

Factors associated with nonadherence to TB chemoprophylaxis in Vitória, Brazil: a historical cohort study*

Fatores associados ao abandono da quimioprofilaxia de TB no município de Vitória (ES): um estudo de coorte histórica

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Abstract

Objective: To describe the factors associated with nonadherence to TB chemoprophylaxis in patients older than 15 years of age treated via referral TB control programs. **Methods:** A historical cohort study was carried out based on medical charts related to cases treated via referral TB control programs in the city of Vitória, Brazil, between 2002 and 2007. Cases of infection with *Mycobacterium tuberculosis* were stratified into two groups: health care workers (HCW group); and individuals who were not health care workers (NHCW group). **Results:** A total of 395 patients were included in the study: 35 in the HCW group and 360 in the NHCW group. The mean age in the HCW and NHCW groups was 34.8 and 32.4 years, respectively ($p = 0.36$). Of the 35 patients in the HCW group, 29 (82.9%) were female, compared with 180 (50.0%) of the 360 patients in the NHCW group. In the HCW and NHCW groups, respectively, 15 (42.9%) and 169 (46.9%) of the patients were contacts of TB cases. In addition, 9 (25.7%) and 157 (78.5%) the HCW and NHCW group patients, respectively, were HIV-infected. Nonadherence to chemoprophylaxis was 37.1% and 21.9% in the HCW and NHCW groups, respectively ($p = 0.045$). In the multivariate analysis, the factors associated with nonadherence were being a health care worker (OR = 8.60; 95% CI: 2.09-35.41), being HIV-infected (OR = 4.57; 95% CI: 1.2-17.5) and having had contact with a TB patient (OR = 2.65; 95% CI: 1.15-6.12). **Conclusions:** In order to improve adherence to TB chemoprophylaxis, new TB control program strategies are needed, especially for health care workers and HIV-infected patients.

Keywords: Tuberculosis; Chemoprevention; Isoniazid.

Resumo

Objetivo: Descrever os fatores associados ao abandono de quimioprofilaxia de TB em maiores de 15 anos atendidos em programas de referência de controle da doença. **Métodos:** Realizou-se um estudo de coorte histórica com análise de prontuários preenchidos entre 2002 e 2007 nos programas de referência de controle da doença no município de Vitória (ES). Os casos de infecção por *Mycobacterium tuberculosis* foram estratificados em dois grupos— profissionais de saúde (grupo PS) e indivíduos não profissionais de saúde (grupo NPS). **Resultados:** Um total de 395 indivíduos foi incluído no estudo: 35 no grupo PS e 360 no grupo NPS. A média de idade nos grupos PS e NPS foi de 34,8 e 32,4 anos, respectivamente ($p = 0,36$). A maioria de pacientes no grupo PS eram mulheres (29; 82,9%), enquanto 180 pacientes no grupo NPS eram mulheres (50,0%). Nos grupos PS e NPS, 15 e 169 pacientes (42,9% vs.46,9%), respectivamente, tiveram contatos de pacientes com TB, e 9 e 157 (25,7% vs.78,5%) eram portadores de HIV, respectivamente. O abandono da quimioprofilaxia foi de 37,1% e 21,9% nos grupos PS e NPS, respectivamente ($p = 0,042$). Na análise multivariada, os fatores associados ao abandono da quimioprofilaxia foram ser profissional de saúde (OR = 8,60; IC95%: 2,09-35,41), indivíduos HIV positivos (OR = 4,57; IC95%: 1,2-17,5), ser contato de paciente com TB (OR = 2,65; IC95%: 1,15-6,12). **Conclusões:** Os programas de controle de TB necessitam de novas estratégias em relação à adesão à quimioprofilaxia, principalmente para os profissionais de saúde e pacientes HIV positivos.

Descritores: Tuberculose; Quimioprevenção; Isoniazida.

