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PERSISTENCE AND CHANGES IN EMERGING COVID-19 SPACE-TIME CLUSTERS IN BRAZILIAN MUNICIPALITIES IN 2020-2021

PERSISTÊNCIA E MUDANÇAS EM *CLUSTERS* ESPAÇO-TEMPORAIS EMERGENTES DE COVID-19 NOS MUNICÍPIOS BRASILEIROS EM 2020-2021

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ABSTRACT

The impacts of COVID-19 in Brazil are evident and exacerbate the country´s inequalities. This study aimed to analyze the persistence and changes in the log-likelihood ratio (LLR), radius, duration, observed and expected number of cases, p-values, number of municipalities, population, and the relative risk of space-time clusters of COVID-19 cases identified in Brazilian municipalities in the epidemiological weeks with peak transmission in 2020 and 2021. The study period was from the epidemiological week (EW) 09-2020 to EW 29-2021 (23 February 2020 to 24 July 2021). The prospective space-time scan was performed during the EW with peaks in case numbers and repeated in the five subsequent EWs to verify clusters' persistence and changes over space and time. COVID-19 clusters were identified in a large part of Brazil´s territory. Over the analyzed period, the clusters´ disposition patterns became increasingly similar, and the clusters were identified in akin locations. The detected clusters also became more persistent, with longer duration; and stronger, with higher LLR. The methodology identified areas with greater risk of COVID-19 that should be prioritized for better allocation of health resources to mitigate transmission.

Keywords: COVID-19. Space-time clusters. Epidemiological surveillance. Spatial analysis. Space-time scan.

RESUMO

Os impactos da COVID-19 no Brasil são evidentes e exacerbam as desigualdades do país. Este estudo teve como objetivo analisar a persistência e as mudanças nas na razão de log-verossimilhança (LLR), raio, duração, número de casos observados e esperados, valores de p, número de municípios, população e no risco relativo dos aglomerados espaço-temporais dos casos de COVID-19 identificados nos municípios brasileiros nas semanas epidemiológicas com pico de transmissão em 2020 e 2021. O período do estudo foi da semana epidemiológica (SE) 09-2020 a SE 29-2021 (23 de fevereiro de 2020 a 24 de julho de 2021). A varredura prospectiva espaço-temporal foi realizada durante as SE's com picos no número de casos e repetida nas cinco SE's subsequentes para verificar a persistência dos *clusters* e as mudanças no espaço e no tempo. *Clusters* de COVID-19 foram identificados em grande parte do território brasileiro. Ao longo do período analisado, os padrões de disposição dos *clusters* tornaram-se cada vez mais semelhantes e os *clusters* foram identificados em localizações similares. Os clusters detectados também se tornaram mais persistentes, com maior duração; e fortes, com maior LLR. A metodologia identificou áreas com maior risco de COVID-19 que devem ser priorizadas para melhor alocação de recursos de

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saúde para mitigar a transmissão.

Palavras-chave: COVID-19. Clusters espaço-temporais. Vigilância epidemiológica. Análise espacial. Análise espaço-temporal.

INTRODUCTION

COVID-19 is a predominantly respiratory disease caused by SARS-CoV-2, the novel coronavirus. The first outbreak of the disease occurred in December 2019 based on the identification of a series of cases of pneumonia with unknown etiology in Wuhan, China (HUANG *et al.*, 2020). Despite efforts by the Chinese government to contain the disease, the virus soon spread to other countries, and on 11 March 2020, the World Health Organization declared COVID-19 a pandemic (KAMEL BOULOS; GERAGHTY, 2020).

The first case in Brazil was reported on 26 February that same year, and new cases were soon reported throughout the country. As of July 2021, Brazil was the country with the third most cases and the second most deaths from COVID-19 (JOHNS HOPKINS UNIVERSITY, 2020). In a country like Brazil with continental dimensions and wide cultural, demographic, and socioeconomic heterogeneity, the impacts from COVID-19 became increasingly evident and called attention to the existing regional and intraregional inequalities (FREITAS *et al.*, 2020; NIQUINI *et al.*, 2020).

During the emergence of new infectious diseases such as COVID-19, it is important for epidemiological surveillance to adopt approaches that allow assessing the progression of the disease in space and time, such as the space-time scan statistic (KULLDORFF, 1997). This technique is a well-established methodology that is a great ally of Public Health and has been widely employed in studies on different diseases, such as measles (YIN *et al.*, 2007), thyroid cancer (KULLDORFF, 2001), tuberculosis (SANTOS NETO *et al.*, 2015), and Dengue, Zika, and Chikungunya (FREITAS *et al.*, 2020). This technique allows the detection of statistically significant clusters of disease and thus areas with increased risk of illness or death (KULLDORFF, 2001).

To detect active or emerging clusters at the time of the analysis, the prospective space-time scan statistic can be applied. An important positive point in this analysis is the possibility of repeating the scan several times as new data become available, thus allowing the identification and monitoring of new clusters to verify changes in their characteristics in time and space. This can be a powerful tool for the epidemiological surveillance during ongoing epidemics. Prospective space-time scan has been used by various authors during the COVID-19 pandemic (DESJARDINS *et al.*, 2020; FERREIRA *et al.*, 2022; MARTINES *et al.*, 2021). When performed periodically, the methodology allows verifying the persistence and changes in the clusters´ characteristics over space and time, which can help answer questions on the best locations and periods to implement measures to control the disease, to decrease transmission (HOHL *et al.*, 2020).

