# Authors' reply

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In the first part of our article, we presented the annual data for the period from January 2003 to December 2014 regarding all 861,901 reported cases of pulmonary tuberculosis (PTB) in individuals aged 10 years or older, as recorded in the Brazilian Ministry of Health National Case Registry Database on October 18, 2016.[1] These data showed a decrease in the total number of cases of PTB, a decrease in the number of new cases of PTB, and a continuous decrease in cure rates, as well as a steady increase in the rates of recurrence, multidrug-resistant TB, and mortality (death from tuberculosis among patients diagnosed with PTB), together with high rates of treatment abandonment.[1] There was no sample selection, and, therefore, selection bias is not possible. We included all available official data, that is, the entire population treated in the period.

Subsequently, we used interrupted time series analysis (ITSA) to determine whether or not there was an association between the irrefutable worsening in the figures regarding PTB and the changes in tuberculosis treatment implemented in 2009.[2,3] At no time did we use the word "causality" mentioned in the letter to the editor. The distinction between "association" and "causality" has been well described in the literature.[4]

The most important variable in assessing infectious disease treatment outcomes is the treatment itself. Therefore, this condition was met in our study. According to Linden,[5] when multiple observations of an outcome variable are available in the pre- and post-intervention periods, ITSA offers a quasi-experimental research design with a high degree of internal validity. According to the literature, one of the strengths of ITSA is the low interference from typical confounding variables that remain reasonably constant (e.g., socioeconomic variables) or change slowly (e.g., Family Health Program coverage or supervised treatment), because these variables are taken into consideration in the long-term trend model.[6] Naturally, the use of the entire population (rather than a sample) strengthened the validity of our study by allowing the control of confounding variables omitted from the statistical analysis, which rejects the low statistical power hypothesis. In fact, because of its robustness, ITSA is used to assess the effects of community interventions, public policies, and regulatory actions; in addition, systematic reviews of the literature have increasingly been including studies that used ITSA as a data analysis tool.[7]

The lack of tuberculin testing (which is used to diagnose latent tuberculosis) and the implementation of the Xpert MTB/RIF assay (which is used to diagnose tuberculosis in patients with negative sputum smear microscopy results) do not affect treatment outcomes in patients with active PTB.

In the "Methods" section of our study,[1] it can be seen that the time frame considered for the implementation of the changes in tuberculosis treatment was from December 2009 to December 2010 (three months after the implementation validation study's date of completion mentioned by the authors of the letter to the editor).

The suggestion that the inferences drawn in our article could not be drawn is in contrast with the literature.[8] In the interpretation of a statistical test, the rejection of the null hypothesis (i.e., when the p value is significant) means that the variables are not independent (i.e., there is a relationship among them), and therefore the opposite is true.[8] Thus, the terms used regarding the inference used in our text are entirely appropriate and correct.

The observation that there are confidence intervals that include null values but show p values less than 0.05 (Figures 2C and 2G) is valid.[1] However, the conclusion from this observation is wrong. It can be easily perceived that there was a misprint (a minus sign is missing before "4.76"). This can be proved by calculating the p value from the confidence interval.[9] When placing a minus sign ($\beta = -8.20$; 95% CI: $-11.58$ to $-4.76$), we find a p value of 0.000003300, that is, $p < 0.0001$, as described in our study; this shows that the reported interval does not include null values. The same is true for Figure 2G and for the slope of the line where the parameters are positive ($p = 0.00001356$, i.e., $p < 0.0001$). Therefore, there were no misinterpretations or methodological limitations in our study, and the data analyzed allow all of the inferences and conclusions drawn in our article.

We thank the authors of the letter to the editor for the critical review of our article. The review allowed us to dispel doubts, clarify concepts, address aspects that we had not addressed, and contribute to the better understanding of ITSA, thereby significantly increasing the strength of the evidence that we presented.

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