

# Effectiveness and trend forecasting of tuberculosis diagnosis after the introduction of rapid molecular testing in a city in south-eastern Brazil

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## Research article

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## Abstract

## Background

To evaluate the effectiveness of a rapid molecular test for the detection of tuberculosis and to predict the behaviour of the disease in a municipality of Brazil where tuberculosis is endemic.

## Methods

An ecological study was carried out in Ribeirão Preto-SP on a population of tuberculosis cases notified between 2006 and 2017. Monthly tuberculosis incidence rates and the Average Monthly Percentage Change (AMPC) were calculated. In order to identify changes in the series, the breakpoint technique was performed; the rates were modelled and predictions of the incidence of tuberculosis until 2025 were made.

## Results

AMPC showed a fall of 0.69% per month in tuberculosis and human immunodeficiency virus (TB-HIV) co-infection, a fall of 0.01% per month in general and lung tuberculosis and a fall of 0.33% per month in extrapulmonary tuberculosis. With the breakpoint technique, general and pulmonary tuberculosis changed in structure in late 2007, and extrapulmonary tuberculosis and TB-HIV co-infection changed in structure after 2014, which is considered as the cut-off point. The IMA(3) models were adjusted for general and pulmonary tuberculosis and TB-HIV co-infection, and the AR(5) models for extrapulmonary TB, and predictions were performed.

## Conclusions

It is necessary that the algorithms for the care of a person with tuberculosis are followed and the diagnostic means used correctly in order to break the chain of transmission of tuberculosis and reduce its indexes.

## Background

Tuberculosis (TB) is an illness suffered by millions of people annually. It is classed as the infectious disease that kills the highest number of people worldwide, and is the main cause of death among people living with HIV (human immunodeficiency virus) (PLHIV), overcoming AIDS (Acquired Immunodeficiency Syndrome) as the most lethal infectious disease of today[1].

In 2018, the World Health Organization (WHO) estimated that there were seven million new cases of TB in the world, with 57% of these cases being in men, 32% in women and 11% in children under 15 years of age. It is also estimated that there were 1.2 million deaths from tuberculosis and 251 000 deaths due to co-infection by tuberculosis and human immunodeficiency virus (TB-HIV). In Brazil, approximately 73 000 new cases were diagnosed in 2018, there were more than 13 000 cases of relapse of the disease, and about 500 cases of drug addiction[1].

Regarding the diagnostic technologies available in the Brazilian scenario, it is important to highlight that bacilloscopy is the routine test in the Sistema Único de Saúde (SUS), and that a culture test is considered the gold standard for identifying the disease[2]; however, because of the delay in obtaining results due to the slow reproduction of the bacillus (on average four to eight weeks) and the high complexity, a culture is rarely used for making decisions related to the treatment of a person affected by the disease[3–4].

After almost a century of stagnation regarding TB diagnostic techniques, the WHO, in 2010, approved the use of the GeneXpert® MTB/RIF system to perform rapid molecular testing for tuberculosis (TRM-TB). This is an amplification test for nucleic acids that is used to detect the DNA (deoxyribonucleic acid) of *Mycobacterium tuberculosis* (MTB) and to screen strains resistant to rifampicin, one of the main antibiotics used in the treatment of TB[5].

In a survey of the scientific literature conducted in the main databases, no studies were found that assessed the impact of TRM-TB in the detection of cases of the disease in the routine activities of health teams. However, studies show that the test performed by the GeneXpert® MTB/RIF system is highly sensitive[6] and is also the most cost-effective[7–9], as it provides faster results without requiring sample treatment or specialized human resources, thus allowing treatment to begin immediately[10].

For this reason, this study aimed to evaluate the effectiveness of GeneXpert® MTB/RIF in the detection of pulmonary tuberculosis, extrapulmonary TB and TB-HIV co-infection, and to predict the behaviour of the disease if the routine activities of the health teams in a municipality of south-eastern Brazil are maintained.

## Methods

## Research design and scenario

This was an ecological study[11] carried out in Ribeirão Preto, a municipality in the interior of São Paulo. As regards the care of people in the municipality with TB, the Basic Health Units (BHSs) are responsible for carrying out active searches for respiratory symptoms, with the collection of sputum smear microscopy and/or X-ray requests. However, the treatment and follow-up of TB cases is performed in specialized outpatient clinics for infectious patients[12].

It is noteworthy that in Ribeirão Preto, TRM-TB using the GeneXpert® MTB/RIF system was implemented and started to be used as a diagnostic technology for TB in November 2014, and this was the cut-off point considered in the study.

## Population

The study population consisted of TB cases notified to the Tuberculosis Patient Control System (TBWeb) from 2006 to 2017, which were made available through the Epidemiological Surveillance Division of the Ribeirão Preto Municipal Secretariat.

