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Trend change estimation for interrupted time series with heteroscedastic and autocorrelated errors: application in syphilis occurrences in Brazil

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ABSTRACT. The impact evaluation of exogenous policies over time is of great importance in several areas. Unfortunately, an adequate time-series analysis has not always been taken into account in the literature, mainly in health problems. When regression models are used in the known interrupted time-series approach, the required error assumptions are in general neglected. Specifically, usual linear segmented regression (lmseg) models are not adequate when the errors have nonconstant variance and serial correlation. To instigate the correct use of intervention analysis, we present a simple approach extending a linear model with log-linear variance (lmvar) to estimate lineartrend changes under heteroscedastic errors (lmsegvar). When the errors are autocorrelated, the Cochrane-Orcutt (CO) modification is implemented to correct the estimated parameters. As an application, we estimate the impact in temporal trend of the Brazilian Rede Mãe Paranaense (RMP) program in gestational syphilis occurrences in the state of Parana, Brazil. The comparison of the proposed linear segmented model (lmsegvar+CO) modeling both the average and variance, with the usual segmented linear model (lmseg), where just the average is modeled, shows the importance of taking heteroscedasticity and autocorrelation into account.

Keywords: heteroscedasticity; intervention time series analysis; linear regression segmented model; nonconstant variance; serial correlation.

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Introduction

In ecological studies of the type before-after design along time, it is necessary to use appropriate statistical methods, such as regression models for time series (Draper & Smith, 1981) or ARIMA class models (‘autoregressive integrated moving average models’ - Box & Jenkins, 1976). When the evaluation of the impact of external effects (also called exogenous variables) is the most important aim, using linear regression models for time series instead of ARIMA models can maintain the advantage of the easy interpretation of abrupt or gradual changes after intervention occurrences, mainly regarding the trend estimations.

However, simple regression models like the one introduced by Finlay and Wilkinson (1963) and later extended by Eberhart and Russell (1966), do not allow the evaluation of trend changes in the variable of interest in moments/periods in time under the occurrence of external factors. In this sense, the segmented regression model, initially proposed by Quandt (1958), was developed and used in several ways (Thistlethwaite & Campbell, 1960; Ransay, Matowe, Grilli, Grimshaw, & Thomas, 2003). Its approach in the context of time series has strengthened the before-after studies in several areas, receiving different specifications and nomenclatures, such as interrupted time series analysis, intervention analysis, discontinuous regression analysis, among others (Kontopantelis et al., 2015). In health, some recent studies can be cited (Kontopantelis et al., 2015; Taljaard, McKenzie, Ramsay, & Grimshaw, 2014; Valsamis, Husband, & Chan, 2019).

In segmented linear regression models, it is assumed that the mean is linear in the pre- and post-intervention periods and that the characteristics of the population are maintained in the study period (Kontopantelis, Doran, Springate, Buchan, & Reeves, 2015). It is also assumed that the errors are independent

and that the variance is constant. If these assumptions are violated, inferences and misinterpretations may occur (Chen et al., 2019).

Unfortunately, assumption verifications have not always been taken into account in the literature, mainly in health problems. To instigate the correct use of intervention analysis, we present an extension of the linear segmented regression model to model heteroscedasticity and also to correct the serial correlation. For non-constant variance modeling, while keeping simple regression models, we considered approaches that have been discussed in the literature by (Harvey, 1976; Aitkin, 1987; Verbyla, 1993; Nijmeijer & Cator, 2018). Regarding the presence of autocorrelation, although more elaborate models can be constructed, we considered a simpler possibility using the Cochrane-Orcutt (CO) modification (Cochrane & Orcutt, 1949).

The proposed model is presented, and to make the verification of the usual model assumptions easy to users of non-exact sciences, the descriptions of traditional statistical tests and model comparison measures are also kept.

As an application, we used occurrences of syphilis, which is a public health problem due to difficulties in accessing adequate treatment, limited resources, stigma, low quality of health services, and the unsatisfactory segment of sexual partners (Sales, Dilts, & Silva, 2019).

During the gestational period, it is estimated that syphilis presents more than 300,000 fetal and neonatal deaths per year in the world and increases the risk of premature death in another 215,000 children (Brasil, 2018). Studies show that late diagnosis, non-treatment, or inadequate treatment of pregnant women are the main difficulties encountered to reduce vertical transmission of syphilis (Araújo, Andrade, Barros, & Bertoncini, 2019).

