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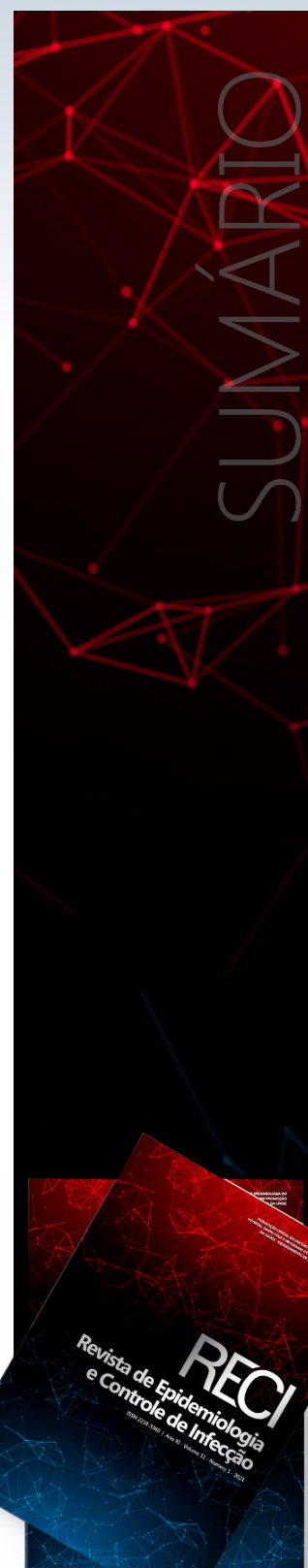
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Prevalence of infectious diseases in a municipal hospital in Belem, northern Brazil

Prevalência de doenças infecciosas em um hospital municipal em Belém, Norte do Brasil

Prevalencia de enfermedades infecciosas enun hospital municipal de Belém, norte de Brasil

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ABSTRACT

Background and objectives: Infectious diseases are still a public health problem in Brazil. Therefore, this study aimed to determine the prevalence of infectious diseases in a reference hospital in the city of Belem, Para, Brazil. **Methods:** From May 2018 to August 2019, the number of cases of individuals with compulsory infections was observed. **Results:** Regarding the research period in which data were obtained from May 2018 to August 2019, a total of 263 cases were affected in the hospital and in 2019 there was an increase in the number of cases and 373 records were reported. The following results were obtained: in 2018, the highest rate of infection was caused by influenza at the rate of 17%, and in 2019 it remained at the same percentage rate and ranked secondly. **Conclusion:** These data are very important for the epidemiological knowledge of the population, elucidating the highest case rates and lowering other diseases related to this study, as well as their harms and treatment.

Descriptors: Admission. Endemicity. Hospital. Notification.

RESUMO

Justificativa e objetivos: As doenças infecciosas ainda são um problema de saúde pública no Brasil. Por isso, este estudo teve como objetivo determinar a prevalência de doenças infecciosas em um hospital de referência na cidade de Belém, Pará, Brasil. **Métodos:** Foi observado, no período de maio de 2018 a agosto de 2019, número de casos de indivíduos acometidos com infecções de caráter compulsório. **Resultados:** Em relação ao período da pesquisa, no qual foram obtidos os dados de maio de 2018 a agosto de 2019, os resultados apontam que, nos meses de maio a dezembro de 2018, foram acometidos 263 casos no hospital e, em 2019, houve o aumento do número de casos, sendo notificados 373 registros. Obtiveram-se os seguintes resultados: no ano de 2018, a maior taxa de infecção foi causada pela influenza, com a taxa de 17%; em 2019, se manteve com a mesma taxa de percentual, ficando em segundo lugar. **Conclusão:** Esses dados são de suma importância para o conhecimento epidemiológico

da população, elucidando sobre os maiores índices de casos e o decréscimo de outras doenças relacionadas a este estudo, bem como seus agravos e tratamento.

Descritores: *Internação. Endemicidade. Hospital. Notificação*

RESUMEN

Justificación y objetivos: las enfermedades infecciosas siguen siendo un problema de salud pública en Brasil. Por lo tanto, este estudio tuvo como objetivo determinar la prevalencia de enfermedades infecciosas en un hospital de referencia en la ciudad de Belém, Pará, Brasil. **Métodos:** desde mayo de 2018 hasta agosto de 2019, se observó el número de casos de personas con infecciones obligatorias. **Resultados:** En cuanto al período de la encuesta en el que se obtuvieron datos de mayo de 2018 a agosto de 2019, los resultados indican que de mayo a diciembre de 2018, 263 casos fueron afectados en el hospital y en 2019 hubo un aumento en el número de casos y se reportaron 373 registros. Se obtuvieron los siguientes resultados: en 2018, la tasa más alta de infección fue causada por la influenza a una tasa del 17%, y en 2019 se mantuvo en la misma tasa porcentual y ocupó el segundo lugar. Seguimiento de tuberculosis, donde el 15% de los casos notificados se registraron en 2018. En comparación con 2019 (19%) hubo un aumento del 4% en el número de personas afectadas, ocupando el primer lugar en el ranking de enfermedades notificadas. Seguimiento por el virus del SIDA donde se registró el 8% de los casos registrados, en comparación con 2019 (6%) se observó hasta ahora una disminución del 2% en el número de casos. **Conclusión:** Estos datos son muy importantes para el conocimiento epidemiológico de la población, ya que dilucidan las tasas de casos más altas y disminuyen en otras enfermedades relacionadas con este estudio, sus enfermedades y su tratamiento.

Palabras Clave: *Internamiento. Endemicidad. Hospital. Notificación*

INTRODUCTION

Infectious diseases are still a public health problem in Brazil, although the proportion of total deaths from this cause has fallen from 50% to 5% over the past eighty years. A large proportion of deaths from infectious diseases in Brazil are caused by respiratory infections, and deaths from these infections have become more common in adults than in children.^{1,2}

Infectious and parasitic diseases are a cause of infant death closely related to socioeconomic and environmental factors. For certain population groups, its occurrence is more significant due to the precarious living conditions. This group of diseases stands out as one of the main causes of hospital admissions and infant mortality in Brazil and worldwide.^{3,4-6}

The occurrence of these diseases reveals the population's health and life levels, which can be used as health indicators for the planning of public policies. Information on mortality rates, where they occur and who is most affected provides a crucial contribution to debates on policies, planning, interventions, as well as the prioritization of new research in health technologies, undoubtedly an essential measure for health analysis of a population.^{7,8}

Tuberculosis (TB) is an infectious disease, caused by the bacterium *Mycobacterium tuberculosis*, which mainly affects the lungs and can develop in other organs of the body, such as bones, kidneys and meninges, and the clinical manifestations are directly related to the affected organ.⁹

Meningitis is an infectious disease characterized by inflammation of the meninges, having several causal factors, infectious or not. Among the infectious causes, the main ones are of viral or bacterial etiology.¹⁰

Chagas' disease belongs to the group of neglected diseases, which are caused by endemic infectious agents, especially in developing countries, in poor populations without adequate basic sanitation. According to data from the World Health Organization (WHO), more than a billion people are infected with one or more etiologic agents that cause neglected diseases, which represents one sixth of the world population.¹¹

Dengue, a negligible tropical disease, considered the vector-borne disease with the highest growth in the world, occurs in a total of 128 countries, with about 4 billion people at risk. It is considered a Public Health problem in Brazil and has great epidemic potential, currently affecting all regions of the country, with emphasis on the Northeast.¹²⁻¹⁴

AIDS (Acquired Immunodeficiency Syndrome), transmitted by the HIV virus, is characterized by the weakening of the body's defense system and the appearance of opportunistic diseases. The HIV virus is transmitted through unprotected sexual intercourse (vaginal, anal or oral) with an HIV-positive person, through the sharing of contaminated sharps, such as needles, nail pliers, among others, from an HIV-positive mother without treatment for her child during pregnancy, childbirth or breastfeeding. In Brazil, from 2000 to June 2018, a total of 116 292 pregnant women were notified infected with HIV, of which 7882 notifications occurred in 2017, with a detection rate of 2.8/1000 live births (Department of Surveillance, Prevention and Control of Sexually Transmitted Infections, HIV/AIDS and Viral Hepatitis, from Health Surveillance Secretariat, Ministry of Health).^{15,16}

Considering this scenario, this study aimed to determine the prevalence of infectious diseases in a reference hospital in the city of Belém, Pará, Brazil.

METHODS

A cross-sectional, quantitative study was carried out, in which data were obtained from the Mario Pinotti Municipal Hospital and Emergency Service (HPSMMP), in Belem, in the state of Para.

The analyzes were carried out from May 2018 to August 2019. The results of the test had been reported in the system, claiming the most current years and the infectious and contagious pathologies. Considering that the data were in a standardized table, it was decided to include the months and periods mentioned.