In the state of São Paulo, a decision has been made to use a single system for the notification and monitoring of people with TB. In TBWeb, which started to be used effectively from 2006, notifications are made online; the main advantage of this system is the uniqueness of each patient's records, and the automatic communication in cases of transfer and hospitalization[13].

Confirmed cases of TB among individuals residing in Ribeirão Preto were considered. Only one record per person was adopted as the selection criterion, with the most current record being selected if there was more than one entry in the system.

The notified TB cases were separated in order to show the different behaviours of the time series for different groups in the municipality: general TB, pulmonary TB, extrapulmonary TB and TB-HIV co-infection.

## Analysis plan

### Calculation of incidence rates

The monthly incidence rates of TB in the municipality were calculated as the number of cases in the month (corrected by the number of days in that month) divided by the corresponding estimated population for the investigation period (2006 to 2017), thus resulting in 144 monthly time observations[14]. Subsequently, the Average Monthly Percentage Change (AMPC) of incidence rates was calculated, identifying, in average percentage terms, any increase or decrease in rates during the study period.

### Detection of structural changes

In an analysis of time series, in addition to the usual variability observed over time, the data can also be influenced by various types of event that can cause structural changes. Thus, in order to identify possible changes in the series, the R CRAN package *strucchange* was used[15].

Basically, a  $y_t$  series is considered and it is assumed that there are  $m$  breakpoints in the series, in which the coefficients change from one stable regression relationship to another. There are, therefore,  $m + 1$  segments in which the regression coefficients are constant and the model can be rewritten as:

$$y_t = x_t^T \beta_j + u_t \quad (t = t_j + 1, \dots, t_{j+1}, \quad j = 1, \dots, m + 1)$$

with  $x_t$  being the vector of the covariables,  $\beta_j$  (where  $j$  denotes the segment index) the corresponding regression coefficients, and  $u_t$  white noise (that is, an uncorrelated series, with zero mean and constant variance)[16].

### Modelling and forecasting future values

To model the TB rates, and to predict their future values, incidence rates smoothed by first-order moving averages were considered, as proposed by Becketti[17], using the model for linear time series called the autoregressive integrated moving average (ARIMA) model. The analysis steps proposed by Box and Jenkins[18] were adapted for the chosen model, based on the data structure itself: Identification, Estimation, Verification and Forecasting.

An ARIMA model  $(p, d, q)$  allows the variability of a time-related, linear, stationary ( $d=D=0$ ) or non-stationary (otherwise) process to be described.

The letters  $p$  and  $q$  represent, respectively, the number of parameters of the autoregressive parts and the moving averages within the period, and the letter  $d$  represents the degrees of simple differentiation necessary to transform a non-stationary series into a stationary one[19].

An ARIMA model can be written as follows:

$$\Delta(B^s)\Phi(B)(1-B)^d(1-B^s)^p T(X_t) = \Psi(B^s)\Theta(B)Z_t$$

where:

$$\Phi(B) = 1 - \phi_1 B - \phi_2 B^2 - \dots - \phi_p B^p, \Theta(B) = 1 - \theta_1 B - \theta_2 B^2 - \dots - \theta_q B^q$$

are, respectively, the autoregressive and the moving average polynomials.  $T$  is the transformation to stabilize the variance, if this is necessary, and  $Z_t$  represents the white noise process (a non-correlated process, with zero mean and constant variance).

The KPSS unit root test was performed to determine whether the series was stationary or not, using a significance level of 5%. For a non-stationary series, it is necessary to resort to the usual transformation techniques (Box-Cox and simple differentiations) in order to transform the series into a stationary one and then to determine, through the empirical autocorrelation and partial autocorrelation functions, the  $p$  and orders of the ARIMA model.

To estimate the model parameters, the maximum likelihood method was used. For the validation of the model, namely in the analysis of residues, the usual tests of absence of autocorrelation (Portmanteau tests: Ljung-Box and Box-Pierce), randomness (Rank and Turning Point tests), normality (Kolmogorov-Smirnov test) and the  $t$  test of average nullity were performed.

It is worth mentioning that the choice of the best model was made taking into account the lowest values of the Akaike information criterion (AIC). Subsequently, data and trend forecasts were made for an eight-year period (2018 to 2025).

A set of tests using the last two years (2016 to 2017) was used to assess the predictive performance of the models. The following measures were considered in order to evaluate this predictive performance: Root Mean Square Error (RMSE), which indicates the difference between the values predicted by a model and the observed values, Mean Absolute Error (MAE), which is a measure of the accuracy of a forecast in the estimation of trends, and Mean Absolute Percentage Error (MAPE), which is the percentage of the predicted values that are incorrect. Forecasts were then made based on the adjusted models for the eight-year period (2018 to 2025).

