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 Rabahi[1,2], José Laerte Rodrigues da Silva Júnior[2,3], Marcus Barreto Conde[4,5]

1. Faculdade de Medicina, Universidade Federal de Goiás, Goiânia (GO) Brasil.
2. Centro Universitário de Anápolis, Anápolis (GO) Brasil.
3. Universidade de Rio Verde, Aparecida de Goiânia (GO) Brasil.
4. Faculdade de Medicina de Petrópolis, Petrópolis (RJ) Brasil.
5. Faculdade de Medicina, Universidade Federal do Rio de Janeiro, Rio de Janeiro (RJ) Brasil.

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 total number of cases ($\beta = 2.17$; 95% CI: -3.80 to 8.14; $p = 0.47$) and in the number of new cases ($\beta = -0.97$; 95% CI: -5.89 to 3.94; $p = 0.70$), as well as having no association with treatment abandonment rates ($\beta = 0.40$; 95% CI: -1.12 to 1.93; $p = 0.60$). The changes in tuberculosis treatment also showed a trend toward an association with decreased cure rates ($\beta = -4.14$; 95% CI: -8.63 to 0.34; $p = 0.07$), as well as an association with increased mortality from pulmonary tuberculosis ($\beta = 0.77$; 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.[1] In addition, there were 1.4 million deaths from tuberculosis, 400,000 of which were due to tuberculosis/HIV coinfection; therefore, tuberculosis remains one of the 10 leading causes of death worldwide.[1] 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.[1]

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.[2-5] 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).[3,5] 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).[2-4]

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).[3,4] 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.[3]

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

Correspondence to:
Marcelo Rabahi. Avenida B, 483, CEP 74605-220, Goiânia, GO, Brasil.
Tel.: 55 62 99975-3381. Fax: 55 62 3521-3333. E-mail: mfrabahi@gmail.com
Financial support: None.

secondary data collected from the *Sistema de Informação de Agravos de Notificação da Tuberculose* (SINAN-TB, Brazilian Tuberculosis Case Registry Database).[6-8] 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.[9] 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:

$$Yt = \beta0 + \beta1Tt + \beta2Tt + \beta3XtTt + \in t$$

where Yt is an aggregate outcome variable, measured at t equally spaced time points; Tt is time elapsed since the beginning of the study; Xt (indicator) represents the intervention; XtTt is an interaction term; and $\in t$ is the random error. In the present study, which involved only one group, $\beta0$ represents the intercept of the line on the vertical axis (initial level of the outcome variable); $\beta1$ is the slope or trajectory of the outcome variable before the intervention; $\beta2$ represents the change in the level of outcome immediately after the introduction of the intervention; and $\beta3$ represents the difference between the pre- and post-intervention slopes. Therefore, significant values of p at $\beta2$ indicate an immediate intervention effect, and significant values of p at $\beta3$ 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 β 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 retreatment 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".[4] 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

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 ($\beta = 2.17$; 95% CI: -3.80 to 8.14; $p = 0.47$) and in the number of reported new cases of tuberculosis ($\beta = -0.97$; 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 ($\beta = -4.14$; 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 ($\beta = 0.40$; 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 ($\beta = -7.28$; 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 ($\beta = 0.13$; 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 ($\beta = -0.86$; 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 ($\beta = 0.39$; 95% CI: 0.03 to 0.75; $p = 0.04$) and statistical analysis comparing the pre- and post-intervention periods ($\beta = 0.77$; 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.[10-12] 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.[10-12] However, the rates of cure, drug resistance, and treatment abandonment have remained below the goal since the 1980s.[3,10-12] 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.[13-16] 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

JBP

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

Table 1. Annual data on pulmonary tuberculosis in Brazil for the period between January of 2003 and December of 2014.[a]