The diseases observed are of Compulsory Notification at the Epidemiological Surveillance Service: Chikungunya, Dengue, Chagas Disease, Schistosomiasis, Hepatitis, AIDS, Influenza, Exogenous Intoxication, Visceral Leishmaniasis, Leptospirosis, Malaria, Meningitis, Accidental Tetanus, Tuberculosis, Varicella, Violence, Varicella, Interpersonal violence, Zika, Human rabies, Work accident, Whooping cough, Acute flaccid paralysis, Typhoid fever, Measles, Hansen's disease, Toxoplasmosis and Rubella.

The data collected through epidemiological notifications of the diseases and conditions notified by the HPSMMP, referring to infection indicators, were in a Microsoft Office Excel 2007 spreadsheet, for the application of the prevalence rate of the diseases of compulsory notification. As it was a research that had neither access to the patients' medical records nor direct contact with them, it did not need to be submitted to REC. Thus, because these data were only numerical, we do not know their gender, color and age, so there was no need for ICF and TCUD. Data analysis was carried out by promoting the rate calculation (percentage).

RESULTS

From May to December 2018 and from January to August 2019, a total of 636 individuals with various infections were observed in the HPSMMP, with emphasis on the distribution of the number of diseases according to the Epidemiological Surveillance Service (Figure 1). The analyzes were calculated according to the prevalence percentage, in which the percentage obtained was applied at the percentage rate so that the prevalence of these infections could be identified. It should be noted that the five most frequent diseases were considered, and secondly, diseases caused by bacteria. As an example, tuberculosis cases, which represent 15% of infectious diseases in 2018, are observed.

Only an increase of five of these infections was observed in 2019. Influenza is one of the diseases with a percentage of 17% in 2018, which remained in 2019 with the same percentage rate, ranking secondly. As stated in the method, data were obtained from the Mario Pinotti Municipal Hospital and Emergency Service (HPSMMP), located in Belem, in the state of Para. The comparison of diseases reported in 2018 to 2019 is shown, showing the level of increase and decline regarding some diseases in the different years (Figure 1).

Some diseases were not included in the figure, as they had no comparison from the other year, as Chagas disease and Hepatitis, both with 6% prevalence in 2018.

DISCUSSION

In Brazil, in 2009, a total of 88464 cases of Severe Acute Respiratory Syndrome (SARS) were reported, of

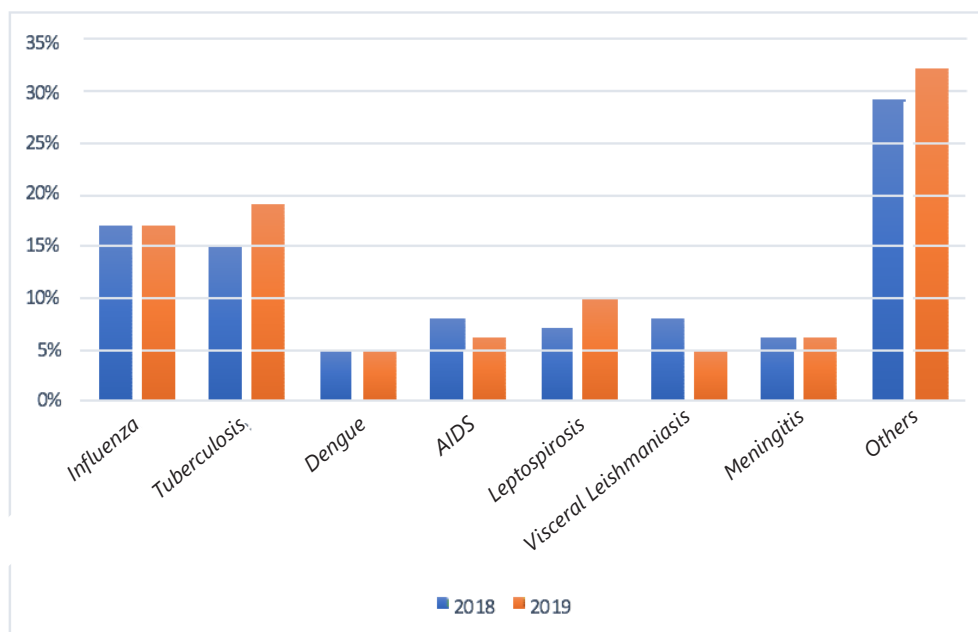


Figure 1. Most prevalent diseases with epidemiological notification from May 2018 to August 2019.

which 50482 were confirmed as influenza A (H1N1), with 2060 deaths.¹⁷ After the pandemic year in 2009, influenza A (H1N1) was more frequent in 2012 and 2013. In the following two years, 2014 and 2015, the predominant influenza virus was influenza A (H3N2). Again, in 2016, influenza A (H1N1) is the main agent, and its circulation occurred before the seasonality period. In 2017, the predominance among influenza viruses was A (H3N2), which exceeded the circulation pattern of 2014 and 2015 (Brazil, 2017).¹⁸ In the state of Rio de Janeiro, there were 5293 cases of SARS, with a total of 2777 confirmed cases.¹⁷ According to the WHO, it is estimated that the occurrence of cases of influenza varies from mild to severe and may even lead to death. Hospitalization and death occur mainly among high-risk groups. Worldwide, these annual epidemics are estimated to result in about 3 to 5 million cases of serious illness and about 290000 to 650000 deaths.¹⁹

The second disease reported with the highest number of cases observed in 2018 (15%) was tuberculosis. Compared to 2019 (19%), there was a 4% increase in the number of individuals affected, moving to the first position in the ranking of notified diseases. In the country, the disease is a serious public health problem, with deep social roots.²⁰ In 2017, it is estimated that 10 million people became ill from tuberculosis (TB) and that the disease caused 1.3 million deaths worldwide, which keeps TB among the top 10 causes of death on the planet.²¹

In 2018, the third disease found in greater number was AIDS (8%), compared to 2019 (6%), with a decrease of 2% in the number of cases so far. The latest estimate for the number of people living with HIV and AIDS in the world was approximately 37 million. In 2017, there were at least 1.8 million cases of new infections and a total of 940 thousand deaths among adults and children due to AIDS.²² From June 1980 to June 2017, 882 810 AIDS cases in Brazil has already been notified to the Ministry of Health, with the highest concentration of cases in the Southeast, South and Northeast, with 52.3%, 20.1% and 15.4%, respectively. The Middle-West and North regions had approximately 6% of the total cases in the period.²³

As for leptospirosis, a 3% increase in the number of cases was observed in 2019, compared to 2018. This infection is caused by a bacterium of the genus *Leptospira*, being transmitted to men by the urine of rodents, with a high incidence in certain areas.²⁴ In a study on the time-space distribution of leptospirosis and risk factors in Belem, the relationship between environmental and socioeconomic risk factors with the occurrence of the disease was reported.²⁵ This fact confirmed the need for continuity of studies on leptospirosis and its socio-environmental determinants, regarding its breakdown at local scales, so that it is possible to establish measures to mitigate the disease in its various aspects.

The infectious diseases found in Brazil, which especially affect the North region, are extremely important for the population's epidemiological knowledge. Thus, the data presented here can contribute to actions for the prevention of these diseases, elucidating the highest rates of cases and the decrease in other diseases related

to this study, its problems and treatment, so that society know about the diseases that most affect the population.

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Clinical characteristics of hospitalized pediatric patients with COVID-19 in a reference hospital in Manaus, Amazonas, Brazil

Características clínicas de pacientes pediátricos internados com COVID-19 em hospital de referência na cidade de Manaus, Amazonas, Brasil

Características clínicas de los pacientes pediátricos ingresados con COVID-19 en un hospital de referencia de la ciudad de Manaus, Amazonas, Brasil

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ABSTRACT

Background and Objectives: considering other pathological processes caused by viral infection and its impacts on affected children, it becomes relevant to identify aspects related to COVID-19 in pediatrics. In this regard, this study aimed to describe the clinical characteristics of pediatric admissions related to COVID-19 in a reference hospital in children's health in the city of Manaus. **Methods:** this is an ecological and descriptive study based on admissions data. The analyzed variables were: number of hospitalizations of COVID-19; month of hospitalization; age group of patients (categorized as: less than 1 year; 1 to 4; 5 to 9; 10 to 14 years); number of deaths; number of discharges, evasions or transfers; diagnostic method for COVID-19; mortality rate; number of atypical clinical manifestations; description of the manifestations. **Results:** thirty-five children diagnosed with COVID-19 were identified. Atypical manifestations are present in 20% of cases. There was a difference between the number of deaths and the number of discharges or transfers, with May presenting the highest number of cases. **Conclusion:** the study identified an increase in the frequency of hospitalization of children infected with COVID-19, raising an alert for a possible relationship between the disease and atypical manifestations, such as neurological disorders. The incipient scientific production, due to the recent history of the COVID-19 pandemic, reveals the need for further studies in the pediatric population as well as the development of measures to promote and monitor health and development in this population.

