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Short Report

Tuberculosis infection among cocaine crack users in Brazil

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ABSTRACT

Background: WHO recommends treatment for latent tuberculosis infection (LTBI) in the homeless and people who use drugs (PWUD). The optimal test for LTBI screening is uncertain.
Methods: A cross-sectional study was conducted among the homeless and drug-rehabilitation clinic clients chronically using crack in Western Brazil. Participants were interviewed and offered HIV testing plus tuberculin skin testing (TST) and QuantiFeron®-Gold-in-Tube (QFT). We considered LTBI when either TST or QFT were positive. Factors associated with LTBI were adjusted in a multivariate model.
Results: Among 372 subjects with at least one valid test, 216 (58%) had LTBI. TST was not read in 18.4%; QFT was indeterminate in 2.5%. TST detected 27 (26%) extra LTBI cases among 75 QFT-negative individuals. PWUD had over three-fold odds for LTBI. TST was 4.5 times more likely to be positive in BCG-vaccinated individuals.
Conclusion: Given the high risk of progression to disease in this population, the high rates of loss to TST reading and the possibility of false-positive TST results from BCG vaccination, we endorse current CDC recommendations to use QFT for LTBI screening among the homeless and PWUD. However, because adding TST to a negative QFT increased LTBI detection considerably, TST should be considered in QFT-negative individuals.

Introduction

Vulnerable populations share the same health difficulties, among them reduced access to healthcare, marginalization, mental health problems and susceptibility to tuberculosis (TB)/HIV and other infectious disease (World Health Organisation, 2016). People who use drugs (PWUD) and the homeless are among vulnerable and difficult-to-reach populations (World Health Organisation, 2016). The syndemic HIV/TB/drug use has accelerated the spread of each single epidemic, threatening in particular the above-mentioned populations, and constitutes a major component of the Global Health agenda (Murray & Lopez, 2013). When latently infected with TB, PWUD and the homeless are particularly susceptible to progression to active TB. However, TB can be prevented if LTBI is detected and treated. Thus, the World Health Organization (WHO) recommends the systematic screening of latent tuberculosis infection (LTBI) in this - and other - vulnerable groups (World Health Organisation, 2016). However, there is no gold standard test for LTBI. The tuberculin skin testing (TST) has been used for more than a century, despite its high rates of both false-negative and false-positive results. The more recently commercialized interferon-γ release assays (IGRA) quantify, in serum samples, the amount of interferon release after in-vitro stimulation of T-cells with antigens present only in *M. tuberculosis* (early secretory antigenic target 6, culture filtrate protein 10, and TB7.7), which should provide less false-positive results. Moreover, unlike TST, results can be obtained with only one visit. Thus, the USA Centers for Disease Control and Prevention (CDC) currently recommends the use of IGRA in difficult-to-reach populations (Centers for Disease Control & Prevention, 2013). In Brazil, extreme socio-economic inequities lead to concomitant vulnerabilities: drug users are often homeless, have a past history of imprisonment and are HIV-infected (Brasil, 2014). TB is 48-fold more frequent in the Brazilian homeless than in the general population (Zuim, 2011). We conducted a cross-sectional study among the homeless and PWUD to estimate: (i) the prevalence of LTBI according to different criteria, (ii) the added

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value of TST to QuantiFeron®-Tuberculosis-Gold-in-Tube (QFT) for the diagnosis of LTBI when preformed in series and (iii) the factors associated with LTBI.

Methods

Setting

There are 370.000 regular users of cocaine crack and similar inhaled drugs (hereafter denominated crack) in the Brazilian state capitals, corresponding to 0.81% of the population living in this setting (Brasil, 2014). Forty-seven percent of them live in the Western Region of the country (border with Latin American drug producer countries). The present study was conducted in three cities in this region: Campo Grande, capital of the state, Corumbá, border with Bolivia and Ponta Porã, border with Paraguay, both in the South American drug route.

Study design and population

This study is part of a broader cross-sectional study conducted from October/2013 to July/2015 to evaluate the prevalence of various infectious diseases in this vulnerable population. Eligible participants were the homeless as well as patients from drug rehabilitation clinics who had used cocaine crack or other similar inhaling drug for at least 25 days in the past six months. They were approached by the study team in clinics, shelters and streets, introduced by healthcare workers from the rehabilitation clinics and *Consultorio na Rua* (healthcare staff that provide on-site assistance to the homeless). Those 18 years or older who signed an informed consent were included. Those who were under drug effect at the moment they were approached, those with mental illnesses, pregnant women and indigenous people were excluded. For the current analysis, those who ultimately were diagnosed with active TB were also excluded. Those who refused blood collection remained in the study if they had a TST. Likewise, those who could not have a TST because of tuberculin shortage during the study (discontinuation by main manufacturer, *Statens Serum Institute*, Denmark) remained in the study (Tebruegge et al., 2016).

