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ORIGINAL ARTICLE

Impact of smoking on sputum culture conversion and pulmonary tuberculosis treatment outcomes in Brazil: a retrospective cohort study

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ABSTRACT

Objective: To evaluate the impact of smoking on pulmonary tuberculosis (PTB) treatment outcomes and the two-month conversion rates for *Mycobacterium tuberculosis* sputum cultures among patients with culture-confirmed PTB in an area with a moderate incidence of tuberculosis in Brazil. **Methods:** This was a retrospective cohort study of PTB patients diagnosed and treated at the Thoracic Diseases Institute of the Federal University of Rio de Janeiro between 2004 and 2012. **Results:** Of the 298 patients diagnosed with PTB during the study period, 174 were included in the outcome analysis: 97 (55.7%) were never-smokers, 31 (17.8%) were former smokers, and 46 (26.5%) were current smokers. Smoking was associated with a delay in sputum culture conversion at the end of the second month of TB treatment (relative risk = 3.58 [95% CI: 1.3-9.86]; p = 0.01), as well as with poor treatment outcomes (relative risk = 6.29 [95% CI: 1.57-25.21]; p = 0.009). The association between smoking and a positive culture in the second month of treatment was statistically significant among the current smokers (p = 0.027). **Conclusions:** In our sample, the probability of a delay in sputum culture conversion was higher in current smokers than in never-smokers, as was the probability of a poor treatment outcome.

Keywords: Tuberculosis; Treatment outcome; Smoking.

INTRODUCTION

According to the World Health Organization, 10.4 million people developed tuberculosis and 1.4 million people died from tuberculosis in 2015.[1] In order to change this reality, the major goal of the World Health Organization strategy since 2015 has been to eradicate the global epidemic of tuberculosis by 2035, reducing the number of cases and deaths by 90% and 95%, respectively.[2] To that end, a treatment success rate of 90% remains the primary goal.[2] However, delays in the diagnosis of pulmonary tuberculosis (PTB) and the large proportion of patients who do not adequately complete treatment remain barriers to achieving these goals.[3] In addition, clinical variables and comorbidities, such as diabetes, HIV infection, alcohol abuse, and the extent of the disease on chest X-rays, can also affect the infectivity, diagnosis, and prognosis of these patients.[4,5] In this context, smoking has been associated not only with a two-fold higher risk of development of active tuberculosis but also with poor treatment outcomes.[6-8]

The smoking epidemic remains one of the greatest global public health threats, with more than 5 million annual deaths being directly associated with tobacco use.[9] Approximately 80% of more than 1 billion smokers worldwide live in low- to middle-income countries, where PTB is not controlled and is highly prevalent.[10] In 2013, the estimated prevalence of smoking in Brazil among individuals aged 15 years or older was 16.1%.[11] This is significant, given that Brazil is one of the 20 countries with the highest absolute numbers of tuberculosis cases worldwide and is also the country with the highest number of cases in Latin America (84,000 estimated new cases in 2015, representing an estimated incidence of 41/100,000 population).[1] In addition, two studies in Brazil demonstrated an association between smoking and delayed culture conversion in PTB patients, although the effects of smoking on treatment outcomes were not analyzed.[12,13] *Mycobacterium tuberculosis* sputum culture conversion at 2 months is an important marker for cure and an important primary outcome marker in most (if not all) clinical trials in PTB.[14,15] However, smoking, a possible confounding variable, has not been evaluated or considered even in recent clinical trials of new tuberculosis treatment regimens.[16-18]

Recently, a consensus statement on the treatment of PTB issued by the American Thoracic Society/Centers for Disease Control and Prevention/Infectious Disease Society of America suggested that smokers with cavitation

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on baseline chest X-ray or culture positivity at 2 months could be considered for extended tuberculosis treatment.[19] This suggestion is based on scientific evidence demonstrating a high risk of PTB recurrence in these patients.[20,21] According to data obtained from the Brazilian National Tuberculosis Control Program, the only comorbidity that should be regarded as a reason for extended PTB treatment is HIV infection.[22] Therefore, the objective of the present study was to evaluate the impact of smoking on *M. tuberculosis* sputum culture conversion rates at 2 months and on PTB treatment outcomes among patients with culture-confirmed PTB in an area with a moderate incidence of tuberculosis in Brazil.