Descriptors: *Coronavirus Infections; Child Health; Epidemiology.*

RESUMO

Justificativa e Objetivos: considerando outros processos patológicos causados por infecção viral e seus impactos nas crianças afetadas, torna-se relevante identificar aspectos ligados à COVID-19 em pediatria. Nesse sentido, este estudo tem como objetivo descrever as características clínicas das internações pediátricas relacionadas à COVID-19 em hospital de referência em saúde infantil na cidade de Manaus. **Métodos:** estudo de caráter descritivo, baseado em dados de internações. As variáveis analisadas foram: número de internações de COVID-19; mês de internação; faixa etária dos pacientes (categorizadas em: menor de 1 ano; 1 a 4; 5 a 9; 10 a 14 anos); número de óbitos; número de altas, evasões ou transferências; método diagnóstico para COVID-19; taxa de mortalidade; número de manifestações clínicas atípicas; descrição das manifestações. **Resultados:** foram identificadas 35 crianças diagnosticadas com COVID-19. Manifestações atípicas estiveram presentes em 20% dos casos. Houve diferença entre o número de óbitos e número de altas ou transferências, com o mês de maio apresentando o maior número de casos. **Conclusão:** o estudo identificou um aumento na frequência de internação de crianças infectadas por COVID-19, levantando um alerta para possível relação da doença com manifestações atípicas, como afecções neurológicas. A incipiente produção científica, devido ao recente histórico de pandemia por COVID-19, revela a necessidade de novos estudos na população pediátrica, assim como a elaboração de medidas de promoção e monitoramento de saúde e desenvolvimento nessa população.

Descritores: *Infecções por Coronavirus; Saúde da Criança; Epidemiologia.*

RESUMEN

Justificación y Objetivos: considerando otros procesos patológicos provocados por la infección viral y su impacto en los niños afectados, cobra relevancia identificar aspectos relacionados con el COVID-19 en pediatría. En este sentido, este estudio tiene como objetivo describir las características clínicas de las hospitalizaciones pediátricas relacionadas con COVID-19 en un hospital de referencia para la salud infantil en la ciudad de Manaus. **Métodos:** estudio ecológico, de carácter descriptivo, basado en datos de hospitalización. Las variables analizadas fueron: número de hospitalizaciones por COVID-19; mes de hospitalización; rango de edad de los pacientes (categorizados como: menos de 1 año; 1 a 4; 5 a 9; 10 a 14 años); número de muertes; número de alta, evasión o traslados; método de diagnóstico para COVID-19; tasa de mortalidad; número de manifestaciones clínicas atípicas; descripción de las manifestaciones. **Resultados:** se identificaron 35 niños diagnosticados con COVID-19. Las manifestaciones atípicas estuvieron presentes en el 20% de los casos. Hubo una diferencia entre el número de muertes y el número de altas o traslados, siendo el mes de mayo el que presentó el mayor número de casos. **Conclusiones:** el estudio identificó un aumento en la frecuencia de hospitalización de niños infectados por COVID-19 y alertó sobre una posible relación entre la enfermedad y manifestaciones atípicas, como trastornos neurológicos. La incipiente producción científica, debido a la historia reciente de la pandemia COVID-19, revela la necesidad de realizar más estudios en la población pediátrica, así como el desarrollo de medidas para promover y monitorear la salud y el desarrollo de esta población.

Palabras clave: *Infecciones por Coronavirus; Salud Infantil; Epidemiología.*

INTRODUCTION

In December 2019, the disease caused by the coronavirus 2 severe acute respiratory syndrome (Sars-CoV-2), COVID-19 (Coronavirus Disease 2019), was reported for the first time in the Chinese province of Wuhan. Since then, the number of infected cases has grown on a large scale and soon the disease was classified by the World Health Organization (WHO) as a public health emergency of international concern.¹

COVID-19 is a disease that evolves with clinical aspects ranging from asymptomatic conditions to severe acute respiratory infection. The diagnosis is hindered by the low specificity of symptoms in the initial phase, such as the absence of fever and radiological abnormalities. The WHO reports that most people will have mild respiratory symptoms, but the elderly population and those with associated conditions may develop more severe symptoms and need advanced support.^{2,3}

In children, the clinical manifestations are similar to

those of adults. Some children progress with gastrointestinal symptoms, but generally the infection progresses from mild to moderate. In the first national-level epidemiological study aimed at the pediatric public, which assessed more than 2,000 children infected with COVID-19 in China, only 5.9% of cases were classified as serious and only one child died.^{4,5}

This same study also showed that infection with the new coronavirus did not show any significant difference between genders. Moreover, it showed that the majority of cases were mild infections and in the average age group of 7 years. However, children under five years of age were the most affected by severe and critical cases of the disease.⁵

Another study that sought to analyze case series also showed that most infected children evolve with greater gastrointestinal symptoms compared to adults. Other associated impairments, such as neurological and genetic disorders, have not been reported.⁶

Recent Brazilian data show that the frequency of hospitalization of children with respiratory symptoms in 2020 is lower compared to previous years. Despite this, the most up-to-date regional epidemiological bulletins point to an increase in the number of children diagnosed with COVID-19 compared to the period of appearance of the first cases in Brazil. States such as São Paulo (SP), Amazonas (AM), Ceará (CE), Pernambuco (PE), and Amapá (AP) are important centers of the pandemic.⁷⁻¹⁰

AM has a higher incidence and lethality rate than the national average, thus showing an expressive growth in the number of children infected by COVID-19. While SP maintains around 1.0% of all confirmed cases in children under 19, AM reaches 10%.^{8,9-11}

In view of this scenario, it is essential to understand the factors that led to this condition as well as to elucidate the evolution of cases of COVID-19 in children. Thus, the main objective of this study was to describe the profile of pediatric admissions related to COVID-19 in a reference hospital for children's health in the city of Manaus, AM.

METHODS

This is an ecological, descriptive study, based on data from admissions linked to COVID-19 in a reference hospital for children's health in the city of Manaus, AM, from March 1 to May 20, 2020. Therefore, data from the COVID-19 Bulletin was published by the Center for Epidemiology and Hospital Infection Control of the institution, which has an installed capacity for hospital/outpatient assistance, with approximately 77 beds in orthopedics, general surgery, anesthesiology, and intensive care.^{12,13}

Such hospital unit is located in a region of the capital of Amazonas that is very affected by the disease, with an incidence greater than 200 per 100 thousand inhabitants. Besides, it is a strategic location close to the main airports of the city and the municipalities in the metropolitan region that access the city of Manaus via land transport.¹¹

The variables used for analysis were: number of COVID-19 hospitalizations; month of hospitalization; age group of hospitalized patients (categorized as: less than 1 year; 1 to 4; 5 to 9; 10 to 14 years); number of deaths; number of discharges, evasions or transfers; diagnostic method for COVID-19; mortality rate; number of atypical clinical manifestations; description of the manifestations.

The information obtained by the aforementioned Bulletin was accessed on May 21, 2020 and converted into tables, using Microsoft Excel, version 16.1, in which descriptive statistical analysis was performed. The data were presented in the form of absolute numbers, frequency relative and 95% confidence interval (CI). As there was no access to individual data, it was not possible to calculate a point estimate (p value). Therefore, the interval estimate (95% CI) of the variables was used for statistical inference, with those categories without intersection between their 95% CI being considered significant differences.

This study was carried out based on secondary data, with no access to nominal data of patients or any others

that establish their identification. In this context, it was not necessary to submit to the Research Ethics Committee (REC), according to Resolution 466 of December 12, 2012 of the Brazilian National Health Council (*Conselho Nacional de Saúde*).¹⁴

RESULTS

Between March and May 2020, a total of 35 children with a diagnosis of COVID-19 were hospitalized. In general, a higher percentage of them started hospitalization in May, despite the shorter time (less days) compared to the other months (Figure 1), and with a predominance of the age group of 2 to 4 years. Most of them were transferred or discharged, and atypical clinical manifestations were present in sporadic cases (minority).

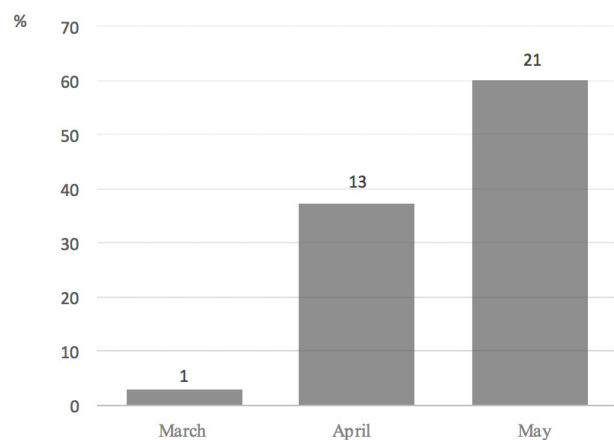


Figure 1. Distribution of COVID-19 cases according to the month of hospitalization from March 1 to May 20

Table 1 shows the frequency and CI of the number of pediatric patients hospitalized with COVID-19 in relation to the month of diagnosis, age group, hospital outcome (transfer, evasion, discharge, or death), diagnostic method, and clinical manifestations (present or absent).