However, despite the clear importance of the identification of areas at high risk for COVID-19 to the epidemiological surveillance, the spatial and spatio-temporal approaches were not widely used by authors during the pandemic, especially during its beginning (GIULIANI *et al.*, 2020).

Given the above, the current study aimed to analyze the persistence and changes in the log-likelihood ratio (LLR), radius, duration, observed and expected number of cases, p-values, number of municipalities, population, and the relative risk of space-time clusters of COVID-19 cases identified in Brazilian municipalities in the epidemiological weeks with peak transmission in 2020 and 2021.

METHODOLOGY

Study Design

The study design is ecological, analytical, and exploratory, and the units of analysis were space-time clusters of COVID-19 cases identified in the selected periods.

Data Source

Brasil.io, available on the site with the same name (Brasil.IO, 2020), was used to obtain the number of COVID-19 cases in Brazilian municipalities by epidemiological week (EW) of notification from EW 09-2020, when the first case was identified, to EW 29-2021, including the period from 23

February 2020 to 24 July 2021. The Brasil.io platform is updated daily, and its source is the official data reported by the Health Departments of Brazil´s 27 states. The official population estimates of the Brazilian municipalities were retrieved from the Instituto Brasileiro de Geografia e Estatística (IBGE) website (The Brazilian Institute of Geography and Statistics, in English).

Data Analysis

COVID-19 cases by municipality were collected in Brasil.io and aggregated by epidemiological week (EW) in a database containing the municipality’s code, its estimated population, the number of confirmed cases, and the epidemiological week. The analysis covered the period from EW 9-2020, when the first COVID-19 case was reported in Brazil, to EW 29-2021, including the period from 23 February 2020 to 24 July 2021.

Graphs were prepared using Microsoft Excel to observe the evolution of COVID-19 cases by EW of notification, to identify transmission peaks. Having done this, the EWs with peaks in cases were selected to perform prospective space-time scan (KULLDORFF, 2001) in the SaTScan software (v.10.0.1) to detect clusters of COVID-19 cases. We opted to perform the analysis in the weeks of peak transmission to allow observing which areas presented increased risk in the pandemic´s most critical moments in Brazil.

Prospective space-time scan was performed, based on the Poisson discrete model, which considers the number of cases and the population at risk over time. The study thus assumed that the distribution of cases follows Poisson distribution.

The proposed method is based on mobile cylinders positioned over the municipal seats of Brazil´s municipalities, the heights of which represent the temporal scan and the circular bases of which (with radius R) represent the spatial scan. The cylinders expand until they encompass a given percentage of the total population at risk or reach the established maximum limits. As the cylinders expand, tests of statistical significance are performed to verify whether the region demarcated by the circumference corresponds to a cluster. The likelihood function is maximized over all municipalities and window sizes, with the one with the maximum likelihood (highest LLR) being the most likely cluster and the one with the lowest probability of having occurred due to chance. The likelihood ratio for this distribution-based window is obtained via the Monte Carlo method. The 'p-value is obtained by comparing the 'rank' of the maximum likelihood real data set with the maximum likelihood of the random data sets (KULLDORFF, 1997).

The epidemiological weeks with peak transmission selected for space-time scan were EWs 30 and 51 of 2020 (2020-30 and 2020-51) and EWs 12 and 24 of 2021 (2021-12 and 2021-24). Although the peak EWs were selected, the method considers the entire previous period present in the dataset, that is, from EW 09 of 2020, which began on 23 February. Thus, EW 2020-30 encompasses the period from 23/02/2020 to 25/07/2020; EW 2020-51 encompasses the period from 23/02/2020 to 19/12/2020; EW 2021-12 the period from 23/02/2020 to 27/03/2021; and EW 2021-24 the period from 23/02/2020 to 19/06/2021.

Prospective space-time scan detects active and statistically significant clusters (p-value < 0.05), i.e., with excess relative risk, up to the last day in which the data were collected and discards clusters with excess relative risk without statistical significance (DESJARDINS *et al.*, 2020). We thus chose to perform the scan at peak moments to allow observing where the active clusters were located at critical moments in the pandemic.

As a result, this scan presents the primary cluster, the one with the highest log-likelihood ratio (LLR), which is the most probable, and secondary clusters (ranked according to their LLR), their radiuses, their initial and final epidemiological weeks, the observed and expected numbers of cases, p-values, number of municipalities, the population in the clusters, and the relative risk (RR) of the identified clusters. It is important to highlight that the relative risk of the cluster is not homogeneous within it and that each municipality encompassed by the cluster has different relative risks. Thus, the RR of some municipalities encompassed by the primary cluster was pointed out.

This relative risk is calculated as the division between the number of observed and expected cases in the cluster, divided by the ratio between the number of observed and expected cases outside the cluster. That is:

$$RR = \frac{c \ / \ E\ [c]}{(C - c) \ / \ (E\ [C] - E\ [c])} = \frac{c \ / \ E\ [c]}{(C - c) \ / \ (C - E\ [c])}$$

Where “c” is the number of cases or deaths in each cluster and “C” is the total number of cases in the dataset.

Various parameters were tested in SaTScan for this study, and we ultimately selected the maximum sizes for each cluster as 10% of the total population at risk and 1,000 km as the maximum radius, to avoid clusters too large for interpretation, as well as 50% of the study period. Each cluster duration was set to a minimum of 1 EW and the clusters must contain a minimum of two confirmed cases of COVID-19. The other parameters were set at default.

