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ORIGINAL ARTICLE

# A time-series ecological study protocol to analyze trends of incidence, mortality, lethality of COVID-19 in Brazil

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## Abstract

**Introduction:** since the first case of COVID-19 was confirmed in February 2020, Brazil has reported more than 20 million cases and more than 600,000 deaths on October 31, 2021. The behavior of the pandemic was also different in the various states, from the less developed to the more developed, such as the state of São Paulo.

**Objective:** to describe step-by-step time series for analyzing trends in mortality, lethality and incidence of COVID-19 in Brazil.

**Methods:** a protocol for an ecological study of time series, covering the 26 states and the federal district (Brasilia).

**Results:** the descriptions have the potential to provide information for the government and society in decision-making about knowledge and conduct, clinical, epidemiological and research investments in health care services for the Brazilian people. It is focused on fully understanding the spread of SARS-COV-2 infection in the Brazilian territory and developing a database for public and universal access for comparative studies between countries and continents.

**Conclusion:** databases built from ecological studies are essential for a full understanding of the virus behavior, its transmissibility, lethality and mortality, and a repository for data collected and integrated from multiple sources. They are relevant tools for the search of information and decision-making in global health.

**Keywords:** COVID-19, protocol, time-series, epidemiology, indicators.

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### Authors summary

#### Why was this study done?

The COVID-19 pandemic has hit Brazil hard, and the country has faced serious challenges to control the spread of the infection and prevent deaths from it. However, there is a lack of studies that analyze mortality, lethality, and incidence trends across Brazilian states. There is a need for evidence to support the decision-making process to control the pandemic.

#### What did the researchers do and find?

Researchers will conduct a time series ecological study for each Brazilian state to analyze indicators of incidence, mortality, case lethality of COVID-19 during a given period time, which will be split into two separate waves. Researchers will then analyze determinants that influence the dynamics of those indicators during the period.

#### What do these findings mean?

The findings will provide useful information to government and health authorities to make decisions to control the spread of infection by SARS-CoV-2.

## INTRODUCTION

After the COVID-19 disease was declared a pandemic by the World Health Organization (WHO) in March 2020, governments and health authorities all over the world faced the difficult task of making decisions that seek to minimize the health, social and economic consequences of the pandemic. For example, closing borders, businesses, schools, non-essential establishments, and at the same time seeking strategies regarding when to reopen those activities and establishments<sup>1</sup>.

Brazil is ranked second in fatalities after the United States. Since the first case of COVID 19 was confirmed in February 2020<sup>2</sup>, cases reached more than 20 Million and there were more than 600.000 deaths as of October 31, 2021 (Coronavirus panel).

The country has a vast territory of more than 8,5Km<sup>2</sup>, Brazilian Institute of Geography and Statistics – IBGE<sup>3</sup> and shares borders with ten countries in South America. The pandemic has shown different trends in the various regions of the country and the less economically developed regions have been heavily affected<sup>4</sup>.

The strategies to control the spread of the virus and consequently reduce mortality generally show a lack of coordination between the federal and state governments (University of Miami, COVID Observatory)<sup>5</sup>. Yet, decision-makers need estimates of the number of cases, fatalities, and lethality of the disease that may not be

perfect but well-founded to allow them to make more accurate decisions. For this reason, it is essential to analyze the trends of COVID-19 incidence, mortality and lethality indicators, as well as examine the variability of these indicators over time and how they are modified according to age, sex, and place.

The analysis of those data in a given period supports estimates of disease transmission trends in the future. The conduct of ecological time-series studies may thus play an important role in forecasting those trends<sup>6</sup> and support timely decision-making by health authorities. To conduct such analysis, we created an umbrella protocol to study future scenarios of COVID-19 incidence, mortality, and lethality for each of the 26 Brazilian states and a Federal District (Brasilia).

The objective of this study is to present the protocol for the development of time series ecological studies to analyze the trend of indicators of mortality, lethality and incidence of COVID-19 in all Brazilian states.

## METHODS

This is a population-based umbrella project, where each state of Brazil will be analyzed separately, following a standard protocol for ecological time-series studies. The country has 26 states and a Federal District, distributed into five well-delimited regions (figure 1).

