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Comparison of Interferon-γ Release Assay to Two Cut-Off Points of Tuberculin Skin Test to Detect Latent *Mycobacterium tuberculosis* Infection in Primary Health Care Workers

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Abstract

**Background:** An interferon-γ release assay, QuantiFERON-TB (QFT) test, has been introduced an alternative test for the diagnosis of latent *Mycobacterium tuberculosis* infection (LTBI). Here, we compared the performance of QFT with tuberculin skin test (TST) measured at two different cut-off points among primary health care work (HCW) in Brazil.

**Methods:** A cross-sectional study was carried out among HCWs in four Brazilian cities with a known history of high incidence of TB. Results of the QFT were compared to TST results based on both ≥5 mm and ≥10 mm as cut-off points.

**Results:** We enrolled 632 HCWs. When the cut-off value of ≥10 mm was used, agreement between QFT and TST was 69% (k = 0.31), and when the cut-off of ≥5 mm was chosen, the agreement was 57% (k = 0.22). We investigated possible factors of discordance of TST vs QFT. Compared to the TST-/QFT+ group, risk factors for discordance in the TST+/QFT− group with TST cut-off of ≥5 mm included age between 41–45 years [OR = 2.70; CI 95%: 1.32–5.51] and 46–64 years [OR = 2.04; CI 95%: 1.05–3.93], BCG scar [OR = 2.72; CI 95%: 1.40–5.25], and having worked only in primary health care [OR = 2.30; CI 95%: 1.09–4.86]. On the other hand, for the cut-off of ≥10 mm, BCG scar [OR = 2.26; CI 95%: 1.03–4.91], being a household contact of a TB patient [OR = 1.72; CI 95%: 1.01–2.92] and having had a previous TST [OR = 1.66; CI 95%: 1.05–2.62], were significantly associated with the TST+/QFT− group. No statistically significant associations were found among the TST+/QFT+ discordant group with either TST cut-off value.

**Conclusions:** Although we identified BCG vaccination to contribute to the discordance at both TST cut-off measures, the current Brazilian recommendation for the initiation of LTBI treatment, based on information gathered from medical history, chest radiograph and physical examination, should not be changed.

Introduction

Although the incidence of tuberculosis (TB) has gradually declined over the last 20 years worldwide, it remains a major infectious cause of morbidity and mortality in developing countries [¹]. Health care workers (HCW) are one of the groups at risk of *Mycobacterium tuberculosis* (Mt) infection, or latent TB infection (LTBI), due to their occupational exposure [²–⁴]. This risk has been associated with duration of exposure during their health care
service, working in higher risk settings such as emergency rooms, inpatient units and laboratories, as well as delay in diagnosis and absence of work-related environmental preventive control measures [5–8].

Therefore, the screening of HCWs for LTBI is critical in an infection control program [9]. Since 2004, the National Control Tuberculosis Program of Brazil redirected efforts for TB control from the inpatient setting to primary care clinics. With this change, the strategy emphasizes efforts on expanding case detection, improving treatment adherence and reducing treatment default [10]. In Brazil, biosafety guidelines are in place for hospital settings, but they are absent in other health care settings. Data from a previous study of tuberculin skin test (TST) survey carried out among HCW at primary care facilities in Brazil demonstrated a prevalence of LTBI of 26% [11]. Several limitations to the estimate of LTBI based on TST have been identified, which include cross-reaction from BCG and exposure to environmental mycobacteria in places like Brazil [12,13].

Interferon-gamma release assays (IGRAs), based on the release of interferon-gamma (IFN-γ) by lymphocytes in response to specific Mtb antigens, were developed to overcome some of the above limitations of TST. One commercial IGRA, QuantiFERON test (QFT), is based on Mtb-specific antigens ESAT-6, CFP-10 and TB7-7, and is considered more specific than TST as the antigens used are not shared by any of the BCG vaccines or by most environmental mycobacteria [14].

According to the new Brazilian guidelines a TST cut-off point ≥5 mm should be considered as a positive result [15]. This change could potentially affect the agreement between TST and QFT results, especially in a TB-endemic setting where BCG is used. Here, we compared the performance of QFT to TST measured at two different cut-off points among primary HCWs, and assessed their concordance and discordance, as well as factors associated with these test results.

Methods

Study design and setting

A cross-sectional study was conducted from 2011 to 2012 in four Brazilian cities with a high incidence of TB: Vitória-ES (39.98/100,000), Cuiaba-MT (51.77/100,000), Salvador-BA (59.87/100,000) and Manaus-AM (71.26/100,000) [16].

Study population

The study population comprised primary HCW (physicians, nurses, nurse technicians and community health workers [CHW]). The exclusion criteria included known HIV status, HIV infection based on rapid test, prior TB, and being pregnant.

Variables

The HCW interviews and demographic data, including factors associated with positive TST or QFT results were acquired in person by trained registered nurses (RN) (Questionnaire S1 and S2). These included gender, age (19–30; 31–55; 36–40; 41–45; 46–64 years), presence of BCG scar, professional category (physicians, nurse, nurse technician or CHW), work only at a primary health care, contact with a household member with TB, alcohol abuse, prior TST, smoker or ex-smoker, years served in health care profession at primary health care (<5 or ≥5 years) and comorbidity.

Interferon-γ release assay

After the questionnaire was completed and a signed consent form obtained, 3 mL of blood was collected for the Quantiferon TB Gold in-tube test (QFT) (1 mL in each tube). The test was performed according to the manufacturer’s instructions (Cellestis Ltd, Carnegie, Victoria, Australia). The samples were transported to the reference laboratory at each capital (Municipal Laboratory Cuiaba-MT; Municipal Laboratory of Salvador-BA; Laboratory of Immunology of the Infectious Diseases Center of the Federal University of Espírito Santo, Vitória-ES and Manaus in the Laboratory of Microbiology of the Tropical Medicine Foundation Dr. Heitor Vieira Golden-Amazonas) within 4–6 h of collection and incubated for 16–24 h at 37°C. The samples were centrifuged at 3000 x g (relative centrifugal force) for 15 min, and the collected plasma was stored at −20°C until use.