We have chosen to present possible trajectories for the forecasts, instead of the usual average forecasts (since when the series are stationary or show trends and/or seasonality, the forecasts do not usually tend towards the process average), through a simulation of the adjusted model. Both for the simulation of future trajectories and for the calculation of the respective confidence intervals of the predictions, errors were considered as random variables, normally distributed, with mean and standard deviation equal to their estimated values.

All the analyses were performed using the statistical software R Studio® version 3.5.2 (<https://rstudio.com>).

## Results

Between 2006 and 2017, 2259 TB cases were reported in Ribeirão Preto, the majority of which were pulmonary (77.9%). Figure 1 shows the time series of incidence rates per 100 000 inhabitants.

**Figure 1.** Tuberculosis incidence rates in Ribeirão Preto, São Paulo, Brazil (2006–2017)

Table 1. Profile of tuberculosis cases according to classification and average monthly percentage variation of rates, Ribeirão Preto, São Paulo, Brazil (2006–2017)

Table 1  
shows the frequency of distribution of TB cases grouped by type, the annual rate and the AMPC.

Tuberculosis	Absolute frequency (%)	Annual rate (100.000 inhab)	Average Monthly Percentage Change (%)
General	2259 (100%)	31.7	-0.01
Pulmonary	1760 (77.9%)	23.2	-0.01
Extrapulmonary	497 (22.0%)	6.4	-0.33
TB-HIV co-infection	510 (22.6%)	6.7	-0.69

Figure 1 shows a drop in the incidence rate of TB-HIV co-infection, which can be proved through the AMPC, which shows a drop of 0.69% per month, as seen in Table 1. It is also possible to verify that general and pulmonary TB decreased by 0.01% per month, and that extrapulmonary TB decreased by 0.33% per month, although these falls are less noticeable when analysing Fig. 1.

With the breakpoint technique, it is possible to identify the time series structure changes. For general and pulmonary TB, the series structure changed in late 2007, whereas the series for the incidence rates of extrapulmonary TB and TB-HIV co-infection show a break after 2014, which is the cut-off

point considered in this study because it marks the beginning of TB diagnosis using the TRM-TB. Figure 2 shows the breakpoint technique and the various confidence intervals.

**Figure 2.** Changes in the structure of the time series regarding the incidence rates of tuberculosis in Ribeirão Preto, São Paulo, Brazil (2006–2017)

With the KPSS unit root test, a value of 0.65 was obtained for general TB (the series is non-stationary), 0.65 for pulmonary TB (non-stationary series), 0.37 for extrapulmonary TB (stationary series) and 1.03 for TB-HIV co-infection (non-stationary series). Thus, it was necessary to use the transformations for the series identified as non-stationary.

For general TB, pulmonary TB and TB-HIV co-infection, the best adjusted models were of ARIMA type (0,1,3), or simply IMA(3). For general TB, only the constant and the coefficient of order three were significant; for pulmonary TB, only the coefficient of order three was significant; and for TB-HIV co-infection, the coefficients of orders two and three were significant. For extrapulmonary TB, the best model found was an ARIMA(5,0,0), or simply AR(5) model, with all the coefficients being significant except for the coefficient of order two.

After choosing the best models, we proceeded to analyse the residues. It is possible to observe (Fig. 3 and Table 2) that the residues are statistically unrelated and that the remaining assumptions of the models are validated (independent and identically distributed residues, with a normal distribution of zero mean and constant variance), considering a significance level of 5%.

Table 2  
Analysis of residues from the temporal modeling of tuberculosis rates, Ribeirão Preto, São Paulo, Brazil (2006–2017).

Test Statistics (p-value)				
Test	General TB	Pulmonary TB	Extrapulmonary TB	TB-HIV co-infection
Ljung-Box	0.04 (0.83)	0.24 (0.61)	0.14 (0.70)	1.54 (0.21)
Box-Pierce	0.044 (0.83)	0.24 (0.62)	0.13 (0.70)	1.51 (0.21)
Rank test	0.82 (0.40)	0.82 (0.40)	-2.16 (0.30)	0.97 (0.33)
Turning Point	-0.33 (0.74)	-0.92 (.035)	1.06 (0.28)	0.66 (0.50)
Difference Sign Test	0.14 (0.88)	-0.71 (0.47)	-1.00 (0.31)	-0.71 (0.47)
Bartlett B test	0.45 (0.98)	0.57 (0.90)	0.95 (0.31)	0.76 (0.59)
Kolmogorov – Smirnov	0.04 (0.92)	0.04 (0.96)	0.04 (0.88)	0.06 (0.60)
T test of means	-0.63 (0.52)	-1.32 (0.18)	0.07 (0.94)	-1.10 (0.27)

**Figure 3.** Residue analysis (schedule, ACF and histogram) of the models estimated for the tuberculosis rates, Ribeirão Preto, São Paulo, Brazil, 2006–2017.

