

# Concordance of tuberculin tests and interferon gamma release assays in the prison population<sup>1,2</sup>

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## ABSTRACT

**Objective:** To study the agreement of Tuberculin Skin Tests (TST) and Interferon Gamma Release Assays (IGRA) when screening tuberculosis infection amongst inmates recently admitted to prison.

**Materials and Methods:** Prospective study conducted in a prison during the months of May and June 2009. Inmates without a TB history, with previous TST negatives or without prior TSTs were included. Participants signed an informed consent form and the study was approved by an independent Ethical Committee. TST (positive 10  $\geq$  mm) and IGRA (Quantiferon TB-Gold) were performed and standardized data collection was carried out. The agreement between both tests was analyzed using the Kappa index. **Results:** A total of 181 people were included. 62% were foreign-born, 17% had previous BCG vaccination; 8.4% were IDUs and 4% HIV-infected. Foreign born subjects were more frequently vaccinated and presented less drug use and HIV infection than people born in Spain. ( $p=0.02$ ,  $p=0.02$  and  $p=0.01$  respectively). TST results were positive in 24% and IGRA in 26%. Both tests were performed in 149 people (82%). Discordant results were observed in 15.8%. Agreement of the Kappa coefficient was 0.6 (CI 0.4-0.7). Agreement was better in the native population ( $K=0.8$ ) and worse in BCG vaccinated ( $K=0.4$ ) and foreign-born subjects ( $K=0.8$ ).

**Conclusion:** Overall agreement was moderate and was less amongst vaccinated subjects and those born abroad. Extension of the study could be useful to evaluate which test better predicts the risk of progression to active TB and the cost-benefit of both tests among the prison population.

**Key Words:** prisons; tuberculin test; interferon-gamma; tuberculosis; latent tuberculosis; comparative study; prevalence; HIV.

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## INTRODUCTION

Tuberculosis (TB) is one of the most important causes of death in the world, especially in poor countries<sup>1,2</sup>. In industrialized countries, although its incidence has significantly dropped throughout recent years, there are still population groups (such as homeless, alcoholics, illegal immigrants, etc.), which are especially vulnerable to this disease<sup>3</sup>. In order to achieve an appropriate control of TB, the following are necessary: a) early detection and treatment of patients with active TB; and b) detecting infected patients, who, since 2000, are referred as latent TB infection patients<sup>4,5</sup> and who are at risk of developing active TB.

As a means of identifying infected patients, traditionally the tuberculin skin test (TST) has been used. There is a wide experience related to this test, which is simple and cheap to carry out, since the WHO standardized it since 1951.

TST has a sensitivity rate close to 100% in individuals with normal immune response, but can cause false positive results in patients infected by non-TB mycobacteria, such as those individuals vaccinated with BCG. On the other hand, it can also cause false negative results in those individuals with cell mediated immunity disorders, such as HIV infected patients, amongst others. Some other disadvantages concerning the TST are: the increase of healthcare workload, since it requires a second visit 48 to 72 hours later in order to interpret the test, and the limitations concerning the application technique, which must be intradermal and not subcutaneous, with resulting result interpretation and a potential booster effect due to repetitive testing. In order to avoid any of this inconvenience, new infection identification techniques have been created, based on in vitro detection of interferon gamma (IFN- $\gamma$ ) produced by T cells after the stimulation of *M. tuberculosis* specific antigens. These techniques, defined IGRAS (Interferon Gamma Release Assays) are more specific than TST but have proven dissimilar sensitivity. The objective of our report is to research within a population with a high incidence of TB infection, such as the prison population, the concordance of TST, regularly used in prison, and IGRAS.

## MATERIAL AND METHODS

This is a prospective and cross-sectional study, which was carried out three days per week during the months of May and June 2009 and which included the inmates of a preventive imprisonment facility which complied with the following criteria: a) no previous

TB history; and b) no previous TST or previously negative TST for patients who had undergone the test in  $\leq 15$  days.

The patients who fulfilled the aforementioned criteria, underwent TST by means of the Mantoux intradermal reaction, by applying 2U of PPD RT 23. It was interpreted as a positive result whenever the reaction, after 48-72h, was 10mm or more. Furthermore, blood samples were taken to undergo QuantiFERON®-TB Gold. The quantification of IFG was always carried out in the Laboratory of the Public Health Agency of Barcelona and was considered positive if it was  $\geq 0.35$  IU/ml. Extractions were done during three days per week, between May 4<sup>th</sup> and June 29<sup>th</sup> 2009. All those patients under study were provided with an information document and were asked to sign an "informed consent" form, which had been drawn up in several languages. The study counted upon the approval of the Research Ethics Committee of the Foundation *Gol y Gorina*, external to the Prison Administration.