The samples collected in Cuiaba, Manaus and Salvador were transported in cryobox inside cooler containing ice packs to the Laboratory of Immunology, Infectious Diseases Center of Federal University of Espírito Santo in less than 6 hours, and stored at −20°/−70°C until the IFN-γ assay was performed. The optical density (OD) of each test was read with a 450 nm filter with a 620 nm reference filter, with an ELISA plate reader.

Results were interpreted according to the manufacturer instructions. The cut-off value for a positive test was 0.35 IU/mL of IFN-γ in the plasma after stimulation, regardless of the result of the mitogen control. The result of the test was considered indeterminate if an antigen-stimulated sample tested negative and if the value of the positive control was less than 0.5 IU/ml after subtraction of the value of the nil control. Values in between were considered indeterminate.

The HIV rapid test was performed in the laboratory with this same blood sample (Rapid Check HIV 1 & 2/NDI-UFES Vitória-ES-Brazil).

Tuberculin skin test

Immediately after the standardized interview was completed and blood was drawn for QFT, a Mantoux skin test containing 0.1 mL of PPD RT23 (Tuberculin PPD Evans 2 TU) was administered intradermally by a trained RN. The induration was measured after 48–72 hours after administration of the PPD and interpreted by the same nurses, according to Brazilian National Institute recommendation [15].

Data Analysis

Results of each test were interpreted independently and the QFT results were interpreted without knowledge of the results of the TST. The concordance between the TST and QFT test results was measured by kappa (κ) statistics. A κ value of ≤0.4 was regarded as poor, >0.75 as excellent, and in between as fair to good agreement [17]. Furthermore, we applied the McNemar’s test for evaluating the discordance. Factors associated with positive TST, QFT, TST+/QFT− and TST−/QFT+ results were evaluated by prevalence odds ratios (OR). A logistic regression model was used to adjust for exposure variables chosen on the basis of biological plausibility and on statistical and epidemiological criteria. A p value of less than 0.05 was defined to indicate a statistically significant difference in bivariate and multivariate analysis. Fisher’s exact test was used to compare the discordant results (TST+/QFT− and TST−/QFT+) depending on the categorized IFN concentration.

Ethical approval

The Universidade Federal do Espírito Santo (UFES) Institutional Review Board approved the study design under registration number 007/10. A written informed consent was obtained from all participating patients.
Results

Between 2011 and 2012, 664 HCWs were enrolled (Figure 1); however, 22 (3.3%) participants were excluded because they did not return for TST reading, 2 (0.3%) refused to have blood drawn, 7 (1.1%) had active TB or were under TB treatment and 1 (0.2%) was HIV positive (positive rapid test).

Therefore, 632 (95%) of 664 HCW were included in this study. Median age was 42 years (40.8–42.4 years); 546 (86.4%) had vaccine BCG scars; and the median time of work as primary HCW was 9 years (range 1–39), 278 (46%) worked only at primary health care facilities. Of 354 (54%) HCW who worked in other health care facilities, 336 (90%) worked in a hospital ward. Of these, 67 (20%) worked in a pulmonary hospital ward.

When TST results were considered separately, the overall prevalence of LTBI among HCWs according to cut-off points of \( \geq 5 \) mm and \( \geq 10 \) mm were 60.8% [CI 95%: 57%–64%] and 40% [CI 95%: 36%–43%], respectively. In contrast, only 172 (27%) of 664 HCW tested positive by the QFT [CI 95%: 23%–30%].

Regarding concordance, when the cut-off point of \( \geq 10 \) mm was chosen, 114 (26%) HCW tested positive by both tests and 322 (74%) tested negative by both tests. When the cut-off used was \( \geq 5 \) mm, 219 (60.5%) tested negative by both tests and 143 (39.5%) tested positive by both tests. Overall agreement between \( \geq 10 \) mm and \( \geq 5 \) mm cut-off points was 69% and 57%, with \( \kappa \) values of 0.31 [CI 95%: 0.24–0.39] and 0.22 [CI 95%: 0.16–0.28], respectively. Indeterminate results of the QuantiFERON-TB Gold In-Tube Test were not reported.

Among the 632 HCW with valid results for both tests, 270 (42.7%) had discordant results for the TST cut-off of \( \geq 5 \) mm; 241 (89.3%) were TST+/QFT− and 29 (10.7%) were TST−/QFT+. For the cut-off of \( \geq 10 \) mm TST, 196 (31%) had discordant

Figure 1. Study flow diagram. Tuberculin Skin Test-TST; Quantiferon TB Gold in tube test-QFT.

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results, and 138 (70.4%) were TST+/QFT− and 58 (29.6%) were TST−/QFT+. The discordance between the QFT and TST results, assessed by McNemar’s test, was significant for both cut-off points (p<0.001).

Next, we investigated possible factors associated with positive TST or QFT results, and discordance of TST vs QFT at the two cut-off points (TST+/QFT− and TST−/QFT+).

By bivariate analysis, a cut-off of ≥5 mm was significantly associated with age (in years) between 36–40 [OR = 1.79; CI 95%: 1.04–3.10], 41–45 [OR = 2.52; CI 95%: 1.41–4.50] and 46–64 [OR = 2.59; CI 95%: 1.60–4.20]; presence of BCG scar [OR = 1.57; CI 95%: 0.99–2.48]; previous TST [OR = 1.44; CI 95%: 1.02–2.04]; smoking [OR = 2.57; CI 95%: 1.23–5.15] and working for greater than 5 years in health care profession at a primary health care setting [OR = 1.7; CI 95%: 1.19–2.44]. By multivariate analysis, age 41–45 [OR = 2.11; CI 95%: 1.13–3.93] and 46–64 [OR = 2.02; CI 95%: 1.14–3.58], and years served in health care profession at primary health care settings [OR = 1.66; CI 95%: 1.12–2.47] remained significant. BCG vaccination scar was also associated with a positive TST result at cut-off of ≥5 mm [OR = 1.78; CI 95%: 1.09–2.90] (Table 1).

By bivariate analysis, a TST cut-off of ≥10 mm showed significant association with age (in years) between 41–45 years [OR = 1.90; CI 95%: 1.05–3.45] and 46–64 years [OR = 2.21; CI 95%: 1.33–3.68]; being a nurse technician [OR = 1.66; CI 95%: 1.16–2.36]; having a household contact with TB [OR = 1.81; CI 95%: 1.27–2.57]; prior TST [OR = 1.57; CI 95%: 1.12–2.20]; smoking [OR = 1.94; CI 95%: 1.08–3.48]; and years served in health care profession at primary health care settings [OR = 1.68; CI 95%: 1.16–2.45]. In multivariate analysis, only household contact with TB [OR = 1.89; CI 95%: 1.24–2.87] and years served in health care profession at primary health care settings [OR = 1.77; CI 95%: 1.17–2.67] were associated (Table 2).