The quality of the forecasts was analysed by comparison with the subset of tests (years 2016 and 2017) as seen in Table 3.

Table 3  
 Predictive analysis of tuberculosis rate models,  
 Ribeirão Preto, São Paulo, Brazil (2006–2017)

	RMSE	MAE	MAPE
General TB	0.27	0.21	8.5
Pulmonary TB	0.23	0.18	9.81
Extrapulmonary TB	0.11	0.09	19.41
TB-HIV co-infection	0.09	0.07	15.31

Figure 4 presents the final models for the series, and it is possible to observe that all the adjustments are able to capture in a very satisfactory way the variability of all the series under analysis.

**Figure 4.** Models adjusted for tuberculosis rates (2006–2017), forecast and respective 95% confidence intervals (2018–2025), Ribeirão Preto, São Paulo, Brazil

## Discussion

The study aimed to assess the effectiveness of GeneXpert® MTB/RIF in the detection of pulmonary tuberculosis, extrapulmonary TB and TB-HIV co-infection, and to predict the behaviour of the disease if the routine activities of health teams in this municipality of south-eastern Brazil are maintained. Among the limitations of the study is the use of secondary data sources, which can lead to incomplete data or typos.

With the analysis of AMPC (Table 1) it is possible to note that, among the groups analysed in the present study, TB-HIV co-infection showed the greatest drop (0.69% per month). This drop can be explained by the greater sensitivity of the TRM-TB. Studies show that for samples with negative smear microscopy, the sensitivity of the TRM-TB for a sputum sample is 72.5% and for three samples it reaches almost 91%[2].

The hypothesis is raised that another reason for this drop in rates is related to the greater adherence of PLHIV to antiretroviral therapy or positive changes in drug regimens in order to decrease their viral load; this would result in an increase in PLHIV immunity and, thus, the hindering of MTB infection[20–22].

With the breakpoint analysis it was possible to identify that the incidence rates for extrapulmonary TB and TB-HIV co-infection changed in structure after 2014, which is the cut-off point considered in this study as it marks the beginning of TB diagnosis through the TRM-TB. This indicates that, among other possible variables, the implementation of the GeneXpert® system in SUS may have influenced the change in TB behaviour in the city because the test, being more sensitive, makes the diagnosis of cases more reliable.

Across the world, the most commonly used tests for the diagnosis of TB are the sputum smear and sputum culture tests. As it is simpler, faster and less costly, bacilloscopy ends up being more commonly used as a routine test by health systems, but it is worth mentioning that it has low sensitivity, especially in cases with low bacillary load[23–24].

A culture test can detect between 70% and 90% of cases; however, it requires at least 14 to 60 days to obtain a diagnosis. Because of this long period for obtaining a diagnosis, cultures are rarely used for making decisions regarding the treatment of a person with TB[23–25].

The main advantages of the TRM-TB performed using the GeneXpert® system is that the result can be released within two hours and will already indicate whether the patient is resistant or sensitive to rifampicin[26]. Thus, it is possible that the incorporation of the GeneXpert® system in SUS could be the reason behind changes in the disease indexes and the consequent change in structure in the time series. This would mainly be due to the high sensitivity, specificity and rapid diagnosis time of the GeneXpert® system when compared to the usual tests.

Using the Box–Jenkins[18] methodology, a well-estimated model that provides adequate forecasts can be a very useful tool to assist with decision-making by both public managers and society[27]. From the adjustment of the models, it was possible to verify and make forecasts for the TB rates in Ribeirão Preto; although the estimates indicate a slight fall, TB will continue to be a serious public health problem.

Considered a priority by the Brazilian government since 2003, TB has been the subject of several national agreements and has been made a priority of the National Tuberculosis Control Program (NTCP). There has been an increase in the detection of cases through the strengthening of the primary health care services system[28].

According to the TB diagnosis algorithm recommended by the Ministry of Health, all new suspected cases of pulmonary TB must be tested using TRM-TB. If both MTB and resistance to rifampicin are detected, another confirmatory TRM-TB should be performed, combined with a culture test and sensitivity test (ST), and the patient should be referred for specialist attention. If MTB and sensitivity to rifampicin are detected, a culture test and ST, and treatment with the basic TB regimen, should be performed[4].

The TRM-TB performed by the GeneXpert® MTB/RIF system has several positive points when compared to classic methods for TB diagnosis; however, further studies will improve the understanding of this test and contribute to the diagnosis of TB. The study advances our knowledge as it presents the impact of TRM-TB on routine health services, and it is important to note that studies of this nature are able to support decisions about the maintenance and/or sustainability of technologies in a real, uncontrolled context.