Sample size

Considering a population of 51.263 crack users, 95% significance and 30% prevalence of LTBI by any method, the calculated sample size was 321. We aimed to test 353, considering a 10% rate of loss to follow up.

Procedures

Research staff selected eligible participants through a quick interview for inclusion/exclusion criteria. After signing the informed consent, participants answered a questionnaire applied by previously trained interviewers. Questionnaires contained sociodemographic characteristics, smoking, alcohol and illicit drug habits, including daily doses and duration, and history of past imprisonment. Participants were examined for a BCG scar and blood was collected for HIV and QFT (as well as other serology tests, not reported in the current analysis). Research trained nurses applied TST, withdraw blood and processed samples for rapid HIV testing and initial QFT procedures within one hour after the interview. TST was read 24–48 h later by the same nurses, blinded to QFT results. Laboratory technicians who performed QFT were blinded for TST results. QFT was performed in the first collected samples (with no selection criterion besides blood withdrawal refusal). TST was performed as long as tuberculin was available in the country, with no selection criteria.

TST was considered positive if induration was ≥ 5 mm. QFT was performed according to the manufacturer's instructions. QFT result was considered positive if the IFN-γ level after stimulation with *M. tuberculosis* antigens minus the negative control was ≥ 0.35 IU/mL and 25% higher than the IFN-γ concentration in the non-stimulated control sample; negative if the IFN-γ level was < 0.35 IU/mL; and indeterminate if the IFN-γ production in the non-stimulated sample was ≥ 8.0 IU/mL or the PHA minus the IFN-γ concentration in the non-stimulated sample was < 0.5 IU/mL. Finally, HIV screening was conducted using enzyme-linked immunoassay (Murex HIV 1.2.0). Reactive samples were confirmed using a quick immunoblot test (Imunoblot Rápido DPP HIV 1/2, Bio-Manguinhos, Fiocruz).

Study outcomes

The main outcome was the prevalence of LTBI. Participants who tested positive both to TST and QFT were considered to have "certain" LTBI. Those with discordant tests were considered to have "probable" LTBI. LTBI was ruled out in those with concordant negative tests.

Analyses

To calculate the added value of a TST applied in series to those with a negative QFT for detecting probable LTBI, we calculated the proportion of probable LTBI in participants with a negative QFT test (proportion of TST + /QFT- over those tested and positive for both). We analyzed factors associated with LTBI (probable and certain), regardless of test applied, as recommended by WHO (Gilpin, Korobitsyn, Migliori, Raviglione, & Weyer, 2018). The association between independent variables and LTBI was measured by the adjusted odds ratio (aOR) and their 95% confidence intervals (CI) in a multivariate logistic regression model.

Results

Participants

We interviewed 728 PWUD (crack) for the broader study, of whom four were excluded for active TB. Of the remaining 724, the first 366 were invited to perform QFT (to complete 14 plates) of whom 345 had valid results (21 or 5.7% had undetermined results, Figure S1). Three hundred and nine were offered TST of whom 252 had valid results (57 or 18.4% did not return for reading). Thus, 372 participants with a valid result of at least one LTBI test constituted the study population, of whom 225 had valid results of both tests. Their mean age was 34.7 (± 9.5) years, 92.9% were male, 93.3% had a BCG scar and eight (3.6%) were HIV-positive. Median daily consumption of crack stones was 10 (range 1–54, one stone being estimated to have between one and five grams of active drug), 35 (15.5%) were homeless. TST was positive in 47.2% (119/252) and QFT in 54.2% (187/345). Among the 372 participants who underwent at least one test, 58.0% (216/372) had LTBI. Among the 225 who underwent both tests, TST was positive in 48.0% (108/225) and QFT in 54.7% (123/225). Certain LTBI was diagnosed in 81/225 (36.0%) and "probable" LTBI (discordant tests) in 69/225 (30.7%), for 150/225 participants (66.7%, or 46% additional diagnoses when a second test was performed). Thus, if used in series, with the second test being performed after a first negative test, the detection of LTBI would have increased by 18.7% with QFT and by 12% with TST.

Table 1 displays factors associated with LTBI, regardless of the test used. The use of injectable drugs had the strongest association with LTBI (aOR = 3.3), followed by presence of BCG scar (aOR = 2.7), previous imprisonment (aOR = 2.0) and older age (aOR = 1.8). BCG was not associated with a positive QFT test (aOR = 1.2, Table S1) but was with a TST (aOR = 4.6, Table S2).

Discussion

In the current study, we found a high prevalence of LTBI in crack