METHODS

This was a retrospective cohort study carried out at the Tuberculosis Outpatient Clinic of the *Instituto de Doenças de Tórax da Universidade Federal do Rio de Janeiro* (IDT/UFRJ, Federal University of Rio de Janeiro Thoracic Diseases Institute), a referral center for the diagnosis and treatment of and clinical research on tuberculosis (formerly known as site 29, Hopkins-Brazil, of the Tuberculosis Clinical Trials Consortium of the Centers for Disease Control and Prevention) in the city of Rio de Janeiro, Brazil, involving patients with PTB between 2004 and 2012. The incidence rate of tuberculosis in Rio de Janeiro during the study period ranged from 83.7/100,000 population in 2004 to 69/100,000 population in 2012.[23]

Data collection, definitions, and subject selection

As part of the routine of the Tuberculosis Outpatient Clinic of theIDT/UFRJ, data regarding demographic aspects, cavitation on chest X-ray, and comorbidities were recorded in the patient medical charts. As for comorbidities, patients were assessed for diabetes mellitus (DM) on the basis of laboratory testing and a history of diagnosis of or treatment for DM. Patients were also assessed for smoking status and consumption, as well as for alcohol use (Cut down, Annoyed, Guilty, and Eye-opener questionnaire, known by the acronym CAGE). In addition, HIV serology testing was offered to all tuberculosis patients. Symptomatic subjects and/or those with abnormal chest X-rays were, on the first visit, instructed to provide two unsupervised sputum samples for AFB smear microscopy (Ziehl-Neelsen staining) and *M. tuberculosis* culture (Löwenstein-Jensen medium). Symptomatic subjects with abnormal chest X-rays who were unable to provide spontaneous sputum underwent sputum induction with hypertonic saline solution. Sputum samples, whether spontaneous or induced, were obtained at admission (baseline) and at eight weeks after treatment initiation for further smear microscopy and culture. Antimicrobial susceptibility testing was carried out on the baseline samples. Tuberculosis treatment is routinely administered under direct supervision to all patients at the Tuberculosis Outpatient Clinic of the IDT/UFRJ, and these patients are followed for 12 months after completion of the tuberculosis treatment.

The medical chart numbers of the patients with a diagnosis of PTB who were admitted to the Tuberculosis Outpatient Clinic of the IDT/UFRJ between October 1, 2004 and December 31, 2012 were obtained from the outpatient clinic database. A data collection instrument was created specifically for the present study, having been pre-tested and modified during a pilot study conducted in March 2012 and involving 15 medical charts (data not shown). The following data were obtained by medical chart review: smear microscopy and *M. tuberculosis* culture results; chest X-ray findings; demographic data (gender and age); level of education; alcohol consumption; HIV status; and comorbidities (cancer, immunosuppression, liver disease, and renal failure). Patients were categorized by their self-reported smoking status as smokers (current or former smokers) and nonsmokers. Current smokers were defined as subjects who were smoking at the time of diagnosis of PTB or who had quit smoking within 12 months prior to diagnosis and had smoked at least 100 cigarettes during their lifetime.[24] Former smokers were defined as those who had quit smoking more than 12 months prior to diagnosis of PTB. Subjects who reported never having smoked were defined as nonsmokers. Smoking history was expressed in pack-years. A diagnosis of DM was established if the subject had a history of DM and was on insulin and/or an oral hypoglycemic agent or had been diagnosed with DM during PTB treatment (on the basis of two or more fasting blood glucose levels ≥ 126 mg/dL on different days or a glycosylated hemoglobin level ≥ 6.5%). Sputum culture conversion was defined as culture negativity at 2 months. Treatment outcomes were categorized as treatment success (cure or treatment completion) or poor treatment outcomes (death, treatment default, or treatment failure). Recurrence was defined as a new PTB episode confirmed by culture positivity for *M. tuberculosis* within 12 months after treatment completion.[25] Subjects with culture positivity for *M. tuberculosis* and aged ≥ 18 years were included in the study.

For the outcome analysis, patient exclusion criteria were as follows: being pregnant during treatment; testing positive for HIV serology; data required for evaluation being missing; having an antimicrobial susceptibility test result that showed *M. tuberculosis* strains resistant to any drug in the standard regimen; and having received different treatments from the standard regimen: rifampin and isoniazid for 6 months, as well as pyrazinamide and ethambutol in the first 2 months, as recommended by the Brazilian National Tuberculosis Control Program.

