Evaluation of the impact that the changes in tuberculosis treatment implemented in Brazil in 2009 have had on disease control in the country

Marcelo Fouad Rabahi1,2, José Laerte Rodrigues da Silva Júnior2,3, Marcus Barreto Conde4,5

ABSTRACT

Objective: To analyze the impact that the 2009 changes in tuberculosis treatment in Brazil had on the rates of cure, tuberculosis recurrence, mortality, treatment abandonment, and multidrug-resistant tuberculosis (MDR-TB).

Methods: An ordinary least squares regression model was used in order to perform an interrupted time series analysis of secondary data collected from the Brazilian Tuberculosis Case Registry Database for the period between January of 2003 and December of 2014.

Results: The 2009 changes in tuberculosis treatment in Brazil were found to have no association with reductions in the number of new cases (β = 2.17; 95% CI: −3.80 to 8.14; p = 0.47) and in the number of new cases (β = 0.40; 95% CI: −1.12 to 1.93; p = 0.60). The changes in tuberculosis treatment also showed a trend toward an association with increased cure rates (β = 4.14; 95% CI: −8.63 to 0.34; p = 0.07), as well as an association with increased mortality from pulmonary tuberculosis (β = 0.77; 95% CI: 0.16 to 1.38; p = 0.01). Although there was a significant increase in MDR-TB before and after the changes (p < 0.0001), there was no association between the intervention (i.e., the changes in tuberculosis treatment) and the increase in MDR-TB cases.

Conclusions: The changes in tuberculosis treatment were unable to contain the decrease in cure rates, the increase in treatment abandonment rates, and the increase in MDR-TB rates, being associated with increased mortality from pulmonary tuberculosis during the study period.

Keywords: Tuberculosis, pulmonary/epidemiology; Tuberculosis, pulmonary/drug therapy; Tuberculosis, pulmonary/mortality; Interrupted time series analysis; Drug resistance, multiple; Drug compounding.

INTRODUCTION

According to the World Health Organization, there were 10.4 million new cases of tuberculosis worldwide in 2015, with 1 million cases among children and 1.2 million cases among people living with HIV. In addition, there were 1.4 million deaths from tuberculosis, 400,000 of which were due to tuberculosis/HIV co-infection; therefore, tuberculosis remains one of the 10 leading causes of death worldwide. Brazil is among the 20 countries that together account for 84% of all incident cases of tuberculosis (in absolute numbers) and 87% of all incident cases of tuberculosis among people living with HIV worldwide.

Because of an increase in primary resistance to isoniazid (H) and rifampin (R), the Brazilian National Ministry of Health made a decision to change the basic treatment regimen for tuberculosis, which had been the same since the 1970s. Therefore, as of December of 2009, the basic regimen consisted of a fixed-dose, single-tablet combination of R, H, pyrazinamide (Z), and ethambutol (E) for two months, followed by a combination of R and H for four months (2RHZE/4RH regimen). In addition, the daily dose of H was reduced from 400 mg to 300 mg (for individuals weighing 50 kg or more), and that of Z was reduced from 2,000 mg to 1,500 mg (for individuals weighing 50 kg or more).

By adding E to the previous drug regimen (i.e., RHZ), the Brazilian National Ministry of Health expected to increase cure rates and prevent an increase in multidrug resistance (i.e., resistance to R and H). The Brazilian National Ministry of Health also expected that fixed-dose combination (FDC) tablets would increase patient comfort (by reducing the number of tablets to be taken), prevent patients from taking the drugs separately, and reduce treatment abandonment rates, thus increasing treatment adherence.

The objective of the present study was to analyze the impact that the 2009 changes in tuberculosis treatment in Brazil had on the rates of cure, treatment abandonment, mortality, and multidrug-resistant tuberculosis (MDR-TB).