The patients were always visited by the same physician. When TST proved positive, the corresponding TB screening was carried out according to the protocols implemented in the prison. Patients were submitted a questionnaire which included the following variables: a) age; b) nationality (Spanish vs. others); c) prison re-admissions; d) heroine and/or cocaine consumption; e) administration (injecting vs. others), when applicable; and f) HIV serology.

The concordance between the TST and IGRAS was researched. As a means of concordance research the Kappa index has been used ( $\kappa = P_o - P_e / 1 - P_e$ ; where  $P_o$  stands for the concordance observed on a per unit basis and " $P_e$ " is the concordance proportion randomly expected). In order to assess the degree of concordance according to the Kappa index, the limits established by Landis and Koch<sup>6</sup>, have been used.

## RESULTS

221 patients were researched, and 181 (89%) were included in the study. All of them were men, due to the imprisonment conditions of the facility. The average age was 32 years (ranged between 19 and 66). 62% were foreign-born, mostly from the Maghreb Countries (38%); South America (30%) and Eastern Europe (12%). Foreigners were younger than the Spanish patients on the whole (30.7 in contrast to 35.1 years old;  $p=0.002$ ). 17% of the patients included had a history of BCG vaccination, 8.4% were IDUs or ex-IDUs and 4% were HIV-infected patients.

Foreign inmates were more frequently vaccinated by BCG than the Spanish inmates (22% in contrast to 9%;  $p=0.02$ ), and were less frequently injecting heroine and/or cocaine users (5% in contrast to 15% in the Spanish population;  $p=0.02$ ), they were also less infected by HIV (0.9% in contrast to 8.7%;  $p=0.01$ ). Moreover, and as far as HIV is concerned, 86% of those who were infected, were at the moment or had previously been IDUs.

TST turned positive in 26.8% of all cases and IGRAS were so in 24.8% (See Table I). Information on both tests was available in 149 cases (82%). 33.6% of all inmates (20% of the Spanish and 41.5% of the foreign-born inmates) presented at least one positive test. Two patients, both presenting negative TST, obtained undefined results in the IGRAS. In the positive IGRAS, the median amount of Quantiferon was 2.04 IU (range: 0.36-31.19). The total amount of disagreeing tests was 15.8%. The Kappa Index was 0.6 (0.4-0.7), which depicted an assessment with a moderate-fair interpretation (see Table II).

Test	Mantoux +	Mantoux -
IGRAS +	27 (18,1%)	10 (6,7%)
IGRAS -	13 (8,7%)	99 (66,4%)

■ Disagreeing results (15,8%).

Kappa Index: 0,6 (0,4-0,7).

Table I. TB infection distribution according to test and concordance degree.

Kappa Index Assessment	
$\kappa$ value	Agreement degree
<0,20	Poor
0,21-0,40	Slight
0,41-0,60	Moderate
0,61-0,80	Fair
0,81-1,00	Substantial

Table II. Interpretation scale for  $\kappa$  values.

The agreement between both tests varied depending on the sub-group considered (see Table III), therefore proving higher in Spanish inmates ( $\kappa=0.8$ ) and lower in vaccinated patients ( $\kappa=0.5$ ). It must be taken into account that 20 disagreeing results were reported in the immigrant group, while within the Spanish group, only 3 were so ( $p=0.01$ ).

## DISCUSSION

The prevalence of tuberculosis infection within our study varies according to the criteria used, but anyway, it is very high. In fact, the prevalence observed in this study is higher than that observed within inmates from other developed countries such as Italy (17.9%)<sup>7</sup> or Austria (13%)<sup>8</sup>, even though the cut-off point in these cases was  $\geq 5$  mm. And even though such cut-off point makes any comparison with previous studies carried out 15 years ago with inmates in Cataluña<sup>9</sup>, difficult, it is worth highlighting that the difference between prevalence rates ( $>25\%$  between both studies) seems to clearly indicate that inmates currently admitted to prison have lower rates of TB infection than those admitted then. Nevertheless, it might be possible that a factor limiting further reduction as far as TB infection is concerned, is the increase of foreign prison population which has been observed throughout recent years (62% of those researched in our study). This population generally comes from poor countries presenting higher infection rates. Several studies carried out with immigrant population arriving at or living in Barcelona have proven the high prevalence of TB infection within this group, even when there are important differences depending on the country they come from<sup>10-12</sup>.

