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ORIGINAL ARTICLE

Morbidity trend and space-time clusters of COVID-19 occurrence in children and adolescents

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Abstract

Objective: To analyze the morbidity trend and space-time distribution clusters of confirmed COVID-19 cases in children and adolescents.

Method: An ecological study of COVID-19 cases confirmed in the Information System from 2020 to 2022 in the age group from 0 to 19 years old, residents in Mato Grosso municipalities, Brazilian Midwest region. A trend analysis of the monthly morbidity rate of cases/100,000 inhabitants was used, following *Prais-Winsten*'s regression. A space-time distribution of the Bayesian incidence rate per 100,000 inhabitants was performed, in addition to a space-time scan to identify high-risk clusters.

Results: Of all 79,592 COVID-19 cases studied, 51.6% were in females and 44.21% in people aged 15−19 years old. The mean monthly rate was 265.87 cases per 100,000 inhabitants, with a stationary trend in the period analyzed (Monthly Percentage Variation [MPV]) = 12.15; $CI_{95\%[MPV]}$: -0.73;26.70). The morbidity rate due to COVID-19 was higher in the female gender (283.14/100,000 inhabitants) and in the age group from 15 to 19 years old (485.90/100,000 inhabitants). An increasing trend was observed with a greater monthly time variation of 14.42% ($CI_{95\%[MPV]}$: 1.28;29.28)] among those aged from 10 to 14 years old. The primary cluster, which was also the one with the highest Relative Risk (RR = 5,16, *p*-value = 0.001), included 19 municipalities located in the North health macro-region.

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Conclusion: The findings indicated a monthly stationary trend in the study population, an increase in the age group from 10 to 14 years old, and areas at a higher risk for the disease in the North health macro-region of the state.

Introduction

The infection by the new "Severe Acute Respiratory Syndrome Coronavirus-2″ (SARS-CoV-2) virus had its first cases recorded in the province of Wuhan, China, in December 2019, rapidly becoming a global health emergency and, consequently, demanding collective efforts in the scientific community and society to minimize human distress.[1,2]

COVID-19 affected several age groups, including children and adolescents, with relevant direct and indirect impacts for this population, vulnerable to various health complications.[3,4] Among the respiratory signs and symptoms, the most frequent are those related to upper airway infection, which can reach the lower respiratory tract with a need for mechanical ventilation in some cases.[5]

Virus spread among children and adolescents has the same infection probability as in adults; however, the symptoms mostly occur in mild clinical forms. However, there can be disease deterioration to the severe phase (dyspnea with central cyanosis) or rapid progression to acute respiratory discomfort syndrome in the critical phase of the disease, with a proportion of confirmed cases between 2.5% and 0.4% in these phases, respectively.[6]

In 2020, the estimated incidence and mortality due to confirmed COVID-19 cases in Brazil in the age group from 0 to 19 years old based on the microdata from the official bulletins in 27 Brazilian states was 559 cases/100,000 inhabitants, with higher estimates in the North (1015 cases/100,000 inhabitants) and Midwest (711 cases/100,000 inhabitants) regions. A total of 800 deaths were recorded in this age group, representing nearly 0.7% of the COVID-19-related deaths in the country, with an estimated mortality of 0.8/100,000 inhabitants in the Midwest.[7]

In the Brazilian Midwest region, the state of Mato Grosso had the following estimated incidence and mortality rates for all confirmed cases until January 31st, 2022: 130.84/100,000 inhabitants and 0.005/100,000 inhabitants, respectively. Of all confirmed cases in the state, 11.5% were in individuals between 0 and 20 years old, with 55.6% prevalence in females and 8.5% presenting associated comorbidities.[8]

COVID-19 affected groups of people with variable severity and caused premature deaths, leading to family and society distress and, consequently, to deterioration in the global panorama during the ongoing pandemic, generating increased economic and psychological burdens. In addition, children's and adolescents' greater exposure to new infectious agents due to the disease, such as greater contact in social environments, precarious hygiene conditions, and sharing of objects, contributed to the disease's high transmissibility and, consequently, to the deterioration of the pandemic situation.[9,10]

Added to the aforementioned context, some children and adolescents live in extremely dense demographic regions with precarious living and sanitation conditions, which increases the COVID-19 infection risk, associated with the prevalent comorbidities of the disease like pulmonary diseases, obesity, and cardiovascular diseases.[8,10]

Given the scarcity of studies on the child and adolescent population, it is fundamental to conduct an epidemiological monitoring study with trend analysis and identification of clusters at higher risk for illness to manage the preventive and care actions, mainly in geographical and social areas still affected by the disease, with a view to future epidemic cycles.