By bivariate analysis, positive QFT result was statistically significantly associated with age between 46–64 years [OR = 2.40; CI 95%: 1.34–4.28]; household contact with TB [OR = 2.03; CI 95%: 1.36–3.03]; smoking [OR = 2.16; CI 95%: 1.19–3.94]; years served in health care profession at primary health care settings [OR = 1.75; CI 95%: 1.14–2.68]; and comorbidity [OR = 1.50; CI 95%: 1.01–2.22]. The presence of BCG scar was statistically significant with a lower probability of having a positive QFT result [OR = 0.55; CI 95%: 0.34–0.88]. The female gender showed a lower probability of testing positive by QFT [OR = 0.59; CI 95%: 0.35–1.00]. In multivariable analysis, years served in health care profession at primary health care settings [OR = 1.70; CI 95%: 1.07–2.71] remained statistically significant (Table 2). The presence of BCG scar [OR = 0.54; CI 95%: 0.32–0.90] and female gender [OR = 0.47; CI 95%: 0.26–0.85] remained less likely to be positive by QFT (Table 3).

Variables to determine the factors associated with discordance between the TST for both cut-offs and QFT are shown in Tables 4 and 5.

At a cut-off of ≥5 mm, the multivariate test showed that the group with TST+/QFT− discordance was more likely to be between the age 41–45 years [OR = 2.70; CI 95%: 1.32–5.51], 46–64 years [OR = 2.04; CI 95%: 1.05–3.93], have a BCG scar [OR = 2.72; CI 95%: 1.40–5.25] and worked only in primary health care [OR = 2.30; CI 95%: 1.09–4.86]. The group with discordance of TST−/QFT+ revealed no statistically significant association with any of the variables evaluated (Table 4).

At a cut-off of ≥10 mm, the group with discordance of TST+/QFT− was significantly likely to have a BCG scar [OR = 2.26; CI 95%: 1.03–4.91], being a household contact of a TB patient [OR = 1.72; CI 95%: 1.01–2.92] and having had a previous TST [OR = 1.66; CI 95%: 1.05–2.62]. The TST−/QFT+ group showed no statistically significant association with any of the variables (Table 5).

We compared the discordant results (TST+/QFT− and TST−/QFT+) depending on the IFN-γ concentration at both cut-offs of TST (Table 6). Among the TST−/QFT+ group, 29 (12%) and 58 (15%) of HCWs, respectively, had a TST cut-off of ≥5 mm and ≥10 mm. Of these, 7 (24.14%) and 10 (17.24%), respectively, had borderline IFN-γ concentration (0.2–0.5 IU/ml).

Discussion

Our study shows that the prevalence of LTBI among HCW in primary HCW in four state capitals of Brazil varied according to definition based on different TST cut-off points. The prevalence at ≥5 mm and ≥10 mm cut-off was, 60.8% and 40% respectively, and 27% if QFT was used. Despite these differences, the prevalence among HCW was higher than the estimated prevalence of LTBI among the Brazilian general population [1]. These findings are consistent with other studies carried out in Brazil. A prospective cohort study was performed by Moreira et al (2010) in Brazil, which estimated that among community health workers involved in disease control, the incidence of positive TST reaction during the follow-up was 41.7% in those exposed to patients with active tuberculosis [11].

Regarding the high prevalence of positive TST or IGRA among Brazilian primary HCW, it is important to highlight that the screening of HCW for LTBI is not fully implemented in healthcare facilities in Brazil. Less than 33% had previously received the tuberculin test.

Our study had some limitations: first, there is no “gold standard” for detecting LTBI, and second, we did not evaluate a possible booster effect of TST, although the Brazilian TST guideline does not require assessing booster effect on HCW [18]. Nevertheless, the strength of the present study was the large sample size and its multi-regional survey design.

In previous studies, several risk factors have been associated with high prevalence of positive TST and QFT [11,19,20]. Although older age has been reported to be associated with positive results with both tests [21,22], our study found this association only with the cut-off of ≥5 mm. Household contact with index cases of TB was associated with a positive TST at a cut-off of ≥10 mm, which was also shown by other studies [19,21,22].

Another associated factor was occupation or working as HCW for more than five years, which was significantly associated with positive TST results regardless of TST cut-offs, as well as with QFT. This finding concurs with other reports [19,23–25]. We also found that being a female is associated with a lower prevalence of LTBI when QFT is used, also reported by another study [26]. The reason for this association is unclear.

The observed concordance between TST (≥5 mm and ≥10 mm) and QFT results was lower than that reported by Pai et al. (2005) (κ = 0.61) among health professionals in India, a country endemic for TB also with a high BCG vaccination coverage [27]. Studies by other research groups have found low concordance between the same two TST cut-offs with QFT [28,29,30,31].

In this study, TST+/QFT− discordance was more frequent than TST−/QFT+ discordance.

We summarized all the risk factors significantly associated with various combinations of TST and QFT results (Table 7). In a study carried out in Salvador-Brazil with household TB contacts that was based on TST cut-off of ≥10 mm, the discordant subgroup TST+/QFT− shared characteristics similar to those observed in the concordant group TST+/QFT+ instead of the
In our study, the TST+/QFT− group, at the cut-off of ≥5 mm TST, was older, had a BCG scar, and worked only in the primary health care. At the cut-off of ≥10 mm, the TST+/QFT− group was more likely to have a BCG scar, be a household contact of TB, and had TST done previously. A study carried out in the United States among HCWs with increased risk of LTBI discusses the possibility of TST+/QFT−