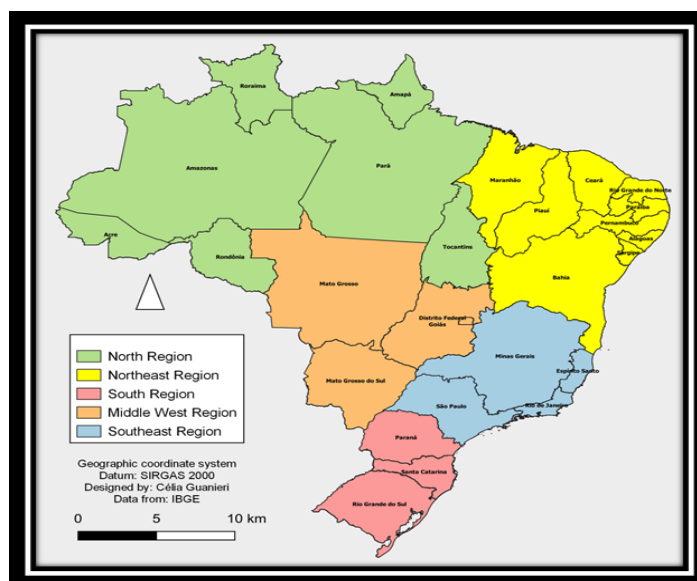
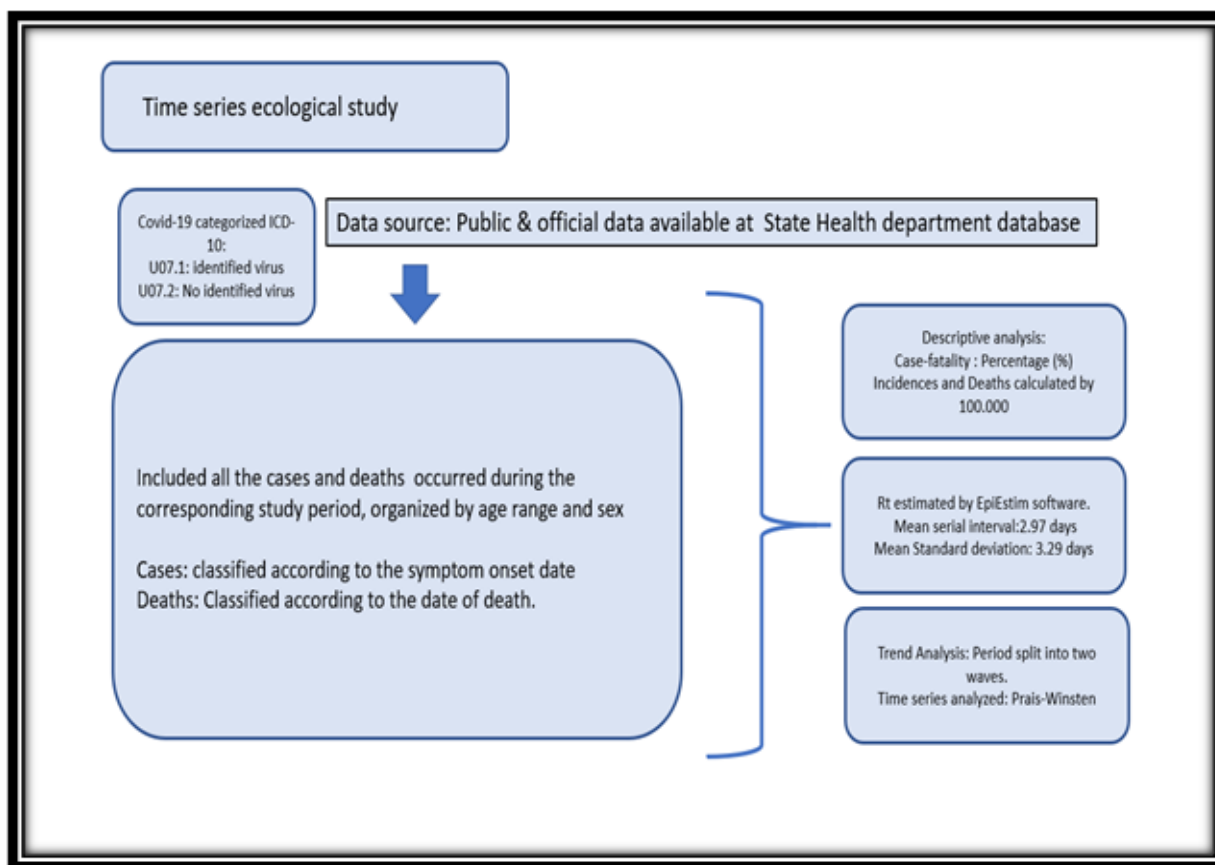


Figure 1: Map of Brazil

Each study will be based on secondary data collected from the official database of the Ministry of Health. Figure 2 shows an overview of the main steps of the protocol that will be followed in each state.

All notifications of cases and deaths of COVID-19 reported during the selected study period will be included

using the International Classification of Diseases 10th edition (ICD-10) of “U07.1 COVID-19, identified virus” or “U07.2 COVID-19, virus not identified”<sup>7</sup>, according to clinical, laboratory or epidemiological confirmation. The cases will be classified according to symptoms and deaths data and organized by date of reporting.



**Figure 2:** Overview of the main protocol stages to analyze incidence, mortality, and case-fatality by COVID-19 in Brazil

Two researchers will extract the data independently to minimize collection bias and guarantee data quality and reliability. In case of disagreements, a third researcher will verify the data. The retrieved data will be organized in an Excel spreadsheet. The effective reproduction number (Rt) will be estimated using the R studio software EpiEstim package<sup>8</sup>, version 2.2.4, a previously time-dependent reproduction number for epidemics guided by Thompson

*et al.*<sup>9</sup>. We employed a mean serial interval of 2.97 days with a mean standard deviation of 3.29 days, as described in prior studies<sup>10,11</sup>.