The study objective was to analyze the morbidity trend and space-time distribution clusters of confirmed COVID-19 cases among children and adolescents from 0 to 19 years old in Mato Grosso municipalities, Midwest Brazil, between 2020 and 2022.

Methods

An ecological study with analysis of space-time morbidity trends and identification of spatial clusters of confirmed COVID-19 cases in children and adolescents living in the municipalities from the state of Mato Grosso, Brazilian Midwest, from 2020 to 2022.

The state of Mato Grosso is located in the Brazilian Midwest region. Its population in 2021 was 3567,234 inhabitants, with 1091,847 (30.61%) aged between 0 and 19 years old.[11] Currently, the state has the third highest *per capita* Gross Domestic Product (GDP) in Brazil.[12] It has 141 municipalities distributed across seventeen health regions which, to organize the health system during the pandemic, were grouped into six health macro-regions (Annex 01- Supplementary material), implemented in the sixth version of the Contingency Plan for COVID-19 Control in Mato Grosso.[13]

The children and adolescents in the study were those aged from 0 to 19 years old corresponding to confirmed COVID-19 cases (*n* = 79,592) recorded in the INDICASUS information system, made available by the epidemiological surveillance office of the Mato Grosso State Health Department (SES/MT) from March 6th, 2020, to April 16th, 2022, and living in Mato Grosso municipalities.

The COVID-19 cases considered were those confirmed through the following laboratory tests: RT-PCR Test, Rapid Test-IgM/IgG and Rapid Test-Antigen Research (Nasal Swab), CLIA-Chemiluminescence, ECLIA-Electrochemiluminescence, ELISA-IgM and FIA-Immunofluorescence.

The variables of interest for the study were gender (female and male), age group (0−4, 5−9, 10−14, and 15−19 years old), clinical situation (symptomatic and asymptomatic) and presence of comorbidities (yes and no). Of the comorbidities recorded in the database, the following were analyzed: arterial hypertension; diabetes *mellitus*;

cardiovascular, pulmonary, and kidney disease; neoplasms; and obesity.

The COVID-19 monthly incidence rates in the population studied were estimated (per 100,000 inhabitants) and calculated according to relative population and age group, as per intercensal projections by the Brazilian Institute of Geography and Statistics for 2020 and 2021.[11] To characterize the time trend estimates, a logarithmic transformation of the coefficients (Y) was performed, as it allows for reducing heterogeneity of the variance of the residuals from the linear regression analysis, that is, the values of the difference between the points on the mean line and the time series points.

The Prais-Winsten procedure was used for generalized linear regression analysis. This model foresees first-order autocorrelation correction. The Monthly Percentage Variation (MPV) of the trend estimate was calculated with the following expression: $MPV = (-1 + 10^b).100\%$. Where "b" is the monthly growth rate. The MPV confidence interval (CI) was defined when $CI_{95\%[MPV]}$: $(-1 + 10^{b \pm t.sd}).100\%$. Where the "b" and "sd" standard deviation values were extracted from the regression analysis and the "t" value from the Student's t distribution. The increasing, decreasing or stationary trend was expressed as MPV, with the respective confidence intervals (95%). When the rate was positive, the time series was considered increasing; when negative, it decreased; and stationary when there was no significant difference between its value and zero.[14] *STATA*, version 16, was used.

The incidence rates were calculated by the municipality and represented in thematic maps, aggregated into 4 periods: 1, from 03/2020 to 08/2020; 2, from 09/2020 to 03/2021; 3, from 04/2021 to 09/2021; and 4, from 10/2021 to 04/2022. The incidence rates per 100,000 inhabitants were calculated using the Local Empirical Bayesian method, with the aid of GeoD, version 1.2. A neighborhood matrix based on the contiguity criterion was built for the Bayesian estimate.