## Conclusions

The TRM-TB performed by the GeneXpert® MTB/RIF system is the method currently recommended by the Ministry of Health for the diagnosis of TB. Its main advantage is that it gives a faster and more accurate diagnosis when compared to other classic diagnostic methods, such as bacilloscopy and culture tests.

It is necessary for NTCP managers to encourage practitioners to follow the algorithm to assist people with TB, so that the diagnostic means are used correctly, a more accurate and rapid diagnosis can be found, and treatment can begin as soon as possible. In this way, the goals proposed by the WHO can be achieved.

## Abbreviations

TB - Tuberculosis

HIV - Human immunodeficiency virus

PLHIV - People living with HIV

AIDS - Acquired immunodeficiency syndrome

WHO - World Health Organization

TB-HIV - Coinfection of tuberculosis and human immunodeficiency virus

SUS - Sistema Único de Saúde

TRM-TB -Rapid molecular testing for tuberculosis

DNA - deoxyribonucleic acid

MTB - *Mycobacterium tuberculosis*

BHS - Basic Health Units

TBWeb - Tuberculosis Patient Control System of São Paulo state

AMPC - Average monthly percentage change

ARIMA - autoregressive integrated moving average

AIC - Akaike information criterion

RMSE - Root mean square error

MAE - Mean absolute error

MAPE - Percentage Error

NTCP - National Tuberculosis Control Program

## Declarations

## Ethics approval and consent to participate

In compliance with Resolution 499/2012 of the National Health Council, the study was approved by the Research Ethics Committee of Nursing College of Ribeirão Preto, University of São Paulo under the Certificate of Ethical Appraisal number 87696318.3.0000.5393 issued on April 30, 2019. Consent to participate not applicable, because we work with secondary data of cases diagnosed with tuberculosis and reported on TBWeb (tuberculosis case notification system used in the state of São Paulo).

## Consent for publication

Not applicable

## Availability of data and materials

The data that support the findings of this study are available from Municipal Health Secretariat of Ribeirão Preto but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Municipal Health Secretariat of Ribeirão Preto.

## Competing interests

The authors declare that they have no competing interests.

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## Authors' contributions

TZB, DG, RAA participated on the conception, planning, analysis, interpretation and writing of the work; ACRV, YMA, ATIB participated on the writing of the work; Author LHA, FLS, LLLS, JAC participated on interpretation and writing of the work. All authors have read and approved the final manuscript.

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Municipal Tuberculosis Control Program of Ribeirão Preto

