Ciência & Saúde Coletiva
cienciaesaudecoletiva.com.br
ISSN 1413-8123. v.29, n.5
DOI: 10.1590/1413-81232024295.02662023EN

THEMATIC ARTICLE

The hidden severity of the COVID-19 pandemic in children and adolescents in Brazil: a territorial analysis of hospital mortality

Amanda Cilene Cruz Aguiar Castilho da Silva (https://orcid.org/0000-0001-8557-4924) [1]
Ronir Raggio Luiz (https://orcid.org/0000-0002-7784-9905) [2]
Regina Célia Gollner Zeitoune (https://orcid.org/0000-0002-0276-8166) [3]
José Rodrigo de Moraes (https://orcid.org/0000-0003-4814-5076) [4]
Arnaldo Prata-Barbosa (https://orcid.org/0000-0002-4726-9782) [5]
Jessica Pronestino de Lima Moreira (https://orcid.org/0000-0003-1987-3584) [6]

Abstract *This article aims to describe the geographical distribution of hospital mortality from COVID-19 in children and adolescents during the 2020-2021 pandemic in Brazil. Ecological, census study (SIVEP GRIPE) with individuals up to 19 years of age, hospitalized with SARS due to COVID-19 or SARS not specified in Brazilian municipalities, stratified in two ways: 1) in the five macro-regions and 2) in three urban agglomerations: capital, municipalities of the metropolitan region and non-capital municipalities. There were 44 hospitalizations/100,000 inhabitants due to COVID-19 and 241/100,000 when including unspecified SARS (estimated underreporting of 81.8%). There were 1,888 deaths by COVID-19 and 4,471 deaths if added to unspecified SARS, estimating 57.8% of unreported deaths. Hospital mortality was 2.3 times higher in the macro-regions when considering only the cases of COVID-19, with the exception of the North and Center-West regions. Higher hospital mortality was also recorded in non-capital municipalities. The urban setting was associated with higher SARS hospital mortality during the COVID-19 pandemic in Brazil. Living in the North and Northeast macro-regions, and far from the capitals offered a higher risk of mortality for children and adolescents who required hospitalization.*

Key words *COVID-19, Pandemics, Child, Adolescent, Ecological Studies*

[1] Instituto de Puericultura e Pediatria Martagão Gesteira, Universidade Federal do Rio de Janeiro (UFRJ). R. Bruno Lobo 50, Cidade Universitária. 21941-912 Rio de Janeiro RJ Brasil. amanda.cilene@ippmg.ufrj.br
[2] Instituto de Estudos em Saúde Coletiva, UFRJ. Rio de Janeiro RJ Brasil.
[3] Escola de Enfermagem Anna Nery, UFRJ. Rio de Janeiro RJ Brasil.
[4] Departamento de Estatística, Universidade Federal Fluminense (UFF). Niterói RJ Brasil.
[5] Departamento de Pediatria, Instituto D'Or de Pesquisa e Ensino. Botafogo RJ Brasil.
[6] Faculdade de Farmácia, UFF. Niterói RJ Brasil.

Introduction

COVID-19, which was declared a pandemic by the World Health Organization in March 2020, has intensely affected the entire world population. In November 2022, Brazil was in 4th place in total cases, with 34,582,063 notifications, behind only the United States (USA), India, and France, with 685,334 lives, remaining in 2nd place in the number of deaths since May 23, 2020, behind only the USA[1].

Most children and adolescents have had mild to moderate illnesses[2,3]. However, some of them have progressed to severe forms of COVID-19, such as Severe Acute Respiratory Syndrome (SARS)[4,5], which is conceptualized as a flu-like syndrome associated with signs of severity such as dyspnea, respiratory distress or a drop in saturation[6], and can lead to death. By November 2022, this age group accounted for 17,358 hospitalizations due to COVID-19 (9.1%) and 87,867 hospitalizations if these are added to cases of unspecified SARS (SARS-NS), corresponding to 25.3% of all hospitalizations due to these causes[1].