Statistical analysis

The results were analyzed with IBM SPSS Statistics software, version 21.0 (IBM Corporation, Armonk, NY, USA), and Stata software, version 11.0 (StataCorp LP, College Station, TX, USA). The exposure variable was

smoking, and the nonexposure variable was absence of a smoking history. The confounding variables considered in our study were DM, cavitation on chest X-ray, and alcohol abuse. The outcome variables evaluated were culture positivity for *M. tuberculosis* at 2 months (yes or no), PTB treatment outcome (poor or treatment success), and PTB recurrence (yes or no). Relative risks (RRs) and 95% confidence intervals were calculated for each outcome. Dichotomous variables were analyzed with the chi-square test and Fisher's exact test, with a level of significance set at 5%. Continuous variables were analyzed with the Kruskal-Wallis test for independent samples, and logistic regression was used for the multivariate analysis.

Ethics

The Research Ethics Committee of the Clementino Fraga Filho University Hospital of the Federal University of Rio de Janeiro approved the present study on March 15, 2012 (Memorandum no. 391/12; Protocol no. 137/11).

RESULTS

Of the 298 patients with a diagnosis of PTB who were enrolled in the outpatient clinic database during the study period, 12 were ineligible for inclusion (culture negativity for *M. tuberculosis*). In addition, 41 subjects were excluded because they tested positive for HIV serology (n = 8) or had baseline resistance to rifampin, isoniazid, pyrazinamide, or ethambutol (n = 33). Those who did not receive the standard treatment regimen because they were participating in a clinical trial testing new drugs were also excluded (n = 71). Of the remaining 174 patients diagnosed with PTB, 77 (44.3%) were in the exposure group (31 former smokers and 46 current smokers) and 97 (55.7%) were in the control group (nonexposure; Figure 1).

The patients included in the study were predominantly male, with a median age of 35 years (interquartile range: 35-49 years), and the presence of cavitation on baseline chest X-ray was highly prevalent (Table 1). The prevalence of DM was 17% among all subjects (30/174). Current smokers had fewer years of schooling and showed a lower prevalence of DM than did nonsmokers. The prevalence of alcohol abuse was higher among those with a (previous or current) history of smoking. There was no significant difference among nonsmokers, former smokers, and current smokers with respect to the presence of cavitation on baseline chest X-ray.

Two-month culture results were available for 137 subjects, and the prevalence of culture positivity at 2 months was 25.5% (35/137). DM and smoking were significantly associated with this outcome in the univariate analysis (RR = 2.59 [95% CI: 0.98-6.89]; p = 0.05; and RR = 2.87 [95% CI: 1.25-6.59]; p = 0.01, respectively). However, in the multivariate model, only smoking remained significantly associated with culture positivity at 2 months (RR = 3.58 [95% CI: 1.30-9.86]; p = 0.01; Table 2). Thus, the likelihood of culture positivity at 2 months was greater among current smokers than among nonsmokers (p = 0.02; Figure 2). In addition, we identified a dose-response relationship between tobacco consumption and culture positivity at 2 months. The proportion of tobacco consumption was similar between former smokers and current smokers (p = 0.6).