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## Figures

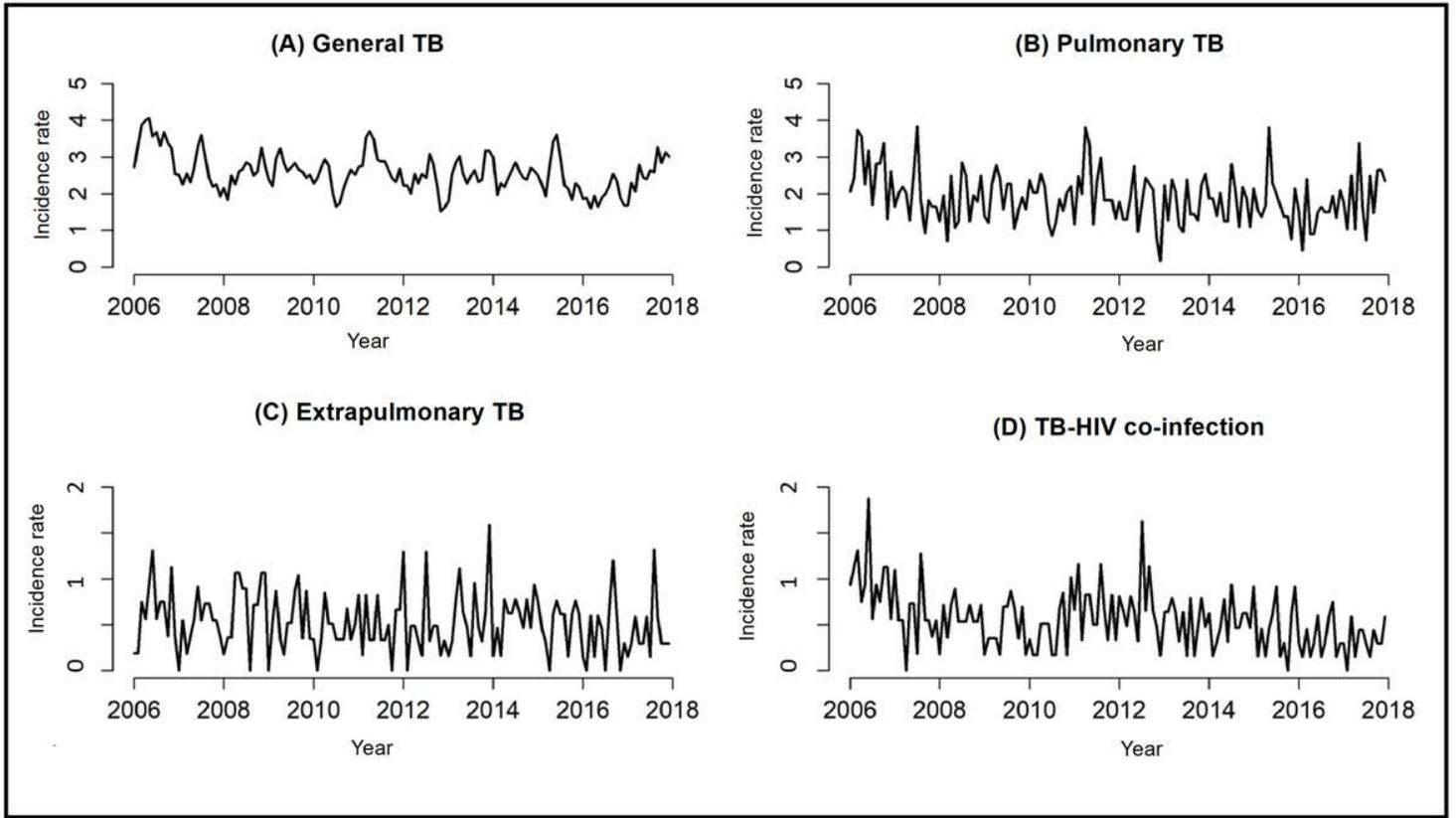


Figure 1

Tuberculosis incidence rates in Ribeirão Preto, São Paulo, Brazil (2006-2017)