In Brazil, the distribution of hospitalizations and deaths has not been uniform. The Brazilian territory is continental in size, with different patterns of COVID-19 hospitalization and evolution occurring in different geographical areas of the country. Socioeconomic inequalities[7] and disparities in access to and supply of health services, such as hospital beds and intensive care[8], also contribute to these discrepancies[9]. Thus, segmentation into geographical macro-regions – North, Northeast, Southeast, South, and Center-West – makes it possible to better study these inequalities. However, great heterogeneity is also found within Brazil's macro-regions and even states. The large agglomerations of capital cities and neighboring municipalities (state metropolitan regions) share the same care network and are more developed, with greater availability of health services. On the other hand, the municipalities in the interior – the majority of Brazilian municipalities – can be seen as more isolated, with a smaller healthcare network and, for the most part, more distant from the capital, which can make it difficult for their residents to access healthcare services.

In view of this scenario, the aim of this study was to describe the geographical distribution of hospital mortality from COVID-19 in children and adolescents among the five Brazilian geopolitical macro-regions and among the capitals and municipalities of the metropolitan regions and the noncapital cities of the Brazilian states during the COVID-19 pandemic.

Method

This is an ecological study, using Brazilian municipalities as units of analysis, stratified in two ways: 1) in the five macro-regions (North, Northeast, Southeast, South, and Center-West); and 2) in three categories of municipalities: capital cities, municipalities belonging to the metropolitan region or integrated economic development regions, and noncapital cities, within each state.

Data from the Influenza Epidemiological Surveillance System (SIVEP GRIPE) of DATASUS/Ministry of Health was used. This is a surveillance database used to monitor SARS cases, which has included those caused by the SARS-CoV-2 virus since March 2020[6], becoming the official system for reporting and monitoring hospitalizations and deaths from severe cases of COVID-19. Notification of SARS cases is mandatory in Brazil, and health professionals are responsible for filling in the notification forms[10]. SARS cases are defined as individuals hospitalized with cough or odynophagia associated with dyspnea, saturation less than 95%, or respiratory distress, or who have died, regardless of hospitalization. The presence of fever is not required for COVID-19 cases[6]. To build the database for this study, the 2020 and 2021 SIVEP GRIPE files were accessed on 01/31/2022. All cases of SARS due to COVID-19 and unspecified SARS in children and adolescents up to 19 years old (census), notified to SIVEP GRIPE between 01/01/2020 and 12/31/2021 were used. Thus, only cases of unspecified SARS were counted in January and February 2020. It was methodologically decided to include SARS-NS in the analysis as a probable underreporting of COVID-19, given the duration of the pandemic. Hospital mortality was the main outcome.

All 5,570 Brazilian municipalities were categorized according to the Classification of Urban Agglomerations by the Brazilian Institute of Geography and Statistics (IBGE) (2021) into the following urban population agglomerations: 27 capital cities, 22 metropolitan regions (MR) or integrated economic development regions (RIDE), containing 1,407 municipalities, and 26 conglomerations of noncapital cities (except capital cities and metropolitan regions), containing 4,136 noncapital municipalities[11]. Thus, 75 aggregates of ecological units were considered in this

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study. The composition of some metropolitan regions or RIDEs is noteworthy: Piauí concentrates the Grande Teresina RIDE with 12 municipalities (excluding Teresina) and one more municipality from Maranhão; Goiás concentrates the Federal District RIDE with 29 municipalities (excluding Brasília) and four more municipalities from Minas Gerais[11]. There are no metropolitan region municipalities in Acre, Mato Grosso do Sul, and the Federal District, and there are no noncapital municipalities in Santa Catarina and the Federal District[11].

Data on the projected population of Brazil and the states by sex and age for the period 2000-2030, made available by IBGE[12], through Tabnet/DATASUS, was accessed in October 2022, to identify individuals up to 19 years of age residing in Brazil in 2020 and 2021 by municipality, to construct the hospitalization rate per 100,000 inhabitants. The average population size for 2020 and 2021 was used.