The prevalence of TB infection observed in this study by means of both techniques (24% and 26% with TST and IGRAS respectively) implies a moderate-fair concordance between them ( $\kappa=0.6$ ; CI: 0.4-0.7) and this agreement is similar to the one observed in previous studies with immunocompetent population ( $\kappa=0.59$ <sup>13</sup> and  $0.65$ <sup>14</sup>), in transplanted patients ( $\kappa=0.6$ <sup>15</sup>), healthcare staff ( $\kappa=0.56$ )<sup>16</sup> and close to the one observed in children ( $\kappa=0.78$ <sup>17</sup>). Nevertheless, it is dissimilar to the studies carried out in HIV infected patients, where low agreement rates have been achieved ( $\kappa=0.37$ <sup>18</sup> and  $0.38$ <sup>19</sup>), yet very similar concordances have been observed with immunocompetent population ( $\kappa=0.52-0.6$ <sup>20</sup> or  $0.54$ <sup>21</sup>). This proves that the specificity of these tests is very high, yet its sensitivity is very variable and probably, as other authors have already stated, further and broad studies are needed to determine the appropriate role of IGRAS in clinically complex situations as those entailed by immunodeficient patients<sup>22-24</sup>. On the other hand consensus and concluding results have been achieved as far as the disagreement between TST and IGRAS in the BCG vaccinated population ( $\kappa=0.02$ <sup>25</sup>) due to the fact that IGRAS use antigens codified in the RD1 region of *M. tuberculosis*,

Group	Cases	TST+/IFN+	TST+/IFN-	TST-/IFN+	TST-/IFN-	Kappa
Vaccinated	22	3	4	1	14	0.4 (0-0.8)
Not Vaccinated	120	22	4	11	83	0.6 (0.5-0.8)
Spanish	55	8	0	3	44	0.8 (0.8-1)
Immigrants	94	19	10	10	55	0.5 (0.3-0.7)
Total	149	27	10	13	99	0.6 (0.4-0.7)

TST: Tuberculin Skin Testing; IFG: Interferon Gamma.

Table III. Concordance between TST and IFG in the researched groups

which the BCG vaccination lacks, and which seem to have an extraordinary ability in the detection of infected patients<sup>14</sup>. The BCG vaccination, which is widely extended in developing countries, is probably responsible for the low concordance ( $\kappa=0.43^{26}$  and  $0.40^{27}$ ) observed in studies carried out with immigrant populations. Our study also proved lower concordance rates in both sub-groups than in the non-vaccinated or national populations.

In any case, it must be noted that the comparison between different studies on the concordance of TST and IGRAS is not easy, since they have been carried out with different population types, different clinical situations, different positive TST criteria and even different types of IGRAS. It can be stated that in vitro technologies provide several obvious advantages (they are quicker, more reproducible, preserve confidentiality, are less subjective to interpretation bias, have no cross-reactivity with BCG, do not produce booster effect and avoid the losses of those cases which did not attend to the TST interpretation), but they are also more expensive, require trained staff and are not exclusively specific for *M. tuberculosis*, since they share antigens with *M.kansasii*, *M.szulgei* and *M.marinum*<sup>23</sup>. Even though the implementation of these techniques can be expensive they are probably more efficient and rentable in a wide range of scenarios and, on a medium-term, they can entail an important saving of healthcare resources, since they reduce the number of false positive results and subsequent costs<sup>14</sup>.

Current indications for IGRAS are not unified. There are few rulings which explicitly use evidence-based levels<sup>28, 29</sup> and few systematic revisions<sup>30</sup>, as well as few countries (16, Spain amongst them), which have made specific recommendations on the

use of these tests. The recommendations are generally of one of the following types: a) the substitution of TST by IGRAS; b) indistinct use; or c) the two steps strategy (TST followed by IGRAS), although there is no common and universally unified ruling. The most extended stance on this issue is probably that IGRAS should not replace TST for the time being, yet they must complement it in some cases. Nevertheless in some closed institutions, such as prisons, assessing which test better predicts the risk of developing TB is of paramount importance, especially due to the type of population imprisoned and the high prevalence of TB infection. Therefore, and in view of the results achieved with this study, it is recommended to further assess other prisons, so that it can be determined what test better predicts the risk of TB progression, as well as the cost-benefit rate of both tests in our country's prison population.

## CORRESPONDECE

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