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Introduction

In Brazil, a country that, together with another 21 developing countries, accounts for 80% of TB cases worldwide, TB is a major health problem.⁽¹⁾ According to the World Health Organization, 9.2 million new cases of TB were reported worldwide in 2006.⁽²⁾ Based on data from the Information Technology Department of the Unified Health Care System, there were approximately 55 new cases per 100,000 population in Brazil in 2006. In the state of Espírito Santo, Brazil, there were 1,222 new cases of TB in 2006. In the same year, the incidence was 150 cases in the state capital, Vitória.

In individuals infected with *Mycobacterium tuberculosis* and at increased risk of developing TB, one of the therapeutic measures for prevention is chemoprophylaxis, which is defined as the use of drugs capable of preventing an individual infected with a microorganism from developing the disease.⁽³⁾ The approach is based on the daily administration of 5-10 mg/kg of isoniazid (maximum dose: 300 mg/day) to individuals who are already infected but show no signs of the disease.⁽¹⁾

The effectiveness of isoniazid chemoprophylaxis has been established in double-blind, placebo-controlled, randomized clinical trials carried out since the 1960s. In a study conducted in Alaska, estimated effectiveness for one-year treatment was 75% in the first 4 years of follow-up, and a long-lasting protective effect was shown: 70% after 15 years and 50% after 19 years.⁽⁴⁾ Isoniazid chemoprophylaxis has a protective effect against active TB since it provides a 40-80% reduction in the risk of developing the disease in individuals infected with *M. tuberculosis* and presenting positive results on the tuberculin skin test (TST).⁽¹⁾

However, the mass use of chemoprophylaxis is still controversial due to the high number of individuals infected with *M. tuberculosis* (approximately 57 million).⁽¹⁾ The Brazilian National Ministry of Health adopts two chemoprophylaxis modalities⁽¹⁾: primary chemoprophylaxis, recommended for neonates born to mothers with active TB or neonates who will have direct contact with active TB cases; and secondary chemoprophylaxis, which consists of daily administration of isoniazid (10 mg/kg) for 6 months.

According to the National Ministry of Health, the indications for secondary chemoprophylaxis

include the following: being younger than 15 years of age, with no signs consistent with active TB, a contact of active TB cases, and a TST reactor (induration ≥ 10 mm) who has not received the BCG vaccination; being a child who has received BCG vaccination and is TST reactive (induration ≥ 15 mm); being a member of an indigenous population, a contact of active TB cases, and a strong TST reactor, regardless of age or vaccination status—in such individuals, chemoprophylaxis should be instituted after a clinical evaluation is performed and the possibility of active TB is ruled out through smear microscopy and X-ray; being immunocompromised, due to the use of drugs or to immunosuppressive diseases, and a household contact of TB cases—in such individuals, chemoprophylaxis should be instituted under strict medical supervision; being a strong reactor to the TST with no signs of active TB but presenting concomitant clinical conditions that are associated with a high risk of developing TB—such conditions including insulin-dependent diabetes mellitus, severe nephropathy, sarcoidosis, lymphoma, alcoholism and silicosis. Among HIV-infected individuals, chemoprophylaxis is indicated for those who are household or institutional contacts of active TB cases, regardless of the TST results, for those who are asymptomatic and TST reactive (induration ≥ 5 mm), for those who are TST nonreactive (induration < 5 mm) and present CD4 counts lower than 350 cells/mm³ or total lymphocyte counts lower than 1,000 cells/mm³ and for those with radiological findings of TB-related lung scarring or with a documented history of TST reactivity.

Secondary chemoprophylaxis is also indicated for individuals with recent TST conversion (within the last 12 months), that is, individuals who presented an increase in induration equal to or greater than 10 mm. Among such individuals, infected health care workers are prioritized to receive TB chemoprophylaxis in order to minimize the risk of developing the active form of the disease.^(5,6)

One problem that has already been detected in other studies is patient adherence to treatment.⁽⁷⁾ It has been pointed out that the main difficulty in adhering to chemoprophylaxis is the fact that it is a 6-month regimen, even for patients who do not have any symptoms of the disease. Therefore, the objective of the present

study was to evaluate the factors associated with adherence to secondary TB chemoprophylaxis in patients older than 15 years of age treated via referral TB control programs in the city of Vitória, Brazil. The patients were stratified into two study groups: health care workers and other individuals infected with *M. tuberculosis*.