SatScan, version 10.0,[15] was used to perform a circular space-time scan to identify clusters, having as input parameter the discrete Poisson probability distribution, definition of a 200 km radius, and using plane coordinates (X, Y) for the state's municipalities. Statistical significance was performed with Monte Carlo simulation.

For estimating the Relative Risk (RR) and respective *p*-values (≤ 0.05) of each cluster, a value was calculated that represents to which extent an area is more likely to have the event in relation to the other areas of the entire territorial extension studied.[15] The municipalities' RRs were also calculated to better understand the dynamics of each cluster identified. All maps were generated in ArcGis 9x (ESRI Corp).

The research protocol was approved by the Research Ethics Committee (CEP) of the Federal University of Mato Grosso — CEP SAÚDE/UFMT, under opinion No. 4,351,125.

Results

During the study period, 79,592 confirmed COVID-19 cases were analyzed in children and adolescents in municipalities from the state of Mato Grosso. Among these cases, the diagnoses were mostly confirmed with the Nasal Swab-Antigen rapid test in the state, corresponding to 45.42% (n = 36,151) of the tests performed in the aforementioned age group and period. There was a predominance of performing the RT-PCR test for the diagnosis of COVID-19 cases among the municipalities from the North, West and Midwest macro-regions.

Among the COVID-19 cases confirmed through laboratory tests, 51.6% were females and 44.21% were from 15 to 19 years old, followed by the age group from 10 to 14 years old (23.08%) (Table 1).

The mean monthly rate was 265.87 cases/100,000 inhabitants, with a stationary trend during the period analyzed (MPV=12.15; $CI_{95\%[MPV]}$: $-0.73;26.70$). The morbidity rate due to COVID-19 was higher in females (283.14/100,000 inhabitants) and in the age group from 15 to 19 years old (485.90/100,000 inhabitants). In both genders, there was a stationary trend in the COVID-19 cases with MPV values of 11.96% ($CI_{95\%[MPV]}$: $-0.93;26.70$) in females and 12.34% ($CI_{95\%[MPV]}$: $-0.52;26.86$) in males. As for age group, it is observed that the first three categories (0−4, 5−9 and 10−14 years old) showed an increasing trend, evidencing higher MPV values [14.42% ($CI_{95\%[MPV]}$: 1.28;29.28)] among the individuals aged from 10 to 14 years old (Table 1).

Table 1 Time series analysis corresponding to the morbidity rate due to COVID-19 in children and adolescents (per 100,000 inhabitants) and according to gender and age group, Mato Grosso (2020−2022).

Variables	Morbidity n (%)		Rate March 2020	Rate March 2022	Rate Mean	MPV[a]	CI$_{95\%[MPV]}$[b]		Interpretation
General	79,592	(100)	3.94	135.01	265.87	12.15	−0.73	26.70	Stationary
Gender									
Female	41,077	(51.61)	4.03	133.96	283.14	11.96	−0.93	26.54	Stationary
Male	38,515	(48.39)	3.85	136.02	248.21	12.34	−0.52	26.86	Stationary
Age group									
0−4 years old	13,005	(16.34)	7.36	129.24	168.38	10.63	0.11	22.26	Increasing
5−9 years old	13,026	(16.37)	3.84	131.77	138.43	13.09	0.80	26.88	Increasing
10−14 years old	18,367	(23.08)	1.82	131.24	207.72	14.42	1.28	29.28	Increasing
15−19 years old	35,194	(44.21)	3.14	146.38	485.90	12.17	−2.40	28.91	Stationary

Source: INDICASUS database; Mato Grosso (SES/MT).
Note:
  [a] Monthly percentage variation.
  [b] Confidence interval.

Table 2 Time series analysis corresponding to the morbidity distribution due to COVID-19 in children and adolescents, according to clinical situation and comorbidity, Mato Grosso (2020−2022).

Variables	Morbidity		March 2020	March 2022	MPV[a]	CI$_{95\%[MPV]}$[b]		Interpretation
	n	(%)	%	%				
Clinical situation								
Symptomatic	71,862	(90.29)	100	94.41	−0.17	−0.59	0.25	Stationary
Asymptomatic	7730	(9.71)	0	5.59	2.02	−2.10	6.31	Stationary
Comorbidity								
Yes	2628	(3.30)	9.52	2.05	−6.52	−9.33	−3.62	Decreasing
No	76,964	(96.70)	90.48	97.95	0.41	0.10	0.73	Increasing

Source: INDICASUS database; Mato Grosso (SES/MT).
Note:
[a] Monthly percentage variation.
[b] Confidence interval.