The indicators shown in the tables were calculated as follows: (1) *hospitalization rate*: number of hospitalizations due to SARS-NE + COVID-19 (or just COVID-19) of residents up to the age of 19 in a given geographic area, multiplied by 100,000, divided by the number of residents up to the age of 19 in the same geographic area; (2) *hospital mortality rate*: number of deaths from SARS-NS + COVID-19 (or just COVID-19) of residents up to the age of 19 in a given geographic area, divided by the number of hospitalized residents up to the age of 19 in the same geographic area, with a diagnosis of SARS-NS + COVID-19 (or just COVID-19), multiplied by 100; (3) *hospital mortality ratio*: COVID-19-only mortality of residents up to the age of 19 in a given geographic area, divided by the mortality of the COVID-19 + SARS-NS group of residents up to the age of 19 in the same geographic area.

Statistical analysis was carried out using IBM SPSS Statistics software version 24 (IBN Corp. Armonk, NY, USA). The maps were drawn up using the TabWin 4.15 program and the graphs were created using the R studio program version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria).

This study uses public data and therefore, according to CNS Resolution 510 of 2016, is exempt from submission to a research ethics committee and the use of an informed consent form.

Results

Table 1 shows the hospitalization rate per 100,000 inhabitants, number of deaths, and hospital mortality due to COVID-19 and COVID-19 + unspecified SARS (COVID-19+SRAG-NS), according to geographic macro-regions. Methodologically assuming that cases of unspecified SARS are potentially underreporting of COVID-19, an overall percentage of underreported deaths of 57.8% was estimated, with great variation between the regions and greater underreporting in the Southeast (62.8%) and lower in the North (44.5%). There were 1,888 deaths considering only confirmed COVID-19 cases and 4,471 deaths when unspecified SARS cases were added to these.

When unspecified SARS and COVID-19 cases are added together, the number of hospitalized cases per 100,000 inhabitants was five and a half times higher than the rate of confirmed COVID-19 cases in Brazil (241.0 versus 44.0). The highest hospitalization rates per 100,000 inhabitants were found in the Southeast (317.4) and South (223.4), when considering COVID-19+SRAG-NS, and in the North (60.6) and Center-West (52.0), when considering only confirmed COVID-19 cases. Hospital mortality, considering only confirmed COVID-19 cases, was 7.2% nationwide, reaching 10.3% in the Northeast. Lower percentages of hospital mortality were found in the Center-West (4.9%) and Southeast (5.8%). When cases of unspecified SARS were included, mortality was 3.1% in Brazil, with a higher rate in the North (5.3%). In Brazil as a whole, the hospital mortality ratio was 2.3 higher in the confirmed COVID-19 SARS group, compared to the COVID-19+SARS-NS group, with great disparities between the regions, but all of them showing a higher mortality ratio for confirmed cases, ranging from 2.8 in the Southeast to 1.4 in the North (Table 1).

Table 2 shows hospital mortality in cases of SARS due to confirmed COVID-19 and COVID-19+SARS-NS, by type of urban agglomeration and state. It can be seen that hospital mortality in Brazil was higher in municipalities further away from the capitals, both for confirmed COVID-19 and COVID-19 + SARS-NS cases, to a greater extent among noncapital municipalities. Roraima is the state that stands out negatively in all urban contexts. The capital, Boa Vista, had a 35% hospital mortality rate when considering only confirmed COVID-19 cases, and 19.2% when including unspecified SARS cases. This proportion

Table 1. Hospitalization rate per 100,000 inhabitants, deaths and hospital mortality due to COVID-19 + unspecified SARS and COVID-19, according to geographic macro-regions, in children and adolescents. Brazil, 2020-2021.