**Table 1.** Variables associated with positive results of tuberculin skin test-TST (≥5 mm) health care workers-HCW.

| Variables                                | Test, N | No positive n (%) | Crude OR* | 95% CI** | OR* Adjusted | 95% CI** |
|------------------------------------------|---------|-------------------|-----------|-----------|--------------|----------|
| Gender                                   |         |                   |           |           |              |          |
| Male                                     | 67      | 43 (64.18)        | Reference |           | Reference    |          |
| Female                                   | 565     | 341 (60.35)       | 0.84      | 0.50–1.43 | 0.70         | 0.39–1.25 |
| Age group (years)                        |         |                   |           |           |              |          |
| 19–30                                    | 101     | 45 (44.55)        | Reference |           | Reference    |          |
| 31–35                                    | 102     | 59 (57.84)        | 1.70      | 0.97–2.97 | 1.38         | 0.77–2.49 |
| 36–40                                    | 110     | 65 (59.09)        | 1.79*     | 1.04–3.10 | 1.60         | 0.89–2.86 |
| 41–45                                    | 97      | 65 (67.01)        | 2.52*     | 1.41–4.50 | 2.11*        | 1.13–3.93 |
| 46–64                                    | 222     | 150 (67.57)       | 2.59*     | 1.60–4.20 | 2.02*        | 1.14–3.58 |
| Presence of BCG scar                     |         |                   |           |           |              |          |
| No                                       | 86      | 44 (51.16)        | Reference |           | Reference    |          |
| Yes                                      | 546     | 340 (62.27)       | 1.57*     | 0.99–2.48 | 1.78*        | 1.09–2.90 |
| Professional category                    |         |                   |           |           |              |          |
| CHW***                                   | 302     | 175 (57.95)       | Reference |           | Reference    |          |
| Nurse technician                         | 219     | 144 (65.75)       | 1.39      | 0.97–1.99 | 0.86         | 0.45–1.64 |
| Nurse                                    | 78      | 49 (62.82)        | 1.22      | 0.73–2.04 | 0.89         | 0.40–1.94 |
| Physicians                               | 33      | 16 (48.48)        | 0.68      | 0.33–1.40 | 0.44         | 0.16–1.20 |
| Work only at Primary Health Care         |         |                   |           |           |              |          |
| No                                       | 354     | 203 (57.34)       | Reference |           | Reference    |          |
| Yes                                      | 278     | 181 (65.11)       | 1.38      | 1.00–1.91 | 1.67         | 0.89–3.13 |
| Contact with a household member with TB  |         |                   |           |           |              |          |
| No                                       | 501     | 293 (58.48)       | Reference |           | Reference    |          |
| Yes                                      | 121     | 81 (66.94)        | 1.43      | 0.94–2.18 | 1.31         | 0.84–2.03 |
| Unknown                                  | 10      | 10 (100.00)       | Omitted   |           | Omitted      |          |
| Alcohol abuse                            |         |                   |           |           |              |          |
| No                                       | 393     | 229 (58.27)       | Reference |           | Reference    |          |
| Yes                                      | 239     | 155 (64.85)       | 1.32      | 0.94–1.84 | 1.19         | 0.83–1.70 |
| Prior TST                                |         |                   |           |           |              |          |
| No                                       | 420     | 243 (57.86)       | Reference |           | Reference    |          |
| Yes                                      | 212     | 141 (66.51)       | 1.44*     | 1.02–2.04 | 1.29         | 0.88–1.88 |
| Smoker                                   |         |                   |           |           |              |          |
| No                                       | 475     | 275 (57.89)       | Reference |           | Reference    |          |
| Yes                                      | 50      | 39 (78.00)        | 2.57*     | 1.28–5.15 | 1.93         | 0.92–4.02 |
| Ex-smoker                                | 107     | 70 (65.42)        | 1.37      | 0.88–2.13 | 1.17         | 0.73–1.88 |
| Years served in health care profession at primary health care |         |                   |           |           |              |          |
| <5                                       | 168     | 86 (51.19)        | Reference |           | Reference    |          |
| ≥5                                       | 464     | 298 (64.22)       | 1.71*     | 1.19–2.44 | 1.66*        | 1.12–2.47 |
| Comorbidity                              |         |                   |           |           |              |          |
| No                                       | 477     | 289 (60.59)       | Reference |           | Reference    |          |
| Yes                                      | 155     | 95 (61.29)        | 1.02      | 0.71–1.49 | 0.85         | 0.56–1.28 |

OR* = Odds ratio; CI** = Confidence interval; * = p value < 0.05; CHW*** = community health worker.
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discordance to represent an exposure to *M. tuberculosis* in the remote past [33]. Our study and the study in American HCWs do not show any data that might suggest that TST+/IGRA– negative results might be caused by remote infection. The discordant TST+/QFT– result is more consistent with strong association of BCG with positive TST [34]. However, our observation differs from the result of the study of household