Table 2 shows that the clinical situation with the highest morbidity proportion corresponded to symptomatic children and adolescents (*n* = 71,862; 90.29%). Both the symptomatic and asymptomatic case trends were stationary over the study period. In relation to the "comorbidity" variable, there was a prevalence of cases with no comorbidities (*n* = 76,964; 96.70%), with an increasing trend in the time series analyzed (MPV=0.41; CI$_{95\%[MPV]}$: 0.10;0.73).

For the spatial distribution, the cases analyzed were those from March 2020 to April 2022. During this period, a higher proportion of cases was verified among residents from the capital: Cuiabá (13.56%; *n* = 10,811).

At the beginning of the study, the rates varied from 18 to 279.8 cases/100,000 inhabitants, with the highest values in the central region of the state, which corresponds to the Mid-Northeast, North and South health macro-regions. In the second and third periods, increased incidence rates were observed in all macro-regions, mainly in municipalities from the North and East macro-regions. In the last period, there was a reduction in incidence, with higher values in the municipalities from the North, East and South macro-regions (Figure 1).

The space-time scan identified 7 statistically significant high-risk clusters for COVID-19 incidence in children and adolescents and included most of the municipalities (*n* = 104). Of these, 6 were identified between January and February 2022, and only Cluster 4, which includes 5 municipalities and has the lowest RR (RR = 2.12, *p*-value = 0.001), was between February 2021 and February 2022 (Figure 2).

The cluster with the highest RR (Cluster 1, RR = 5.16, *p*-value = 0.001) included 19 municipalities, most of them located in the North macro-region of the state and one from the Mid-North. Clusters 2 and 6 (RR: 4.71, *p*-value = 0.001 and RR: 3.55, *p*-value = 0.001, respectively) included 17 (Cluster 2) and 10 (Cluster 6) municipalities, mostly from the East and South health macro-regions, with only one municipality from Cluster 6 in the Mid-North macro-region (Figure 2).

Discussion

The study results indicated that COVID-19 was more incident among female children and adolescents between 15 and 19 years old, from 2020 to 2022 in Mato Grosso. The COVID-19 monthly incidence estimate was stationary in the general study population and increasing in those aged less than 15 years old and in the cases with no comorbidities. Among all municipalities, the area at the highest risk for the disease included 19 municipalities, located in the central area of the state and from the North and Mid-North health macro-regions.

Previous studies also evidenced female predominance among the cases.[16,17] As for age, other authors report that the transmission rate is higher in older children (10−19 years old), with consistently lower incidence reported among those between the ages of 0 and 10.[16,18]

The higher incidence in this age group can be explained by their inclusion in other environments, in addition to school, as the Consolidation of Labor Laws (CLT) considers ages between 15 and 19 years old suitable for the labor market as young apprentices,[19] favoring higher chances of disease transmission. In addition, adolescents tend to relate more socially when compared to the other age groups under study.

Even with lower rates among younger age groups, the under-14 group presented an increasing trend during the period analyzed. Such a finding suggests that it can be due to the delay in releasing vaccination against COVID-19 for this age group, as well as to a resumption of face-to-face classes without complete vaccination schedules, increasing the virus transmission risk among children.[20] Vaccination is important to interrupt the transmission chain and reduce severe cases, thus avoiding high public expenditures on hospitalizations and deaths,[21] reducing the distress caused to the patients and family members involved.