Methods

A historical cohort study was carried out based on the medical charts of patients treated via referral TB control programs in the city of Vitória, Brazil, between 2002 and 2007. Information on indications for chemoprophylaxis and on follow-up during treatment was obtained.

The primary health care clinics in the city of Vitória were studied, as was the Tuberculosis Control Program of the Cassiano Antônio de Moraes University Hospital of the Federal University of Espírito Santo.

Patients were stratified into two study groups: the first group comprised those for whom chemoprophylaxis had been indicated and who were health care workers (HCW group); whereas the second group comprised those for whom chemoprophylaxis had been indicated and who were not health care workers (NHCW group). All other patients older than 15 years of age for whom secondary chemoprophylaxis had been indicated were included in the NHCW group. Those younger than 15 years of age were excluded in order to avoid study bias, since this population requires adult supervision to ensure the intake of medication and this fact could affect the results.⁽⁸⁾

A data collection form, containing variables such as gender, age, TST result, presence of comorbidities, history of contact with a TB patient, HIV serology, chemoprophylaxis side effects and outcome of chemoprophylaxis, was developed. In addition, the consistency and

completeness of the information were evaluated, and only information considered complete was analyzed. Completeness was evaluated based on the annotations on the medical chart related to the case—annotations that should contain explicit information regarding the study variables.

On the TST, positivity was defined as an induration reading equal to or greater than 10 mm. In HIV-infected patients, positivity was defined as an induration greater than 5 mm.⁽⁹⁾

The data were initially entered into a Microsoft Excel spreadsheet and subsequently transferred to the STATA statistical program, version 9.0 (Stata Corp., College Station, TX, USA). In the data analysis, qualitative variables are presented as absolute and relative frequencies, whereas quantitative variables are presented as mean and standard deviation. The groups were compared using the chi-square test or Fisher's exact test, when necessary, and the Student's t-test. The level of significance was set at 5%. In the logistic regression analysis, all of the variables selected based on univariate analysis were included in the model. A p value < 0.20 was set for entry into the model, and a p value < 0.05 was set for statistical significance in the final model.

In order to protect the identity of the study subjects, only the initials of the participants were used during data collection. The present study was approved by the Ethics Committees of the Federal University of Espírito Santo Health Sciences Center and the Municipal Health Department of Vitória.

Results

In the period studied, 578 individuals submitted to chemoprophylaxis were evaluated. Of those, 183 were excluded for being younger than 15 years of age. In the NHCW group, the main indication for chemoprophylaxis was HIV infection (in 44% of the cases). Other indications

Table 1 – Distribution of participants referred for chemoprophylaxis in the two groups, by demographic variable.

Variable	Health care workers	Not health care workers	OR (95% CI)	p
Female gender, n (%)	29 (82.9)	180 (50.0)	0.20 (0.06-0.52)	0.002*
Male gender, n (%)	6 (17.1)	180 (50.0)		
Age, mean ± SD	34.8 ± 10.6	32.6 ± 13.8	-	0.36**

*Chi-square test and Fisher's exact test. **Student's t-test.

included TST conversion (in 27% of the cases), immunosuppressive diseases or use of drugs (in 15%), severe nephropathy (in 10%) and insulin-dependent diabetes mellitus (in 4%). In the HCW group, chemoprophylaxis had been indicated for all patients due to TST conversion.

The study population comprised 395 individuals, 35 of whom belonged to the HCW group and 360 of whom belonged to the NHCW group. The verification process of consistency and completeness resulted in the exclusion of variables, and, for the analysis, the sample size included only the variables considered complete. Regarding gender, we found that 29 (82.9%) of the patients in the HCW group were female, compared with 180 (50.0%) of the patients in the NHCW group. Regarding age, 34 patients in the HCW group and 347 patients in the NHCW group were analyzed. In the HCW group, the median was 33 years (range, 21-55 years), with a mean of 34.8 ± 10.6 years. In the NHCW group, the median was 31 years (range, 15-82 years) and the mean was 32.6 ± 13.8 years. The difference between the groups in terms of mean age was not significant (Table 1).