Geographic macro-regions	COVID-19 + unspecified SARS			Only COVID-19			Percentage of deaths underreported[§]	Hospital mortality ratio (B/A)
	Hospitalization rate per 100,000 inhabitants**	Number of deaths	Hospital mortality (A)	Hospitalization rate per 100,000 inhabitants**	Number of deaths	Hospital mortality (B)		
Brazil	241	4,471*	3.1%	44.0	1,888	7.2%	57.8%	2.3
North	151.9	528	5.3%	60.6	293	7.3%	44.5%	1.4
Northeast	190.1	1,599	4.8%	39.5	709	10.3%	55.7%	2.1
Southeast	317.4	1,575	2.1%	43.4	586	5.8%	62.8%	2.8
South	223.2	446	2.6%	36.6	177	6.2%	60.3%	2.4
Center-West	208.5	319	3.2%	52.0	123	4.9%	61.4%	1.5

Note: *In 2020, there was no information on the person's region of residence in 4 notifications of deaths and 11 of hospitalizations. **Hospitalizations for unspecified SARS + COVID-19 or only COVID-19 of residents in a given geographic area, multiplied by 100,000, divided by the number of residents up to the age of 19 in the same geographic area. §This study methodologically considered unspecified SARS as latent underreporting. Calculation method: 1- (COVID-19 deaths/COVID-19 deaths + unspecified SARS), multiplied by 100.

Source: SIVEP-GRIPE and IBGE/Directorate of Research. Population and Social Indicators Coordination. Management of Studies and Analysis of Demographic Dynamics.

is much higher than that found in other states. Few capitals exceeded 10% hospital mortality among confirmed COVID-19 cases, such as São Luís-MA (11.9%), Maceió-AL (11.0%) and Recife-PE (10.8%). Among municipalities belonging to metropolitan regions, Roraima also stands out with a 44% hospital mortality rate, with few states having more than 10%, all belonging to the North or Northeast regions, among confirmed COVID-19 cases. In noncapital municipalities, hospital mortality was 66% in Roraima, 20.9% in Maranhão, and 20.0% in Acre. In noncapital cities of the Southeast, South, and Center-West regions, the only state above 10% was Espírito Santo, with 25%. Some municipalities stood out for showing a significant increase in the mortality ratio in cases of confirmed COVID-19 compared to cases of COVID-19+SARS-NS, such as noncapital cities in the state of Espírito Santo, with a ratio of 3.9, in the Metropolitan Region of Minas Gerais, with 3.7, in the Metropolitan Region of Rio de Janeiro, with 3.2 and the capital city of Santa Catarina, with 4.3.

Figure 1 shows the spatial distribution of hospital mortality from COVID-19 by Brazilian municipality (Figure 1A: COVID-19+SARS-NS and Figure 1B COVID-19 only). There is greater heterogeneity in the map of COVID-19 cases only, with areas with no deaths in all macro-regions, contrasting with others with mortality above 10%. Greater areas of mortality can be identified in the municipalities of the North and Northeast. When integrating data from unspecified SARS with confirmed COVID-19, there is a greater distribution of deaths and a reduction in hospital mortality.

Discussion

This study demonstrated the great variability in the indicators of hospitalization and deaths from COVID-19 and unspecified SARS in Brazil, during the COVID-19 pandemic in 2020 and 2021, both by geographic macro-region and by state, stratified into three urban agglomerations: capital cities, metropolitan regions, and noncapital cities.

Living in municipalities in the North and Northeast offered a higher risk for Brazilian children and adolescents who required hospitalization during the COVID-19 pandemic, especially when considering only confirmed COVID-19 cases. In general, hospital mortality was much higher (more than double) in the Brazilian macro-regions when only COVID-19 cases were considered, compared to COVID-19 cases integrated with unspecified SARS, with the exception of the North and Center-West regions, where rates were also comparatively higher, but to a lesser extent. There was also a higher hospital mortality rate in noncapital cities (in both groups), especially in Roraima, which reached more than 65% mortality for confirmed COVID-19 cases and

Table 2. Hospital mortality (HM) from COVID-19 + unspecified SARS and COVID-19 alone among children and adolescents, by state, according to urban context of residence. Brazil, 2020-2021.