| Variables                                           | Test, N | No positive n (%) | Crude OR*   | 95% CI**    | OR* Adjusted | 95% CI** |
|-----------------------------------------------------|---------|-------------------|-------------|-------------|--------------|----------|
| Gender                                              |         |                   |             |             |              |          |
| Male                                                | 67      | 30 (44.78)        | Reference   |             |             |          |
| Female                                              | 565     | 222 (39.29)       | 0.79        | 0.47–1.32   | 0.66         | 0.38–1.17 |
| Age group (years)                                   |         |                   |             |             |              |          |
| 19–30                                               | 101     | 28 (27.72)        | Reference   |             |             |          |
| 31–35                                               | 102     | 37 (36.27)        | 1.48        | 0.81–2.68   | 1.19         | 0.64–2.22 |
| 36–40                                               | 110     | 44 (40.0)         | 1.73        | 0.97–3.10   | 1.53         | 0.83–2.82 |
| 41–45                                               | 97      | 41 (42.27)        | 1.90*       | 1.05–3.45   | 1.37         | 0.72–2.61 |
| 46–64                                               | 222     | 102 (45.95)       | 2.21*       | 1.33–3.68   | 1.47         | 0.81–2.65 |
| Presence of BCG scar                                |         |                   |             |             |              |          |
| No                                                  | 86      | 32 (37.21)        | Reference   |             |             |          |
| Yes                                                 | 546     | 220 (40.29)       | 1.13        | 0.71–1.82   | 1.18         | 0.72–1.95 |
| Professional category                               |         |                   |             |             |              |          |
| CHW***                                              | 302     | 109 (36.09)       | Reference   |             | Reference    |          |
| Nurse technician                                    | 219     | 106 (48.40)       | 1.66*       | 1.16–2.36   | 1.38         | 0.73–2.61 |
| Nurse                                               | 78      | 29 (37.18)        | 1.04        | 0.62–1.75   | 0.93         | 0.42–2.05 |
| Physicians                                          | 33      | 8 (24.24)         | 0.56        | 0.24–1.29   | 0.44         | 0.15–1.28 |
| Work only at Primary Health Care                    |         |                   |             |             |              |          |
| No                                                  | 354     | 130 (36.72)       | Reference   |             | Reference    |          |
| Yes                                                 | 278     | 122 (43.88)       | 1.34        | 0.97–1.85   | 1.25         | 0.67–2.34 |
| Contact with a household member with TB             |         |                   |             |             |              |          |
| No                                                  | 501     | 182 (36.33)       | Reference   |             | Reference    |          |
| Yes                                                 | 121     | 65 (53.72)        | 1.81*       | 1.27–2.57   | 1.89*        | 1.24–2.87 |
| Unknown                                             | 10      | 5 (50.0)          | 1.75        | 0.50–6.13   | 1.61         | 0.43–6.06 |
| Alcohol abuse                                       |         |                   |             |             |              |          |
| No                                                  | 393     | 149 (37.91)       | Reference   |             | Reference    |          |
| Yes                                                 | 239     | 103 (43.10)       | 1.24        | 0.89–1.72   | 1.17         | 0.82–1.67 |
| Prior TST                                           |         |                   |             |             |              |          |
| No                                                  | 420     | 152 (36.19)       | Reference   |             | Reference    |          |
| Yes                                                 | 212     | 100 (47.17)       | 1.57*       | 1.12–2.20   | 1.41         | 0.97–2.03 |
| Smoker                                              |         |                   |             |             |              |          |
| No                                                  | 475     | 179 (37.68)       | Reference   |             | Reference    |          |
| Yes                                                 | 50      | 27 (54.0)         | 1.94*       | 1.08–3.48   | 1.52         | 0.81–2.86 |
| Ex-smoker                                           | 107     | 46 (42.99)        | 1.24        | 0.81–1.90   | 0.99         | 0.62–1.57 |
| Years served in health care profession at primary health care |     |                   |             |             |              |          |
| <5                                                  | 168     | 52 (30.95)        | Reference   |             | Reference    |          |
| ≥5                                                  | 464     | 200 (43.10)       | 1.68*       | 1.16–2.45   | 1.77*        | 1.17–2.67 |
| Comorbidty                                          |         |                   |             |             |              |          |
| No                                                  | 477     | 187 (39.20)       | Reference   |             | Reference    |          |
| Yes                                                 | 155     | 65 (41.94)        | 1.12        | 0.77–1.61   | 0.95         | 0.64–1.43 |

OR* = Odds ratio; CI** = Confidence interval; *= p value < 0.05; CHW*** = community health worker.

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Table 2. Variables associated with positive results of tuberculin skin test-TST (≥10 mm) in health care workers-HCW.
contacts in Salvador-Brazil, which did not show an association with BCG vaccination with TST cut-off of $10$ mm [32].

On the other hand, the TST+/IGRA+ result, observed in 29 (12%) and 58 (15%) of HCWs, respectively when a cut-off point of 5 mm and $10$ mm was used, was suggested to be associated

### Table 3. Variables associated with positive test results with the Quantiferon TB Gold in tube test - QFT in health care workers - HCW.

| Variables                        | Test, N | No positive n (%) | Crude OR* | 95% CI** | OR* Adjusted | 95% CI** |
|----------------------------------|---------|-------------------|-----------|----------|--------------|----------|
| **Gender**                       |         |                   |           |          |              |          |
| Male                             | 67      | 25 (37.31)        | Reference | Reference|              |          |
| Female                           | 565     | 147 (26.02)       | 0.59*     | 0.35–1.00| 0.47*        | 0.26–0.85|
| **Age group (years)**            |         |                   |           |          |              |          |
| 19–30                            | 101     | 18 (17.82)        | Reference | Reference|              |          |
| 31–35                            | 102     | 23 (22.55)        | 1.34      | 0.67–2.67| 1.19         | 0.58–2.45|
| 36–40                            | 110     | 31 (28.18)        | 1.80      | 0.94–3.50| 1.63         | 0.81–3.27|
| 41–45                            | 97      | 24 (24.74)        | 1.52      | 0.76–3.01| 1.26         | 0.61–2.64|
| 46–64                            | 222     | 76 (34.23)        | 2.40*     | 1.34–4.28| 1.90         | 0.97–3.70|
| **Presence of BCG scar**         |         |                   |           |          |              |          |
| No                               | 86      | 33 (38.37)        | Reference | Reference|              |          |
| Yes                              | 546     | 139 (25.46)       | 0.55*     | 0.34–0.88| 0.54*        | 0.32–0.90|
| **Professional category**        |         |                   |           |          |              |          |
| CHW***                           | 302     | 78 (25.83)        | Reference | Reference|              |          |
| Nurse technician                 | 219     | 69 (31.51)        | 1.32      | 0.90–1.94| 1.37         | 0.68–2.74|
| Nurse                            | 78      | 21 (26.92)        | 1.06      | 0.60–1.85| 1.42         | 0.61–3.34|
| Physicians                       | 33      | 4 (12.12)         | 0.40      | 0.13–1.16| 0.32         | 0.08–1.22|
| **Work only at Primary Health Care** |       |                   |           |          |              |          |
| No                               | 354     | 93 (26.27)        | Reference | Reference|              |          |
| Yes                              | 278     | 79 (28.42)        | 1.35      | 0.98–1.85| 0.94         | 0.48–1.85|
| **Contact with a household member with TB** | | | | | |
| No                               | 501     | 130 (25.95)       | Reference | Reference|              |          |
| Yes                              | 121     | 40 (33.06)        | 2.03      | 1.36–3.03| 1.31         | 0.83–2.06|
| Unknown                          | 10      | 2 (20.0)          | 1.75      | 0.50–6.13| 0.47         | 0.09–2.37|
| **Alcohol abuse**                |         |                   |           |          |              |          |
| No                               | 393     | 102 (25.95)       | Reference | Reference|              |          |
| Yes                              | 239     | 70 (29.29)        | 1.18      | 0.82–1.70| 1.17         | 0.79–1.72|
| **Prior TST**                    |         |                   |           |          |              |          |
| No                               | 420     | 109 (25.95)       | Reference | 1        |              |          |
| Yes                              | 212     | 63 (29.72)        | 1.20      | 0.83–1.74| 1.00         | 0.67–1.50|
| **Smoker**                       |         |                   |           |          |              |          |
| No                               | 475     | 119 (25.05)       | Reference | Reference|              |          |
| Yes                              | 50      | 21 (42.00)        | 2.16*     | 1.19–3.94| 1.77         | 0.93–3.36|
| Ex-smoker                        | 107     | 32 (29.91)        | 1.27      | 0.80–2.02| 0.98         | 0.60–1.62|
| **Years served in health care profession at primary health care** | | | | | |
| <5                               | 168     | 33 (19.64)        | Reference | Reference|              |          |
| $\geq$5                          | 464     | 139 (29.96)       | 1.75*     | 1.14–2.68| 1.70*        | 1.07–2.71|
| **Comorbidity**                  |         |                   |           |          |              |          |
| No                               | 477     | 120 (25.16)       | Reference | Reference|              |          |
| Yes                              | 155     | 52 (33.55)        | 1.50*     | 1.01–2.22| 1.31         | 0.85–2.00|