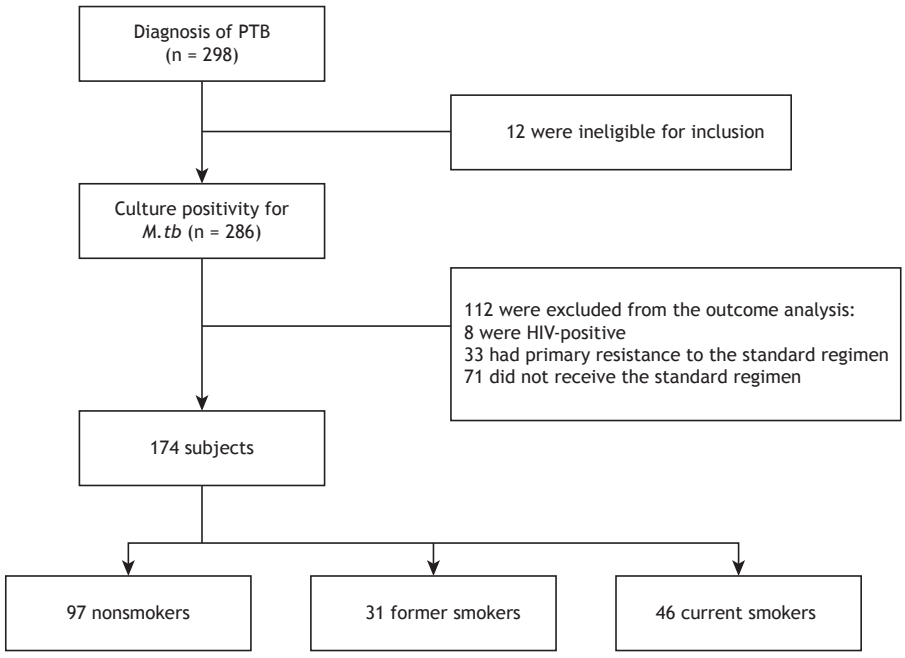

Figure 1. Pulmonary tuberculosis (PTB) patient evaluation flowchart. *M.tb: Mycobacterium tuberculosis.*

Treatment outcomes were available for 164 patients: treatment success was observed in 146—cure, in 26; and treatment completion, in 120—and a poor outcome was observed in 18—failure, in 5; death, in 4; and default, in 9. Thus, the treatment success rate was 89%. There was 1 case of recurrence within 1 year after treatment completion. Smoking was the only independent factor associated with a poor treatment outcome (RR = 6.29 [95% CI: 1.57-25.21]; p = 0.009; Table 3). Current smokers were more likely to have a poor treatment outcome than were former smokers and nonsmokers (p = 0.04 and p = 0.002, respectively; Figure 3).

DISCUSSION

The clinical characteristics of our study sample were representative of what is expected for PTB patients. The male predominance, the median age of 35 years, few years of schooling, and the rate of alcohol abuse above 20% of the sample are comparable to what has been previously reported in other studies.[8,12,13] Notably, the prevalence of DM among the PTB patients was higher than that found in the general population of Brazil in 2014 (17% vs. 7.6%).[26] Although a descriptive study in Brazil found a DM prevalence of 8%, our findings were similar to those of descriptive studies conducted in China and in India (16.2% and 14%, respectively).[27-29] The prevalence of smoking among the PTB patients was also higher (44.3%) than that in the general Brazilian population (15%).[11] Likewise, our data were consistent with the smoking prevalence of 44% found in South Africa, another middle-income country with a high number of tuberculosis cases.[30] The presence of cavitation on baseline chest X-ray was highly prevalent, but this finding was similar between the exposure and nonexposure groups.

In our study, the prevalence of alcohol abuse was higher among former smokers and current smokers than among nonsmokers. A higher prevalence of alcohol abuse among individuals with a (previous or current) history of smoking than among those who were nonsmokers has also been reported previously.[8,21] Because alcohol abuse is a confounding variable for PTB treatment outcomes, it is commonly analyzed together

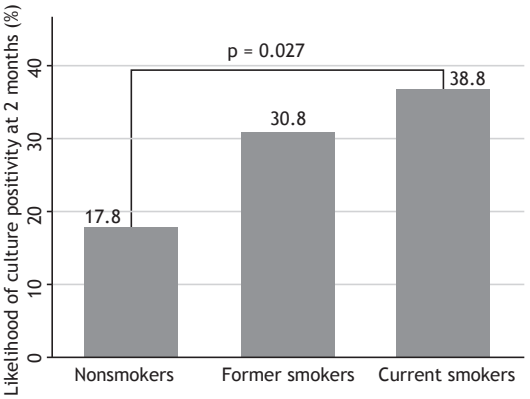

Figure 2. Smoking status and culture positivity at 2 months.

Table 1. Characteristics of pulmonary tuberculosis patients (n = 174).[a]

Characteristic	Total sample (N = 174)	Nonsmokers (n = 97)	Former smokers (n = 31)	p*	Current smokers (n = 46)	p**
Male gender	114 (66)	52 (54)	25 (71)	0.09	37 (80)	0.002
Age, years	35 [25-49]	30 [24-41]	51 [34-57]	< 0.001	40 [25-52]	0.2
Schooling, years[b¤]						
≤ 7	43 (25)	21 (22)	7 (23)	0.9	15 (32)	0.1
8-10	65 (38)	31 (33)	13 (43)	0.3	21 (46)	0.2
> 10	62 (36)	42 (45)	10 (33)	0.2	10 (22)	0.008
Diabetes mellitus	30 (17)	13 (46)	10 (32)	0.1	7 (15)	< 0.001
Alcohol abuse[c]	48 (29)	13 (13)	11 (35)	0.006	24 (52)	< 0.001
Cavitation on baseline CXR[c]	118 (69)	65 (67)	18 (58)	0.3	35 (76)	0.2

CXR: chest X-ray.¤ [a]Values expressed as n (%) or as median [interquartile range]. [b]Information not available for 4 patients. [c]Information not available for 7 patients. *Nonsmokers vs. former smokers. **Nonsmokers vs. current smokers.