METHODS

We used an ordinary least squares regression model in order to perform an interrupted time series analysis (ITSA) of
secondary data collected from the Sistema de Informação de Agravos de Notificação da Tuberculose (SINAN-TB, Brazilian Tuberculosis Case Registry Database). We collected monthly data for the period between January of 2003 and December of 2014. We used the Stata statistical software package, version 13.1 (StataCorp LP, College Station, TX, USA). ITSA was performed as described by Linden. In brief, regression coefficients were estimated by the ordinary least squares method, producing Newey-West standard errors. Subsequently, the Cumby-Huizinga test was applied to the error distribution in order to test for residual autocorrelation, which was adjusted for by Prais-Winsten regression, when necessary. Seasonality was accounted for by the use of dummy variables in order to define each month of the year, dummy variables being used as adjustment factors in the analysis. Given that an ITSA of a single group does not have a comparable control group, the pre-intervention trend projected for the post-intervention period serves as a counterfactual. Trend analysis was used in order to determine whether there was a statistically significant difference between the pre- and post-intervention slopes outside the intervention period. The following formula was used:

\[ Y_t = \beta_0 + \beta_1 T_t + \beta_2 T_t + \beta_3 X_t X_t + \epsilon_t \]

where \( Y_t \) is an aggregate outcome variable, measured at \( t \) equally spaced time points; \( T_t \) is time elapsed since the beginning of the study; \( X_t \) (indicator) represents the intervention; \( X_t T_t \) is an interaction term; and \( \epsilon_t \) is the random error. In the present study, which involved only one group, \( \beta_0 \) represents the intercept of the line on the vertical axis (initial level of the outcome variable); \( \beta_1 \) is the slope or trajectory of the outcome variable before the intervention; \( \beta_2 \) represents the change in the level of outcome immediately after the introduction of the intervention; and \( \beta_3 \) represents the difference between the pre- and post-intervention slopes. Therefore, significant values of \( \beta_2 \) indicate an immediate intervention effect, and significant values of \( \beta_3 \) indicate an intervention effect over time.

Interrupted time series plots show (monthly) study variable data (dots) and data regression (straight line). Figure 1 shows pre-, mid-, and post-intervention data (from January of 2003 to November of 2009, from December of 2009 to December of 2010, and from January of 2011 to December of 2014, respectively), the intervention being tuberculosis treatment changes. We used an intervention time frame (from December of 2009 to December of 2010) rather than an intervention time point because that was the estimated time required to implement the new treatment in all health care facilities in Brazil. In addition, tuberculosis treatment lasts at least six months (being as long as nine months in some cases), and patients whose treatment was started in the month prior to the change would continue to receive the old treatment for at least another five months. If the slope (gradient) of the trend line is the same before and after the intervention (i.e., tuberculosis treatment changes), it means that the trend in the data for the study variable remains the same despite the intervention. A decrease in the slope of the line after the intervention suggests a downward trend in the data, whereas an increase in the slope of the line after the intervention suggests an upward trend in the data. However, statistical analysis is the only means of determining whether (potential) changes in the data and an upward or downward shift in the regression line after the intervention are significant, i.e., whether they are related to or independent of the intervention. The results of our statistical analysis were expressed as \( \beta \) regression coefficients. The confidence interval was 95%, and the significance level was 5%.

Only data on pulmonary tuberculosis were included, given that most of the tuberculosis cases that are diagnosed by sputum smear microscopy, Mycobacterium tuberculosis culture, or a combination of the two are pulmonary tuberculosis cases rather than extrapulmonary tuberculosis cases, which are commonly diagnosed on the basis of patient response to empirical treatment. Given that the new treatment was used only in individuals who were 10 years of age or older, those who were younger than 10 years of age were not included in the analyses. We collected data on the following variables: total number of cases of pulmonary tuberculosis; number of new cases of pulmonary tuberculosis; number of cases of tuberculosis recurrence; number of cases of treatment abandonment after treatment abandonment; treatment outcomes (cure, treatment abandonment, mortality from tuberculosis, and mortality from other causes); number of cases of MDR-TB; number of HIV tests performed; number of cultures for M. tuberculosis; number of positive HIV test results; and number of positive cultures for M. tuberculosis. The SINAN-TB defines cure as the sum of the cases of patients who were discharged and patients who completed the six months of treatment. Up until 2010 (when tuberculosis treatment was changed), tuberculosis recurrence was defined as development of a new tuberculosis case within twelve months after cure. In 2011, the Programa Nacional de Controle da Tuberculose (PNCT, Brazilian National Tuberculosis Control Program) definition of tuberculosis recurrence was changed to “a case of active tuberculosis in a previously treated and cured patient, regardless of the time elapsed since the previous treatment”.