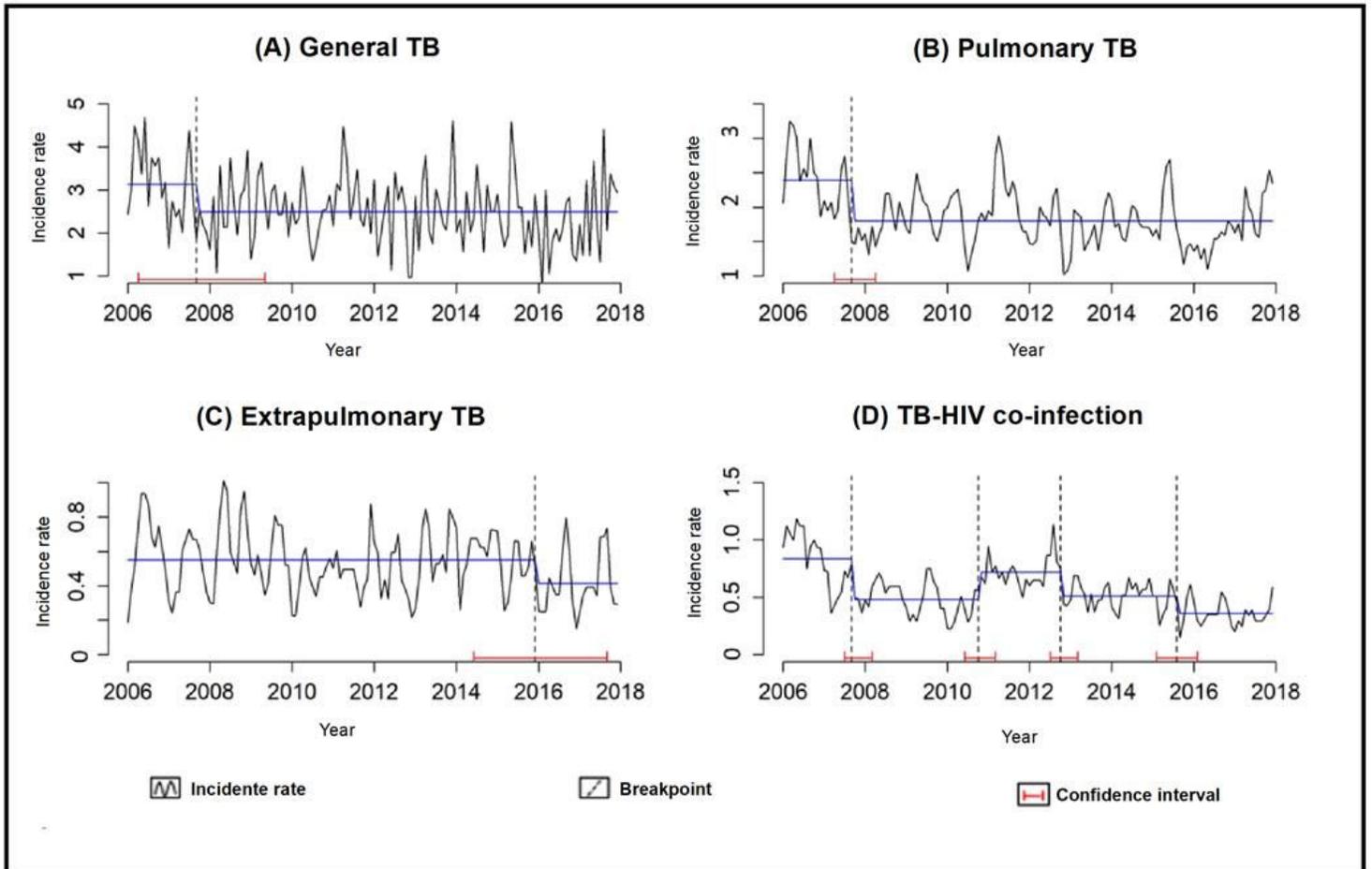


Figure 2

Changes in the structure of the time series regarding the incidence rates of tuberculosis in Ribeirão Preto, São Paulo, Brazil (2006-2017)