Immunization in the age group included in the study was initiated in 2021 and, according to the Immunization Performance Panel against COVID-19 in Mato Grosso, until October 15th, 2022, vaccination coverage of the first dose applied in adolescents from 12 to 17 years old was 82.41%, 44.87% in the age group from 5 to 11 and, from 3 to 4 years old, coverage was 2.26%. The panel also shows that the areas with higher coverage values of the 4th dose (2nd booster dose) applied correspond to the same areas with the reduced incidence among children and adolescents in the last study period, suggesting that the strategies adopted across the
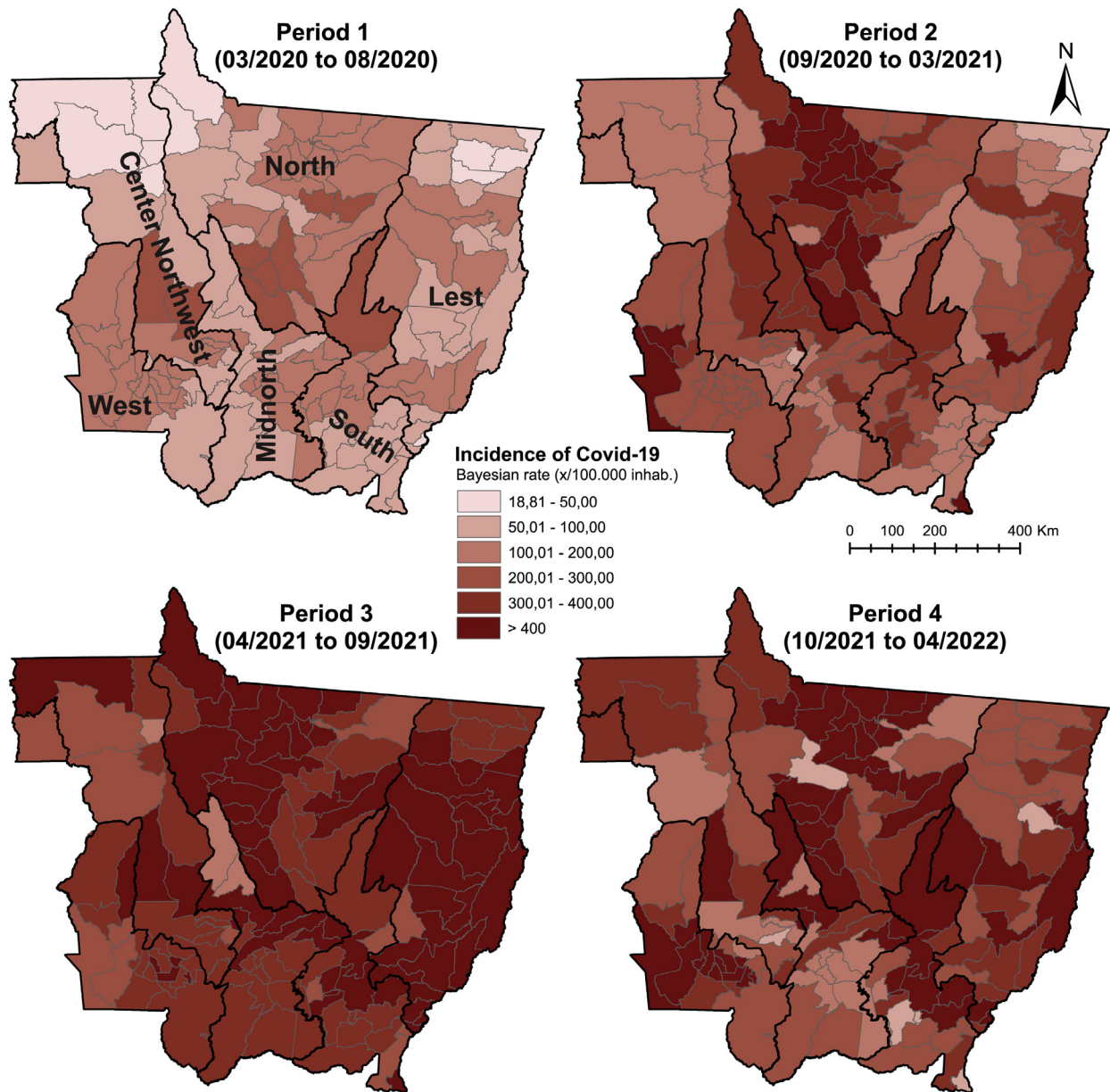
Figure 1 Space-time distribution of the COVID-19/100,000 inhabitants Bayesian incidence rates among children and adolescents aged from 0 to 19 years old, Mato Grosso, Brazil (2020–2022). Source: Data from the INDICASUS Information System; Mato Grosso (SES/MT).

locations are decisive in the COVID-19 surveillance process.[20]