Year	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Type of entry in the database												
Total number of cases of pulmonary TB	75,890	75,201	74,456	72,078	68,891	71,369	71,486	70,524	72,400	68,763	70,626	70,217
New cases of pulmonary TB	62,497	61,980	61,507	59,050	57,045	59,047	58,924	57,567	58,943	55,962	56,980	56,152
Recurrence within < 1 year after discharge	5,186	4,967	4,716	4,995	4,468	4,528	4,512	4,787	5,365	5,250	5,353	4,995
Retreatment after treatment abandonment	4,591	4,568	4,325	4,250	3,940	4,412	4,626	4,919	4,989	5,235	6,347	7,032
Transfer	2,823	3,247	3,512	3,514	3,237	3,215	3,226	2,982	2,904	1,894	1,585	1,659
Unknown	794	439	396	269	201	167	198	269	199	214	232	191
Pulmonary TB outcome												
Cure[b]	51,891 (79.5)	51,486 (79.8)	52,529 (80.0)	50,474 (79.5)	48,069 (78.6)	49,710 (78.6)	49,376 (77.3)	48,965 (77.1)	51,195 (77.7)	48,537 (76.7)	49,324 (76.1)	47,319 (75.7)
Treatment abandonment[b]	8,649 (13.2)	8,438 (13.1)	8,018 (12.3)	7,953 (12.5)	7,939 (13.0)	8,559 (13.5)	9,200 (14.4)	9,037 (14.2)	9,114 (13.8)	9,223 (14.6)	9,856 (15.2)	9,422 (15.1)
Total number of deaths[b]	4,650 (7.1)	4,458 (6.9)	4,689 (7.2)	4,898 (7.7)	4,916 (8.1)	4,763 (7.6)	4,981 (7.8)	5,020 (7.9)	5,073 (7.7)	4,875 (7.7)	5,065 (7.8)	5,083 (8.1)
Death from TB[b]	85 (0.1)	104 (0.2)	262 (0.4)	1,287 (2.0)	2,482 (4.1)	2,382 (3.8)	2,389 (3.7)	2,480 (3.9)	2,317 (3.5)	2,425 (3.8)	2,547 (3.9)	2,525 (4.0)
Death from other causes[b]	4,565 (7.0)	4,354 (6.7)	4,427 (6.8)	3,611 (5.7)	2,434 (4.0)	2,381 (3.8)	2,592 (4.1)	2,540 (4.0)	2,756 (4.2)	2,450 (3.9)	2,518 (3.9)	2,558 (4.1)
Transfer	6,216	5,869	5,864	5,115	4,795	5,103	5,395	5,088	5,142	3,717	3,886	4,270
MDR-TB	122 (0.2)	157 (0.2)	175 (0.3)	195 (0.3)	257 (0.4)	242 (0.4)	350 (0.5)	469 (0.7)	496 (0.8)	633 (1.0)	611 (0.9)	680 (1.1)
Total number of Mtb cultures	14,077 (19)	15,131 (20)	16,061 (22)	15,415 (21)	15,316 (22)	15,995 (22)	9,223 (24)	19,940 (28)	21,682 (30)	21,820 (32)	23,221 (33)	22,334 (32)
Positive Mtb cultures	5,514 (39)	5,812 (38)	6,662 (41)	7,289 (47)	7,531 (49)	8,220 (51)	17,348 (53)	10,561 (53)	11,403 (53)	11,824 (54)	12,917 (56)	13,712 (61)
Total number of HIV tests	32,813 (43)	35,196 (47)	37,513 (50)	38,455 (53)	39,608 (57)	43,298 (61)	45,742 (64)	47,962 (68)	50,983 (70)	50,418 (73)	54,251 (77)	54,257 (77)
TB/HIV coinfection	4,697 (14)	4,565 (13)	4,681 (12)	4,842 (13)	5,243 (13)	5,557 (13)	5,668 (12)	6,167 (13)	6,441 (13)	6,368 (13)	6,564 (12)	6,775 (12)