In this context, in 2012, the Rede Mãe Paranaense (RMP) Program was implemented, based on the conceptual framework of the Health Care Networks (SAN), adopted in Paraná state as a model of attention to improve access and quality in actions provided for the population. Thus, we are going to investigate the impact of this program in occurrences of gestational syphilis, comparing the traditional linear segmented regression, the linear segmented model for non-constant variances (lmsegvar), and also the lmsegvar model with CO modification.

Material and methods

It is an ecological study of the type before-after design on gestational syphilis with intervention evaluation implemented by the RMP program in 2012.

The gestational syphilis data were obtained from the Department of Informatics of the Brazilian Unified Health System (Sinan/Datasus - www2.datasus.gov.br/DATASUS/index.php?area= 0203&id=29878153), from January 2008 to December 2018, in the State of Paraná, Brazil. The monthly occurrence rates in pregnant women were calculated for every 100,000 women, represented by the ratio:

$$\frac{Syphilis\ in\ Pregnant\ Women\ per\ Month}{Female\ Resident\ Population} \times 100{,}000$$

Because we have only one intervention (RMP Program), we build a segmented regression model with two segments separated by one interruption point in January 2012, when the RMP Program began:

$$Y_t = \mu_t + \varepsilon_t = \beta_0 + \beta_1 T_t + \beta_2 X_t T_t + \varepsilon_t, \quad (1)$$

where:

Y_t is a random variable for the observed time series with the outcome rate at each t, which varies from 1 to n = 132 observations, Y_t is normally distributed with average μ_t and variance-covariance matrix $\boldsymbol{\Sigma}$, $Y_t N(\mu_t, \Sigma)$.

ε_t is the Gaussian random error, $\varepsilon_t N(0, \sigma_\varepsilon^2)$.

T_t is the time since the beginning of the study in January 2008 considering the months as fractions of the years (T_1 = 2008.0; T_2 = 2008.01; ...; T_n = 2018.9),

X_t is a dummy variable representing the intervention where X_t = 0 in the pre-intervention period (t = 1, ..., 55) and X_t = 1 after January 2012, (t = 56, ..., 132),

β_0 represents the intercept or estimated rate at the beginning of the study (January 2008);

β_1 is the estimated slope or trend of the outcome variable up to the introduction of the intervention (January 2012);

β_2 represents the change in slope or trend of the outcome after the introduction of the intervention up to the end of the study.

In Equation 1, we have a standard segmented linear model for time series, here called 'lmseg', which means the matrix Σ is diagonal ($\Sigma_{ij} = 0$ if $i \neq j$) and with the same variance for all t, $\Sigma_{ij} = \sigma^2$ if i = j. But in the case of nonconstant variance in Yt and, consequently, εt, instead of the standard linear model, the diagonal inputs may be different. This means Σ is still a diagonal matrix but each Y_t has its own variance σ_t^2. To take non-constant variances into account, another equation is included to model σ regarding T_t.

In the same way as the expected value vector, μ_t, is linearly dependent on the values of the covariates in the matrix model X_{μ_t}: $\mu_t X_{\mu_t} \beta_{\mu_t}$, the vector σ_t depends on the covariates in the model matrix X_{σ_t} as presented in the equation:

$$log\sigma_t = X_{\sigma_t}\beta_{\sigma_t}, \quad (2)$$

where:
log σ_t = (log σ_1 , ..., log σ_n).

The logarithm in Equation 2 is the 'natural' one, i.e., with basis e. The vectors $\beta_{\mu_t}$and β_{σ_t} have the parameters for μ_t and σ_t, respectively. Depending on the behavior of the mean and variance, a predictor can be included only in X_μ, in X_σ, or in both X_μ and X_σ (Nijmeijer & Cator, 2018). In the time-series approach, parameters are included in X_σ only for the period or periods where the variance is not constant (heteroscedasticity), which can be only one period of the analysis, pre- or post-intervention, or both. In this work, as the heterocedastic period is only after the intervention, just the covariate $X_t T_t$ is included in X_{σ_t} while both T_t and $X_t T_t$ is in X_μ.

To interpret the trend in the period after the intervention (X_t = 1), the estimated change β_2 has to be added to the previous period β_1, i.e. $\beta_1 + \beta_2$. The segmented linear regression model for time series with nonconstant variance by Equation 1 and 2 was called 'lmsegvar'.