Information on medication side effects was identified in few medical charts. In 8 (22.86%) of the 35 medical charts of patients in the HCW group, some data on medication side effects had been recorded. However, the treatment had to be discontinued in only 1 patient. In the medical

Table 2 - Comparison of the two groups in terms of comorbidities, based on data obtained from the Tuberculosis Case Registry database report forms and from the medical charts of participants.

Comorbidity	Not health care workers n (%)	Health care workers n (%)
Smoking	9 (2.5)	-
AIDS	38 (10.6)	1 (2.9)
Use of corticosteroids	8 (2.2)	4 (11.4)
Alcoholism	7 (2.0)	3 (8.6)
Diabetes	12 (3.3)	27 (77.1)
Two comorbidities	6 (1.7)	-
Three comorbidities	3 (0.8)	-
Other	17 (4.7)	-
Not reported	267 (74.2)	-
Total	360 (100)	35 (100)

charts of patients in the NHCW group, there was no record of such an occurrence.

The individuals in the HCW group belonged to the following professional categories: nursing team (nurse, nursing technician, nursing assistant), 14 individuals (40.0%); student in the area of health care, 6 individuals (17.1%); physician, 3 individuals (8.5%); professor in the area of health care, 2 individuals (5.7%); physical therapist, 1 individual (2.9%); dentist, 1 individual (2.9%); psychologist, 1 individual (2.9%); and other categories (laboratory technician and pathology technician), 7 individuals (20.0%).

Table 3 - Distribution of the study participants in the two groups by history of contact with a TB patient, HIV serology, tuberculin skin test result and outcome of chemoprophylaxis.

Variable	Health care worker n (%)	Not a health care worker n (%)	OR (95% CI)
History of contact with a TB patient			
Yes	15 (46.9)	169 (46.9)	1.2 (0.55-2.56)*
No	20 (57.1)	191 (53.1)	
HIV test result			
Positive	9 (52.9)	157 (78.5)	0.3 (0.09-0.98)**
Negative	8 (47.1)	43 (21.5)	
PPD result			
Strongly positive	35 (100.0)	357 (99.2)	0 (0-13)***
Weakly positive	0 (0.0)	3 (0.8)	
Outcome of chemoprophylaxis			
Released from treatment	22 (62.9)	281 (78.16)	2.1 (0.92-4.58)****
Nonadherence	13 (37.1)	79 (21.9)	
Total	35 (100.0)	360 (100.0)	

*p = 0.64. **p = 0.017 (n = 217). ***p = 0.58. ****p = 0.042.

Table 4 - Logistic regression analysis of the study variables, adjusted for nonadherence to chemoprophylaxis.

Variable	Adjusted OR*	95% CI	p
Health care worker	8.60	2.09-35.41	0.003
Contact	2.65	1.15-6.12	0.022
Age	0.96	0.93-0.99	0.009
HIV	4.57	1.20-17.50	0.027
Gender	1.28	0.61-2.70	0.507

*OR adjusted for all of the remaining variables.

Comorbidities were reported in 8 (22%) of the 35 health care workers studied. Of those 8, 1 (12.5%) was a smoker, 4 (50.0%) were diagnosed with AIDS and 3 (37.5%) were diagnosed with other diseases (lymphoma, neoplasia or Wegener's granulomatosis). For the remaining individuals in the HCW group, this information was not available.

As can be seen in Table 2, comorbidities were identified in 100 (27.8%) of the 360 patients in the NHCW group: AIDS, in 38; diabetes, in 12; smoking, in 9; concomitant use of corticosteroids, in 8; alcoholism, in 7; and other diseases (neoplasia, systemic lupus erythematosus, ankylosing spondylitis, rheumatoid arthritis, etc.), in 17. In addition, we observed that, among those individuals, 6 had two comorbidities (diabetes and smoking, alcoholism and AIDS, alcoholism and diabetes, alcoholism and smoking or AIDS and smoking) and 3 had at least three comorbidities (AIDS, alcoholism and smoking).