Table 2. Predictors of culture positivity at 2 months (n = 137).

Predictor	Univariate analysis[a]	p	Multivariate analysis[a]	p
Male gender	1.06 (0.46-2.46)	0.884	0.96 (0.35-2.66)	0.941
Age	1.02 (0.99-1.05)	0.166	1.01 (0.97-1.04)	0.701
>10 years of schooling	1.69 (0.76-3.76)	0.200	2.32 (0.91-5.91)	0.077
Diabetes mellitus	2.59 (0.98-6.89)	0.056	2.33 (0.76-7.14)	0.140
Other comorbidities[b]	1.28(0.50-3.28)	0.607	1.39 (0.49-3.88)	0.535
Alcohol abuse	0.73 (0.29-1.80)	0.494	0.47 (0.16-1.34)	0.157
Cavitation	1.80(0.70-4.60)	0.220	1.79 (0.66-4.85)	0.253
Smoking	2.87 (1.25-6.59)	0.013	3.58 (1.30-9.86)	0.014

[a]Values expressed as relative risk (95% CI). [b]Cancer, immunosuppression, liver disease, and renal failure.

Table 3. Predictors of poor treatment outcome[a] (n = 164).

Predictor	Univariate analysis[b]	p	Multivariate analysis[b]	p
Male gender	1.14 (0.37-3.47)	0.821	0.97 (0.28-3.39)	0.967
Age	0.98 (0.95-1.02)	0.426	0.97 (0.92-1.01)	0.169
>10 years of schooling	0.8 (0.26-2.43)	0.691	1.04 (0.29-3.68)	0.957
Diabetes mellitus	0.7 (0.15-3.27)	0.646	0.84 (0.15-4.61)	0.841
Other comorbidities[c]	0.55 (0.12-2.54)	0.441	0.85 (0.16-4.41)	0.846
Alcohol abuse	1.16 (0.38-3.56)	0.795	0.68 (0.19-2.41)	0.546
Cavitation	0.42 (0.15-1.20)	0.105	0.37 (0.12-1.13)	0.081
Smoking	3.75 (1.15-12.22)	0.028	6.29 (1.57-25.21)	0.009

[a]Death, treatment failure, or default. [b]Values expressed as relative risk (95% CI). [c]Cancer, immunosuppression, liver disease, and renal failure.

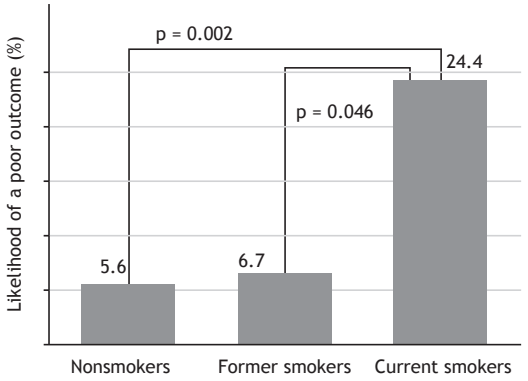

Figure 3. Smoking status and poor tuberculosis treatment outcomes.

with smoking. Like in other studies, multivariate analysis in our study demonstrated that smoking (rather than alcohol abuse) was the variable associated with a poor PTB treatment outcome.[21,31,32]

In our study sample, only smoking was independently associated with delayed 2-month *M. tuberculosis* culture conversion. , The association between smoking and delayed *M. tuberculosis* culture conversion among PTB patients was also observed in China and in Spain,[21,33] which suggests that smoking could be evaluated as a predictive variable in future studies, affecting culture conversion and PTB treatment failure. Thus, this may also be an important aspect for consideration in future publications on the treatment of tuberculosis, given that the rate of *M. tuberculosis* culture conversion is one of the most commonly used predictors of outcomes in clinical trials in PTB.[14] In addition, Maciel et al. demonstrated that smoking more than 20 cigarettes per day was independently associated with delayed 2-month culture conversion.[13] Similarly, we also observed a dose-response relationship between these two variables.