Therefore, in 2011, the SINAN-TB and PNCT definitions of tuberculosis recurrence came to be the same (personal communication). Although the previous definition was operational and included cases of exogenous reinfection, it was aimed at identifying cases of true recurrence, caused by the same bacterial strain that caused the first episode of tuberculosis, as a result of incomplete sterilization of the infecting bacilli. As a result of the new definition, the recurrence cases reported after 2010/2011 differed from those reported before that. This introduced a confounding factor that precludes the evaluation of the impact of the intervention on that variable. The rates of cure and treatment abandonment were calculated in relation to the total number of cases of pulmonary tuberculosis in Brazil in 2009 that had had on disease control in the country.
After exclusion of cases in which the outcome was unknown. Given that this was an ecological study, no research ethics committee approval was required.

RESULTS

Table 1 shows SINAN-TB data on pulmonary tuberculosis in individuals 10 years of age or older for the 2003-2014 period. Figure 1 shows graphical representations of cure, treatment abandonment, MDR-TB, and mortality rates in the study period. Beginning in 2003, there was a continuous decrease in cure rates and a steady increase in treatment abandonment, mortality, and MDR-TB rates (Figure 1).

Figure 2 shows interrupted time series plots demonstrating the impact of the intervention (tuberculosis treatment changes) on tuberculosis-related variables. As can be seen in Figure 2A, there was a statistically significant decrease in the total number of reported cases of tuberculosis before the intervention (p < 0.0001); however, after the intervention, that decrease was no longer significant (p = 0.09). There was a significant decrease in the number of reported new cases of pulmonary tuberculosis before the intervention (p < 0.0001), and that decrease remained significant after the intervention (p = 0.01). However, our ITSA showed that the reductions in the total number of reported cases of tuberculosis (β = 2.17; 95% CI: −3.80 to 8.14; p = 0.47) and in the number of reported new cases of tuberculosis (β = −0.97; 95% CI: −5.89 to 3.94; p = 0.70) occurred independently of the intervention.

Figure 2C shows that there were significant decreases in cure rates before and after the intervention (p < 0.0001 for both). Although our statistical analysis showed that those decreases occurred independently of the intervention (β = −4.14; 95% CI: −8.63 to 0.34; p = 0.07), the fact that the value of p was = 0.07 shows a trend toward an association between tuberculosis treatment changes and decreased cure rates. Figure 2D shows that treatment abandonment rates were high throughout the study period regardless of the intervention (β = 0.40; 95% CI: −1.12 to 1.93; p = 0.60). It is of note that there was a significant decrease in treatment abandonment rates during the period in which the intervention was implemented (β = −7.28; 95% CI: −11.6 to 2.93; p = 0.001). As can be seen in Figure 2E, there was no statistical association between tuberculosis treatment changes and MDR-TB cases (β = 0.13; 95% CI: −0.03 to 0.29; p = 0.12). However, there were significant increases in the numbers of MDR-TB cases before and after tuberculosis treatment changes (p < 0.0001 for both).

As can be seen in Table 1, the reported number of deaths from tuberculosis was found to have increased from 85 in 2003 to 2,482 in 2007, a finding that suggests that there was an SINAN-TB criterion change or reporting problem. Therefore, we analyzed the total number of deaths (i.e., the sum of deaths from pulmonary tuberculosis and other causes) in the study period (from 2003 to 2014) and performed a separate analysis of deaths from pulmonary tuberculosis and other causes from 2007 to 2014 (rather than from 2003 to 2014).

