approach for the estimation of LCM

We used the studies by Ling *et al.* [16] and Joseph *et al.* [8] as a reference and the following procedures for the construction of the LCM:

- We assigned 1 and 0 values to the positive and negative results, respectively, for both the TST and QFT. Frequencies for concordant and discordant results of the two tests were calculated (Fig. 1).
- We modelled the observed data using a multinomial distribution where the probabilities of the four combinations of the TST and QFT results can be expressed in terms of sensitivity and specificity and the prevalence of LTBI [equation (1) in the Technical Appendix].
- The LCM has the assumption of conditional independence between TST and QFT within the LTBI + and LTBI- groups. We did not control for dependence in the analysis but we are confident that the Bayesian LCM will allow for reasonable inferences [17].
- The LCM is not identifiable because there are five unknown parameters (the sensitivity and specificity of both tests and the prevalence) which exceed three degrees of freedom (four test combinations minus 1). To avoid this problem using a Bayesian approach, informative prior distributions were assigned for two of the model parameters (TST sensitivity and specificity).
- We obtained the percentiles of the prior distributions for the sensitivity and specificity of TST from an article by Pai *et al.* [18]. They worked with a cohort of 719 medical and nursing students and HCWs in India who underwent TST and QFT testing, and we used their LCM analysis results as prior distributions for our study. To estimate the sensitivity of the TST, a Beta distribution (77·8,15·7) was used as informative prior distribution, whose 2·5% and 97·5% percentiles are 0·75 and 0·90, respectively; and for the specificity of TST, a Beta distribution (46·3,10·8) was used as prior distribution whose 2·5% and 97·5% percentiles are 0·70 and 0·90, respectively (Fig. 2). We do not expect TST sensitivity/specificity to behave differently in our study, since the study by Pai *et al.* was also on HCWs and both India and Colombia administer BGC only once at birth.
- A relatively uninformative distribution such as the uniform distribution (Fig. 2) was used for the parameters of the model for which prior information was not available due to, as far as we know, a lack of Latin American studies on this subject (sensitivity and specificity for QFT).

Table 1. *Sociodemographic and occupational characteristics of the healthcare worker (HCW) population*

	Total ($N = 988$)		QFT+,TST+ ($N = 411$; 41·6%)		QFT-,TST- ($N = 312$; 31·6%)		QFT+,TST- ($N = 55$; 5·6%)		QFT-,TST+ ($N = 210$; 21·3%)	
Variables	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Sex										
Female	727	73·6	310	75·4	241	77·2	39	70·9	137	65·2
BCG vaccination status	947	96·7	390	95·8	302	98·1	52	94·6	203	97·1
Education level										
Illiterate/Elementary/High school	147	14·9	83	20·2	31	9·9	9	16·4	24	11·4
Technical/Higher education/Other	841	85·1	328	79·8	281	90·1	46	83·6	186	88·6
Socioeconomic strata (housing)										
Low/Medium-low	645	65·3	287	69·8	196	62·8	42	76·4	120	57·1
Medium-high/High	343	34·7	124	30·2	116	37·2	13	23·6	90	42·9
Job type										
Administrative	242	24·5	100	24·3	67	21·5	15	27·3	60	28·6
Clínical/Para-clinical	746	75·5	311	75·7	245	78·5	40	72·7	150	71·4
Sharing housing with a TB case	55	5·6	33	8·1	15	4·8	1	1·8	6	2·9
Use of respiratory protection	559	56·6	244	59·4	183	58·7	32	58·2	100	47·6
Residential area*										
Low TB incidence	749	78·0	287	71·9	255	84·2	39	70·9	168	82·8
Intermediate TB incidence	195	20·3	105	26·3	43	14·2	15	27·3	32	15·8
High TB incidence	16	1·7	7	1·8	5	1·6	1	1·8	3	1·5
	Median	IQR	Median	IQR	Median	IQR	Median	IQR	Median	IQR
Age, years	43	33–51	44	36–52	37	29–48	47	37–52	44	35–51
Years of hospital employment	14	6–23	16	8–24	10	4–21	14	6–25	16	8–24

BCG, Bacille Calmette-Guérin; IQR, interquartile range.
* The residential area of 28 HCWs was unknown.