To estimate the parameters in this model, the maximum likelihood estimation (MLE) was used, which consists of estimating the parameters so that the estimates maximize the likelihood function (equivalent to minimizing the log-negative likelihood function). More details of parameter estimation considering nonconstant variance in simple regression models can be found in Aitkin (1987), Harvey (1976), Verbyla (1993) or even in the description of the lmvar package of R. At the end of this estimation, it is necessary to verify the assumptions of the model.

To verify the need to consider a segmented linear regression model with nonconstant variance, the Breusch-Pagan-Godfrey test was performed to test the hypothesis of homoscedasticity of the residuals.

This test statistic follows approximately a chi-square distribution with (p-1) degrees of freedom where p is the number of parameters to be estimated and the null hypothesis that the variances of errors are all equal is true. The normal distribution was verified by the Jarque-Bera test, which evaluates both the symmetry and the kurtosis of the distribution:

$$JB = n\left(\frac{\hat{\alpha}_1}{6} + \frac{(\hat{\alpha}_2 - 3)^2}{24}\right), \quad (3)$$

where:
n is the number of observations of the time series and $\hat{\alpha}_1$ and $\hat{\alpha}_2$correspond to the sample coefficients of symmetry and kurtosis. Considering these coefficients must assume values of zero and three, respectively, the value of the JB statistic given by 3 is expected to be equal to zero. Under the null hypothesis that errors are normally distributed, Jarque and Bera (1987) showed that, asymptotically, the statistics given by Equation 3 follows a chi-square distribution with 2 degrees of freedom. Thus, we reject the hypothesis of normality of errors if $JB > X^2$, where $X^2{}_{q,\alpha-1}$ is the $1-\alpha$ quantile of the distribution X^2 with two degrees of freedom.

The serial autocorrelation was checked from the autocorrelation function (ACF) and partial auto-correlation function (PACF), besides the Durbin-Watson (DW) and Breusch-Godfrey (BG) tests for serial correlation.

In the DW test, the null hypothesis is that the autocorrelation coefficient ρ in the residuals $\hat{\varepsilon} = Y_t - \hat{Y}_{t-1}$ is zero. Thus, considering the model $\hat{\varepsilon} = \rho\varepsilon_{t-1} + v_t$, v_t the Gaussian error, the DW statistics is given by:

$$d = \frac{\sum_{t=2}^{n}(\hat{\varepsilon}_t - \hat{\varepsilon}_{t-1})^2}{\sum_{t=1}^{n}(\hat{\varepsilon}|t)^2,} \quad (4)$$

which for n large enough is equivalent to

$$d = 2(1 - r), \quad (5)$$

varying from zero to four since the correlation coefficient r between $\hat{\varepsilon}_t$ and $\hat{\varepsilon}_{t-1}$ varies from r = -1to r = 1. Hence d close to zero indicates the existence of positive autocorrelation in errors. If d is close to four, it represents the existence of negative autocorrelation in errors (Hoffmann & Vieira, 1987). Because of the dependence of any computed DW value on the associated data matrix, exact critical values of d are not tabulated for all possible cases. Instead, Durbin and Watson established upper (d_U) and lower bounds (d_L) for the critical values (Durbin & Watson, 1951). An extension of DW test, the Breusch-Godfrey test, was also applied for serial correlations larger than 1 (Breusch, 1978; Godfrey, 1978).

In the presence of autocorrelation, the measures of adjustment quality are overestimated, the trend estimation tends to be significant and may lead to interpretation errors. Although more elaborate models can be constructed to solve such a problem, a simpler possibility is to use the Cochrane-Orcutt (CO) procedure to estimate the existing correlation and to adjust the regression model so that it is more realistic and meets the required assumptions. To estimate the existing autocorrelation of order 1 (ρ), for example, one can construct an autoregressive AR (1) model for the residual series of the regression model, in which the errors are autocorrelated (Cochrane & Orcutt, 1949). For that, we can take the model in the Equation 1 delayed by one order:

$$Y_{t-1} = \beta_0 + \beta_1 T_{t-1} + \beta_2 X_{t-1} T_{t-1} + \varepsilon_{t-1} \quad (6)$$

Multiplying the Equation 6 by ρ and subtracting from the 1, we get:

$$Y_t - \rho Y_{t-1} = \beta_0(1 - \rho) + \beta_1(T_t - \rho T_{t-1}) + \beta_2 T_t - \rho X_{t-1} T_{t-1} + u_t, \quad (7)$$

where:
$u_t = \varepsilon_t - \rho\varepsilon_{t-1}$. This result of a 'near-difference' results in a model without first order serial correlation.