TB: tuberculosis; MDR-TB: multidrug-resistant tuberculosis; and Mtb: *Mycobacterium tuberculosis*. [a]Values expressed as n or n (%). [b]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.
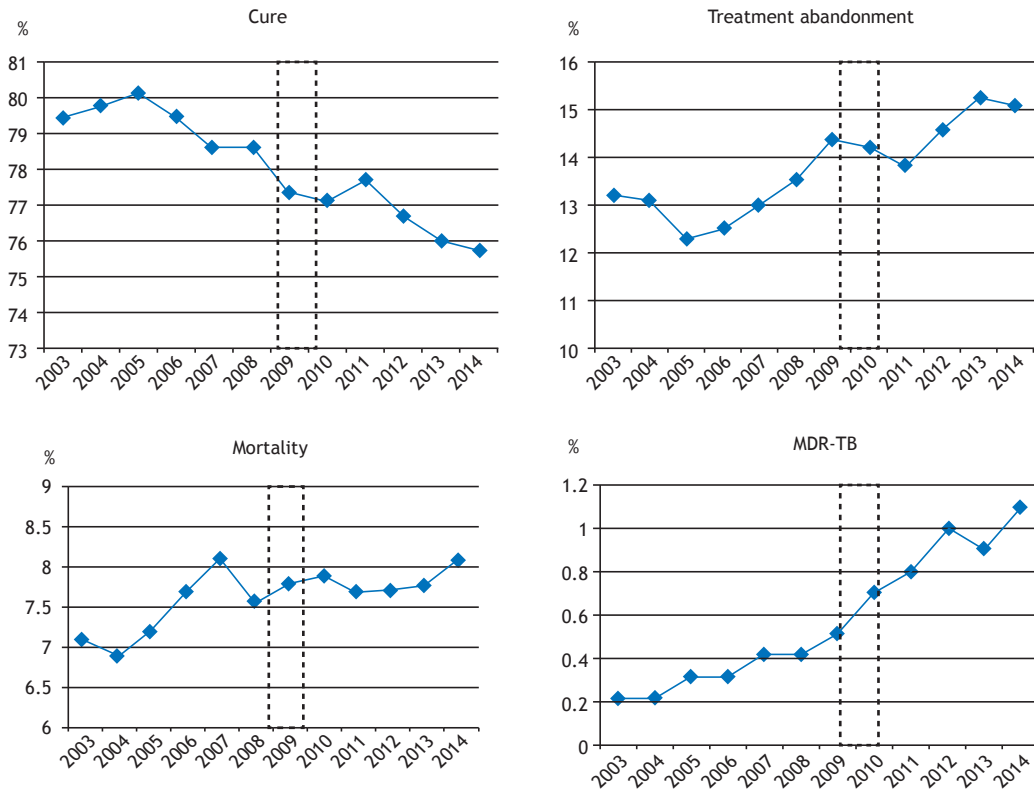
Figure 1. Graphical representations of cure, treatmet abandonment, mortality, and multidrug-resistant tuberculosis (MDR-TB) rates in the 2003-2014 period. The vertical axis (ordinate) represents the proportions relative to the total number of cases of pulmonary tuberculosis during the study period. The horizontal axis (abscissa) represents the variable "years". The dashed rectangle represents the transition from the old to the new tuberculosis treatment in Brazil.