The analysis of the TST results revealed that most of the 395 patients analyzed were strong reactors. Of the 35 patients in the HCW group, all (100%) were strong reactors, compared with 357 (99.2%) of the 360 patients in the NHCW group. Regarding history of contact with a TB patient, 15 (42.9%) of the patients in the HCW group and 169 (46.9%) of the patients in the NHCW group were classified as contacts. Information regarding HIV serology was available for only 17 (48.6%) of the patients in the HCW group and 200 (55.6%) of the patients in the NHCW group. Among those patients, the HIV serology was positive in 9 (52.9%) of the 17 HCW group patients, compared with 157 (78.5%) of the 200 NHCW group patients (Table 3).

The evaluation of the outcome of chemoprophylaxis in the groups studied revealed that

281 (78.1%) of the 360 individuals in the NHCW group were released from treatment, compared with only 22 (62.9%) of the 35 individuals in the HCW group. In the HCW and NHCW groups, respectively, 13 and 79 individuals (37.1% and 21.9%) did not complete the course of chemoprophylaxis. This difference, despite presenting a level of significance of less than 5%, presented a borderline confidence interval (Table 3).

Table 4 presents the logistic regression analysis of the data, adjusted for treatment nonadherence related to other selected factors. The variable "history of contact with a TB patient" was included in the model, despite presenting $p > 0.20$, since it is an important variable in terms of use of chemoprophylaxis. We found that being a health care worker results in an 8.6-fold increase in the risk for treatment nonadherence in relation to not being a health care worker. In addition, we observed that contacts of a TB patient are at higher risk for nonadherence to chemoprophylaxis. Age is a protective factor against nonadherence to chemoprophylaxis. Another finding that deserves attention is that HIV-infected patients have a 4.5-fold higher risk for nonadherence to chemoprophylaxis.

Discussion

Among individuals with latent infection, TB chemoprophylaxis is an effective strategy for the prevention of new cases.⁽¹⁰⁾ The risk of infection and disease caused by *M. tuberculosis* in health care workers has received attention since the 1990s, when the morbidity and mortality rates associated with the disease increased in the general community.⁽¹¹⁾

The significance of the exposure of such individuals to *M. tuberculosis* depends principally on the prevalence of the disease among users of health care facilities, which results in an increase in the number of cases of the disease among health care workers, especially in the nursing team, as has been reported by some authors.^(12,13)

In our study, a gender-related analysis in the HCW group revealed a higher prevalence of TB among females. This finding can be explained by the fact that the nursing team was composed mostly of women,⁽¹⁴⁾ whereas, in the NHCW group, there was a gender balance.

Regarding age, one group of authors analyzed TB cases among health care workers

and observed that the greatest proportion of cases occurred among those in the 35-54 year age bracket.⁽¹⁵⁾ In our study, although we observed only the occurrence of infection, the median age of the population in the HCW group was 33 years, a finding that does not differ from that regarding the incidence of TB in the general population.⁽²⁾

Since 1965, isoniazid has been the drug of choice for TB prophylaxis. However, due to the occurrence of severe hepatotoxicity associated with its use, isoniazid has come to be used only in conjunction with monitoring of liver function. Isoniazid should be discontinued when aminotransferase levels are three to five times higher than normal values. Nevertheless, other studies have demonstrated that only a small portion of the population developed side effects with the use of isoniazid.⁽¹⁰⁾

In the United States, clinical trials carried out by public health care providers revealed that, of the 13,831 individuals who received isoniazid, only 1% developed hepatitis, the incidence being higher among those older than 50 years of age. Chief among the factors related to risk of developing hepatitis, in addition to age, was alcoholism.⁽¹⁶⁾ In the present study, despite a considerable lack of information, we found that chemoprophylaxis was discontinued due to the hepatotoxicity in only one of the health care workers, a 44-year-old individual who did not report alcoholism.