- Using the medians of age and years of employment (Table 1), the results of laboratory tests were processed for four groups of HCWs: age <43 years, age ⩾43 years, <15 years of employment, ⩾15 years of employment. The LCM results were presented for each group.
- Once the posterior distributions were obtained, we calculated the median and the credible intervals (CrIs) for prevalence, sensitivity and specificity for TST and QFT. In a Bayesian approach, the CrIs are the equivalent of the confidence intervals (CIs) used in the frequentist approach.

All the procedures described above were performed using OpenBUGS software, v. 3.2.3 revision 2012 (Bayesian inference Using Gibbs Sampling; Free Software Foundation, USA). The analysis presented here is the result of 20 000 Markov chain Monte Carlo (MCMC) iterations using the multivariate forward updater algorithm with a thinning of five iterations and a burn-in of 10 000 iterations. We checked the convergence of chains using the diagnostics tool provided by OpenBUGS (see the code in the Technical Appendix).

Ethical considerations

The authors assert that all the procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees (Bioethics Review Committee of The National School of Public Health – University of Antioquia: C13255-161040 and the Management Committee at ESE Metrosalud) on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All the workers and managers of the healthcare institutions who agreed to participate gave their written informed consent (individual and institutional) accepting to take the survey, laboratory tests and clinical and X-ray follow-up as indicated in the protocols. The procedures to assess the presence of active TB were the estimation of comorbidity and the annual risk of active TB for all workers, using an algorithm developed by Menzies *et al.* [19] (The Online TST/

IGRA Interpreter, v. 3.0; www.tstin3d.com). Chest X-rays were given to all workers with either one or both positive tests results, after which they were evaluated by an internist and/or pneumologist to establish individual prescriptions. TB smear and culture of sputum were given to respiratory symptomatics. In the case of LTBI, the national guidelines of Colombia postponed the decision on the systematic treatment and monitoring of LTBI in HCWs, probably following the conditional status of that recommendation in the WHO guidelines due to the '*low quality of evidence*' [20–22].

RESULTS

Some basic demographic and occupational characteristics are described in Table 1. The median age of the HCWs with positive concordant results (TST+, QFT+) was 43 (IQR 33–51) years, and for those with negative concordant results was 44 (IQR 36–52) years. No differences in the history of BCG vaccination were found. Just over 75% of HCWs performed clinical and support activities and 98% lived in areas of the city with low (<50 × 100 000) and intermediate TB incidence (50–100/100 000 inhabitants). Of the HCW respondents, 5·6% had contact with active TB cases at their residence. These characteristics had about the same distribution in HCWs with discordant results. The concordance between TST and QFT was 73·2% (kappa: 47·1% 95% CI 44·0–50·3).

Figure 1 summarizes the frequency of positive concordant (TST+,QFT+), negative concordant (TST-,QFT-), and discordant (TST-,QFT+), (TST+,QFT-) results. Altogether, the discordant results had a frequency of 27% ($n = 265$).

The frequency histograms for TST showed a bimodal distribution with assymetry to the left (coefficient of skewness: −0·3) due to the number of HCWs who did not develop any induration, especially in those aged <43 years. The average induration was 9·6 mm (s.d. = 6·0). Figure 3 shows the histograms by age and years of employment, which had a similar distribution.

Figure 4 and Table 2 summarize the shape of the distribution and the posterior probabilities calculated by the model. The posterior probability that both tests are positive P(TST+,QFT+) was 41·0% (95% CrI 38·0–44·0) and the prevalence obtained by the model P(LTBI+) was 62·1% (95% CrI 53·0–68·2). The probability of having LTBI given positive results in both tests P(LTBI+|TST+,QFT+) was 99·6% (95% CrI 98·1–99·9), and for the negative results P(LTBI+|TST-,QFT-) was 5·7% (95% CrI 2·5–9·2).

The posterior TST sensitivity was 88·5% (95% CrI 85·2–92·1), and the specificity was 80·8% (95% CrI 68·9–89·6). For QFT, a posterior sensitivity of 74·3% (95% CrI 67·8–85·6), and a specificity of 97·6% (95% CrI 91·6–99·9) were obtained.