crisis in the country, might affect the decrease in the incidence rate of tuberculosis (or even increase it) in the coming years.[1] 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.[3] According to the literature, treatment failure is unlikely to occur in patients with resistance to H treated with the RHZ regimen.[17,18] 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.[19-21] 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).[22] 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.[3] 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).[23] 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
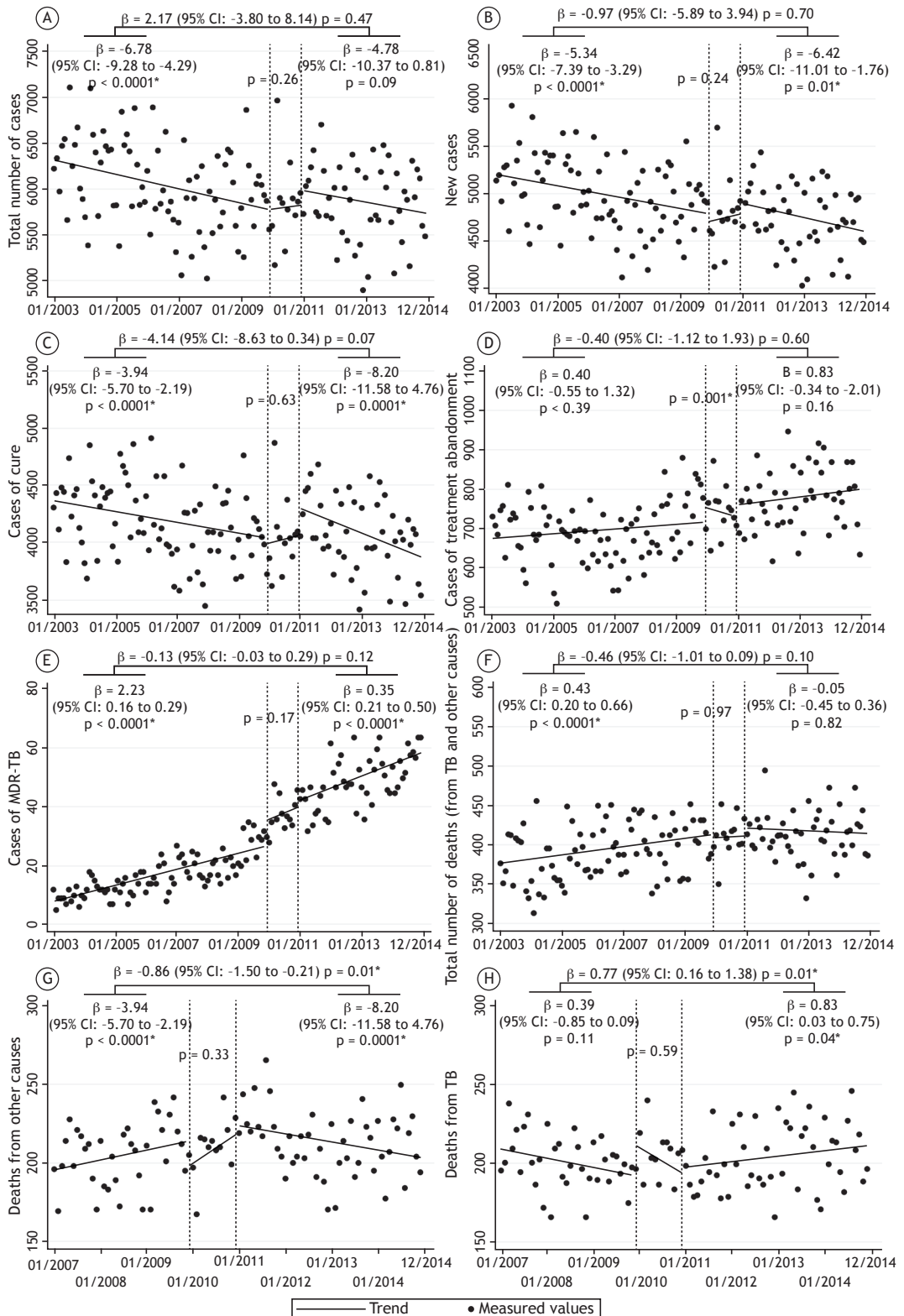
Figure 2. Interrupted time series regressions for the following variables: total number of cases of pulmonary tuberculosis (in A); new cases (in B); cases of cure (in C); cases of treatment abandonment (in D); cases of multidrug-resistant tuberculosis (MDR-TB, in E); total number of deaths (in F); deaths 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.[26] 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 antituberculosis 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 reinfection. 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.