Regarding the age groups of hospitalized patients, there was no statistical difference between the categories, although most children are up to 4 years old (21, equivalent to 60% of cases). The mortality rate for the cases studied was 5.7% (95% CI: 1.6% -18.6%), with a statistically significant difference between the number of deaths and the number of discharge or transfers, according to CI. The diagnostic methods did not differ in the sample; however, according to the source of information, it was not possible to know whether patients who were diagnosed using RT-PCR (Polymerase Transcriptase Reverse Chain Reaction) performed the rapid test or vice versa, which precludes a more complex analysis of diagnostic methods.

Most children did not present atypical clinical manifestations, which was significant in relation to the absent

Table 1. Characteristics of hospitalization/patient with COVID-19 according to frequency and confidence interval.

Characteristics of hospitalization/patient	Absolut frequency	Relative Frequency (%)	Confidence Interval 95% (CI 95%)
Age group			
< 1 year	10	28.6	16.3 – 45.1
2 to 4 years	11	31.4	18.6 – 48.0
5 to 9 years	06	17.1	8.1 – 32.7
10 to 14 years	08	22.9	12.1 – 39.0
Hospital outcome			
Transfer	14	40.0	25.6 – 56.4
Discharge	17	48.6	33.0 – 64.4
Evasion	02	5.7	1.6 – 18.6
Death	02	5.7	1.6 – 18.6
Diagnostic method			
Rapid Test	19	54.3	38.2 – 69.5
RT-PCR	16	45.7	30.5 – 61.8
Atypical clinical manifestations			
Presents	07	20.0	10.0 – 35.9
Absents	28	80.0	64.1 – 90.0

*Atypical manifestations present: 01 case of meningitis; Seizure 01; 01 case of Guillain Barré Syndrome; 01 case of acute diffuse glomerulonephritis; 01 case of Exanthematic Febrile Syndrome; 01 case of gastroenteritis; 01 case of nonspecific abdominal pain.

cases. According to the data extraction document, of the seven children with atypical manifestations, three of them had neurological changes (8.6%), namely: 01 case of meningitis, 01 seizure, and 01 Guillain-Barré Syndrome. The remaining cases were (only 01 patients each) acute diffuse glomerulonephritis, Exanthematic Febrile Syndrome, gastroenteritis, and nonspecific abdominal pain.

DISCUSSION

This study is one of the pioneers in the formal presentation and discussion of cases of children infected with COVID-19 in the Amazon region. In general, the results showed a tendency towards an increase in the frequency of cases of infected children from April onwards and continuing through May, which may indicate a follow-up to the rising regional and national epidemiological curve and the total number of cases. In March and April, AM had a higher incidence of cases among the states in northern Brazil. Such a finding may fit the results of the research by Mendonça et al. (2020), which demonstrated that the highest frequency of hospitalizations due to respiratory diseases in northern states occurs from March to June due to climatic issues that involve a longer period rain and increased humidity, making the environment more favorable to viral transmissibility.^{8-11,15,16}

Huang and colleagues (2020) report that as the epidemic spread in China, the number of infected children has increased. However, differently from other Brazilian

regions very affected by the pandemic, the findings of this research seem to show a disproportionate growth of the affections in the pediatric public in relation to the total of confirmed cases in this period, in Manaus, which may be related to the regional characteristics of frequency of admissions due to respiratory diseases.^{1,9-11}

In a study that sought to investigate the characteristics of children infected with COVID-19 in Italy, which assessed data from 11 Italian pediatric hospitals, Garazzino and collaborators (2020) identified 168 cases until April, of which 110 were hospitalized. In the United States, between February and April 2020, of the total cases of COVID-19 infection confirmed by laboratory examination (almost 150,000), 1.7% (2,572) were of individuals under 18 years old. Such research did not present information capable of defining whether there was an increase in the frequency of infection in children over time.¹⁷⁻¹⁸

The data found in this study show us that most patients admitted to the assessed unit were either transferred or discharged. The transfers of these children are probably not related to the need for care at a higher level of complexity, but to the fact that the hospital in the study was not defined by the state government as a reference to caring for patients infected with COVID-19. Furthermore, in a research that assessed the symptoms of the disease in the pediatric population, most of results conclude that the infection is mild to moderate, which contributes to clarifying the large number of hospital discharge found.¹⁷⁻¹⁹

The infected children had two types of tests as a diagnostic method, the rapid test and the RT-PCR. The first is to detect antibodies against Sars-CoV-2 antigens. The second is the laboratory method for identifying the virus, being carried out by collecting respiratory material. According to data from the assessed institution, it does not have the necessary machinery to perform tomography, another test that may indicate a lung injury caused by infection with the new coronavirus. Thus, a more comprehensive assessment of sequel left by the disease in children is difficult. Even so, there are no reports showing severe lung injury in the pediatric public due to COVID-19.^{2,20,21}

The mortality rate for the assessed cases was 5.7%, a number corresponding to the percentage of severe cases found in a Chinese cohort and equal to the number of patients who required hospitalization in the United States in the same period. The most recent national epidemiological bulletin shows that the mortality rate in cases of infection associated with COVID-19 in children was 15.3% in Brazil.^{5,18,20}

Clinical studies that sought to present clinical and epidemiological characteristics of COVID-19 infection reported that patients with severe cases and with a greater chance of having death as an outcome were not in the age group under 18 years old. The mortality rate is variable, and in the child population, it was between 0 and 3%. It is worth mentioning that the assessed sample by these surveys is greater than the study presented here. However, studies on COVID-19 manifestations are still

incipient. Moreover, the number of cases is still on the rise, so it is not possible to predict whether the mortality rate will remain the same.^{2,5,17}

National study data seem to point to differences in the spread of the virus and a consequent increase in the number of cases of infection with respect to spatial and geographical characteristics. Findings from the Center for Disease Control in the United States also pointed to epidemiological differences arising from geographic variations. Official data on the epidemic in Brazil show that northern Brazil is the most affected and that the coefficient of incidence and mortality rate, in AM, are the highest. In this regard, a more stratified approach that includes more information about the profile of the pediatric population affected by COVID-19 is necessary and may assist in planning public policies, aimed at child growth and development as well as in health promotion.^{8,22,23}

Data from the study in question show that 20% of infected children had atypical manifestations (neurological changes, gastroenteritis, nonspecific abdominal pain, etc.). Children under 5 years old seem to have more episodes of vomiting and diarrhea. Although it is not possible to determine the age of patients who evolved with such clinical findings, more attention is needed to the age group under 5 years old, who had a higher frequency of hospitalization by the study. Such special attention is due not only to immunological issues, but also due to aspects of greater growth, development and maturation of the central nervous system related to this age group. That is, the higher the levels of exposure of agents potentially harmful to the development of these children the greater the chances of changes and impairments to their development, not only at the neurophysiological level, but also neurobehavioral, considering that brain plasticity, in greater activity in children up to five years of age, is characterized by the ability to constantly remodel not only function, but also the structure of the brain, influenced by the experience that extends throughout life.^{5,17,24}

Besides that, investigating possible atypical manifestations, especially neurological, is of paramount importance due to the recent Brazilian history, linked to the Zika Virus (ZIKV) epidemic, identified in 2015. Such infection resulted in serious consequences for child development, characterized by the emergence of a congenital syndrome in which the main involvement was the microcephaly of children whose mothers were infected during pregnancy. After that, new strategies were needed to include supportive measures for this population in the health system.²⁵

The study has as a limitation the number of assessed children (35), which will require constant monitoring of the numbers and greater exploration of them, including analysis of individual variables. However, it is useful to describe data and assist in the adoption of criteria aimed at following-up these patients, on an outpatient basis and within the scope of primary care, to monitor possible changes linked to COVID-19 and to relate potential adverse events associated with the acute condition of the disease by the new coronavirus with special attention to

possible neurological changes.

In conclusion, the study identified an increase in the frequency of hospitalization of children infected with COVID-19 as well as the possibility, even if not certified, of a relationship between coronavirus infection and associated atypical factors. The incipient scientific production aimed specifically at the pediatric public affected by this disease, in addition to the recent history of complications in child development caused by maternal contamination by the Zika Virus, suggests the need to create measures to promote health and monitor this population with regard to strengthening Primary Health Care actions aiming at comprehensive and multidisciplinary care.

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CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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AUTHOR'S CONTRIBUTIONS:

Lucas Lima de Moraes e Ayrles Silva Barbosa Gonçalves Mendonça contributed to the planning, conception, design of the article, analysis, writing, revision and final approval of the article;

Tiótrefis Gomes Fernandes contributed to the analysis, writing, revision and final approval of the article;

All authors approved the final version to be published and are responsible for all aspects of the work, including ensuring its accuracy and integrity.