OR* = Odds ratio;  
CI** = Confidence interval;  
*= p value $<0.05$;  
CHW*** = community health worker.

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Table 4. Variables associated with discordant groups (TST+/QFT− and TST−/QFT+) compared to the reference group (TST−/QFT−) at TST cut-off ≥5 mm.

| Variables                        | TST+/QFT− (≥5 mm) | TST−/QFT+ (≥5 mm) |
|----------------------------------|-------------------|-------------------|
|                                  | Test, N | N (%) | Crude OR* | 95% CI** | OR* Adjusted | 95% CI** | Test, N | N (%) | Crude OR* | 95% CI** | OR* Adjusted | 95% CI** |
| Gender                           |         |       |           |          |             |          |         |       |           |          |             |          |
| Male                             | 42      | 22 (52.38) | Reference | Reference | 23          | 3 (13.04) | Reference |       |           |          |             |          |
| Female                           | 417     | 219 (52.52) | 1         | 0.53–1.89 | 0.82        | 0.39–1.68 | 224      | 26 (11.61) | 0.87     | 0.24–3.15 | 0.63       | 0.14–2.74 |
| Age group (years)                |         |       |           |          |             |          |         |       |           |          |             |          |
| 19–30                            | 83      | 31 (37.35) | Reference | Reference | 56          | 4 (7.14)  | Reference |       |           |          |             |          |
| 31–35                            | 79      | 40 (50.63) | 1.72      | 0.91–3.21 | 1.55        | 0.79–3.05 | 43       | 4 (9.38)  | 1.33     | 0.31–5.66 | 1.58       | 0.33–7.52 |
| 36–40                            | 79      | 40 (50.63) | 1.72      | 0.91–3.21 | 1.74        | 0.89–3.38 | 45       | 6 (13.33) | 2.00     | 0.52–7.57 | 2.15       | 0.48–9.65 |
| 41–45                            | 73      | 45 (61.64) | 2.69a     | 1.40–5.15 | 2.70a       | 1.32–5.51 | 31       | 3 (9.68)  | 1.39     | 0.29–6.66 | 1.40       | 0.25–7.81 |
| 46–64                            | 145     | 85 (58.62) | 2.37a     | 1.36–4.13 | 2.04a       | 1.05–3.93 | 72       | 12 (16.67) | 2.6      | 0.79–8.55 | 2.26       | 0.52–9.68 |
| Presence of BCG scar             |         |       |           |          |             |          |         |       |           |          |             |          |
| No                               | 53      | 19 (35.85) | Reference | Reference | 42          | 8 (19.05) | Reference |       |           |          |             |          |
| Yes                              | 406     | 222 (54.68) | 2.15a     | 1.19–3.91 | 2.72a       | 1.40–5.25 | 205      | 21 (10.24) | 0.48     | 0.19–1.18 | 0.43       | 0.16–1.18 |
| Professional category            |         |       |           |          |             |          |         |       |           |          |             |          |
| CHW***                          | 224     | 106 (47.32) | Reference | Reference | 127         | 9 (7.09)  | Reference |       |           |          |             |          |
| Nurse technician                 | 150     | 89 (59.33) | 1.62a     | 1.06–2.46 | 0.77        | 0.36–1.64 | 74       | 13 (17.57) | 2.79a    | 1.13–6.90 | 2.68       | 0.57–12.51 |
| Nurse                            | 56      | 33 (58.93) | 1.59      | 0.88–2.89 | 0.77        | 0.30–2.00 | 29       | 6 (20.69)  | 3.42a    | 1.10–10.54 | 5.57       | 0.93–33.21 |
| Physicians                       | 29      | 13 (44.83) | 0.90      | 0.41–1.96 | 0.46        | 0.15–1.39 | 17       | 1 (5.88)   | 0.81     | 0.09–6.90 | 0.82       | 0.05–11.32 |
| Work only at Primary Health Care |         |       |           |          |             |          |         |       |           |          |             |          |
| No                               | 261     | 122 (46.74) | Reference | Reference | 151         | 12 (7.95) | Reference |       |           |          |             |          |
| Yes                              | 198     | 119 (60.10) | 1.71a     | 1.18–2.49 | 2.30a       | 1.09–4.86 | 96       | 17 (17.71) | 2.49a    | 1.13–5.48 | 1.04       | 0.24–4.45 |
| Contact with a household member with TB |         |       |           |          |             |          |         |       |           |          |             |          |
| No                               | 371     | 190 (51.21) | Reference | Reference | 207         | 26 (12.56) | Reference |       |           |          |             |          |
| Yes                              | 80      | 43 (53.75) | 1.10      | 0.68–1.79 | 0.98        | 0.58–1.65 | 40       | 3 (7.58)  | 0.56     | 0.16–1.96 | 0.53       | 0.13–2.07 |
| Unknown                          | 8       | 8 (100)    | Omitted   | Omitted   | Omitted     | Omitted   | 0        | 0        | Omitted   | Omitted   | Omitted   | Omitted   |
| Alcohol abuse                    |         |       |           |          |             |          |         |       |           |          |             |          |
| No                               | 290     | 143 (49.31) | Reference | Reference | 163         | 16 (9.82) | Reference |       |           |          |             |          |
| Yes                              | 169     | 98 (57.99) | 1.41      | 0.96–2.07 | 1.28        | 0.85–1.94 | 84       | 13 (15.48) | 1.68     | 0.76–3.68 | 2.04       | 0.83–5.03 |
| Prior TST                        |         |       |           |          |             |          |         |       |           |          |             |          |
| No                               | 311     | 155 (49.84) | Reference | Reference | 177         | 21 (11.86) | Reference |       |           |          |             |          |