The clusters detected in peak EWs (2020-30, 2020-51, 2021-12, and 2021-24) were monitored for up to five epidemiological weeks to verify their persistence in space and changes in their characteristics. Space-time scan was thus repeated weekly until completed five weeks after the peak week. For example, to monitor the clusters of cases identified in EWs 2020-09 and 2020-30, we repeated the analysis adding the cases notified in EWs 2020-31, 2020-32, 2020-33, 2020-34, and 2020-35. Importantly, the aim of this stage was not to analyze the clusters singly in each period, but to verify their persistence and changes in their characteristics across space and time, as done by Hohl (2020).

Further in this stage, we analyzed the clusters´ distribution by EW for each target period. We also elaborated a series of graphs with the variations in the clusters´ characteristics over the course of the respective EWs (population in the clusters, observed cases, expected cases, number of clusters, number of municipalities, mean radius of the clusters in km, mean duration in epidemiological weeks, mean LLR, and mean relative risk) (Figure 4).

Since the study used secondary data in the public domain, it dispensed with ethical review by the Institutional Review Board of the Sergio Arouca National School of Public Health (ENSP-Fiocruz), according to Exemption from Ethical Review no. 06/2022.

RESULTS

From the confirmation of the first case in epidemiological week 09 of 2020 to EW 29 of 2021 (23 February 2020 to 24 July 2021), 19,360,825 COVID-19 cases were reported in Brazil. Of this total, 7,652,747 were reported in 2020 and 11,708,078 in 2021. Figure 1 shows the graphs with the curves of cases reported in Brazil in 2020 (a) and 2021 (b).

The increase in the number of cases was slow in Brazil until week 23 of 2020 (31 May to 06 June), when the country began to display an extensive transmission level. Brazil reached the first peak in cases in EW 30 (19-25 July), followed by a downward trend in subsequent weeks and an upward trend in cases from EW 45 (01-07 November) to EW 51 (13-19 December), when the country reached the second peak.

In the initial weeks of 2021, Brazil reported high numbers of cases compared to the previous year, with an upward trend starting in EW 7 (14-20 February). In week 12 (21-27 March), the country reached the third transmission peak, followed by a slight drop and an increase in cases in EW 24 (13-19 June) that lasted until the following week and preceded another drop in case notifications.

The epidemiological weeks with high notification numbers and that were selected for the analyses were EWs 30 and 51 of 2020 and EWs 12 and 24 of 2021.

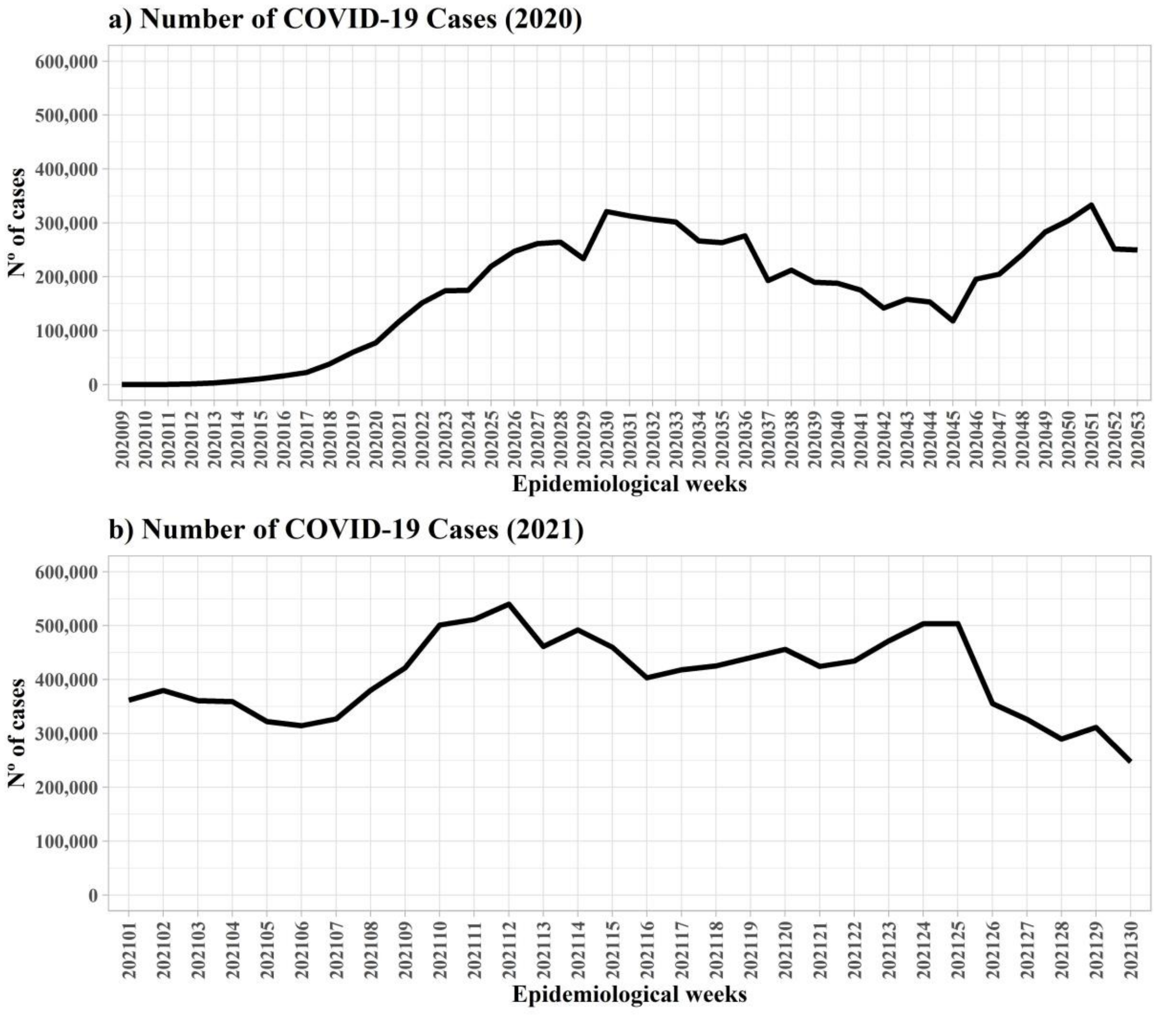
Figure 2 presents the clusters detected in the period from EWs 09-30 of 2020 (23/02-25/07) (a) and from EWs 09-51 of 2020 (23/02-19/12) (b) and clusters detected in the five subsequent epidemiological weeks. The primary cluster identified on the peak transmissions (EW 30 of 2020 and on EW 51 of 2020) is highlighted with the number “1”.