This CO modification is iteratively implemented until a satisfactory estimate of ρ is obtained, determined when in two successive iterations the estimates of ρ do not differ more than a small pre-established value.

Finally, the residuals can be converted into standardized residuals (*z-scores*), i.e., the quotient between the residuals and its estimated standard deviation:

$$z_i = \frac{\hat{\varepsilon}_i}{\hat{\sigma}} i = 1,2,3,\ldots,n \quad (8)$$

which are distributed around a zero mean and with unit standard deviation.

Thus, with the standardized residuals, it is possible to compare them with different models, making use of the properties of the *z-scores*.

Once the model is estimated and its assumptions verified, possible changes in trends after the intervention can be identified and interpreted by checking the significance of β_2 at the α = 5% level. However, besides verifying the required assumptions, there are other factors to consider when evaluating a model (Navarro & Myung, 2004).

To evaluate the adjustment quality and select the model that best fits the data we used the Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), and likelihood ratio test (LR).

Akaike Information Criterion corresponds to a relative measure of the fit quality of a given statistical model, so that it evaluates the quality of the parametric model fit, estimated by the maximum likelihood method:

$$AIC = -2(Maximized\ likelihood\ log) + 2(number\ of\ parameters),$$

$$AIC = -2logL(\hat{\theta}) + 2(p) \quad (9)$$

The Bayesian Information Criterion (BIC) is a criterion that evaluates models in terms of probability a posteriori. So, be $F(x_n|\hat{\theta})$ the chosen statistical model estimated through the maximum likelihood method, then the BIC is represented by:

$$BIC = -2logF(x_n|\hat{\theta}) + klogn \quad (10)$$

The last used measure to compare the quality of fit of the model was the likelihood ratio (LR)test, which compares the logarithm values of the maximized likelihood function without restriction, represented by $L(\beta|Y, X)$, being beta a vector $\beta = (\beta_0, \beta_1, ..., \beta_p)$ and under H_0 represented by $L(\beta_0|Y, X)$. For this test, it is advisable to use it, in case of hypothesis regarding many coefficients $\beta's$. If there is a big difference, then H_0 is rejected.

The statistics defined for this test are given by:

$$LR = -2loge\lambda = 2\left[l\left(\hat{\beta}|Y,X\right) - l\left(\hat{\beta}_0|Y,X\right)\right] \quad (11)$$

For sufficiently large samples, H_0 is rejected, with a probability level of $100\alpha\%$, if $LR > X^2_{q,1-\alpha}$.

The implementation was done in R language using time series packages such as forecast, besides the package lmvar. Also, a function was implemented to apply the CO modification to the segmented linear model for time series with nonconstant variance (lmsegvar). The implementation is available under request to the authors, but an R package is under development for easier reproducibility.

Results and discussion

The temporal behavior for the time series of the rates of pregnant women with syphilis can be evaluated in Figure 1, where increasing trend and nonconstant variance are observed.

Although the non-constant variance is clear in Figure 1, in the first moment, the classic lmseg model was estimated with confirmation and comparison purposes. The obtained estimates from the lmseg model are presented in Table 1. To check the need of including seasonal terms in the model, the autocorrelation functions were built and no statistical statistically cyclical/seasonal autocorrelation was detected. To verify the presence of nonconstant variance, the Breusch-Pagan test was applied, considering that its null hypothesis is that the errors of a classic segmented linear model (lmseg - Equation 1) have constant variance. From this test, p-value < 0.001 was obtained at a 5% significance level, allowing rejecting the hypothesis of homoscedasticity. Therefore, it is confirmed that the assumption of constant variance was not fulfilled.