Comparing Interferon-γ Release Assay with TST in Health Care Workers
| Variables                        | Test, N | N (%) | Crude OR* | 95% CI**     | OR* Adjusted | 95% CI**     | Test, N | N (%) | Crude OR* | 95% CI**     | OR* Adjusted | 95% CI**     |
|---------------------------------|---------|-------|-----------|--------------|--------------|--------------|---------|-------|-----------|--------------|--------------|--------------|
| **Smoker**                      |         |       |           |              |              |              |         |       |           |              |              |              |
| Yes                             | 148     | 86 (58.11) | 1.39     | 0.94–2.07   | 1.20         | 0.77–1.87   | 70      | 8   (11.43) | 0.95       | 0.40–2.27   | 0.58         | 0.21–1.59   |
| No                              | 355     | 178 (50.14) | Reference | Reference   | Reference   | Reference   | 199     | 22 (11.06) | Reference | Reference   | Reference   | Reference   |
| Ex-smoker                       | 75      | 43 (57.33) | 1.33     | 0.80–2.20   | 1.14         | 0.66–1.98   | 37      | 5   (13.51) | 1.25       | 0.44–3.56   | 0.93         | 0.26–3.23   |
| **Years served in health care** |         |       |           |              |              |              |         |       |           |              |              |              |
| profession at primary health    |         |       |           |              |              |              |         |       |           |              |              |              |
| care, <5                        | 135     | 61 (45.19) | Reference | Reference   | Reference   | Reference   | 82      | 8   (9.76)  | Reference | Reference   | Reference   | Reference   |
| ≥5                              | 324     | 180 (55.56) | 1.51*    | 1.01–2.27   | 1.41         | 0.89–2.23   | 165     | 21 (12.73) | 1.34       | 0.57–3.19   | 1.48         | 0.58–3.76   |
| **Comorbidity**                 |         |       |           |              |              |              |         |       |           |              |              |              |
| No                              | 356     | 188 (52.81) | Reference | Reference   | Reference   | Reference   | 187     | 19 (10.16) | Reference | Reference   | Reference   | Reference   |
| Yes                             | 103     | 53 (51.46) | 0.94     | 0.61–1.46   | 0.82         | 0.50–1.33   | 60      | 10 (16.67) | 1.76       | 0.77–4.04   | 1.98         | 0.75–5.19   |

OR* = Odds ratio; CI** = Confidence interval; * = p value <0.05; CHW** = community health worker.

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Table 5. Variables associated with discordant groups (TST+/QFT− and TST−/QFT+) compared to the reference group (TST−/QFT−) at TST cut-off ≥10 mm.

| Variables                        | TST+/QFT− (≥10 mm) | TST−/QFT+ (≥10 mm) |
|----------------------------------|---------------------|---------------------|
|                                  | Test, N N (%)       | Crude OR* 95% CI**  | OR* Adjusted 95% CI** |
| Gender                          | Male 42 9 (21.43)   | Reference           | Reference |
|                                  | Female 418 130 (31.10) | 1.65 0.76–3.55 1.46 | 0.63–3.37 |
| Age group (years)               | 19–30 83 16 (19.28) | Reference           | Reference |
|                                  | 31–35 79 23 (29.11) | 1.71 0.82–3.56 1.50 | 0.69–3.24 |
|                                  | 36–40 79 23 (29.11) | 1.71 0.82–3.56 1.68 | 0.78–3.61 |
|                                  | 41–45 73 26 (35.62) | 2.31* 1.12–4.78 1.80 | 0.82–3.97 |
|                                  | 46–64 146 51 (34.93) | 2.24* 1.18–4.27 1.60 | 0.76–3.36 |
| Presence of BCG scar            | No 53 9 (16.98)     | Reference           | Reference |
|                                  | Yes 407 130 (31.94) | 2.29* 1.08–4.84 2.26a | 1.03–4.91 |
| Professional category           | CHW*** 224 59 (26.34) | Reference           | Reference |
|                                  | Nurse technician 150 57 (38) | 1.71* 1.09–2.67 0.76 | 0.33–1.73 |
|                                  | Nurse 57 17 (29.82) | 1.18 0.62–2.25 0.49 | 0.17–1.40 |
|                                  | Physicians 29 6 (20.69) | 0.72 0.28–1.87 0.38 | 0.10–1.39 |
| Work only at Primary Health Care | No 261 68 (26.05)   | Reference           | Reference |
|                                  | Yes 199 71 (35.68)  | 1.57* 1.05–2.35 2.21 | 0.97–4.99 |
| Contact with a household member with TB | No 371 102 (27.49) | Reference           | Reference |
|                                  | Yes 81 34 (41.98)   | 1.90* 1.16–3.13 1.72a | 1.01–2.92 |
| Alcohol abuse                    | No 291 79 (27.15)   | Reference           | Reference |
|                                  | Yes 169 60 (35.50)  | 1.47 0.98–2.22 1.42 | 0.92–2.20 |
| Prior TST                        | No 311 80 (25.72)   | Reference           | Reference |
|                                  | Yes 149 59 (39.60)  | 1.89* 1.24–2.86 1.66a | 1.05–2.62 |
| Variables | Test, N   | N (%) | Crude OR* | 95% CI** | OR* Adjusted | 95% CI** | Test, N   | N (%) | Crude OR* | 95% CI** | OR* Adjusted | 95% CI** |
|-----------|-----------|-------|-----------|----------|--------------|----------|-----------|-------|-----------|----------|--------------|----------|
| Smoker    |           |       |           |          |              |          |           |       |           |          |              |          |
| No        | 356       | 100 (28.09) | Reference | Reference |              |          | 296       | 40 (13.51) | Reference | Reference |
| Yes       | 29        | 11 (37.93) | 1.56      | 0.71–3.42 | 1.14         | 0.48–2.72| 23        | 5 (21.74) | 1.77      | 0.62–5.05 | 1.42         | 0.46–4.34|
| Ex-smoker | 75        | 28 (37.33) | 1.52      | 0.90–2.57 | 1.18         | 0.67–2.09| 60        | 13 (21.67) | 1.77      | 0.88–3.56 | 1.38         | 0.64–2.94|
| Years served in health care profession at primary healthcare |
| <5        | 135       | 35 (25.93) | Reference | Reference |              |          | 116       | 16 (13.79) | Reference | Reference |
| ≥5        | 325       | 104 (32.0) | 1.34      | 0.85–2.10 | 1.26         | 0.77–2.08| 263       | 42 (15.97) | 1.18      | 0.63–2.21 | 1.01         | 0.51–1.98|
| Comorbidity |         |       |           |          |              |          |           |       |           |          |              |          |
| No        | 357       | 108 (30.25) | Reference | Reference |              |          | 289       | 40 (13.84) | Reference | Reference |
| Yes       | 103       | 31 (30.10) | 0.99      | 0.61–1.60 | 0.82         | 0.48–1.39| 90        | 18 (20.0) | 1.55      | 0.84–2.87 | 1.32         | 0.67–2.60|