Some studies have demonstrated an association between smoking and a poor PTB treatment outcome.[8,21,31] The association between smoking and treatment default has already been described as being independent of alcohol or illicit drug use.[34] Thus, this association may be related to the psychosocial aspect of smoking, because smoking predominates in males and in disadvantaged populations, which are factors associated with poor treatment adherence. Chiang et al.[31] demonstrated that high tobacco consumption (> 20 cigarettes per day) was significantly associated with a lower likelihood of achieving a positive treatment outcome. The functional damage seen in human alveolar macrophages of smokers after *M. tuberculosis* infection could contribute to the delayed culture conversion and poor treatment outcomes observed.[35]

In our sample, current smoking was associated with culture positivity at 2 months and with a poor treatment outcome. Delayed culture conversion is relevant when we consider the tuberculosis transmission process and because it is a risk factor for recurrence.[14,36] Therefore, the results of the present study support the American Thoracic Society/Centers for Disease Control and Prevention/Infectious Disease Society of America suggestion that, among smokers, the presence of cavitation on baseline chest X-ray or culture positivity at 2 months could result in extended tuberculosis treatment.[19] In addition, current smokers in our sample were defined as subjects who were smoking at the time of diagnosis of PTB or who had quit smoking within 12 months prior to diagnosis. Therefore, they continued smoking despite their PTB-related symptoms, which could be interpreted as high tobacco dependence and greater difficulty in quitting smoking.

The present study has limitations. Smoking status was self-reported by the patient during the clinical interview and was not assessed by cotinine levels. Nevertheless, a recent study suggested that self-reporting is an accurate way of determining patient smoking status.[37] In addition, the classification of current smoking among new PTB cases could consider smoking at the time of onset of PTB symptoms, in order to prevent misclassification of current smokers as former smokers.[30] Thus, it is possible that we classified more patients as current smokers than as former smokers, given that we used a cutoff of 12 months of abstinence to define former smokers. Further limitations of the study were that glucose levels were not determined for all PTB patients because of operational difficulties and that the sample size was limited. However, the present study is unique in that it evaluates the impact of smoking in a sample of PTB patients with culture positivity for *M. tuberculosis* in the country with the highest number of tuberculosis cases in Latin America.

All patients were treated under direct supervision with a standard treatment regimen and using data collected in accordance with good clinical practices.

In conclusion, smoking was independently associated with delayed 2-month culture conversion and with a poor treatment outcome. These findings suggest that current smoking in PTB patients could be considered as an additional variable for extending PTB treatment to 9 months in Brazil. Prospective studies with larger sample sizes are needed to confirm our findings.