Profile of deaths from respiratory diseases in the state of Rio Grande do Sul, from 2006 to 2015

Perfil dos óbitos por doenças respiratórias no interior do Rio Grande do Sul, 2006 a 2015

Perfil de muertes por enfermedades respiratorias en el interior de Rio Grande do Sul, 2006 a 2015

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ABSTRACT

Background and objectives: Respiratory diseases affect all age groups and pose a high demand on health services. The present study aimed to analyze the profile of patients who have died from respiratory diseases, between 2006 and 2015, from the 9th Health Coordination of Rio Grande do Sul. **Methods:** This is a cross-sectional and descriptive study using the database of the Informatics Department of the Unified Health System (Datusus) from the Ministry of Health in Brazil. Data collection was carried out in November 2017 and included 10 years up to 2015. The causes of death from respiratory disease were selected according to the International Classification of Diseases 10th revision, Chapter X, vital statistics, mortality from 1996 to 2015. The variables for this research were collected according to chronological distribution, gender, age and period of the year. **Results:** Out of a total of 1,471 deaths from respiratory diseases, 52% were men, most were older adults (61%) with up to 3 years of education (73.3%), which is possibly associated with low income. The main causes of death were chronic diseases of the lower airways and pneumonia, representing 56% and 29% of deaths, respectively. In addition, 34% of deaths occurred during winter. **Conclusion:** The main causes of mortality from respiratory diseases from the 9th Health Coordination were chronic diseases of the lower airways and pneumonia, with higher mortality rates in colder months, among older adults and patients with a lower level of education.

Keywords: Respiratory Tract Diseases. Epidemiology. Mortality Registries.

RESUMO

Justificativa e objetivos: As doenças respiratórias atingem todas as faixas etárias e geram grande demanda dos serviços de saúde. O presente estudo objetivou analisar o perfil dos óbitos por doenças respiratórias na 9^a Coordenadoria de Saúde do Rio Grande do Sul, entre 2006 e 2015. **Métodos:** Trata-se de um estudo transversal e descritivo em que se utilizou o banco de dados do Departamento de Informática do Sistema Único de Saúde (Datusus) do Ministério da Saúde do Brasil. A coleta de dados foi realizada em novembro de 2017, abrangendo os últimos 10 anos.

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A seleção das causas de óbitos por doenças respiratórias foi selecionada de acordo com o Código Internacional de Doenças 10ª revisão, Capítulo X, estatísticas vitais, mortalidade de 1996 a 2015. As variáveis para esta pesquisa foram coletadas de acordo com a distribuição cronológica, sexo, idade e período do ano do óbito. **Resultados:** Do total de 1.471 óbitos por doença respiratória, observou-se que 52% acometeram homens, na maioria idosos (61%) e com até 3 anos de estudo (73%), o que pressupõe baixa renda. As principais causas de óbitos foram as doenças crônicas das vias aéreas inferiores e pneumonia, equivalendo a 56% e 29% dos óbitos respectivamente, sendo 34% dos óbitos ocorridos durante o inverno. **Conclusão:** As principais causas de mortalidade por doenças respiratórias ocorridas na 9ª Coordenadoria de Saúde foram as doenças crônicas das vias aéreas inferiores e pneumonia, com maior ocorrência nos meses mais frios, acometendo mais homens idosos e com menor nível escolar.

Descritores: Doenças Respiratórias. Epidemiologia. Registros de Mortalidade.

RESUMEN

Justificación y objetivos: Las enfermedades respiratorias afectan a todas las edades y generan gran demanda por los servicios de salud. El presente estudio objetiva analizar el perfil de las muertes por enfermedades respiratorias en la 9ª Coordinación de Salud del Rio Grande do Sul, entre 2006 y 2015. **Métodos:** Se trata de un estudio transversal descriptivo con base en informaciones del Departamento de Informática del Sistema Único de Salud (Datusus) del Ministerio de la Salud (Brasil). La recolección de datos se realizó en noviembre de 2017, abarcando los últimos 10 años. La selección de las causas de muertes por enfermedades respiratorias fue estimada seguido la Clasificación Internacional de Enfermedades 10ª Revisión, Capítulo X, estadísticas vitales, mortalidad de 1996 a 2015. Las variables para esta investigación fueron recolectadas de acuerdo con la distribución cronológica, sexo, edad y período del año del óbito. **Resultados:** De las 1.471 muertes por enfermedad respiratoria, fue observado que 52% en hombres (767), la mayoría ancianos (61%), hasta 3 años de estudio (73%), o que presupone bajos ingresos. Las principales causas de muerte fueron las enfermedades crónicas de las vías aéreas inferiores y la neumonía, equivalente al 56% y 29% de los casos, respectivamente, el 34% de las muertes ocurrieron durante el invierno. **Conclusiones:** Las principales causas de mortalidad por enfermedades respiratorias ocurridas en la 9ª Coordinación de Salud en los 10 años fueron enfermedades crónicas de las vías aéreas inferiores y neumonía, con mayor ocurrencia en los meses más fríos, afectando más hombres ancianos con menor nivel escolar.

Palabras clave: Enfermedades Respiratorias. Epidemiología. Registros de Mortalidad.

INTRODUCTION

Respiratory diseases affect individuals of all ages and socioeconomic levels and are associated with high morbidity and mortality rates, which poses a high demand for health services and affect the economy.¹ Respiratory diseases can be chronic or not, and some can be classified as chronic non-communicable diseases (NCDs), which are responsible for a reduction in quality of life.²

There are several agents that cause respiratory diseases, including virus, bacteria, allergens, trauma, and chemical and physical agents. Respiratory system diseases cause airway obstruction and affect both the lower and the upper respiratory tracts.³ Several pathologies can affect the respiratory system: acute respiratory infections, chronic lower respiratory diseases and Chronic Obstructive Pulmonary Disease (COPD).¹

Risk factors for respiratory diseases can be modifiable, such as lifestyle and smoking; or not modifiable,⁴ such as age, gender, demographic status, and socioeconomic characteristics. These data can describe the profile of individuals affected by respiratory diseases.⁵ In addition to these factors, changes in temperature and environment also have been studied for being possibly associated with deaths from respiratory diseases.⁶

A study on the mortality rate of chronic non-communicable diseases in Brazil, based on data from

Datusus, showed that respiratory diseases appeared as the third leading cause of death in the country between 2000 and 2011.² According to the Epidemiological Report of the Ministry of Health (2016), between 2003 and 2013, most hospitalizations and deaths due to respiratory diseases occurred in the South region, with 6,876,361 hospital admissions at the Unified Health System and 685.031 deaths.⁷

Considering the relevance of the theme, the objective of this study was to analyze the profile of patients who died from respiratory diseases between 2006 and 2015 from the 9th Health Coordination of Rio Grande do Sul.

METHODS

Cross-sectional and descriptive study, using Datusus database, managed by the Ministry of Health in Brazil. Based on these data, we analyzed the epidemiological profile of deaths and hospitalizations due to respiratory diseases in the cities of the 9th Health Coordination/Rio Grande do Sul.

Data collection was carried out in November 2017 and included data from a 10 year period, available through Tabnet. The region of the 9th Health Coordination of Rio Grande do Sul (Cruz Alta) is composed by 13 cities, namely: Boa Vista do Cadeado, Boa Vista do Ingra,

Colorado, Cruz Alta, Fortaleza dos Valos, Ibirubá, Jacuizinho, Quinze de Novembro, Saldanha Marinho, Salto do Jacuí, Santa Barbara do Sul, Selbach and Tupanciretã.

The selection of the causes of death from respiratory diseases was estimated according to the International Classification of Diseases 10th revision (ICD-10), Chapter X (Diseases of the respiratory system), vital statistics, mortality from 1996 to 2015. The variables for this research were collected according to the chronological distribution, gender, age, time of study and month of death. As the data was public and secondary, going through the Research Ethics Committee was not necessary.

RESULTS

Among all of 1,471 deaths from respiratory disease registered in Datasus in the 9th Health Coordination (Cruz Alta) from 2006 to 2015, 52% (767) of those affected were male.

For the present study, data from the Brazilian Institute of Geography and Statistics (IBGE) from 2010 was established as the average reference population, with a number of 152,070 inhabitants. In this study, the rate of mortality due to Respiratory Diseases was 9.67/10 thousand inhabitants. The highest incidence of deaths

occurred between the years 2012 and 2014, reaching a rate of 11.6 and 11.5 deaths (for every 10,000 inhabitants) respectively (Figure 1).