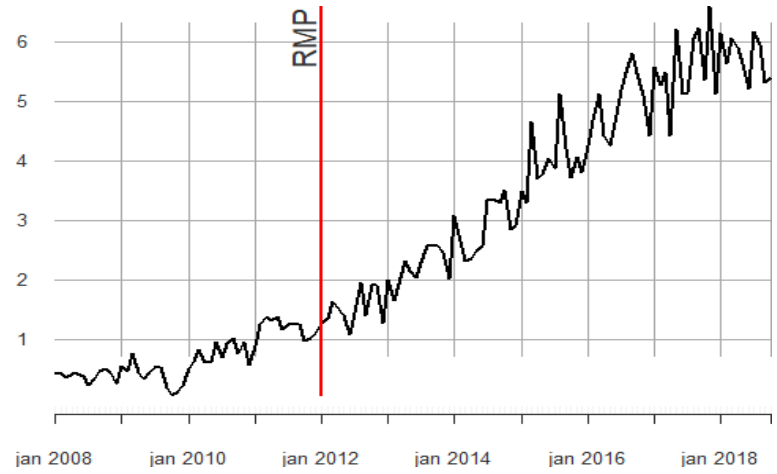

Figure 1. Rate of gestational syphilis occurrences from 2008 to 2018 including periods before and after the RMP Program.

Table 1. Estimated parameters, standard errors (SE), and p-values for the lmseg model.

Parameters	Estimate	SE	p-value
β_0	0.180	0.106	0.090
β_1	0.020	0.003	< 0.001
β_2	0.044	0.004	< 0.001
$\beta_1 + \beta_2$	0.064	0.003	0.001

Thus, it is necessary to construct the intervention model considering the nonconstant variance (lmsegvar - Equation 1 and 2). Table 2 shows the estimates of the parameters of the lmsegvar model while Figure 2 illustrates the estimated model.

When adjusting the models, the estimated parameter of the nonconstant variance was statistically significant (p < 0.0001), as we can see in Table 2. Furthermore, we can also observe an increasing trend

that has been statistically significant since the beginning of the study in 2008 ($\beta 1 > 0$ and $\beta 1 + \beta 2 > 0$). Despite the implementation of the RMP program (intervention), the trend has increased even more ($\beta 2 > 0$ and $p < 0.0001$) after 2012. The average rate increased by about 0.02 per month (0.23 per year) in 100,000 women and, after the intervention in 2012, when the Program was already in operation, an average increase of about 0.06 per month (0.77 per year) was obtained.

For comparison, Figure 3 presents the standardized residuals for gestational syphilis rates over the study period for both lmseg and lmsegvar models. Although both are distributed around zero, the residuals for lmseg indicates heteroscedastic errors, so the variance of errors is nonconstant. Applying the Breusch-Pagan test for the residuals of lmsegvar model, homoscedasticity is verified, but it was not for the traditional linear model lmseg, as presented before.

Figure 4 shows the standard deviation and the 95% confidence interval (CI) for gestational syphilis rates over the study period, from January 2008 to October 2018, highlighting the red linethat corresponds to the standard deviation of errors that is returned from the classic linear model.

Thus, considering the constant variation assumption was not verified for the lmseg model, the next assumptions evaluations are going to be performed only for the lmsegvar model.

Table 2. Estimated parameters, standard errors (SE), and p-values for the lmsegvar model.

Parameters	Estimate	SE	p-value
β_0	0.188	0.062	0.002
β_1	0.019	0.001	< 0.001
β_2	0.045	0.003	< 0.001
$\beta_1 + \beta_2$	0.063	0.004	< 0.001
β_{σ}^2	0.015	0.002	< 0.001