The results of the LCM are presented by age and years of employment. Higher prevalences were obtained for the group of HCWs aged ⩾43 years compared to HCWs aged <43 years; however, the estimated probability of having LTBI P(LTBI+|TST+, QFT+), the discordant results at the expense of QFT P(LTBI+|TST-,QFT+) and the sensitivity and specificity were similar by age group and years of employment (Table 2).

DISCUSSION

To our knowledge, this is the first study of LTBI in a HCW population in Colombia using TST and QTF simultaneously. Using the LCM, the probability of LTBI as measured by two tests (TST+,QFT+) was 41·0% and the prevalence was 62·1%. This prevalence was not surprising and fell within the range of the estimates for HCWs in low-/medium-income countries (33–79%) [23]. In 2013 Nienhaus *et al.* [24] consolidated the results of LTBI prevalence in HCWs using TST and IGRA simultanously, and indicated that the prevalence of concordant results for medium-/high-income countries such as Spain was 30·0%, Italy 21·7%, Portugal 30·5%, and Georgia 50·8%.

There are few studies of LTBI prevalence in HCWs using TST and IGRA simultaneously in countries of intermediate TB incidence and universal coverage of BCG vaccination at birth [25]. Nevertheless, a recent Colombian study [26] found a 66·3% prevalence of LTBI in household contacts of TB cases in the city of Medellín, and 24·3% in the general population. Despite the difficulty of comparing both studies due to the use of different laboratory tests, the prevalence of LTBI in HCWs in our study is similar that of the household contacts of active TB cases, and higher than that of the general population of the city.

The prevalence of LTBI and the fequency of discordant results in our study were similar to those found in countries of high TB incidence in the general population such as Georgia [27]: (TST+,QFT+: 50·2%) (TST+,QFT-: 16·6%) (TST-,QFT+: 3·8%) or India [28] where prevalences of 50% were found for either test, and 30% for both tests in young HCWs