State	Capital			Metropolitan Region			Noncapital cities		
	COVID-19 +unspecified SARS	COVID-19	Hospital mortality ratio	COVID-19+ unspecified SARS	COVID-19	Hospital mortality ratio	COVID-19+ unspecified SARS	COVID-19	Hospital mortality ratio
	MH (A -%)	MH (B -%)	(B/A	MH (A -%)	MH (B -%)	(B/A)	MH (A -%)	MH (B -%)	(B/A)
Brazil	2.5	6.1	2.4	2.7	7.0	2.6	4.5	8.3	1.8
North Region	5.7	7.6	1.3	8.0	9.1	1.1	4.6	6.9	1.5
Rondônia	4.9	9.8	2.0	0.0	0.0	0.0	8.8	15.7	1.8
Acre*	7.2	17.4	2.4	-	-	-	8.3	20.0	2.4
Amazonas	5.2	5.4	1.0	6.8	6.4	0.9	4.0	4.6	1.2
Roraima	19.2	35.3	1.8	36.0	44.4	1.2	40.0	66.7	1.7
Pará	5.7	9.3	1.6	7.1	9.3	1.3	6.1	8.5	1.4
Amapá	6.3	6.3	1.0	4.2	4.7	1.1	1.8	0.6	0.3
Tocantins	3.8	7.4	2.0	7.3	12.9	1.8	1.3	3.8	3.0
Northeast Region	3.5	8.1	2.3	4.6	9.4	2.0	6.7	13.3	2.0
Maranhão	8.4	11.9	1.4	7.1	11.7	1.7	14.4	20.9	1.5
Piauí**	2.6	5.6	2.2	8.8	10.0	1.1	7.7	10.1	1.3
Ceará	3.2	9.7	3.0	4.4	11.7	2.7	6.1	13.6	2.2
Rio Grande do Norte	2.2	9.0	4.0	3.8	9.4	2.4	5.5	9.3	1.7
Paraíba	3.3	7.2	2.2	4.7	5.7	1.2	7.2	13.0	1.8
Pernambuco	3.2	10.8	3.4	3.8	11.1	2.9	6.1	14.3	2.4
Alagoas	5.3	11.0	2.1	8.1	11.9	1.5	5.6	9.4	1.7
Sergipe	2.7	4.8	1.8	2.9	6.7	2.3	8.1	13.1	1.6
Bahia	3.5	6.1	1.7	3.3	6.0	1.8	6.5	12.9	2.0
Southeast Region	1.9	4.8	2.5	2.0	5.9	3.0	3.1	7.2	2.3
Minas Gerais	1.2	2.3	1.8	1.7	6.4	3.7	3.1	7.5	2.4
Espírito Santo	1.6	6.7	4.2	3.3	8.9	2.7	6.4	25.0	3.9
Rio de Janeiro	2.9	7.0	2.4	2.3	7.3	3.2	3.0	5.6	1.9
São Paulo	1.6	3.9	2.4	1.9	5.4	2.8	2.7	6.5	2.4
South Region	1.5	4.5	3.0	2.4	6.5	2.7	3.8	6.6	1.7
Paraná	1.3	3.4	2.6	2.0	5.5	2.8	3.4	7.8	2.3
Santa Catarina*	1.1	4.8	4.3	2.6	7.6	2.9	-	-	-
Rio Grande do Sul	2.2	6.8	3.1	3.2	6.1	1.9	4.3	5.7	1.3
Center-West Region	2.2	4.0	1.8	4.5	8.3	1.9	4.2	4.6	1.1
Mato Grosso do Sul*	2.6	2.5	1.0	-	-	-	3.1	3.2	1.0
Mato Grosso	3.2	4.9	1.5	3.2	4.1	1.3	4.0	3.3	0.8
Goiás***	5.8	9.3	1.6	4.5	9.4	2.1	6.3	9.9	1.6
Distrito Federal*	1.2	2.0	1.7	-	-	-	-	-	-

Note: *According to the IBGE Classification of Urban Agglomerations (2021), the following states do not have a Metropolitan Region: Acre, Mato Grosso do Sul and the Federal District. These do not have noncapital municipalities: Santa Catarina and the Federal District. **Piauí concentrates the RIDE of Santa Catarina with 12 municipalities (excluding Teresina) and 1 municipality from Maranhão. ***Goiás concentrates the RIDE of the Federal District and surrounding area with 29 municipalities (excluding Brasília) and 4 municipalities in Minas Gerais.