ACKNOWLEDGMENTS

REFERENCES

1. World Health Organization [homepage on the Internet]. Geneva: WHO; c2016 [cited 2016 Oct 18]. Global Tuberculosis Report 2016 [about 2 screens]. Available from: http://www.who.int/tb/publications/global_report/en/

2. Conde MB, Melo FA, Marques AM, Cardoso NC, Pinheiro VG, Dalcin Pde T, et al. III Brazilian Thoracic Association Guidelines on tuberculosis. J Bras Pneumol. 2009;35(10):1018-48. https://doi.org/10.1590/S1806-37132009001000011

3. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Vigilância Epidemiológica. Programa Nacional de Controle da Tuberculose [monograph on the Internet]. Brasília: Ministério da Saúde [cited 2016 Oct 18]. Nota técnica sobre as mudanças no tratamento da tuberculose no Brasil para adultos e adolescentes – Versão 2 [Adobe Acrobat document, 5p.]. Available from: http://www1.saude.rs.gov.br/dados/1293729099101Nota%20T%E9cnica%20-%202%AA%20vers%E3o%20%28corrigida%20em%2022-10%29.pdf

4. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Vigilância Epidemiológica. Manual de recomendações para o controle da tuberculose no Brasil. Brasília: Ministério da Saúde; 2011. 284 p.

5. Santos LA, Galesi VM. Mudança no esquema de tratamento da tuberculose. Bepa. 2010;7(73):28-32.

6. Soumerai SB, Starr D, Majumdar SR. How Do You Know Which Health Care Effectiveness Research You Can Trust? A Guide to Study Design for the Perplexed. Prev Chronic Dis. 2015;12:E101. https://doi.org/10.5888/pcd12.150187

7. Wagner AK, Soumerai SB, Zhang F, Ross-Degnan D. Segmented regression analysis of interrupted time series studies in medication use research. J Clin Pharm Ther. 2002;27(4):299-309. https://doi.org/10.1046/j.1365-2710.2002.00430.x

8. Brasil. Ministério da Saúde. Portal da Saúde. Sistema de Informações de Agravos de Notificações [homepage on the Internet]. Brasília: Ministério da Saúde [cited 2016 Oct 18]. Informações de Saúde (TABNET) – Epidemiológicas e Mortalidade [about 2 screens]. Available from: http://www2.datasus.gov.br/DATASUS/index.php?area=0203&id=31009407&VObj=http://tabnet.datasus.gov.br/cgi/tabcgi.exe?sinannet/cnv/tuberc

9. Linden A. Conducting interrupted time series analysis for single-and multiple-group comparisons. Stata J. 2015;15(2):480-500.

10. Ruffino-Netto A. Tuberculosis in Brazil: general information and new perspectives [Article in Portuguese]. Inf Epidemiol Sus. 2001;10(3):129-38. http://dx.doi.org/10.5123/S0104-16732001000300004

11. Hijar MA, Oliveira MJ, Teixeira GM. A tuberculose no Brasil e no mundo. Bol Pneumol Sanit. 2001;9(2):9-16.

12. Brasil. Ministério da Saúde. Coordenação de Pneumologia Sanitária. Manual de normas para o controle da tuberculose. Brasília: Ministério da Saúde; 1995.

13. Ploubidis GB, Palmer MJ, Blackmore C, Lim TA, Manissero D, Sandgren A, et al. Social determinants of tuberculosis in Europe: a prospective ecological study. Eur Respir J. 2012;40(4):925-30. https://doi.org/10.1183/09031936.00184011

14. Myers WP, Westenhouse JL, Flood J, Riley LW. An ecological study of tuberculosis transmission in California. Am J Public Health. 2006;96(4):685-90. https://doi.org/10.2105/AJPH.2004.048132

15. Janssens JP, Rieder HL. An ecologic analysis of incidence of tuberculosis and per capita gross domestic product. Eur Respir J. 2008;32(5):1415-6. https://doi.org/10.1183/09031936.00078708

16. Guimarães RM, Lobo Ade P, Siqueira EA, Borges TF, Melo SC. Tuberculosis, HIV, and poverty: temporal trends in Brazil, the Americas, and worldwide. J Bras Pneumol. 2012;38(4):511-7. https://doi.org/10.1590/S1806-37132012000400014

17. Mitchison DA. How drug resistance emerges as a result of poor compliance during short course chemotherapy for tuberculosis. Int J Tuberc Lung Dis. 1998;2(1):10-5.