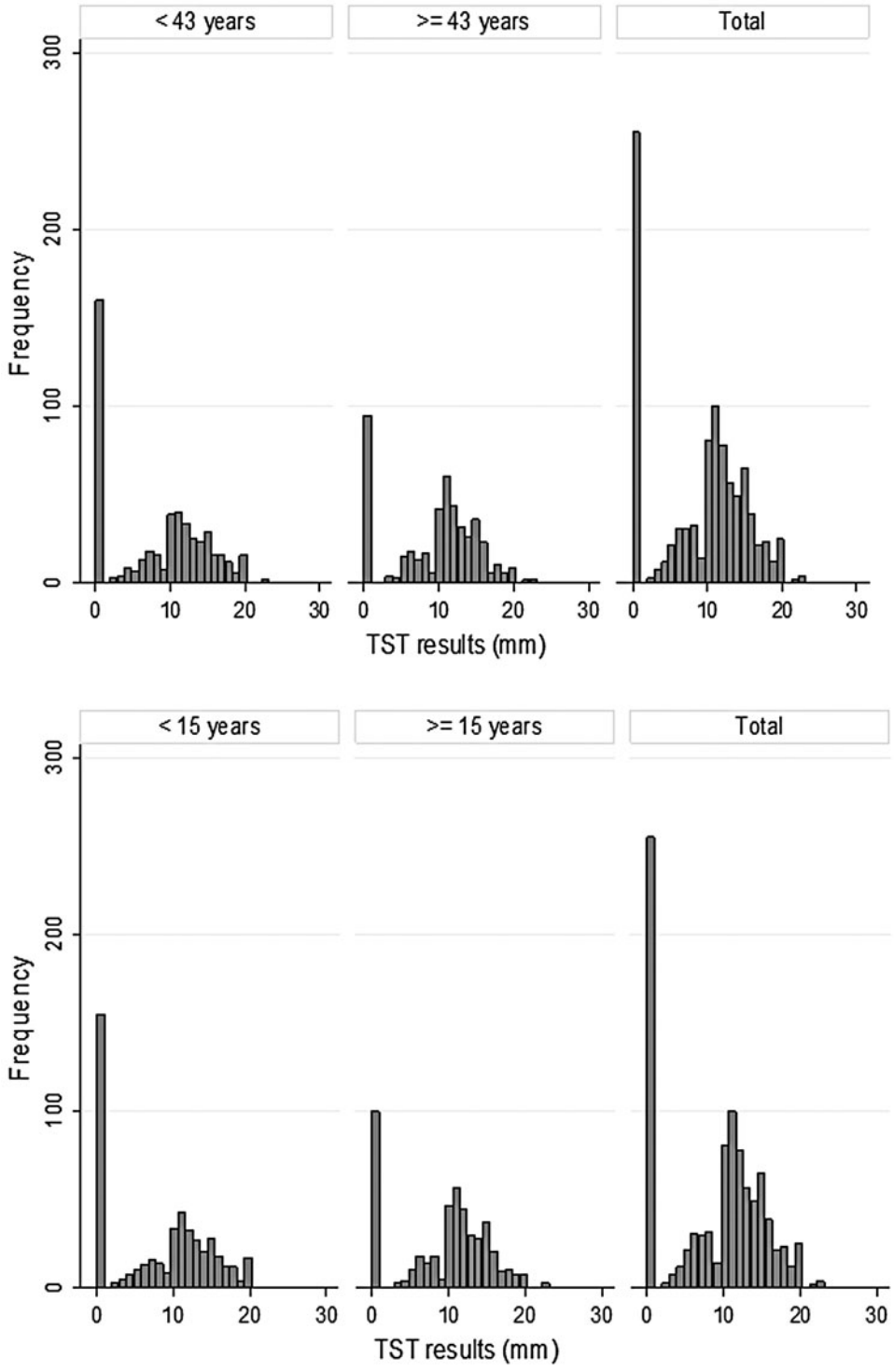

Fig. 3. Frequency histograms of the distribution of the tuberculin skin test (TST) results by age and years of employment.

(median age 22 years). The interpretation of discordant results (TST+,QFT-) (TST-,QFT+) is complex due to the rooted tendency of considering them as TST false positives caused by cross-reactivity with BCG and/or the infection with non-TB mycobacterias [18]. Moreover, although we trained our personnel extensively, some two-reader bias is still possible as described by Menzies [14] and this may impact the proportion of discordant results. It is also necessary to consider other sources of variability of QFT such

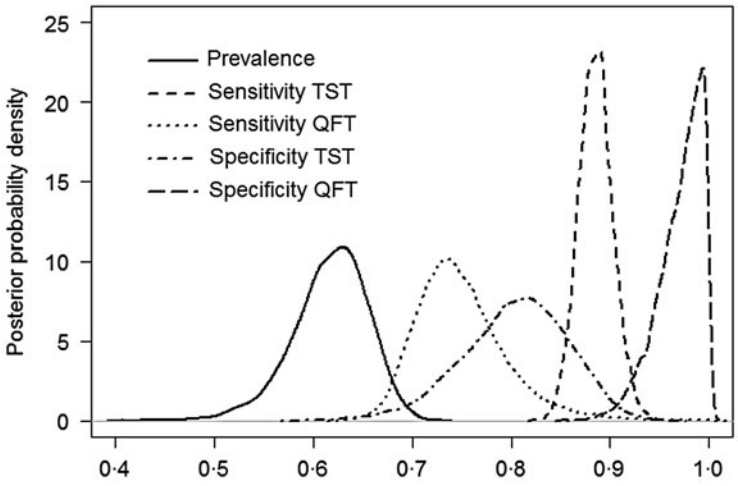

Fig. 4. Posterior distribution estimates for the parameters of the model (prevalence, sensitivity, specificity). Prevalence of latent tuberculosis infection in healthcare workers of the public hospital network in Medellín, Colombia, 2013–2015.

as the drawing, transport and processing of samples [29], and the possibility that the HCWs with QFT- results in our study could correspond to false negatives or reversions [30].

Our results indicate the importance of further studying the weight of occupational and non-occupational (community) exposure in LTBI in HCWs in Colombia. We found a group of 21% of HCWs with discordant (TST+,QFT-) results, 82·8% of whom lived in areas of the city with low TB incidence in the population and had a median age of 44 (IQR 35–51) years. These results are threefold those of Zwerling *et al.* [31] who found 8·6% of discordant results (TST+,QFT-) in a low-incidence country, associated with the non-occupational exposure and the total number of years of hospital employment.