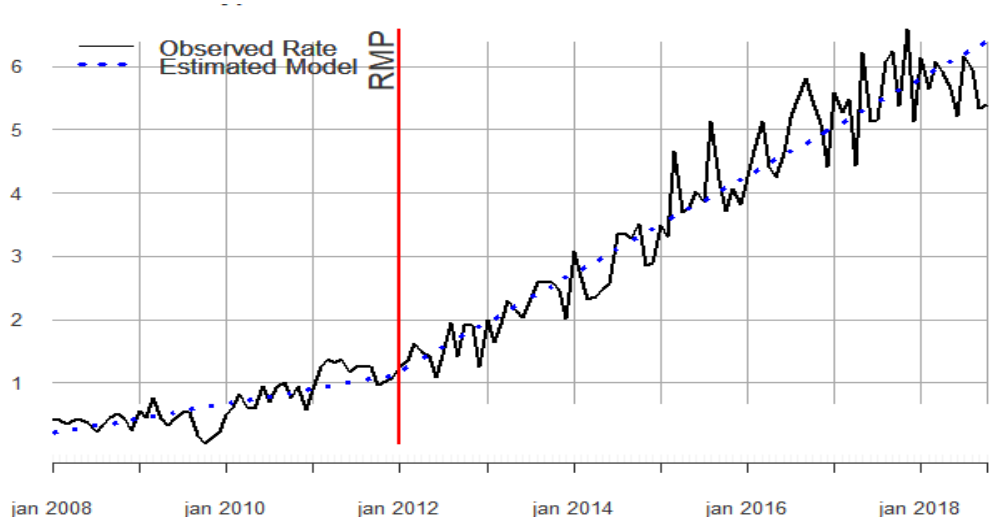

Figure 2. Rates of gestational syphilis occurrences observed before and after the RMP program together with the estimated intervention model with nonconstant variance (lmsegvar).

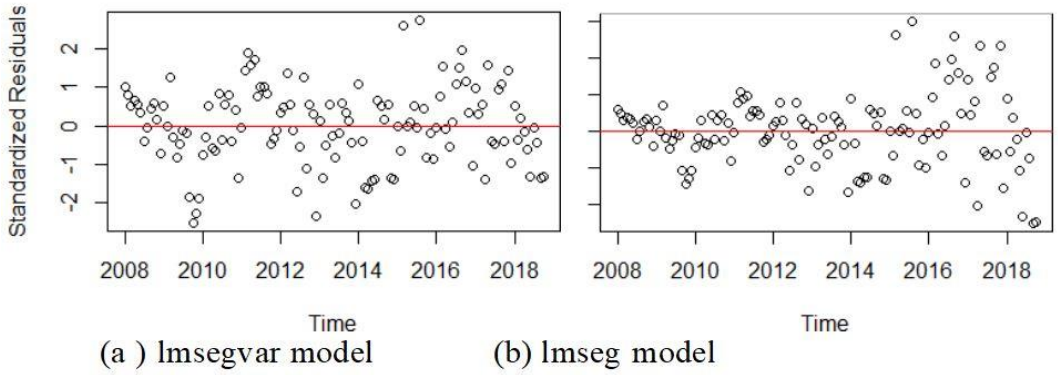

Figure 3. Standardized residuals of gestational syphilis rates versus time.

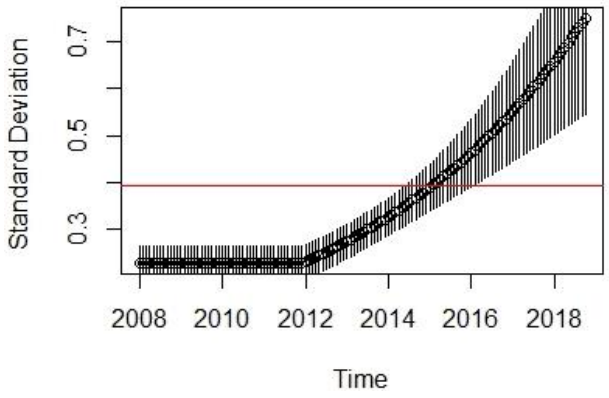

Figure 4. Estimated standard deviation and its 95% confidence interval (CI) for lmsegvar+ CO model. The horizontal line corresponds to the standard deviation of residuals for the lmseg model.

To evaluate the assumption of normality for the residuals of the lmsegvar model, the quantile-quantile plot (Q-Q plot) was additionally used. Thus, by Figure 5, the configuration of the points in the graph is not far from a diagonal line, as expected if the assumption of normality is sustained. To corroborate this statement, the Jarque-Bera test was used, in which the evaluation of the normal distribution was verified in the residuals and the null hypothesis of normality was not rejected (p-value 0.06).

Regarding the evaluation of the independence assumption, from DW test, the calculated d was 1.57. Considering $k = 2$ and $n = 100$, for the tabulated range, d from 1.63 to 1.71 was obtained. Thus, the value of d calculated for pregnant women with syphilis is satisfying the following condition $d < dL$, indicating the existence of autocorrelation between errors, which can be positive or negative. In Figure 6, it is observed that the autocorrelation functions ACF and PACF corroborate the DW test showing significant autocorrelation of order 1. By identifying the autocorrelation in the series of pregnant women with syphilis, the assumption of independence of errors is not being satisfied. In this way, the quality measures of the adjustment are overestimated, in which the tendency estimate tends to be significant, allowing for interpretation errors. To circumvent this scenario, the CO modification (Equation 7) was conducted, in which the existing correlation was estimated, adjusting the regression model so that it is closer to the real and meets the required assumptions. The obtained estimates are shown in Table 3.