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REFERENCES

1. World Health Organization (WHO). Global tuberculosis report 2016. Geneva: WHO; 2016
2. World Health Organization (WHO). The End TB Strategy 2015. Geneva: WHO; 2015.
3. Dye C, Watt CJ, Bleed D. Low access to a highly effective therapy: a challenge for international tuberculosis control. Bull World Health Organ. 2002;80(6):437-44.
4. Harries AD, Zachariah R, Corbett EL, Lawn SD, Santos-Filho ET, Chimzizi R, et al. The HIV-associated tuberculosis epidemic–when will we act? Lancet. 2010;375(9729):1906-19. https://doi.org/10.1016/S0140-6736(10)60409-6
5. Baghaei P, Marjani M, Javanmard P, Tabarsi P, Masjedi MR. Diabetes mellitus and tuberculosis facts and controversies. J Diabetes Metab Disord. 2013;12(1):58. https://doi.org/10.1186/2251-6581-12-58
6. Lin HH, Ezzati M, Chang HY, Murray M. Association between tobacco smoking and active tuberculosis in Taiwan: prospective cohort study. Am J Respir Crit Care Med. 2009;180(5):475-80. https://doi.org/10.1164/rccm.200904-0549OC
7. Chiang CY, Slama K, Enarson DA. Associations between tobacco and tuberculosis. Int J Tuberc Lung Dis. 2007;11(3):258-62.
8. Bonacci RA, Cruz-Hervert LP, García-García L, Reynales-Shigematsu LM, Ferreyra-Reyes L, Bobadilla-del-Valle M, et al. Impact of cigarette smoking on rates and clinical prognosis of pulmonary tuberculosis in Southern Mexico. J Infect. 2013;66(4):303-12. https://doi.org/10.1016/j.jinf.2012.09.005
9. World Health Organization [homepage on the Internet]. Geneva: WHO [updated 2016 Jun; cited 2017 Feb 1]. Tobacco Fact sheet. Available from: http://www.who.int/mediacentre/factsheets/fs339/en/
10. Goldhaber-Fiebert JD, Jeon CY, Cohen T, Murray MB. Diabetes mellitus and tuberculosis in countries with high tuberculosis burdens: individual risks and social determinants. Int J Epidemiol. 2011;40(2):417-28. https://doi.org/10.1093/ije/dyq238
11. Instituto Brasileiro de Geografia e Estatística (IBGE) [homepage on the Internet]. Rio de Janeiro: IBGE [cited 2017 Feb 1]. Pesquisa Nacional de Saúde 2013. [Adobe Acrobat document, 181p.]. Available from: http://biblioteca.ibge.gov.br/visualizacao/livros/liv91110.pdf
12. Nijenbandring de Boer R, Oliveira e Souza Filho JB, Cobelens F, Ramalho Dde P, Campino Miranda PF, Logo Kd, et. al. Delayed culture conversion due to cigarette smoking in active pulmonary tuberculosis patients. Tuberculosis (Edinb). 2014;94(1):87-91. https://doi.org/10.1016/j.tube.2013.10.005
13. Maciel EL, Brioschi AP, Peres RL, Guidoni LM, Ribeiro FK, Hadad DJ, et al. Smoking and 2-month culture conversion during anti-tuberculosis treatment. Int J Tuberc Lung Dis. 2013;17(2):225-8. https://doi.org/10.5588/ijtld.12.0426
14. Mitchison DA. Assessment of new sterilizing drugs for treating pulmonary tuberculosis by culture at 2 months. Am Rev Respir Dis. 1993;147(4):1062-3. https://doi.org/10.1164/ajrccm/147.4.1062
15. Wallis RS, Doherty TM, Onyebujoh P, Vahedi M, Laang H, Olesen O, et al. Biomarkers for tuberculosis disease activity, cure, and relapse. Lancet Infect Dis. 2009;9(3):162-72. https://doi.org/10.1016/S1473-3099(09)70042-8
16. Diancon AH, Dawson R, von Groote-Bidlingmaier F, Symons G, Venter A, Donald PR, et al. Bactericidal activity of pyrazinamide and clofazimine alone and in combinations with pretomanid and bedaquiline. Am J Respir Crit Care Med. 2015;191(8):943-53. https://doi.org/10.1164/rccm.201410-1801OC
17. Merle CS, Fielding K, Sow OB, Gninafon M, Lo MB, Mthiyane T, et al. A four-month gatifloxacin-containing regimen for treating tuberculosis. N Engl J Med. 2014;371(17):1588-98. https://doi.org/10.1056/NEJMoa1315817
18. Rustomjee R, Lienhardt C, Kanyok T, Davies GR, Levin J, Mthiyane T, et al. A Phase II study of the sterilising activities of ofloxacin, gatifloxacin and moxifloxacin in pulmonary tuberculosis. Int J Tuberc Lung Dis. 2008;12(2):128-38.
19. Nahid P, Dorman SE, Alipanah N, Barry PM, Brozek JL, Cattamanchi A, et al. Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis. Clin Infect Dis. 2016;63(7):e147-e195. https://doi.org/10.1093/cid/ciw376
20. Yen YF, Yen MY, Lin YS, Lin YP, Shih HC, Li LH, et al. Smoking increases risk of recurrence after successful anti-tuberculosis treatment: a population-based study. Int J Tuberc Lung. 2014;18(4):492-8. https://doi.org/10.5588/ijtld.13.0694
21. Leung CC, Yew WW, Chan CK, Chang KC, Law WS, Lee SN, et al. Smoking adversely affects treatment response, outcome and relapse in tuberculosis. Eur Respir J. 2015;45(3):738-45. https://doi.org/10.1183/09031936.00114214
22. Brasil. Ministério da Saúde. Portal da Saúde [homepage on the Internet]. Brasília: o Ministério [cited 2017 Feb 1]. Manual de recomendações para o controle da tuberculose no Brasil 2011. [Adobe Acrobat document, 298p.]. Available from: : http://portalarquivos.saude.gov.br/images/pdf/2015/junho/30/MANUAL-DE-RECOMENDACOES-PARA-O-CONTROLE-DA-TUBERCULOSE-NO-BRASIL.pdf
23. Secretaria Estadual de Saúde do Estado do Rio de Janeiro [homepage on the Internet]. Rio de Janeiro: a Secretaria [cited 2017 Feb 1]. Principais indicadores da tuberculose no estado do Rio de Janeiro, 2013 [about 23 screens]. Available from: http://www.riocomsaude.rj.gov.br/Publico/MostrarArquivo.aspx?C=QXgbrHtoUtA%3D
24. Centers for Disease Control and Prevention (CDC). Cigarette smoking among adults–United States, 1992, and changes in the definition of current cigarette smoking. MMWR Morb Mortal Wkly Rep. 1994;43(19):342-6.
25. World Health Organization (WHO). Definitions and reporting framework for tuberculosis–2013 revision. Geneva: WHO; 2013.
26. World Health Organization (WHO). Global status report on noncommunicable diseases 2014. Geneva: WHO; 2014.
27. Khanna A, Lohya S, Sharath BN, Harries AD. Characteristics and treatment response in patients with tuberculosis and diabetes mellitus in New Delhi, India. Public Health Action. 2013;3(Suppl 1):S48-50. https://doi.org/10.5588/pha.13.0025
28. Hongguang C, Min L, Shiwen J, Fanghui G, Shaoping H, Tiejie G, et al. Impact of diabetes on clinical presentation and treatment outcome of pulmonary tuberculosis in Beijing. Epidemiol Infect. 2015;143(1):150-6. https://doi.org/10.1017/S095026881400079X
29. Augusto CJ, Carvalho Wda S, Gonçalves AD, Ceccato Md, Miranda SS. Characteristics of tuberculosis in the state of Minas Gerais, Brazil: 2002-2009. J Bras Pneumol. 2013;39(3):357-64. https://doi.org/10.1590/S1806-37132013000300013
30. Lam C, Martinson N, Hepp L, Ambrose B, Msandiwa R, Wong ML, et al. Prevalence of tobacco smoking in adults with tuberculosis in South Africa. Int J Tuberc Lung Dis. 2013;17(10):1354-7. https://doi.org/10.5588/ijtld.13.0016
31. Chiang YC, Lin YM, Lee JA, Lee CN, Chen HY. Tobacco consumption is a reversible risk factor associated with reduced successful treatment outcomes of anti-tuberculosis therapy. Int J Infect Dis. 2012;16(2):e130-5 https://doi.org/10.1016/j.ijid.2011.10.007
32. Gegia M, Magee MJ, Kempker RR, Kalandadze I, Chakhaia T, Gloub JE, et al. Tobacco smoking and tuberculosis treatment outcomes: a prospective cohort study in Georgia. Bull World Health Organ. 2015;93(6):390-9. https://doi.org/10.2471/BLT.14.147439
33. Gullón Blanco JA, Suárez Toste I, Lecuona Fernández M, Galindo