Several approaches (frequentist and Bayesian) have been described to estimate the prevalence of a disease and the accuracy of diagnostic tests in the absence of a gold standard. The robust estimates obtained by the LCM in our study allowed for a more accurate approach to quantifying the prevalence of LTBI and considered the uncertainty of the sensitivity and specificity of the tests in a population of HCWs not previously studied and vaccinated with BCG. The operational features of TST and QFT obtained in our study are broadly consistent with those obtained by Ling and Pai in HCWs in India [16, 18].

One limitation of our study is the current lack of information about the performance of the tests in the group of HCWs with negative concordant results a year later ('annual conversion'), as well as the lack of information on reversions. Thus, obtaining more informative data in the future would require serial and periodic screening [32]. Moreover, although the quality of prior information may affect LCM results is a known criticism [16], we still believe that we have used the best available information on sensitivity and specificity of TST and QFT tests from a study in HCWs vaccinated with BCG at birth.

Another limitation is that our study does not provide objective data on the control of conditional dependence of both tests. If the TST and QFT were positively correlated, the sensitivity and specificity may be biased. Yet, some authors have found that the magnitude of the bias is mitigated by the Bayesian LCM that adjusts for dependence, and even those models which ignore the dependence allow for reasonable inferences [16, 17, 33].

There are challenges to measuring the exposure gradient in a prevalence study such as this one and we used both age and years of employment as stratification variables. Besides the great variation in the definition of the exposure groups [34], the time of employment of HCWs does not account for their community exposure to TB infection, which may be significant in intermediate-/high-incidence cities such as Medellín. The HCWs' age, on the other hand, reflects the cumulative exposure (occupational plus community exposure) [35], and is easier to use as a means of prioritizing populations at risk in institutional TB control programmes.

Our study is the beginning of a journey along a road not travelled in Colombia thus far. We have previously published a simulation of the risk of infection in hospitals where the HCWs in our study come from [36] and we

Table 2. *Predictive posterior probabilities: prevalence, sensitivity and specificity, and probabilities of concordant and discordant results for healthcare workers (HCWs) and for age groups <43 and ⩾43 years. Prevalence of latent tuberculosis infection (LTBI) in HCWs of the public hospital network in Medellín, Colombia, 2013–2015*

	Age (<43 and ⩾43 years)			Years of hospital employment (<15 and ⩾15 years)		
		95% CrI			95% CrI	
Variable	Median, %	2·50%	97·50%	Median,%	2·50%	97·50%
Probability (TST+,QFT+)	41·04	38·02	44·04	41·04	38·02	44·04
<43	36·13	32·20	40·39	36·75	32·82	40·92
⩾43	44·86	40·70	49·13	44·56	40·43	48·85
Probability (TST+,QFT-)	21·23	18·78	23·89	21·23	18·78	23·89
<43	20·41	17·03	24·05	19·20	15·97	22·84
⩾43	22·12	18·71	25·91	23·53	19·92	27·37
Probability (TST-,QFT+)	6·15	4·86	7·66	6·15	4·86	7·66
<43	5·77	4·17	7·75	6·70	4·93	8·87
⩾43	7·42	5·53	9·73	6·55	4·77	8·67
Probability (TST-,QFT-)	31·51	28·63	34·44	31·51	28·63	34·44
<43	37·57	33·31	41·92	37·24	32·98	41·50
⩾43	25·43	21·71	29·42	25·24	21·51	29·31
Prevalence (LTBI+)	62·06	53·03	68·25	62·06	53·03	68·25
<43	54·15	43·49	62·29	54·27	43·64	62·47
⩾43	69·82	61·08	76·44	70·32	61·83	76·86
Prevalence (LTBI+|TST+,QFT+)	99·59	98·07	99·98	99·59	98·07	99·98
<43	99·54	97·71	99·98	99·37	97·02	99·97
⩾43	99·50	97·56	99·98	99·62	98·09	99·99
Prevalence (LTBI+|TST+,QFT-)	66·65	34·30	84·33	66·65	34·30	84·33
<43	57·94	17·91	80·86	55·84	14·31	80·01
⩾43	75·30	49·74	88·91	76·91	52·05	89·61
Prevalence (LTBI+|TST-,QFT+)	88·18	58·13	99·47	88·18	58·13	99·47
<43	87·19	56·14	99·44	84·57	51·27	99·28
⩾43	86·71	55·06	99·41	88·70	58·67	99·52
Prevalence (LTBI+|TST-,QFT-)	5·67	2·51	9·17	5·67	2·51	9·17
<43	4·11	1·09	7·99	4·17	0·92	8·29
⩾43	8·95	4·58	15·32	8·87	4·55	15·09
Sensitivity (TST+|LTBI+)	88·55	85·22	92·06	88·55	85·22	92·06
<43	88·09	83·75	91·98	86·94	82·44	91·40
⩾43	87·72	83·60	91·69	88·76	84·76	92·29
Sensitivity (QFT+|LTBI+)	74·34	67·85	85·59	74·34	67·85	85·59
<43	75·47	65·79	91·42	77·48	67·59	93·49
⩾43	72·97	66·24	81·75	71·25	64·40	80·05
Specificity (TST-|LTBI-)	80·77	68·94	89·62	80·77	68·94	89·62
<43	80·73	69·88	89·56	80·77	69·95	89·56
⩾43	80·75	69·42	89·51	80·90	68·94	89·77
Specificity (QFT-|LTBI-)	97·63	91·65	99·89	97·63	91·65	99·89
<43	98·02	92·51	99·92	97·22	90·59	99·87
⩾43	95·97	86·04	99·82	96·93	88·44	99·87