As can be seen in Figure 2F, the slope of the trend line after the intervention suggests a nonsignificant reduction in the total number of deaths, which might have been due to a significant reduction in the number of deaths from other causes (Figure 2G) between the pre- and post-intervention periods (β = −0.86; 95% CI: −1.50 to −0.21; p = 0.01). In contrast, with regard to mortality from pulmonary tuberculosis (Figure 2H), the slope of the trend line after the intervention (β = 0.39; 95% CI: 0.03 to 0.75; p = 0.04) and statistical analysis comparing the pre- and post-intervention periods (β = 0.77; 95% CI: 0.16 to 1.38; p = 0.01) showed an association between the intervention and increased mortality from pulmonary tuberculosis.

DISCUSSION

For the 2003-2014 period in Brazil, SINAN-TB data show a decrease in the total number of reported cases of pulmonary tuberculosis, a decrease in the number of reported new cases of pulmonary tuberculosis, and a continuous decrease in cure rates, as well as a steady increase in the rates of recurrence, MDR-TB, and mortality, together with high rates of treatment abandonment. Our ITSA revealed that, in addition to being associated with an increase in the number of deaths from pulmonary tuberculosis, the intervention (the changes in tuberculosis treatment) showed a trend toward an association with a further decline in cure rates, having had no impact on the increase in the number of cases of MDR-TB or on the high rates of treatment abandonment (i.e., having been statistically independent of both). In addition, the possibility of underreporting cannot be ruled out.

The tuberculosis incidence rate has decreased since the 1980s, having decreased from 70.4/100,000 population in 1982 to 43.0/100,000 population in 2010. This might be due to the Emergency Plan for Tuberculosis Control in 1996-1997, the PNCT in 1998 (which extended coverage, implemented supervised treatment, and created a new way of transferring resources to municipalities), and the provision of antiretroviral therapy to patients with tuberculosis/HIV coinfection, among many other measures.

However, the rates of cure, drug resistance, and treatment abandonment have remained below the goal since the 1980s. Therefore, it is possible that other variables are involved in the decrease in the number of reported cases of pulmonary tuberculosis in Brazil. The tuberculosis incidence rate has been shown to be inversely associated with variables such as per capita income and gross domestic product. Therefore, it is possible that economic stability and the increase in gross domestic product in Brazil in the last 25 years have contributed to reducing the number of tuberculosis cases. In this context, the current rates of cure and treatment abandonment (which are far from those recommended by the World Health Organization), together with the current economic...
Table 1. Annual data on pulmonary tuberculosis in Brazil for the period between January of 2003 and December of 2014.

<table>
<thead>
<tr>
<th>Year</th>
<th>Type of entry in the database</th>
<th>Total number of cases of pulmonary TB</th>
<th>New cases of pulmonary TB</th>
<th>Recurrence within &lt; 1 year after discharge</th>
<th>Treatment abandonment</th>
<th>Transfer</th>
<th>Unknown</th>
<th>Pulmonary TB outcome</th>
<th>MDR-TB</th>
<th>Total number of Mtb cultures</th>
<th>Positive Mtb cultures</th>
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TB: tuberculosis; MDR-TB: multidrug-resistant tuberculosis; and Mtb: Mycobacterium tuberculosis. Values expressed as n or n (%). The rates of cure, treatment abandonment, and mortality were calculated in relation to the total number of pulmonary TB cases in which the outcome was known.
Rabahi MF, Silva Júnior JLR, Conde MB

The 2011 change in the definition of tuberculosis recurrence by the PNCT, whereby any patient who had had tuberculosis was considered to have recurrent tuberculosis regardless of the time elapsed between the first and second episodes, was expected to reduce the number of new cases and increase the total number of reported cases. This might explain why the decrease in the number of reported new cases remained significant after 2010 (p = 0.01), whereas the decrease in the total number of reported cases did not (p = 0.09).