The incidence (A) and mortality rate (B) will be calculated per 100,000 inhabitants, and case-fatality (C) represented as a ratio. Those indicators will be calculated according to the formulas below:

(A) $\frac{\text{number of cases}}{\text{population}} \times 100.000$	(B) $\frac{\text{number of deaths}}{\text{population}} \times 100.000$	(C) $\frac{\text{number of deaths}}{\text{number of cases}} \times 100$
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**Legend:** (A) - Incidence rate ; (B) - Mortality rate ; (C) - Case fatality

The mortality rates for the entire period will be stratified by sex and age. The population will be taken from state projections for the year 2020<sup>12</sup>. For the trend analysis, time periods will be split into two separate waves. The first wave will end in the month with the lowest mortality rate, which indicates the end of the wave. Time series analysis and calculation of the mortality and fatality trends will follow the method proposed by Antunes and Cardoso<sup>13</sup>, based on the the Prais-Winsten regression model for population mortality rates.

The following values will be calculated: probability

(p), and Daily Percent Change - DPC, considering a 95% level of significance, as illustrated in the following formula:

(D) $DPC = [-1 + 10^{\beta}] * 100\%$ (E) $IC\ 95\% = [-1 + 10^{\beta_{min}}] * 100\%; [-1 + 10^{\beta_{max}}] * 100\%$
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**Legend:** (D) - Daily Percent Change ; (E) - level of significance

The STATA 14.0 software (College Station, TX, U.S. 2013) will be used for statistical analysis. The

effective reproduction number ( $R_t$ ) will be estimated using R studio software EpiEstim package<sup>8</sup>, version 2.2.4, a time-varying reproduction number for epidemics developed by Thompson and colleagues<sup>9</sup>. As described in previous studies, there will be used a mean serial interval of 2.97 days with a mean standard deviation of 3.29 days<sup>10,11</sup>.

## DISCUSSION

To our knowledge, this is the first umbrella project aimed at analyzing trends in incidence, mortality, and case lethality of COVID-19 in all Brazilian states applying the method of time series ecological design. There is evidence<sup>14</sup> that the examination of the variability of incidence, mortality, and case-fatality in a defined period enables better understanding of the trends of the COVID-19 pandemic, which is essential to assess its severity and risks.

Conversely, the use of the traditional cumulative case-fatality rates may potentially underestimate the real mortality and morbidity<sup>15</sup>, since each state and/or region in Brazil has experienced different trends.

This protocol uses official, public secondary data from the Ministry of Health, which is the best source of information about the COVID pandemic in Brazil. The time series regression method suggested in this protocol will allow the calculation of Daily Percent Change (DPC) in mortality rates, which is useful to assess the trend variability of the pandemic in each state.

On the other hand, the studies developed with this protocol will provide partial information because the pandemic is still ongoing.

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## CONCLUSION

The evidence available in Brazil does not meet the demands of the pandemic of COVID-19. Population studies showing the reality of each state and/or region are relevant to support public health initiatives to prevent and control the spread of this disease.

Results of these studies will provide guidance for decision-makers and are valuable for future research analyzing the trends of incidence, mortality, and case fatality of COVID-19.

The database built from ecological studies are essential for a full understanding of the virus behavior, its transmissibility, lethality and mortality, and a repository for data that’s been collected and integrated from multiple sources. It is a relevant tool for the search of information and decision-making in global health.

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## Conflict of interest

The authors declare no conflicts of interest.

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## Resumo

**Introdução:** a Introdução: Desde que o primeiro caso de COVID-19 foi confirmado em fevereiro de 2020, o Brasil notificou mais de 20 milhões de casos e mais de 600.000 mortes em 31 de outubro de 2021. O comportamento da pandemia também foi diferente nas várias regiões do país, desde aquelas de menor desenvolvimento econômico à de maior desenvolvimento econômico, tal qual o Estado de São Paulo.

**Objetivo:** descrever o passo a passo de séries temporais para análise das tendências de mortalidade, letalidade e incidência de COVID-19 no Brasil.

**Método:** etapas de um protocolo para um estudo ecológico de séries temporais e com cobertura dos 26 Estados e Distrito Federal (Brasília).

**Resultados:** as descrições possuem potencial de prover informações para o governo e sociedade nas tomadas de decisões acerca do conhecimento e conduta, clínica, epidemiológica e de investimentos em pesquisa cuidados à saúde do povo brasileiro, com foco no pleno entendimento da disseminação da infecção pelo SARS-CoV-2 em território brasileiro, bem como desenvolver banco de dados para acesso público e universal para estudos comparativos entre países e continentes.

**Conclusão:** banco de dados construídos a partir de estudos ecológicos são imprescindíveis ao pleno entendimento do comportamento do vírus, sua transmissibilidade, letalidade e mortalidade, bem como constitui-se em repositório para busca de informações e tomadas de decisão em saúde pública.

**Palavras-chave:** COVID-19, protocolo, séries temporais, epidemiologia, indicadores.

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