Source: SIVEP-GRIPE and IBGE/Directorate of Research. Population and Social Indicators Coordination. Management of Studies and Analysis of Demographic Dynamics.

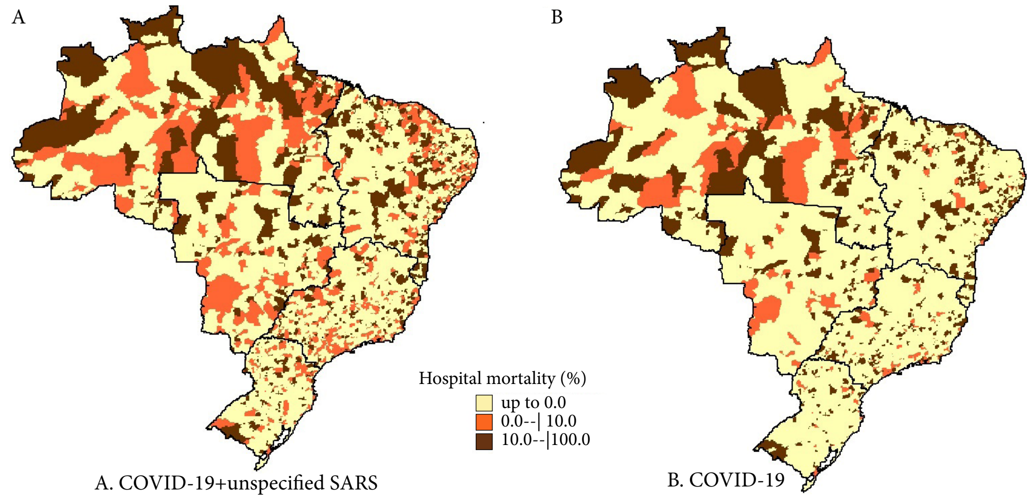

Figure 1. Spatial distribution by Brazilian municipalities of hospital mortality due to COVID-19 among children and adolescents. Brazil, 2020-2021.

Source: SIVEP-GRIPE and IBGE/Directorate of Research. Population and Social Indicators Coordination. Management of Studies and Analysis of Demographic Dynamics.

40% when including cases of unspecified SARS. Although less than 25% of Brazilian municipalities reported deaths in children and adolescents from COVID-19 and unspecified SARS during the pandemic, unfortunately, 73 municipalities reached 100% hospital mortality for COVID-19+SARS-NS cases and 156 for confirmed COVID-19 cases. In addition, 257 individuals under the age of 19 with COVID-19+SARS-NS died without even being hospitalized.

In this study, hospital mortality rates in some states were much higher than those reported in other studies, which described rates between 3%[8] and 7.3%[13]. International studies place this mortality rate between 2% and 4%[14,15], and it is higher in middle and low-income countries (4.0% [95%CI 3.6-4.4%]) than in high-income countries (1.7% [95%CI 1.3 to 2.1%]). Although the mortality rate in Brazil as a whole ranged from 6.1% in the capitals to 8.3% in noncapital municipalities, the scenario was quite different when urban agglomerations and municipalities were considered, as already highlighted. The perception of these contrasts was made possible by the use of a time frame of two full years of the pandemic and the collection of data from an official source covering the entire Brazilian territory, SIVEP GRIPE. The finding of the worst-case scenario in states in the North was also described by Oliveira *et al.*[13], studying individuals up to the age of 19, Baqui *et al.*[7], studying the general population and Silva *et al.*[16], showing a cut-off by age. All of them used SIVEP GRIPE, but with a shorter time frame.