According to Chapter X from the ICD-10, the groups that can be described as diseases of the respiratory system are acute infections of the upper airways, influenza, pneumonia, other acute infections of the lower airways, other diseases of the upper airways, chronic diseases of the lower airways, lung diseases due to external agents, other respiratory diseases that mainly affect the interstitium, necrotic and suppurative disorders of the lower airways, other diseases of the pleura and other diseases of the respiratory system.⁷ In this study, the following groups can be observed as causes of death from the 9th Health Coordination (Cruz Alta): Influenza, Pneumonia, Lower Airway Infections, Chronic Lower Airway Diseases, Asthma and several others.

Between 2006 and 2015, the main causes of mortality in the same region were chronic diseases of the lower airways and pneumonia, which represented 56% (826) and 29% (421) of the cases, respectively. As for gender, the highest percentage of deaths from Chronic Lower Airway Diseases was among men (59% - 487), differing from cases of Pneumonia, which affected more women (41% - 339), as shown in figure 2.

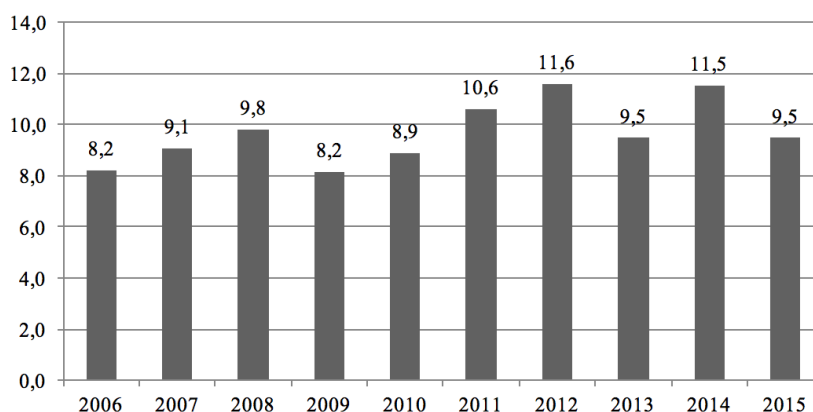


Figure 1. Chronological distribution of the rate of deaths from respiratory diseases between 2006 and 2015, from the 9th Health Coordination/Rio Grande do Sul, according to Datasus (for every 10,000 inhabitants).

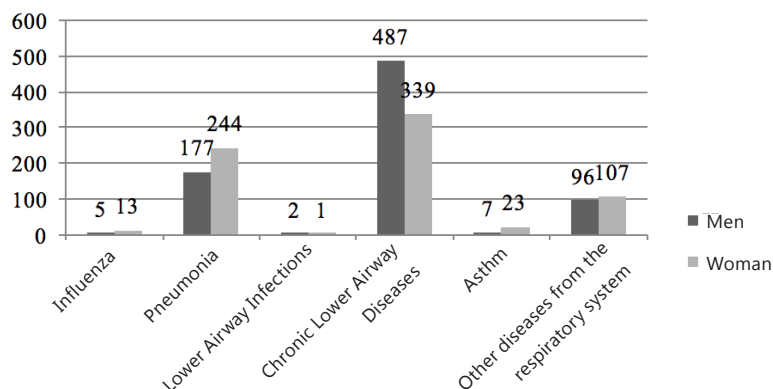


Figure 2. Number of deaths during the study period, grouped by gender, according to data from Datasus (9th Health Coordination / Rio Grande do Sul between 2006 and 2015).

Deaths from respiratory diseases were described according to the month of occurrence, with the objective of observing the seasonal distribution of deaths from respiratory diseases. The months with the highest rates were June (145 deaths), July (188 deaths) and August (168 deaths), representing 501 deaths out of a total of 1,471. Consequently, there was a higher percentage of deaths in the coldest months (Figure 3).

The analysis of the number of deaths according to the age group shows an increase from the age of 45 onwards, with a gradual increase following age. The age

group with the highest number of deaths was 75 years old or more, with a total of 906 cases (61.6%). (Figure 4).

It was found that the highest number of deaths occurred in individuals with a lower level of education. However, 518 (35%) cases had no records regarding the level of education. Of the 953 (65%) individuals who had a record of their level of education, 474 (50%) had 1 to 3 years of education, 225 (24%) had no education and 209 (22%) had 4 to 7 years of education. Among those remaining, 29 (3%) had 8 to 11 years of education and 16 (2%) had 12 years or more of education (Figure 5).

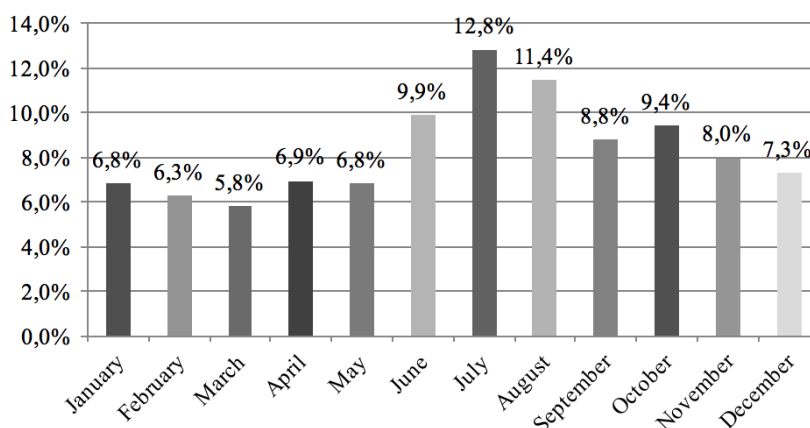


Figure 3. Seasonal distribution of deaths during the study period, presented in months of the year, according to data from Datasus (9th Health Coordination/Rio Grande do Sul, 2006-2015).

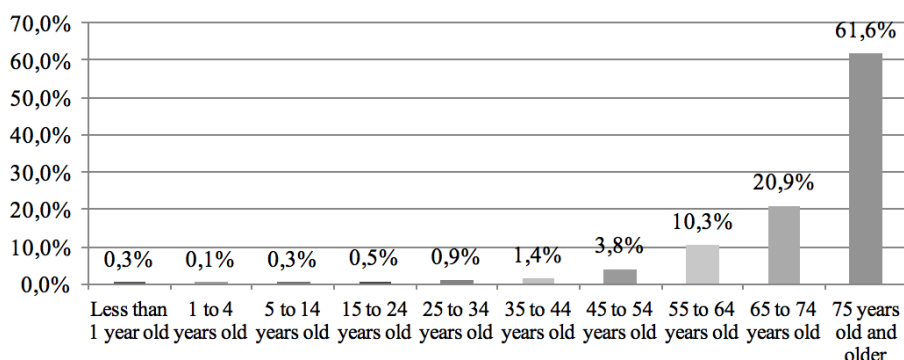


Figure 4. Distribution of the percentage of deaths, described by age groups, 2006-2015, according to Datasus (9th Health Coordination / Rio Grande do Sul).

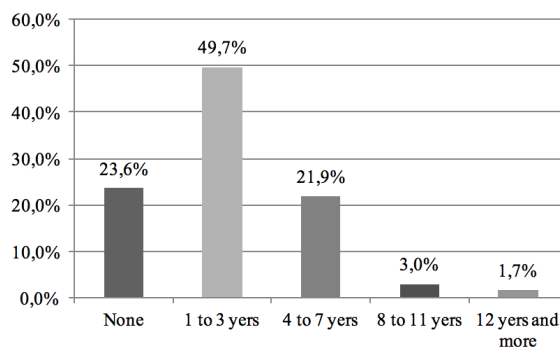


Figure 5. Distribution of deaths according to level of education, in years, according to data from Datasus (9th Health Coordination / Rio Grande do Sul between 2006 and 2015).

DISCUSSION

This study found that deaths from respiratory diseases are more common among men, which was also observed in similar studies. The reasons for this result include lifestyle habits, smoking, alcohol consumption and the greater search for healthcare among females.^{8,9}

Diseases of the respiratory system affected a greater number of older adults in the 9th Health Coordination, with emphasis on the age group of 75 years and older. Other studies found similar results.¹⁰⁻¹¹⁻¹² Another fact that stands out is the high number of diseases of the respiratory system among older adults, concomitant to the growth of this population in Brazil.¹³ A study carried out in the state of Rio de Janeiro analyzed the rates of hospital admissions of individuals aged 60 years or older and found that the second major cause of hospital admissions were diseases of the respiratory system.¹⁴

The overall mortality rate of respiratory diseases found in this study was 0.97/100 thousand inhabitants. According to the Epidemiological Report of the Ministry of Health, the mean number of deaths from respiratory disease in the South was 46/100 thousand inhabitants. According to the year, the number of deaths was 48.9/100 thousand inhabitants in 2003 and 47.0/100 thousand inhabitants in 2013.⁸