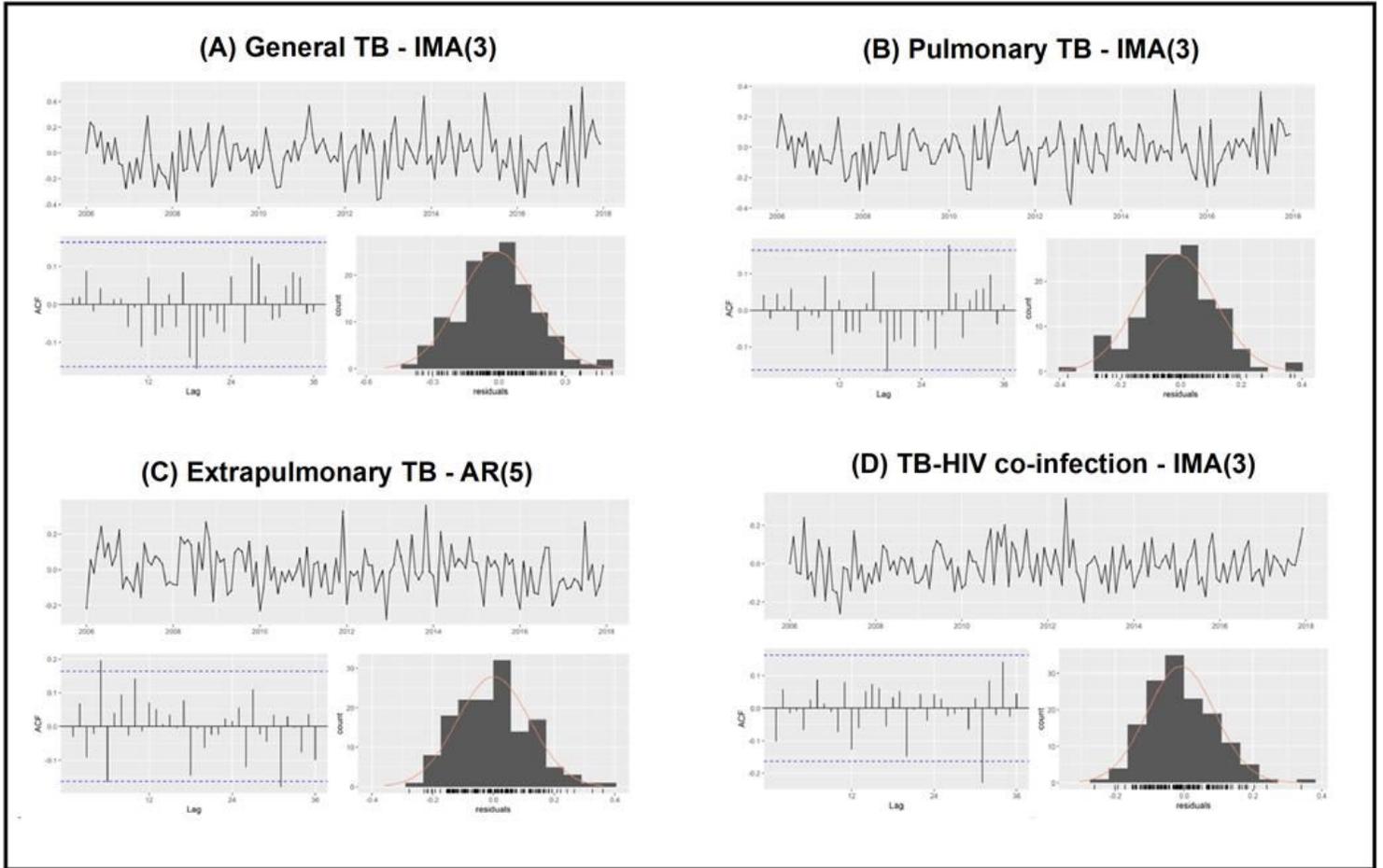
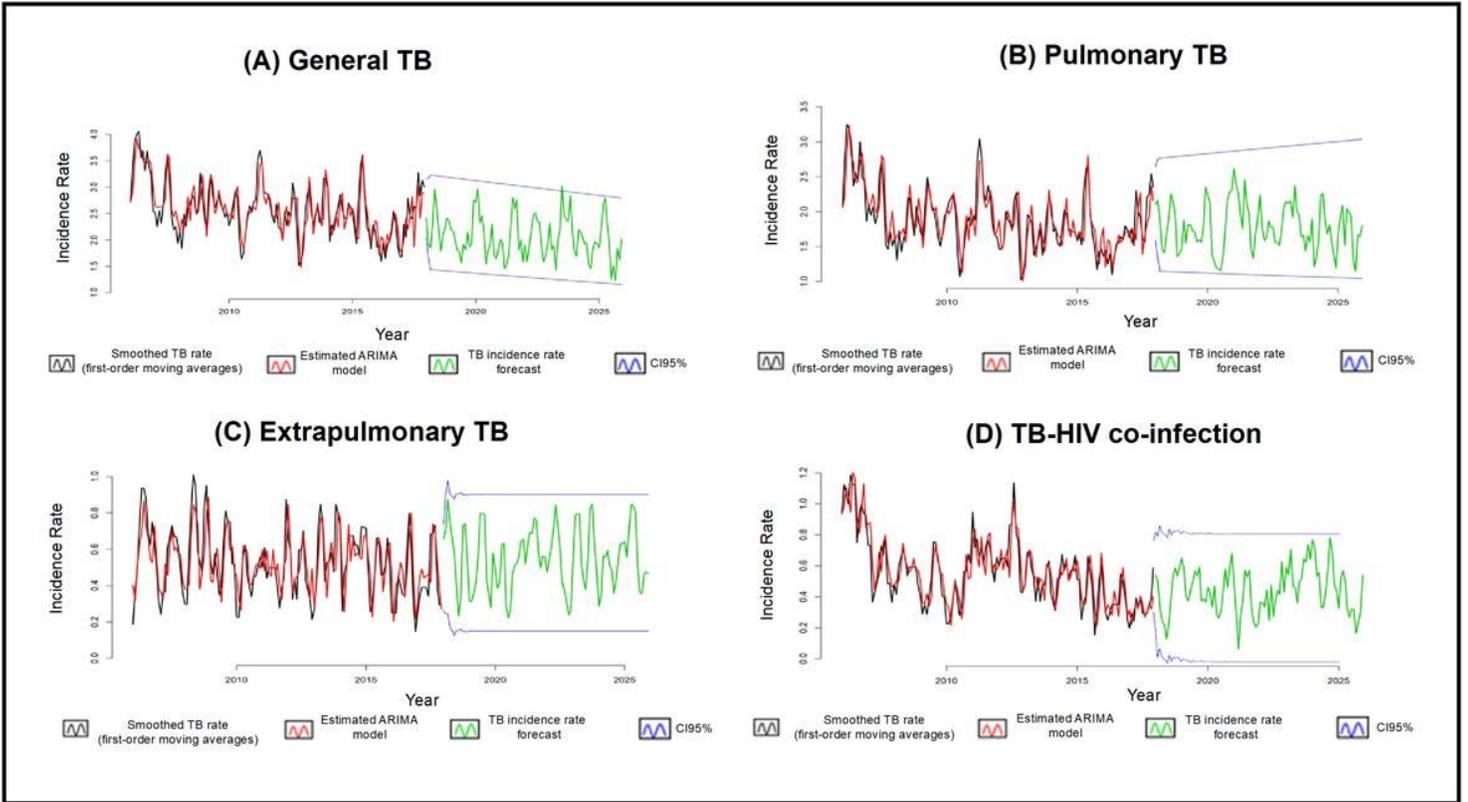


Figure 3

Residue analysis (schedule, ACF and histogram) of the models estimated for the tuberculosis rates, Ribeirão Preto, São Paulo, Brazil, 2006-2017.



**Figure 4**

Models adjusted for tuberculosis rates (2006-2017), forecast and respective 95% confidence intervals (2018-2025), Ribeirão Preto, São Paulo, Brazil