Nine clusters were detected in the analysis of EWs 09-30 of 2020 (23/02-25/07). The first clusters became active in EW 20 (10/05-16/05). At least one municipality per Brazilian state was encompassed by a cluster. The primary cluster (identified in Figure 2-a with the number "1" on the EW 30 of 2020), in other words, the cluster with the highest log-likelihood ratio (LLR), which is the one with the least probability of occurring due to chance, was detected over part of the North and

Northeast regions in Brazil. 608 municipalities were encompassed by cluster 1. Of these, 80.43% had RR greater than 1, ranging from 1.01 to 25.61. The municipalities with the highest relative risks were Pedra Branca do Amapari (RR=25,61) and Serra do Navio (RR=17,24), both in the state of Amapá. Larger clusters were identified in the North of Brazil and medium and smaller clusters in the country´s other regions. Starting in EW 31 (26/07-01/08), the clusters´ distribution changed and remained similar in the following weeks. A cluster emerged that covered the entire state of Roraima, besides smaller clusters mainly in the Southeast region starting in EW 33 of 2020 (09/08-15/08).

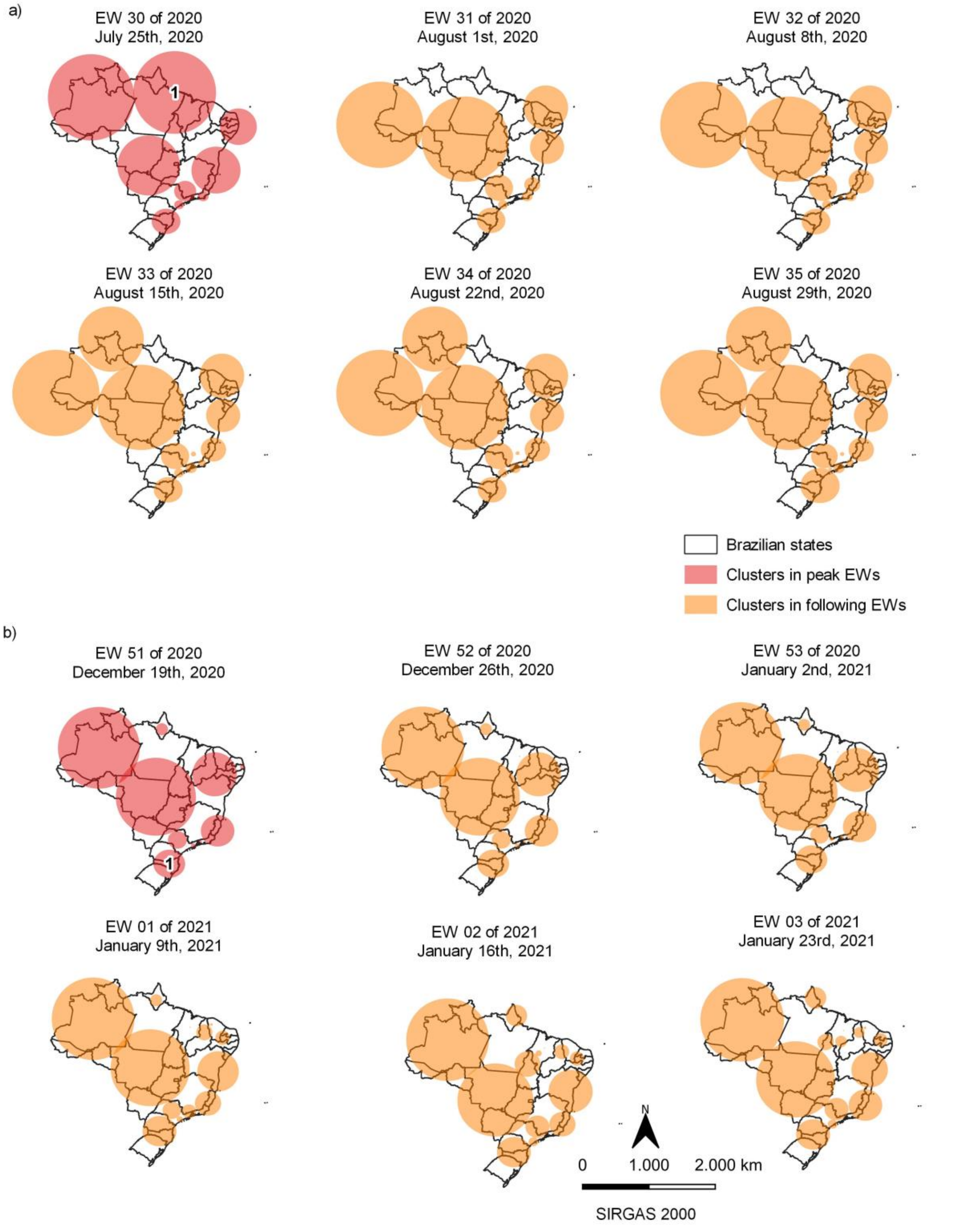
Sixteen clusters of COVID-19 cases were detected in EWs 09-51 of 2020 (23/02-19/12). In this period, the clusters became active starting in EW 48 of 2020 (22/11-28/11). The distribution of these clusters remained quite similar until EW 53, the last epidemiological week of 2020. In EW 01 of 2021 (03/01-09/01), 31 clusters were detected in Brazil. This period saw an increase in some clusters located in the country´s South and Southeast and the emergence of clusters including just one municipality each in the states of Pará and Maranhão. The primary cluster (identified in Figure 2-b with the number "1" on the EW 51 of 2020), with the highest LLR, was detected over the Southern region of the country. This cluster encompassed 724 municipalities, of which 79.69% had RR greater than 1, varying between 1.00 and 9.45. The municipalities within this cluster with the highest RR were Santa Cecília do Sul (RR = 9.45), in the state of Rio Grande do Sul, and Presidente Castello Branco (RR = 6.65), in Santa Catarina.