CrI, Credible interval.

now present the results for each of them. We consider it necessary to widen this study to include HCWs in healthcare centres (primary care) given that they are more likely to encounter unnoticed TB patients.

During the course of the present research we observed encouraging changes in the attitude of HCWs. Some of the hospitals started conducting diagnostic and early isolation activities (administrative controls), which although not the goal of the present research (effect not measured), may be attributed to the hospitaĺs participation in the study: the effect of the project's follow-up of hospital services, the administration of

laboratory tests to HCWs and the construction of the project web page (http://www.epiteorica.com/index.php/tuberculosis-en-hospitales). Assessing the efficacy of these administrative controls would require further studies and measurement of the annual conversion rate of HCWs. In the meantime, a possibility for strenghtening these changes and implementing local TB control plans could be the adaptation of the FAST strategy: 'Find cases Actively by cough surveillance and rapid molecular sputum testing, Separate safely, and Treat effectively based on rapid drug susceptibility testing (DST)' with the goal of reducing time exposure to unnoticed TB patients [37].

In conclusion, our results indicate that a two-test strategy would not be useful in Colombia for the diagnosis of LTBI in HCWs. Although using two tests may improve the sensitivity, the clinical and epidemiological uncertainty generated by the discordant results would make prevalence surveys and pre-employment tests more costly and difficult to interpret. This reinforces the need for developing national guidelines that support the systematic monitoring of Colombian HCWs with a single test, either as a pre-employment test or in the assessment of the prevalence of LTBI in healthcare institutions. Although the Ministry of Health guidelines on TB recommend the use of TST as the test of choice in Colombia [20], it is necessary to conduct local cost-benefit studies to compare with QFT.

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DECLARATION OF INTEREST

None.

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TECHNICAL APPENDIX

We used the multinomial distribution where the probabilities of the four combinations of the two test results can be expressed in terms of the sensitivity and specificity, and the prevalence of LTBI. Thus:

$$n_{ij} \sim \text{multinomial}(\pi_{ij}, N),\ \ i,j=0,1 \text{ and } N=\sum_{i,j} n_{i,j},$$

where n_{ij} represents the number of individuals classified in the status i of the standard test and the status j of the new test. The values '0' and '1' represent that the test was negative and positive respectively.

The values of π_{ij} are given by:

$$\begin{aligned}
\pi_{11} &= P(\text{LTBI}^+)P(\text{TST}^+|\text{LTBI}^+)P(\text{QFT}^+|\text{LTBI}^+) \\
&\quad + [1-P(\text{LTBI}^+)]\,[1-P(\text{TST}^-|\text{LTBI}^-)] \\
&\quad [1-P(\text{QFT}^-|\text{LTBI}^-)] \\
\pi_{10} &= P(\text{LTBI}^+)P(\text{TST}^+|\text{LTBI}^+) \\
&\quad [1-P(\text{QFT}^+|\text{LTBI}^+)] + [1-P(\text{LTBI}^+)] \\
&\quad [1-P(\text{TST}^-|\text{LTBI}^-)]\,P(\text{QFT}^-|\text{LTBI}^-)) \\
\pi_{01} &= P(\text{LTBI}^+)[1-P(\text{TST}^+|\text{LTBI}^+)] \\
&\quad P(\text{QFT}^+|\text{LTBI}^+) + [1-P(\text{LTBI}^+)] \\
&\quad P(\text{TST}^-|\text{LTBI}^-)\,[1-\ P(\text{QFT}^-|\text{LTBI}^-)] \\
\pi_{00} &= P(\text{LTBI}^+)[1-P(\text{TST}^+|\text{LTBI}^+)] \\
&\quad [1-P(\text{QFT}^+|\text{LTBI}^+)] + [1-P(\text{LTBI}^+)] \\
&\quad P(\text{TST}^-|\text{LTBI}^-)\,P(\text{QFT}^-|\text{LTBI}^-) \qquad (1)
\end{aligned}$$

where:

$P(\text{LTBI}^+)$ is the prevalence of LTBI,
$P(\text{TST}^+|\text{LTBI}^+)$ is the sensitivity of TST,
$P(\text{QFT}^+|\text{LTBI}^+)$ is the sensitivity of QFT,
$P(\text{TST}^-|\text{LTBI}^-)$ is the specificity of TST, and
$P(\text{QFT}^-|\text{LTBI}^-)$ is the specificity of QFT

The model of equation (1) was used to predict the following probabilities:

$$P(\mathrm{LTBI}^+|\mathrm{TST}^+,\mathrm{QFT}^+) = \frac{P(\mathrm{LTBI}^+)P(\mathrm{TST}^+|\mathrm{LTBI}^+)P(\mathrm{QFT}^+|\mathrm{LTBI}^+)}{\pi_{11}}$$

$$P(\mathrm{LTBI}^+|\mathrm{TST}^+,\mathrm{QFT}^-) = \frac{P(\mathrm{LTBI}^+)P(\mathrm{TST}^+|\mathrm{LTBI}^+)[1-P(\mathrm{QFT}^+|\mathrm{LTBI}^+)]}{\pi_{10}}$$

$$P(\mathrm{LTBI}^+|\mathrm{TST}^-,\mathrm{QFT}^+) = \frac{P(\mathrm{LTBI}^+)[1-P(\mathrm{TST}^+|\mathrm{LTBI}^+)]P(\mathrm{QFT}^+|\mathrm{LTBI}^+)}{\pi_{01}}$$

$$P(\mathrm{LTBI}^+|\mathrm{TST}^-,\mathrm{QFT}^-) = \frac{P(\mathrm{LTBI}^+)[1-P(\mathrm{TST}^+|\mathrm{LTBI}^+)][1-P(\mathrm{QFT}^+|\mathrm{LTBI}^+)]}{\pi_{00}}$$

OpenBUGS code

```
model.Medellín
{
#================================
# Observed values of multinomial random variable measuring
# joint results of two dichotomous diagnostic tests
#================================
t12[1]<-n11
t12[2]<-n10
t12[3]<-n01
t12[4]<-n00
#================================
# likelihood of observed data
#================================
t12[1:4] ~ dmulti(p12[1:4],N)
#================================
# probabilities of observing different cross-classifications of two dichotomous diagnostic tests
#================================
p12[1]<-pi*(sens1*sens2)+(1-pi)*((1-spec1)*(1-spec2))
p12[2]<-pi*(sens1*(1-sens2))+(1-pi)*((1-spec1)*spec2)
p12[3]<-pi*((1-sens1)*sens2)+(1-pi)*(spec1*(1-spec2))
p12[4]<-pi*((1-sens1)*(1-sens2))+(1-pi)*(spec1*spec2)
#================================
# new predicted value positive
#================================
ppv.new[1]<-(pi*(sens1*sens2))/p12[1]
ppv.new[2]<-(pi*(sens1*(1-sens2)))/p12[2]
ppv.new[3]<-(pi*((1-sens1)*sens2))/p12[3]
ppv.new[4]<-(pi*((1-sens1)*(1-sens2)))/p12[4]
#================================
# prior distributions
#================================
pi~dunif(0,1)
sens1~dbeta(77·85,15·75)
spec1~dbeta(46·33,10·85)
sens2~dunif(0,1)
spec2~dunif(0,1)
}
```