In this study, most of the children and adolescents diagnosed with COVID-19 had no comorbidities and the case notification trend was increasing in them, in accordance with the study by Feldstein et al.,[22] which found prevalence of children and adolescents with no comorbidities (73%). The decreasing trend in the occurrence of the disease among children/adolescents with comorbidities can be explained by the vaccination strategy employed by the Ministry of Health, which prioritizes age and the presence of comorbidities.[23]

Regarding spatial distribution, the study presented the dynamics of the COVID-19 space-time distribution among children and adolescents in Mato Grosso between 2020 and 2022, with higher prevalence in the North (6 municipalities), South (1 municipality) and Mid-Northwest (2 municipalities) macro-regions in the first period, followed by diffused and increased rates in the other municipalities during periods 2 and 3 and a subsequent reduction in all health macro-regions during the last study period.

Although there are still few studies addressing COVID-19 among children and adolescents, it must be considered that there is significant transmissibility in this age group, with rapid spread in Mato Grosso, as evidenced in this study. Some studies suggest that high transmissibility can result from diagnostic failures, possibly explained by the occurrence of mild symptoms or even the absence of symptoms in this age group, thus maintaining the spread of the disease.[24,25]
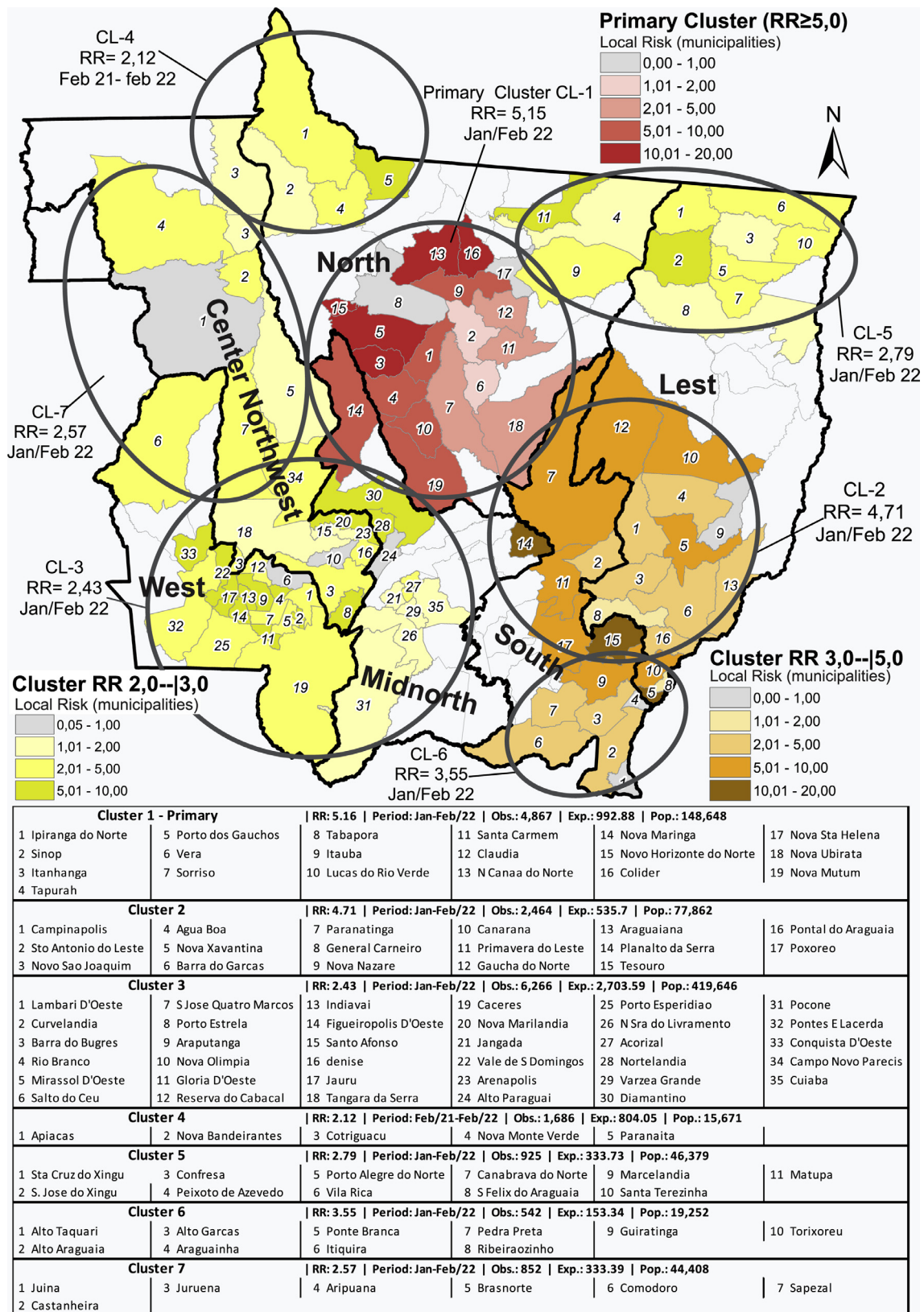
Figure 2 Space-time clusters at high risk for COVID-19 among children and adolescents aged from 0 to 19 years old, Mato Grosso, Brazil (2020−2022). Source: Data from the INDICASUS Information System; Mato Grosso (SES/MT).