Figure 1 – Number COVID-19 cases in 2020 (a) and in 2021 (b)



Source: Own elaboration based on data from the State Health Departments and consolidated by the Brasil.io project.

Figure 2 – Clusters detected in the period from EWs 09-30 of 2020 (23/02-25/07) (a) and from EWs 09-51 of 2020 (23/02-19/12) (b), the primary clusters identified on these EWs (represented with the number "1"), and clusters detected in the five subsequent epidemiological weeks in Brazil



Source: Own elaboration based on data from the State Health Departments and consolidated by the Brasil.io project.

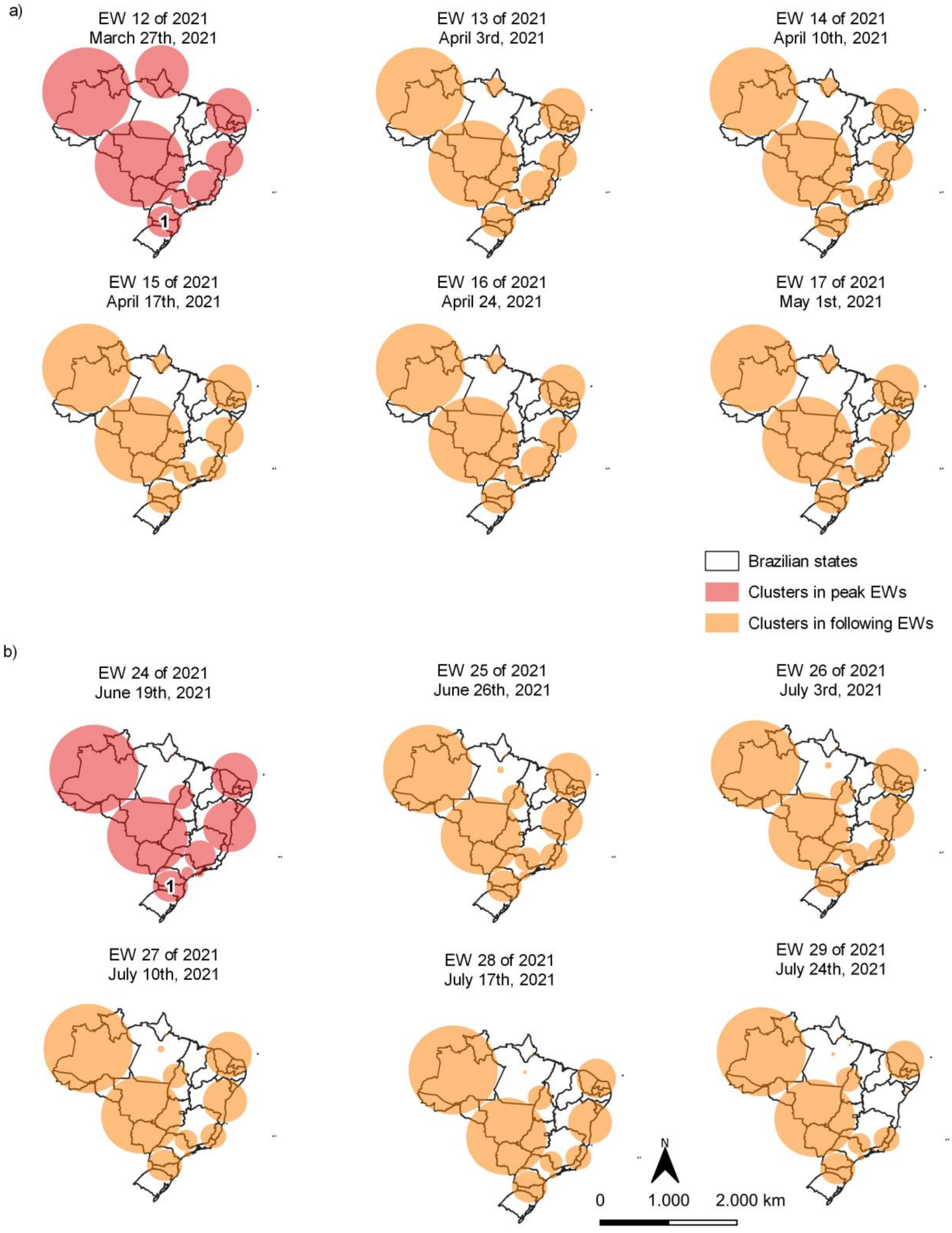
Figure 3 shows the clusters detected from EW 09 of 2020 to EW 12 of 2021 (23/02/2020-27/03/2021) (a) and from EW 09 of 2020 to EW 24 of 2021 (23/02/2020-19/06/2021) (b) and the clusters detected in the five subsequent epidemiological weeks. The primary cluster identified on the peak transmissions (EW 12 of 2021 and on EW 24 of 2021) is highlighted with the number “1”.