OR* = Odds ratio; CI** = Confidence interval; * = p value < 0.05; CHW*** = community health worker.
with recent exposure [35]. In our study, the subgroup with TST–/QFT+ results at both cut-offs showed QFT ELISA values that were borderline between 0.2 and 0.5 IU/ml [36]. These values may represent false-positive QFT results.

It should be noted however that, although TST+/QFT− and TST−/QFT+ discordant results suggest previous exposure (recent or remote) to M. tuberculosis, neither TST nor QFT can distinguish remote from recent infection [37].

A study by Pai and colleagues (2009) concluded that health professionals should be cautious about using a simplistic dichotomous criterion to determine conversion or reversion, and should instead consider the amount of change in absolute IFN-γ responses, as well as relevant clinical information to interpret serial testing results [36].

Several guidelines have sought to standardize the use of IGRA and TST, according to the characteristic of each country and specific population groups [38–40]. In relation to HCW, there are guidelines that define the use of one or the other test to diagnose LTBI. In many high-income countries with low rates of TB, serial testing for LTBI is recommended for persons at increased risk of TB [41]. The advantages are to increase the test specificity in individuals with prior BCG vaccination, and also to reduce cost incurred by the follow-up and treatment of LTBI based on false-positive TST. However, the use of IGRA for serial testing is complicated by the lack of clear data on optimal cut-offs for serial testing and unclear interpretation and prognosis of conversions and reversions, reproducibility or time interval to conversion of IGRA after exposure to tuberculosis [20,40,42,43]. Some studies have shown considerable fluctuations in positive and negative IGRA results from the same individuals [44,45,46].

These discussions around the limitations, advantages and applicability of QFT in clinical practice are important, especially in low and middle income countries with high incidence of tuberculosis, BCG vaccination coverage and the presence of environmental mycobacteria. In our study among Brazilian HCW, we found high positive results by TST, using different TST cut-offs

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### Table 6. Comparing the discordant results (TST+/QFT− and TST−/QFT+) depending on the categorized IFN-γ concentration (IU/mL).

| IFN-γ concentration (IU/mL) | ≥5 mm | P value* | ≥10 mm | P value* |
|----------------------------|-------|----------|--------|----------|
| TST+/QFT−                  |       |          |        |          |
| <0.2                       | 216 (100) |          | 121 (100) |          |
| 0.2–0.5                    | 24 (77.42) | 7 (22.58) | 17 (62.96) | 10 (37.04) |
| >0.5                       | 1 (43.5) | 22 (95.65) | <0.001 | 1 (2.04) | 48 (97.96) | <0.001 |

*Fisher’s exact test.

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### Table 7. Summary table containing all the risk factors found to be significantly associated with various combinations of tuberculin skin test (TST) and QFT results.

| TST/QFT | QFT+ | OR* Adjusted | CI **95% | QFT− | OR* Adjusted | CI **95% |
|---------|------|--------------|---------|------|--------------|---------|
| TST+ (≥5 mm) | Age 46–64 | 3.28 | 1.06–4.42 | Age 41–45 | 2.70 | 1.32–5.51 |
|         | Smoker | 2.97 | 1.17–7.50 | Age 46–64 | 2.04 | 1.05–3.93 |
|         | Years served in health care profession at primary health care >5 years | 2.17 | 1.06–4.42 | Presence of BCG scar | 2.72 | 1.40–5.25 |
| TST+ (≥10 mm) | Contact with a household member with TB | 2.14 | 1.22–3.75 | Presence of BCG scar | 2.26 | 1.03–4.91 |
|         | Years served in health care profession at primary health care >5 years | 2.70 | 1.29–5.65 | Contact with a household member with TB | 1.72 | 1.01–2.92 |
| TST− (≥5 mm) | no variables statistically significant | Reference group |
| TST− (≥10 mm) | no variables statistically significant | Reference group |

OR* = Odds ratio; CI** = Confidence interval.

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points, ≥5 mm and ≥10 mm, and QFT. However, we found a high level of disagreement with QFT, regardless of the TST cutoff. Although we identified that BCG vaccination may partly account for this disagreement, we suggest that Brazilian recommendations to treat LTBI based on information gathered from medical history, TST, chest radiograph and physical examination, should not be changed. Further studies are needed before the QFT is introduced in prospective LTBI screening program for HCWs in Brazil.

Supporting Information

Questionnaire S1 Screening of community health workers. Questionnaire to identify the personal characteristics of community health workers and the level of exposure to Mycobacterium tuberculosis (in portuguese).

(PDF)

Questionnaire S2 Screening of health care workers. Questionnaire to identify the personal characteristics of nursing technicians, nurses and physicians and the level of exposure to Mycobacterium tuberculosis (in portuguese).

(PDF)

Author Contributions

Conceived and designed the experiments: ELNM. Performed the experiments: FMS TNP. Analyzed the data: FMS TNP. Wrote the paper: ELNM TNP LWR RRR.

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