In addition to COVID-19 spread across the Mato Grosso municipalities, it is also possible to identify a change in the disease spatial pattern during the last study period, with a reduction in incidence in some areas, distributed across all health macro-regions. Among the strategies adopted to contain the disease, it is important to highlight mass immunization of the population at risk, in an attempt to reduce disease transmission and possible complications. The action takes place in age group descending order and its distribution follows epidemiological criteria established by the Ministry of Health to control the pandemic.[26,23]

The space-time distribution of the Bayesian incidence rates allowed identifying possible high-rate clusters, confirmed by the space-time scan analysis, with areas with a 5-fold higher risk for the occurrence of the disease in the age group studied. The space-time scan identified high-risk clusters that include most municipalities in the state, showing the fast spatial dissemination of the disease across the state.

The areas identified as at the highest risk for COVID-19 occurrence in children and adolescents correspond to the central part of the state, located in the North macro-region, which currently presents significant economic growth driven by the emergence of new agricultural and economic frontiers; this dynamism also results in rapid spatial dissemination via contagion, for being a communicable disease.[27,28] The intense and rapidly increasing transportation flow existing in this macro-region[29] favors the transmission of contagious diseases like COVID-19, even among younger populations, which present lower COVID-19 illness/deterioration risks.[24]

The spread of infectious diseases like COVID-19 is associated with socioeconomic, environmental, and health service factors. Places with higher demographic density, social inequality, precarious housing conditions, disadvantaged socioeconomic conditions, and flaws in the planning of health actions directly contribute to maintaining the COVID-19 transmission cycle in all age groups.[30]

Identifying space-time patterns becomes complex when dealing with rapidly disseminating diseases like COVID-19. Although these municipalities have smaller territorial spaces, they also present their own demographic, socioeconomic, and political dynamics.[28] Public policies for COVID-19 prevention and control, access to such services and adherence to containment measures can mitigate or accentuate its transmission and effects and, therefore, justify heterogeneity in the spread and confrontation of the pandemic across different locations.

The study has as a limitation its use of secondary data from case notifications, which may incur errors during the data digitization process, in addition to possible underreporting, which directly depends on the surveillance actions implemented *in loco* and the policies for testing and coping with the disease. In addition, in the age group studied, COVID-19 mostly presents itself as mild or asymptomatic cases, increasing underreporting due to a lack of demand for medical care and subsequent confirmation of cases through diagnostic tests.

It is important to highlight that there may be underdiagnosis in children and adolescents ($0 - 19$ years old), as they are asymptomatic or oligosymptomatic, not requiring medical care and, therefore, there is no diagnosis of the disease.[17,18] However, the current study included cases confirmed through laboratory tests, which confers robustness to its main findings.

The findings indicated a monthly stationary trend in the study population, an increase in the age group from 10 to 14 years old, and areas at higher risk for the disease in the North health macro-region of the state.

This study contributes diverse evidence on space-time analyses, allowing visualization of the disease dynamics and areas at higher risk for its occurrence, contributing to orientation and planning of more specific and localized strategic actions to reduce the magnitude of the disease.

However, the importance of other studies is highlighted to complement the analysis of the COVID-19 cases, such as individualized surveys associated with sociodemographic, cultural, behavioral, and environmental aspects.

Conflicts of interest

The authors declare no conflicts of interest.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jped.2023.10.004.

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