It is of note that, in the HCW group, 57% of the patients were not household contacts of TB patients. However, it can be presumed that many health care workers were infected with the bacillus in the workplace, as demonstrated in other studies showing that the development of active TB is likely after primary infection.^(5,10,13)

In Brazil, the fact that health care workers have an increased risk of infection in relation to the general population has been demonstrated by studies showing an association between exposure to TB patients and TST conversion (10-mm increase in relation to initial induration). The principal risk factors were having had nosocomial exposure to patients with pulmonary TB, being a nursing professional and working at a hospital where biosafety measures have not been implemented. Only 1.5% of the health care workers analyzed reported having had contact with TB

in the community, whereas 33% reported having had contact with TB in the workplace.^(5,17)

In the present study, the rate of nonadherence to chemoprophylaxis was higher in the HCW group than in the NHCW group, despite the fact that health care professionals have greater knowledge regarding the disease, the risks associated with their line of work and the efficacy of TB treatment.

In a study of household contacts of patients with pulmonary TB, two new alternatives for chemoprophylaxis were proposed: a 3-month regimen of rifapentine combined with isoniazid; and a 3-month regimen of pyrazinamide combined with rifampin.⁽¹⁸⁾ The combination of rifapentine and isoniazid was effective against latent TB and was significantly less toxic than was the combination of rifampin and pyrazinamide.⁽¹⁹⁾ The use of this new treatment regimen could lead to a decrease in the duration of chemoprophylaxis and to fewer side effects. In addition, it would be a means of increasing adherence, since treatment duration has been reported as one of the causes of nonadherence.⁽²⁰⁾

The risk of developing TB in HIV-infected patients has been estimated at 1.7-7.9 per 100 person-years, which is why the identification of co-infection and the administration of preventive treatment have great relevance.⁽¹⁰⁾ In the present study, the NHCW group presented a high rate of TB/HIV co-infection: 157/200 cases (78.5%). However, this information was missing from 160 of the medical charts. Failure to record this information on the medical forms and medical charts of patients was common, and this is mainly due to the lack of a specific form for this condition. It is known that data reliability, data completeness and data updating improve data quality and facilitate the decision-making process.⁽¹⁷⁾ Nevertheless, when recording this information is not mandatory, as is the case with individuals who are on chemoprophylaxis, data collection proves to be inefficient.

The limitations of our study are mainly related to the use of secondary data. There were a great number of charts in which there were no data for some variables, which might have affected the final analysis, increasing the probability of a type II error. However, even with a loss of power due to incompleteness, our findings show the need for TB control programs that

are more structured in terms of strategies to improve adherence to chemoprophylaxis, especially for health care workers and HIV-infected patients

The analysis adopted for the present study did not allow us to determine why younger individuals are at lower risk for nonadherence to chemoprophylaxis. One of the possible explanations is that, with age, other comorbidities might be present, leading individuals to use other medications concomitantly with chemoprophylaxis, and this could affect adherence. Another noteworthy finding is that nonadherence to chemoprophylaxis was approximately three times higher among contacts of TB patients than among patients who reported no known contact with a TB patient. A possible explanation, in addition to other factors involved in the causal model of TB that were not assessed in the present study, is that the family rallies around TB patients rather than around individuals who are receiving only prophylaxis.

Programs for the control of TB are based on case detection and treatment; however, in consensuses, little emphasis has been placed on prevention of diseases through the institution of chemoprophylaxis.⁽²¹⁾ Although such measures have been recommended, they are not a priority in the programs, as evidenced by the fact that, to date, there is no specific medical form for the evaluation and follow-up of patients infected with *M. tuberculosis*.

In addition, chemoprophylaxis, unlike treatment, does not have a set goal for adherence. The efficacy of chemoprophylaxis in itself justifies the development of a more organized strategy to minimize the rates of nonadherence. To that end, it is necessary that professionals who work in TB control programs be trained and that specific indicators of chemoprophylaxis be created to be used as a management tool. The monitoring and evaluation of such indicators will allow chemoprophylaxis to be one more instrument for TB control, and, therefore, rank similar to treatment in importance. To date, this has not been observed in the routine of health facilities.

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