Twelve clusters were identified from EW 09 of 2020 to EW 12 of 2021 (23/02/2020 -27/03/2021), and the first clusters became active starting in EW 46 of 2020 (08/11-14/11). Large clusters were identified in municipalities in the states of Acre, Amazonas, and Roraima, in the North of Brazil, and mostly in municipalities in the states of Mato Grosso, Mato Grosso do Sul, and Goiás in the Central-West. Intermediate clusters were identified along the Brazilian coast. The primary cluster (represented in Figure 3-a with the number "1" on the EW 12 of 2021) was identified over the Southern region of Brazil and encompassed 890 municipalities. 95,05% of these municipalities showed RR greater than 1, and those with higher RR were Presidente Castello Branco (RR = 10,98) and Jardinópolis (RR = 8,69), both in the state of Santa Catarina. Changes were seen in the radiuses of some clusters, besides a decrease in the number of clusters starting in EW 14 of 2021, but the clusters´ distribution was largely quite similar from EW 12 to EW 17 of 2021 (21/03-01/05).

Ten clusters were identified from EW 09 of 2020 to EW 24 of 2021 (23/02/2020-19/06/2021), which started to be detected in EW 46 of 2020 (08/11-14/11). Two large clusters were detected in the states of Acre, Rondônia, Amazonas, Roraima, Pará, Tocantins, Mato Grosso, Mato Grosso do Sul, Goiás, Minas Gerais, São Paulo, and Paraná. Intermediate and smaller clusters were detected along the Brazilian coast. The primary cluster (identified in Figure 3-b with the number "1" on the EW 24 of 2021) was detected over the Southern region of Brazil and encompassed 890 municipalities. 96,96% of these municipalities had RR greater than 1,00, ranging from 1,00 to 6,51. The municipalities with the highest RR were Kaloré (RR = 6,51), in the state of Paraná, and Presidente Castello Branco (RR = 6,16), in Santa Catarina. Several new clusters with smaller radiuses were identified in the subsequent EWs in the North, Northeast, and Southeast.

The clusters identified in EWs 12-17 and EWs 24-29 (Figure 3) displayed high similarity, indicating a more stabilized moment in the pandemic, where the curves of cases in the municipalities showed a certain degree of synchronicity.

Figure 3 – Clusters detected in the period from EWs 09 of 2020 to EW 12 of 2021 (23/02/2020-27/03/2021) (a) and from EWs 09 of 2020 to EW 12 of 2021 (23/02/2020-19/06/2021) (b), the primary clusters identified on these EWs (represented with the number “1”) and clusters detected in the five subsequent epidemiological weeks in Brazil



Source: Own elaboration based on data from the State Health Departments and consolidated by the Brasil.io project.

Figure 4 shows the graphs with changes in the clusters´ characteristics over the course of the epidemiological weeks.

The population in the clusters (Figure 4a) remained around 135 million in EWs 31-35 of 2020 (26/07-29/08). In the last three epidemiological weeks of 2020, the population in the clusters remained around 100 million, increasing to more than 120 million in the first week of 2021. The clusters identified in EWs 12-17 (21/03-01/05) and 24-29 (13/06-24/07) of 2021 showed a population of around 140 million.

As expected, the number of observed cases (Figure 4b) and expected cases (Figure 4c) in the clusters shows an increase over the course of the epidemiological weeks. However, both decreased slightly in the first weeks of 2021. The clusters identified in EW 28 of 2021 (11/07-17/07) showed the most observed cases (more than 9.2 million) and expected cases (more than 5 million).

An average of 11 clusters were identified in the analyses of EWs 30-35 (19/07-29/08), EWs 12-17 (21/03-01/05), and EWs 24-29 (13/06-24/07) of 2021 (Figure 4d). There was an increase in the number of clusters detected from EW 51 of 2020 to EW 01 of 2021 (13/12/20-09/01/21), followed by a drop. An average of 25 clusters were identified in each epidemiological week during this period.

The curves in the numbers of municipalities in the clusters (Figure 4e) showed similar patterns to the population curves (Figure 4a), except for the analysis of EWs 24-29 of 2021 (13/06-24/07). Overall, approximately 3,400 municipalities were encompassed by the clusters in the analyses of EWs 30-35, EW 51 of 2020 to EW 03 of 2021, and EWs 24-29 of 2021. In EWs 12-17 (21/03-01/05) of 2021, this number increased to a mean of 3,900 municipalities.