The Epidemiological Report, vol. 47. No. 19, carried out in 2016, demonstrated that chronic diseases of the lower airways are associated with the highest number of deaths in the South region.⁸ The main causes of deaths from respiratory diseases in the region of the 9th Health Coordination (Cruz Alta) were chronic diseases of the lower airways (56%) and Pneumonia (29%). Some authors reported, that among respiratory diseases, Pneumonia is largely responsible, if not the main, responsible for the high number of deaths.¹⁵⁻¹⁷ A study analyzed the main causes of hospitalizations and deaths that affected older adults between 2005 and 2015 in Brazil, and pneumonia appeared in the second position, both as a cause of deaths and as a cause of hospitalizations.¹⁶

In March 2010, the ten-valent pneumococcal conjugate vaccine (PCV10) was introduced in Brazil's National Immunization Program. A study evaluated the direct and indirect impact of the vaccine on hospitalizations for pneumonia in all age groups by analyzing time series, and found a significant decrease in hospitalization rates in the population aged 10 to 49 years. However, it did not change the growing trends in hospitalization for pneumonia in older adults \geq 65 years old. The authors concluded that the escalating numbers of hospitalizations for pneumonia among older adults should be investigated for being a public health problem.¹⁵

In this study, cases of Pneumonia affected mostly women, with a rate of 58% of cases. A similar result was found in another study, which was carried out in a city in São Paulo-Brazil and found that prevalence of pneumonia cases was increasing over different periods, with an increase of 57.92% in the female population.¹² A Spanish survey analyzed the epidemiology of pneumonia cases over a period of ten years, aiming to describe the character-

istics of patients diagnosed with the disease and found that, in a sample of 1,290 patients, 56.1% were men.¹⁸

Researchers carried out a temporal study analyzing mortality rates of Pneumonia and found that, in the South Region of Brazil, there was a decrease until the year 2000, followed by growth, whereas in the North and Northeast region, mortality for pneumonia increased during the entire studied period.⁹ A study in the Northeast Region of Brazil evaluated deaths caused by influenza from 1998 to 2007 through data from the Datasus and concluded that the mortality rates of Influenza were high and increasing, differing from the 9th Health Coordination (Cruz Alta) region, where there were only 18 registered cases of influenza, the lowest percentage (1.2%) among the causes of death.¹¹

Climate changes are part of the global reality. In addition, some regions have extreme temperatures, which represent a health threat and may cause or worsen respiratory problems.¹⁹ In a meta-analysis that verified the effects of air temperature on morbidities and mortality among older adults, the authors found that a temperature reduction of 1°C is able to increase mortality from respiratory problems (2.90%). In addition, it was found that pneumonia cases were directly associated with cold weather (6.89%), leading to the conclusion that the risks for the mentioned diseases are directly related to the climate.³ It is also worth mentioning that in addition to the direct relationship between climate change and mortality rates, climate changes also increase the rate of hospital admissions, generating high expenses for the health system.¹⁶

This study found a prevalence of respiratory diseases in the period of June, July, and August (34%) in the region of the 9th Health Coordination, which represents the period of the winter in Brazil. A study compared the climate and respiratory diseases in the city of Patrocínio-MG and found that during the winter months, when the air quality is worse, there is a significant increase in the number of respiratory diseases.²⁰ Another study conducted in the city of Campina Grande, aimed to identify the association between meteorological variables and respiratory diseases in the period between 2004 and 2013 and found that health is directly associated to seasonality, as the respiratory system tends to suffer from changes in air humidity and low temperatures.²¹

Socio-demographic differences were considered an important factor in the characterization of deaths from respiratory diseases. Most of these deaths occurred in individuals with a low level of education, with 1 to 3 years of education, or with no education, which suggests that mortality by respiratory diseases may be associated with low income.²² A survey associated diseases of the respiratory system and low income and concluded that the lower the socioeconomic class, the greater the number of cases of respiratory diseases.¹⁷ A cross-sectional study associated health conditions and risk factors in adults living in Puerto Rico, a place that experienced an economic crisis, and found that 51% of the population received government food benefits and 21% had respiratory health issues.²³

A limitation of this study was the use of secondary data, collected through the Datasus Tabnet (Informatics Department of the Brazilian Unified Health System). This is a tool that provides information on the health of the population, but does not support the total demand for data from managers.²⁴

There is an urge for other forms of prevention and monitoring of respiratory diseases for greater management of cases and better care of the affected population. Procedures must be taken to achieve equality in access to health for the entire population, especially the most vulnerable groups along with their risk factors.²⁵

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AUTHOR'S CONTRIBUTIONS:

Alana Martins da Veiga, Giovani Sturmer, Fabiana de Cássia Romanha Sturmer, Gilson Rodrigues dos Santos contributed to the conception, design of the article, analysis and writing of the article;

Alana Martins da Veiga, Giovani Sturmer, Fabiana de Cássia Romanha Sturmer, Gilson Rodrigues dos Santos contributed to the planning, analysis, review and final approval of the article;

All authors have approved the final version to be published and are responsible for all aspects of the work, including ensuring its accuracy and completeness.

Use of antidepressants and potential drug interactions in cancer patients treated at a hospital in the Southern Brazil

Uso de antidepressivos e potenciais interações medicamentosas em pacientes oncológicos atendidos em hospital do Sul do Brasil

Uso de antidepressivos y posibles interacciones farmacológicas en pacientes con cáncer tratados en un hospital en el Sur de Brasil

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ABSTRACT

Background and Objectives: Cancer is a chronic degenerative disease and its diagnosis is often associated with mental distress, doubts and insecurities that can trigger depressive symptoms, causing the need for pharmacological treatment. However, cancer patients often use multiple medications (polypharmacy), thus increasing the chances of potential drug interactions. The objective of this study was to evaluate the use of antidepressant drugs in oncological inpatients and the potential drug interactions of their prescriptions. **Methods:** Prospective, descriptive, and analytical cross-sectional study conducted with cancer patients aged ≥ 18 years, admitted to a hospital in Southern Brazil, and aware of their diagnosis. Larger and contraindicated drug interactions were analyzed using the Micromedex® and Lexicomp® databases. **Results:** The sample consisted of 50 patients, 54% were female and the mean age was 53.6 (± 15.3) years. Antidepressant drugs were used in 42% of the patients, escitalopram (selective serotonin reuptake inhibitors) being the most prescribed. 90% of the patients had some potential interaction and they occurred with any drug prescribed for treatment. Out of the patients using antidepressants, 62% had contraindicated interactions and all had at least one case of major interaction. The drugs most related to contraindicated drug interactions were dipyrone and metoclopramide. **Conclusion:** The results of this study demonstrated a high number of contraindicated interactions involving antidepressant drugs. The significance of monitoring and adjusting the pharmacotherapy of these patients is crucial.

Keywords: Drug Interactions. Antineoplastic Agents. Antidepressive Agents. Medical Oncology.

RESUMO

Justificativa e Objetivos: O câncer é uma doença crônico-degenerativa cujo diagnóstico constantemente está associado a sofrimento mental, dúvidas e inseguranças, podendo desencadear sintomas depressivos, de forma que às vezes são necessárias medidas farmacológicas para tratar desses sintomas. Entretanto, pacientes oncológicos frequentemente utilizam vários medicamentos (polifarmácia), aumentando as chances de potenciais interações medicamentosas. Este estudo pretendeu avaliar o uso de antidepressivos nos pacientes em tratamento oncológico hospitalizados e as potenciais interações medicamentosas de suas prescrições. **Métodos:** Estudo transversal, prospectivo, descritivo e analítico realizado com pacientes oncológicos com idade superior a 18 anos, internados em um hospital do Sul do Brasil e cientes de seu diagnóstico. As interações medicamentosas maiores e as contraindicadas foram analisadas por meio das bases de dados *Micromedex*[®] e *Lexicomp*[®]. **Resultados:** Na amostra, composta de 50 pacientes, 54% eram do sexo feminino, e a média de idade foi de 53,6 ($\pm 15,3$) anos. Além disso, dentre a amostra, 42% dos pacientes utilizavam medicamentos antidepressivos, sendo o escitalopram (inibidor seletivo da recaptção de serotonina) o mais prescrito; e 90% dos pacientes apresentaram algum tipo de potencial interação, que ocorreram com quaisquer medicamentos prescritos para o tratamento. Dos pacientes que utilizavam antidepressivos, 62% tiveram interações contraindicadas e todos apresentaram pelo menos um caso de interação maior. Os medicamentos mais relacionados a interações medicamentosas contraindicadas foram a dipirona e a metoclopramida. **Conclusão:** Os resultados deste estudo demonstraram um elevado número de interações medicamentosas contraindicadas envolvendo medicamentos antidepressivos. Nesse contexto, verifica-se a importância de monitorar e adequar a farmacoterapia desses pacientes.