By adding a fourth drug (E) to the RHZ regimen, the Brazilian National Ministry of Health expected to increase the cure rate. According to the literature, treatment failure is unlikely to occur in patients with resistance to H treated with the RHZ regimen. Therefore, the addition of E to the drug regimen was unlikely to result in a significant increase in the cure rate. However, the continuous decrease in cure rates since 2003 was not attenuated by the 2009/2010 tuberculosis treatment changes. In addition, our ITSA revealed a trend toward an association between the intervention and a further decline in cure rates. The low rate of cure of pulmonary tuberculosis patients can be attributed to a variety of reasons. One reason is treatment failure. There have been reports of bioavailability and absorption problems affecting FDC formulations of R, particularly in people living with HIV and having a low CD4 count. In a systematic review and meta-analysis published in 2013 and comparing FDC formulations and separate drug formulations for the treatment of tuberculosis, the risk of treatment failure or recurrence was found to be higher in the group of patients receiving treatment with FDC formulations (relative risk = 1.28; 95% CI: 0.99-1.70). In Brazil, tuberculosis treatment changes included a change in formulation (from a separate drug formulation to a FDC formulation) and a reduction in the doses of H and Z.

In another systematic review, published in 2016, FDC formulations were compared with separate drug formulations and no differences were found between the two regarding treatment failure rates; however, there was a trend toward higher recurrence in the group of patients receiving treatment with FDC formulations (relative risk = 1.28; 95% CI: 1.00-1.64). Given that the change in the definition of tuberculosis recurrence and the intervention occurred in the same period, the impact of the intervention on recurrence rates was not evaluated in the present study. Therefore, it is impossible to determine whether the increase in the number of cases of recurrence is due to the changes in tuberculosis treatment or to the inclusion of a larger number of cases of exogenous reinfection. True tuberculosis recurrence is due to incomplete sterilization of the infecting bacilli, which
Evaluation of the impact that the changes in tuberculosis treatment implemented in Brazil in 2009 have had on disease control in the country.

Figure 2. Interrupted time series regressions for the following variables: total number of cases of pulmonary tuberculosis (in A); new cases (in B); cases of cure (in C); cases of treatment abandonment (in D); cases of multidrug-resistant tuberculosis (MDR-TB, in E); total number of deaths (in F); deaths from other causes (in G); and deaths from pulmonary tuberculosis (TB, in H). The dots represent the data collected for each variable each month from January of 2003 to December of 2014, and the straight line represents the data trend. The middle column corresponds to the period in which the intervention was implemented (between December of 2009 and December of 2010). *Statistically significant.
should be killed by R and Z.\(^{(20,24)}\) In order to avoid (true) recurrence, the bioavailability and bioequivalence of FDC tablets should be studied before their use.

Reduced cure rates can also be explained by increased treatment noncompliance. The fact that the treatment abandonment rate remained high regardless of the intervention suggests that the decrease in cure rates was independent of that variable. In addition, it shows that, contrary to what the Brazilian National Ministry of Health intended to achieve, the change to FDC tablets did not result in reduced treatment abandonment rates. This finding is similar to that of a systematic review and meta-analysis performed in 2013, which showed that FDC tablets did not result in increased treatment adherence in any of the five clinical trials in which that variable was analyzed.\(^{(22)}\)