18. Jindani A, Nunn AJ, Enarson DA. Two 8-month regimens of chemotherapy for treatment of newly diagnosed pulmonary tuberculosis: international multicentre randomised trial. Lancet. 2004,364(9441):1244-51. https://doi.org/10.1016/S0140-6736(04)17141-9

19. Blomberg B, Spinaci S, Fourie B, Laing R. The rationale for recommending fixed-dose combination tablets for treatment of tuberculosis. Bull World Health Organ. 2001;79(1):61-8.

20. Mitchison DA. The diagnosis and therapy of tuberculosis during the past 100 years. Am J Respir Crit Care Med. 2005; 71(7):699-706. https://doi.org/10.1164/rccm.200411-1603OE

21. Peloquin CA, Berning SE, Huitt GA, Iseman MD. AIDS and TB drug absorption. Int J Tuberc Lung Dis. 1999;3(12):1143-4.

22. Albanna AS, Smith BM, Cowan D, Menzies D. Fixed-dose combination antituberculosis therapy: a systematic review and meta-analysis. Eur Respir J. 2013;42(3): 721-32. https://doi.org/10.1183/09031936.00180612

23. Gallardo CR, Rigau Comas D, Valderrama Rodríguez A, Roqué i Figuls M, Parker LA, Caylà J, et al. Fixed-dose combinations of drugs versus single-drug formulations for treating pulmonary tuberculosis. Cochrane Database Syst Rev. 2016;(5):CD009913. https://doi.org/10.1002/14651858.CD009913.pub2

24. Controlled clinical trial of short-course (6-month) regimens of chemotherapy for treatment of pulmonary tuberculosis. Lancet. 1972;1(7760):1079-85.

25. Vareldzis BP, Grosset J, de Kantor I, Crofton J, Laszlo A, Felten M, et al. Drug-resistant tuberculosis: laboratory issues. World Health Organization recommendations. Tuber Lung Dis. 1994;75(1):1-7. https://doi.org/10.1016/0962-8479(94)90096-5

26. Xu J, Jin H, Zhu H, Zheng M, Wang B, Liu C, et al. Oral bioavailability of rifampicin, isoniazid, ethambutol, and pyrazinamide in a 4-drug fixed-dose combination compared with the separate formulations in healthy Chinese male volunteers. Clin Ther. 2013;35(2):161-8. https://doi.org/10.1016/j.clinthera.2013.01.003

27. Bastos GM, Cezar MC, Mello FC, Conde MB. Prevalence of primary drug resistance in pulmonary tuberculosis patients with no known risk factors for such. J Bras Pneumol. 2012;38(6):733-9. https://doi.org/10.1590/S1806-37132012000600008

28. Marques M, Cunha EA, Ruffino-Netto A, Andrade SM. Drug resistance profile of Mycobacterium tuberculosis in the state of Mato Grosso do Sul, Brazil, 2000-2006. J Bras Pneumol. 2010;36(2):224-31. https://doi.org/10.1590/S1806-37132010000200011

29. Baliza M, Bach AH, Queiroz GL, Melo IC, Carneiro MM, Albuquerque Mde F, et al. High frequency of resistance to the drugs isoniazid and rifampicin among tuberculosis cases in the city of Cabo de Santo Agostinho, an urban area in Northeastern Brazil. Rev Soc Bras Med Trop. 2008;41(1):11-6. https://doi.org/10.1590/S0037-86822008000100003