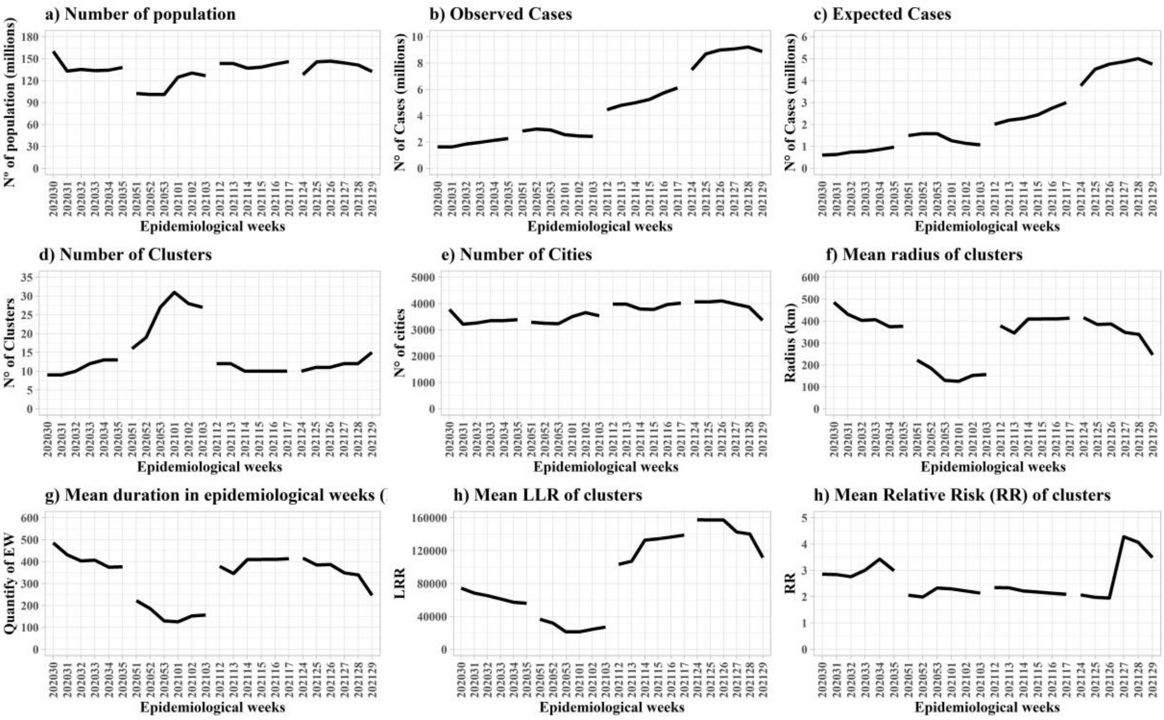
The mean radius of the clusters (Figure 4f) decreased over the course of the EWs in 2020. Clusters with smaller radiuses were identified in the period from EW 51 of 2020 to EW 03 of 2021 (13/12/20–09/01/21), with a range of 125-222km, contrasting with the other periods analyzed, which generally showed mean radiuses greater than 300km.

As expected, the clusters´ duration (Figure 4g) increased over the course of the COVID-19 pandemic process in Brazil. The clusters identified in EWs 30-35 (19/07-29/08) of 2020 lasted an average of 7.9 weeks, those identified from EW 51 of 2020 to EW 03 of 2021 (13/12/20-09/01/21) lasted an average of 15 weeks, those from EWs 12-17 of 2021 (21/03-01/05) lasted an average of 15.9 weeks, and those from EWs 24-29 (13/06-24/07) of 2021 lasted an average of 26.7 weeks.

The clusters´ log likelihood ratio (LLR) (Figure 4h) decreased over the course of the analysis starting at EW 30 of 2020. The clusters identified from EW 51 of 2020 to EW 03 of 2021 (13/12/20-09/01/21) showed the lowest LLRs (on average, 27,000). The clusters identified in EWs 12-17 (21/03-01/05) and EWs 24-29 (13/06-24/07) of 2021 showed higher LLRs, ranging from 103,251 to 157,582.

The mean relative risk (RR) of the clusters (Figure 4i) identified in EWs 30-35 (19/07- 29/08) of 2020 was around 3.00 throughout the analyses. In the period from EW 51 of 2020 to EW 03 of 2021 (13/12/20-09/01/21) and EWs 12-17 (21/03-01/05), the clusters´ mean RR ranged from 1.99 to 2.35. The clusters´ mean RRs were highest in EWs 28 (RR=4.28) and 29 of 2021 (RR = 4.07), respectively, from 11 to 24 July 2021.

Figure 4 – Changes in the clusters' characteristics over the course epidemiological weeks



Source: Own elaboration based on data from the State Health Departments and consolidated by the Brasil.io project.

DISCUSSION

This study involved a prospective space-time scan (KULLDORFF, 1997) in four important periods in the COVID-19 pandemic process in Brazil that showed peaks in the number of reported cases. The approach allows identifying patterns of the disease, which can back interventions and public policies to decrease SARS-CoV-2 transmission and improve health resource allocation. Prospective space-time scan has been used by various authors to detect areas at greater risk of COVID-19 (ALQADI *et al.*, 2021; DESJARDINS; *et al.*, 2020; GOMES *et al.*, 2020; HOHL *et al.*, 2020; KULLDORFF, 2001). The technique has also been applied to specific periods with peaks in COVID-19 cases to monitor clusters of the disease at the most critical moments of the pandemic (FERREIRA *et al.*, 2022; LU *et al.*, 2022).