After the modification of CO (Table 3) for pregnant women with syphilis, a new d calculated for the Durbin Watson test was obtained, being 2.05. Thus, considering the same values of k and n, we have for the tabulated interval d in the same interval from 1.63 to 1.71, thus fitting the first situation when $d > dU$, i.e., evidencing the absence of autocorrelation of errors. For checking serial correlation of orders up to 5, the BG test also did not reject the null hypothesis of absence of autocorrelation. Furthermore, observing the autocorrelation functions ACF and PACF (Figure 7) after the CO modification, we confirm the absence of significant autocorrelations in the first lags, which were the main concern, especially the first one, taking into account the CO modification. The few weak sample autocorrelations that appear are not at relevant lags, such as seasonal lags, and are within what one would expect in a sample autocorrelation function (approximately 5% can be significant even for a random time series - Chatfield, 2004).

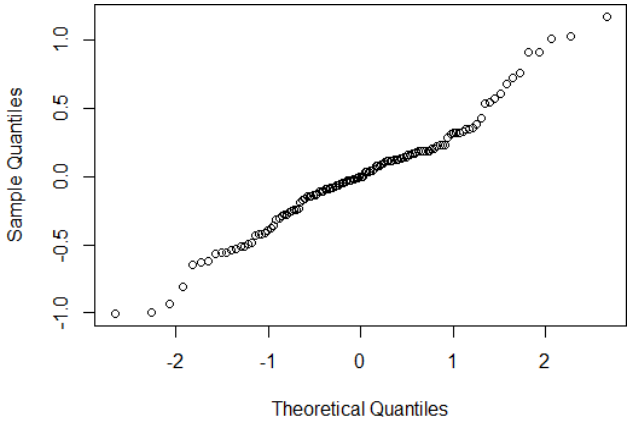

Figure 5. QQ-Plot of the standardized residuals for lmsegvar model.

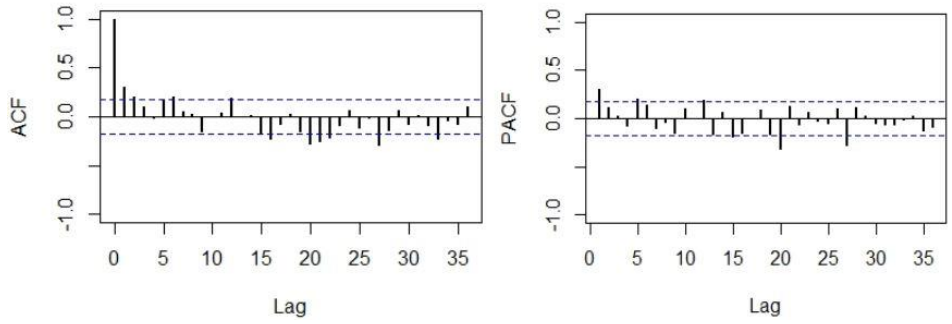

Figure 6. Autocorrelation Function (ACF) and Partial Autocorrelation Function (PACF) of the residuals of gestational syphilis lmsegvar model.

Table 3. Estimated parameter, standard errors (SE), and p-values for the lmsegvar + CO model.

Parameters	Estimate	SE	p-value
β_0	0.129	0.059	0.029
β_1	0.020	0.002	< 0.001
β_2	0.043	0.003	< 0.001
$\beta_1 + \beta_2$	0.063	0.005	< 0.001
β_σ^2	0.016	0.002	< 0.001

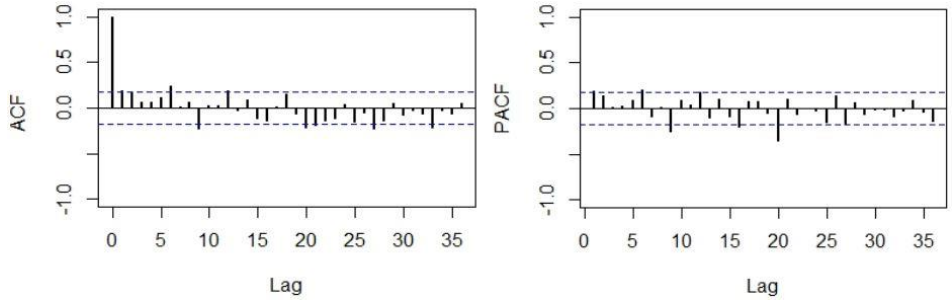

Figure 7. Autocorrelation Function (ACF) and Partial Autocorrelation Function (PACF) of the residuals of gestational syphilis lmsegvar + CO model.