There was a significant increase in the number of MDR-TB cases during the study period. The increase in the number of cultures for \(M.\) \(tuberculosis\) (from 19\% in 2003 to 32\% in 2014) is not sufficient to explain the increase in the number of diagnosed cases of MDR-TB (from 0.2\% to 1.1\%) over the same period. The post-intervention outcome was independent of the intervention; that is, the changes in tuberculosis treatment in Brazil had no impact on MDR-TB rates, which increased significantly before and after the intervention. From a programmatic standpoint, resistance results from \(M.\) \(tuberculosis\) exposure to one drug only or to lower-than-required doses.\(^{(17)}\) Treatment adherence problems (treatment abandonment, incorrect/irregular drug use, or both), as well as inadequate dosing, absorption, or both, are associated with increased acquired resistance.\(^{(17,25)}\) In the study population, incorrect drug use is unlikely because patients received treatment with an FDC formulation, which has been shown to have no association with reduced treatment abandonment rates.\(^{(22)}\) Therefore, the high number of cases of treatment abandonment in the study period might be one of the variables involved in the increased number of cases of MDR-TB in Brazil. However, why was the tuberculosis treatment change in Brazil unable to contain the increase in MDR-TB in the country? The addition of E to the RHZ regimen reduced the risk of further resistance in patients with initial resistance to H alone, in those with simultaneous resistance to H and Z, and in those with resistance to R alone (which is rare) but has no protective effect in cases of simultaneous resistance to H and R (i.e., MDR-TB).\(^{(20)}\) In addition, a bioavailability study conducted in 2013 demonstrated a lack of bioequivalence between FDC and separate drug formulations of H.\(^{(46)}\) These data, together with the aforementioned bioavailability problems affecting FDC formulations of R and the aforementioned reduction in the doses of H and Z, underscore the importance of conducting bioequivalence and bioavailability studies of FDC formulations of tuberculosis therapy.\(^{(19-21)}\) The increase in resistance appears to be associated with malfunctioning tuberculosis control programs.\(^{(25)}\) In this sense, the increase in MDR-TB cases suggests an increase in single-drug resistance and primary multidrug resistance, as demonstrated by studies conducted in different regions of the country.\(^{(27-29)}\)

These findings suggest that there is an urgent need to make \(M.\) \(tuberculosis\) culture and drug susceptibility testing available to all tuberculosis patients in Brazil. The increase in MDR-TB cases might also be due to an increase in the number of TB/HIV coinfection cases. However, despite a significant increase in the proportion of tuberculosis patients tested for HIV (from 43\% in 2003 to 77\% in 2014), the proportion of cases of coinfection decreased (from 14\% in 2003 to 12\% in 2014). Despite being below the goal of 100\%, the proportion of tuberculosis patients tested for HIV increased significantly (to 77\%) in the study period.

The increase in the number of deaths from pulmonary tuberculosis from 2007 onward is a very relevant finding because pulmonary tuberculosis is a treatable disease and antibacteriosis drugs are provided free of charge by the public health care system in Brazil. Although our ITSA showed an association between tuberculosis treatment changes and increased mortality from tuberculosis (as evidenced by the slope of the trend line and the regression coefficient), other variables might also be involved. Nevertheless, this is worrisome in the context of economic crisis, decreased cure rates, increased treatment noncompliance, and increased MDR-TB cases.

The present study has several limitations. This was a study of secondary data, and they might be inaccurate. Molecular testing is not routinely performed under tuberculosis control programs to confirm whether a case of “tuberculosis recurrence” is indeed a case of infection with the same mycobacterial strain that caused the first episode of tuberculosis or whether it is actually a case of re-infection. Although the previous definition of recurrence (i.e., development of a new tuberculosis case within twelve months after cure) was widely accepted, it is no longer used. The analyzed data were not stratified by state or municipality. Therefore, our findings might not be representative of all Brazilian states and municipalities. Although all methodological designs can lead to erroneous conclusions, ITSA appears to be the least likely to in studies evaluating public health interventions.\(^{(6)}\)

In summary, during the study period, there were decreases in the number of reported new cases of pulmonary tuberculosis, the total number of cases, and cure rates, as well as increases in MDR-TB and mortality from pulmonary tuberculosis, together with a high rate of treatment abandonment. Our ITSA showed that the changes in tuberculosis treatment in Brazil did not result in reduced treatment abandonment or MDR-TB rates; they were associated with increased mortality from pulmonary tuberculosis and showed a trend toward a further decline in cure rates.

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