The reasons for these findings are still unclear and require specific studies. However, some hypotheses can be put forward to explain these inequalities, such as socio-economic differences between regions, differences in the basic health conditions of the population, and differences in the structure of care. It is also possible that the difficulty of getting to a hospital is associated with a worse outcome in municipalities further away from the major centers. Measures to restrict the movement of people, especially in the first year of the pandemic, with a reduction in the availability of public transport and a reduction in free demand in primary healthcare networks, may have contributed to making hospital access more difficult. At the beginning of the pandemic, the population was advised to quarantine themselves at home for mild cases and children were considered to have a lower chance of being infected, through information from the WHO, disseminated by the mainstream media[17-19], which may have led to delays in seeking hospital care. The Primary Care Network, which is often the closest access to families, had its services reduced during the pandemic, with most units only performing COVID-19 tests, reducing the possibility of children and adolescents being evaluated early by health professionals for signs and symptoms of severity[20]. Studies conducted in Europe reported that restrictive population displacement measures considerably reduced the number of outpatient visits[21] and hindered children's and adolescents' access to primary and community services, causing many children who needed emergency care to be delayed, leading to a more complicated outcome and even death[21,22].

Notwithstanding the difficulty of access, it is also possible that hospital care routines in the first months of the pandemic, which were still maladjusted due to the incipient knowledge of the new disease and the best form of treatment, contributed to the increase in hospital mortality. Especially with regard to ventilatory support, many initial routines advised against the use of non-invasive ventilation if total isolation of the patient was not possible[17,18,23,24], which may have delayed optimal ventilatory support and contributed to higher mortality rates.

To the best of our knowledge, no other study has described the difference in mortality rates between capitals, metropolitan regions, and noncapital cities in children and adolescents with confirmed cases of COVID-19 and cases of unspecified SARS. Our findings, indicating higher mortality for confirmed cases in noncapital cities, were consistent in all Brazilian macro-regions, with the exception of the North, where the consolidated rate was higher in the capitals and metropolitan regions.

This study has some limitations. Firstly, the use of data from compulsory notification systems, such as SIVEP-GRIPE, despite ensuring a comprehensive scope by using census data from Brazil, may contain possible typing or filling errors, affecting one or more of the various fields of registration although the notifications are constantly being evaluated for corrections by the local teams responsible for each record, which minimizes the impact of possible failures. Secondly, the figures in this study represent the cases notified on the day the database was accessed, but delays in notifications can occur, as health establishments are allowed to notify cases, even if late. Thirdly, the lack of diagnostic confirmation for thousands of potential COVID-19 cases results in them being classified as "unspecified SARS" rather than COVID-19. This classification can have a huge impact on assessing the severity of the pandemic in pediatrics, not only by underestimating the majority of COVID-19 cases and deaths, but mainly by devaluing the real impact of the pandemic on the lives of children and adolescents. We tried to overcome this limitation by describing both confirmed COVID-19 SARS cases and unspecified SARS cases. As a result, it is possible to consider the proportion of "unspecified SARS" cases as an indicator of the underreporting of COVID-19 cases. Finally, since this is an ecological study, the ecological misconception when trying to raise hypotheses to explain the inequalities found cannot be disregarded, but the main focus is not on this, but rather on describing the mortality findings, which were based on census data.

Collaborations

ACCAC Silva and JPL Moreira: conception, planning, analysis, interpretation, and writing. A Prata-Barbosa: planning, interpretation, and writing. RR Luiz: conception, interpretation, and writing. JR Moraes: interpretation and writing, and RCG Zeitoune: writing. All authors approved the final version submitted.

Funding

Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (Capes) – Financing Code 001.

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Article submitted 09/03/2023
Approved 28/08/2023
Final version submitted 30/08/2023

Chief editors: Romeu Gomes, Antônio Augusto Moura da Silva