Although from the assumption evaluations, the choice of the adequate model is clear, it is usualto use other measures for model adjustment quality comparisons. Thus, with this purpose, some criteria were used, such as AIC, BIC, and Likelihood Ratio Test. Consequently, the model that best satisfies these criteria will be adopted, in addition to the necessary assumptions.

Table 4 shows the results of the likelihood ratio test, AIC, and BIC, used for comparing the three models. From the likelihood ratio (LR) tests both models (lmsegvar and lmsegvar+CO) obtained $p < 0.001$, so the models offer a significantly better fitting quality compared to the classic linear segmented model (lmseg), although the lmsegvar+CO model stood out with the highest LR (23.71). The results of AIC and BIC corroborate those of the LR test.

Table 4. Results of the likelihood ratio test, AIC, and BIC.

Model	LR	(p-value)	AIC	BIC
lmsegvar + CO	23.71	(p < 0.001)	79.97	94.27
Lmsegvar	20.51	(p < 0.001)	91.65	105.98
Lmseg		-	130.68	142.15

Thus, the lmsegvar + CO model was chosen because all assumptions were fulfilled and it delivered the best fit for the gestational syphilis series.

This study conducted an intervention analysis to assess the trend impact of the RMP Program on the occurrence of gestational syphilis in the State of Paraná. Given the characteristics of time series, an extension of a segmented linear model to time series was performed to model also the nonconstant variance, i.e., to properly consider the presence of heteroscedasticity.

The choice for the class of segmented linear models was made by the ease of interpretation of thetrend and its changes after the occurrence of interventions, the main focus of this study. Although it facilitates the interpretation of estimated parameters, this model also requires that errors are not autocorrelated. In this sense, the Cochrane-Orcutt (CO) modification was implemented to correct the serial correlation of the residuals of the presented model.

Besides the graphical and hypothesis tests evaluation of the required assumptions, comparisons of the adjustment quality were also made from AIC and BIC criteria, as well as the Likelihood Ratio Test. After the comparison, the model that presented the best adjustment was the linear segmented model with nonconstant variance and CO modification. Furthermore, all necessary assumptions were fulfilled. The normal distribution of the residuals was satisfied by the Jarque-Bera test at a significance level of 5%. Homoscedasticity was verified by the Breusch-Pagan test. To verify the existence of autocorrelation of errors, the Durbin-Watson and Breusch-Godfrey tests were performed at a level of 5% of significance, in addition to the analysis of partial (PACF) and autocorrelation (ACF) functions.

Thus, from an adequate model of intervention for time series, it was possible to verify that there has been a growing and statistically significant trend since the beginning of the study in 2008. And, despite the implementation of the PRM program (intervention), the trends increased even more ($p < 0.0001$). The trend was about 0.02 per month (0.23 per year) in 100,000 women before the intervention and increased to 0.06 per month (0.77 per year) after the intervention in 2012.

This same scenario is present in other regions of Brazil, the study of Rezende and Barbosa (2015), conducted in the State of Goiás, from January 2009 to December 2012, shows an increase in the rate of syphilis in pregnant women and congenital syphilis from 2011. This shows an effective increase in the number of cases or an improvement in information due to the reduction of under-reporting (Alves et al., 2016).

Although a reduction could be expected, the RMP program was very useful to reach more women to be treated. The Program is monitoring, analyzing, and identifying pregnant women with syphilis, reducing sub-notification and congenital transmission.

Conclusion

From an adequate model of intervention for time series, it was possible to verify that there has been a growing and statistically significant trend in the rates of pregnant women with syphilis since the beginning of the study in 2008. After the implementation of the RMP Program, the trends increased even more, showing it was very useful to reach more women to be treated.

Further studies are required to continue assessing the efficacy of the program and its current protocols. Also, the follow-up and updating of the model after the introduction of new data is essential for future guidance regarding the problem in question.

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