We adapted the methodology used by Hohl *et al.* (2020), repeating the prospective space-time scan periodically to analyze the persistence and changes in the characteristics of clusters of COVID-19 cases identified in epidemiological weeks with peak transmission in Brazil. As far as we know, this is the first study to apply this methodology to COVID-19 in Brazil.

Brazilian municipalities began their COVID-19 case counts in different epidemiological weeks, resulting in distinct epidemiological trajectories. This is due not only to the dynamics of SARS-CoV-2 spread (MAGALHÃES *et al.*, 2021), notified first in large metropolises, but also to the lack of diagnostic tests (KAMEDA *et al.*, 2021). Although the World Health Organization recommended mass testing to understand the COVID-19 scenario in Brazil and to attempt to break the virus´ transmission chain (WORLD HEALTH ORGANIZATION, 2020), the Brazilian government showed lack of coordination and unpreparedness to purchase the necessary inputs for conducting tests, resulting in large numbers of unreported cases (OLIVEIRA; ARAÚJO, 2020).

The above-mentioned factors contributed to the slow increase in the number of cases in the first epidemiological weeks of 2020. Brazil recorded a slow increase in the number of cases and reached the first transmission peak in late July, followed by a drop that coincided with the flexibilization of social isolation measures and a new peak in mid-December, close to the year-end holidays and vacation season (DE SOUZA *et al.*, 2021). The year 2021 was marked by a large increase in the number of cases compared to the previous year, which can be explained by the introduction of more transmissible SARS-Cov-2 variants such as Delta and Omicron (ALCANTARA *et al.*, 2022; DA SILVA *et al.*, 2022) and two transmission peaks, one in late March and another in mid-June.

Prospective space-time scan detected clusters in almost the entire Brazilian territory. Analysis of the cluster maps (Figures 2 e 3) shows that the clusters´ distribution becomes increasingly similar over the course of the epidemiological weeks. This suggests greater synchronicity between the curves of cases in the municipalities and a stabilized moment in the pandemic.

Approximately 60% of Brazilian municipalities were encompassed by clusters during the periods analyzed, indicating high risk in most of Brazil´s territory. In general, the number of observed and expected cases increased over the course of the periods analyzed. As the number of clusters increased there was a decrease in the mean size of their radiuses, suggesting the disappearance of a larger cluster and the emergence of smaller clusters. The clusters´ mean RR appeared to have dropped during the period studied until EW 27 of 2021. Over the course of the EWs analyzed, the clusters began to last longer and show higher LLR, indicating more likely clusters.

This manuscript has some limitations. The clusters´ circular format may not be the best option for areas with high spatial heterogeneity. Case counts depended on the municipalities´ testing capacity, which can hinder understanding the real magnitude and spatial distribution of COVID-19. And some clusters displayed very large radiuses, which hinders the interpretation and implementation of local strategies for prevention of the disease.

Another limitation of our study is working with the date of notification and not with the date of symptoms onset of COVID-19 cases. Thus, the results found in this study may be delayed by up to two weeks or more. Even without providing the date of the first symptoms, the Brasil.io database was widely used in studies during the COVID-19 pandemic (BARROZO *et al.*, 2020; CASTRO *et al.*, 2021; MARTINES *et al.*, 2021). We also chose to use this database, because it consolidates the epidemiological bulletins of the State Health Departments in Brazil on a daily basis and provides the number of cases of the disease per epidemiological week and by municipality in a clear and organized manner, thus allowing us to describe the pattern and intensity of COVID in Brazil. An alternative to circumvent this limitation would be to use the database of the Influenza Epidemiological Surveillance Information System (SIVEP-Gripe), an official Brazilian government data source that records cases of Severe Acute Respiratory Syndrome. However, if we used this basis, we would not include mild and moderate cases and our results would only reflect severe cases of COVID-19.

CONCLUSIONS

A prospective space-time scan of Brazilian municipalities was performed to identify clusters of COVID-19 cases and to analyze their persistence and changes in their characteristics from EW 9 of 2020, when the first COVID-19 case was reported in Brazil, until EW 29 of 2021, encompassing the period from 23 February 2020 to 24 July 2021. Clusters of COVID-19 cases were identified in a large part of Brazil´s territory, indicating major spread of SARS-CoV-2 across the country. The clusters´ distribution, which became increasingly similar over the course of the epidemiological weeks, suggests a stabilized period in the pandemic. The number of clusters remained stable during the EWs analyzed, except for the analyses from EW 51 of 2020 to EW 03 of 2021. The clusters´ relative risks appeared to have decreased until EW 27 of 2021. As far as we know, this is the first study that detects prospective space-time clusters of COVID-19 cases in Brazil and analyzes their persistence and changes over space and time. The study contributed to the identification of areas with increased risk of COVID-19. Health decision-makers should prioritize these areas for better allocation of health resources, posts, vaccination campaigns, and other local strategies to decrease transmission of the disease.

We suggest that health authorities continue to monitor COVID-19 cases in Brazil and reinforce the need to carry out new studies that encompass possible aspects that have not been covered in this manuscript, such as the use of official data from the Brazilian government, aspects of vaccination and the emergence of novel strains.

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