Morales R, Fernández Alvarez R, Rubinos Cuadrado G, et al. Tobacco smoking and sputum smear conversion in pulmonary tuberculosis [Article in Spanish]. Med Clin (Barc). 2007;128(15):565-8. https://doi.org/10.1157/13101612

34. Cherkaoui I, Sabouni R, Ghali I, Kizub D, Billioux AC, Bennani K, et al. Treatment default amongst patients with tuberculosis in urban Morocco: predicting and explaining default and post-default sputum smear and drug susceptibility results. PLoS One. 2014;9(4):e93574. https://doi.org/10.1371/journal.pone.0093574
35. O'Leary SM, Coleman MM, Chew WM, Morrow C, McLaughlin AM, Gleeson LE, et al. Cigarette smoking impairs human pulmonary immunity to Mycobacterium tuberculosis. Am J Respir Crit Care Med. 2014;190(12):1430-6. https://doi.org/10.1164/rccm.201407-1385OC
36. Godoy P, Caylà JA, Carmona G, Camps N, Álvarez J, Alsedà M, et al. Smoking in tuberculosis patients increases the risk of infection in their contacts. Int J Tuberc Lung Dis. 2013;17(6):771-6. https://doi.org/10.5588/ijtld.12.0696
37. Brunet L, Pai M, Davids V, Ling D, Paradis G, Lenders L, et al. High prevalence of smoking among patients with suspected tuberculosis in South Africa. Eur Respir J. 2011;38(1):139-46. https://doi.org/10.1183/09031936.00137710