Descritores: Interações de Medicamentos. Antineoplásicos. Antidepressivos. Oncologia

RESUMEN

Justificación y objetivos: El cáncer es una enfermedad crónico-degenerativa, que tiene su diagnóstico frecuentemente asociado a angustia mental, dudas e inseguridad, lo que puede resultar síntomas depresivos, que necesitarán, a menudo, medidas farmacológicas para tratarlos. Sin embargo, los pacientes con cáncer muchas veces usan varios medicamentos (polifarmacia), lo que aumenta las posibilidades de interacciones farmacológicas. Este estudio propone evaluar el uso de antidepressivos en pacientes con cáncer hospitalizados y las posibles interacciones farmacológicas que proceden de sus prescripciones. **Métodos:** Estudio transversal, prospectivo, descriptivo y analítico realizado con pacientes con cáncer de edad superior a 18 años, ingresados en un hospital en el Sur de Brasil y conscientes de su diagnóstico. Las interacciones farmacológicas más grandes y contraindicadas se analizaron utilizando las bases de datos *Micromedex* y *Lexicomp*. **Resultados:** La muestra consistió en 50 pacientes, el 54% eran mujeres y el promedio de edad fue de 53,6 ($\pm 15,3$) años. El 42% de los pacientes utilizaban fármacos antidepressivos, de los cuales el escitalopram (inhibidor selectivo de la recaptación de serotonina) fue el más recetado; el 90% de los pacientes tuvieron alguna interacción que ocurrió con cualquier medicamento recetado para el tratamiento. De los pacientes que usaban antidepressivos, el 62% tuvieron interacciones contraindicadas y todos presentaron, al menos, un caso de interacción mayor. Los fármacos más relacionados con las interacciones farmacológicas contraindicadas fueron dipirona y metoclopramida. **Conclusión:** Los resultados de este estudio demostraron un alto número de interacciones farmacológicas contraindicadas que involucran fármacos antidepressivos. En este contexto, se verifica la importancia de monitorear y ajustar la farmacoterapia de estos pacientes.

Palabras clave: Interacciones Farmacológicas. Antineoplásicos. Antidepressivos. Oncología médica

INTRODUCTION

Depression is a common mental disorder worldwide. It is estimated that more than 300 million people suffer from this disorder. It is characterized by sadness, loss of interest or pleasure, feeling of guilt or low self-esteem, altered sleep and appetite, tiredness, and lack of concentration, and it can become a critical health condition, especially when it has long duration and moderate or severe intensity.¹

Individuals with chronic conditions are more likely to have depressive symptoms. In fact, worldwide, depression is more prevalent among patients with cancer, heart disease, diabetes, stroke, or chronic respiratory problems

than in the general population. Cancer patients are up to three times more likely to suffer from depression than people who do not have the disease. However, it may be difficult to make a definitive diagnosis due to the overlap of clinical symptoms.²⁻⁵

Cancer is the second leading cause of death in the world and in 2018 it accounted for 9.6 million deaths. According to the Brazilian National Cancer Institute (*Instituto Nacional de Câncer* — INCA), an estimated 420,000 new diagnoses of the disease are estimated for 2019, except for non-melanoma skin cancer. It is a chronic-degenerative disease characterized by the uncontrolled and disorderly growth of cells that prevent the normal functioning of the

body. This type of cancer has a multifactorial origin and it is mainly triggered by genetic changes, environmental factors and lifestyle.⁶⁻⁸

The diagnosis of cancer causes intense suffering to patients and generates a greater sense of anguish than other non-neoplastic diseases with a worse prognosis. Patients tend to have high levels of mental suffering, doubts, and insecurity for prolonged periods, which can lead to the development of anxiety disorders, depression, or both.^{5,9}

The prevalence of depressive symptoms among cancer patients varies according to the type of cancer, stage of the disease, and demographic profile of the population. Depression not only compromises the quality of life of patients, but also increases their mortality.^{5,10}

Pharmacological options are often required to treat symptoms related to depressive disorders. Furthermore, antidepressant medications can be used for other purposes, such as pain treatment. However, many antineoplastic medicines share the same metabolic pathways, potentiating their undesirable effects. Concomitant administration of antineoplastic drugs and antidepressants can lead to drug interactions, both pharmacokinetic and pharmacodynamic, reducing the drugs effectiveness or increasing its toxicity. Generally, the patients most exposed to DI are those who use five or more medications (polypharmacy). Cancer patients are most often prone to polypharmacy because they use – in addition to cancer treatment-medicine – drugs to treat side effects of chemotherapy, neoplasia-related syndromes, and other associated diseases.¹⁰⁻¹³

Drug interactions can be considered responsible not only for the clinical deterioration of the patient, but mainly for the increase in hospital measures and the time of hospitalization, affecting the quality of care and making the treatment more expensive for the health care system. It is noteworthy the significance of the entire health team to monitor these DI, in addition to the fundamental role of the pharmacist in this scenario.¹⁴

The prescription of antidepressant medications for patients undergoing cancer treatment can be made by several professionals, which may generate negligence in the observation of potential drug interactions resulting from this use.¹⁰

This study analyzes the use of antidepressants in patients undergoing cancer treatment admitted to a hospital in the Southern Brazil and the potential drug interactions of the prescriptions given to these patients.

METHODS

This is a cross-sectional, descriptive, and analytical study carried out in a teaching hospital, a reference in the treatment of childhood and adult cancer, in addition to be a High Complexity Care Unit in Oncology (Unidade de Assistência de Alta Complexidade – UNACON).

The sampling was non-probabilistic and non-random, performed with patients hospitalized in the proposed period. The collection was carried out in two periods, to continue the existing database, covering the period from August to September 2018, and from April to June

2019. Patients aged ≥ 18 years, who were hospitalized for cancer treatment and who had cognitive conditions to answer the questionnaire were included in the study. The volunteers who agreed to participate in the study signed an informed consent form.

Data were collected by information from the patient's electronic medical records and by a structured bedside interview, whose variables were: name, age, schooling level, occupation, marital status, number of children, breastfeeding, family history of cancer, and continuous use medications. The questionnaires were applied by a pharmacist of the Multiprofessional Residency Program in Cancer Care. The research was approved by the Research Ethics Committee of the University of Passo Fundo, under opinion no. 3,220,803 and CAAE 93508318.1.0000.5342.

The Micromedex[®] and Lexicomp[®] databases were used to evaluate the drug interactions between antidepressant, oncological therapy, and supportive medications. Since some medications were not included in the arsenal of some bases, both were used to analyze the interactions. Considering the clinical relevance, this study was based on the description and detailing of the contraindicated drug interactions, so that the higher-severity drug interactions were only mentioned in terms of their frequency, because they occurred in large numbers, which hindered their detailing.

The severity of the interactions was described according to the Micromedex[®] database classification: "contraindicated," when the drugs cannot be used concomitantly because they cause risk to the patient's life; and "higher," when drug interactions can threaten the patient's life, requiring or not medical intervention to minimize or prevent adverse effects.

The collected data were stored as a database in Excel 2016 software. Continuous variables were expressed as mean and standard deviation, and the categoric ones with relative frequencies and absolute number.

RESULTS

The sample was composed of 50 cancer patients hospitalized and undergoing chemotherapy. The patients' mean age in the study was 53.6 (± 15.3) years, with a minimum age of 22 years and a maximum of 78 years, among which 66% were aged \leq to 60 years. Most patients were women, 54% (n=27), among whom 92.6% (n=25) reported having children, 64.0% (n=16) breastfed, on average, for 16 (± 14.7) months. The sociodemographic characteristics of the study participants are described in table 1.

Among the patients, 54% (n=27) reported having a family history of cancer, whose diagnosis had occurred on average 13.8 (± 2.9) months; 24% (n=12) had distant metastasis and 24% (n=12) had recurrences, in addition to 10% (n=5) who were undergoing palliative treatment.

Acute myeloid leukemia (AML) and large B-cell non-Hodgkin lymphoma (LBCNHL) were the most frequent types of cancer presented by patients in 14% (n=7) and 10% (n=5) of cases, respectively. The

Table 1. Sociodemographic characteristics of the patients in the study, treated in a hospital in the Southern Brazil. Passo Fundo, 2019. (n=50)

Characteristic	n	%
Skin color		
White	49	98
Brown/Mixed race	1	2
Schooling level		
Elementary School	20	40
High School	22	44
Higher Education	16	16
Occupation		
Farmer	12	24
Retired	6	12
Professor	5	10
Others	23	54
Marital status		
Married	32	64
Single	11	22
Widow/widower	4	8
Divorced	3	6
Health insurance plan*		
SUS	31	62
Others	19	38
Associated diseases*		
Yes	34	68

*Dichotomous variables

most used protocols to treat these two forms of disease were "7+3" induction (which includes cytarabine and idarubicin) and R-ICE (rituximab, ifosfamide, carboplatin, etoposide, and mesna), in 28.6% (n=2) and 40% (n=2) of the cases, respectively.

Out of the 50 patients, in only 10 cases there was information on staging, among which 70% (n=4) had stage IV tumors. For cases in which there was no information on staging and grading, 70% (n=35) cases were hemato-

logical cancer, to which this classification does not apply, and for 10% (n=5) of the patients the medical records were not filled with this information.

Among the patients, 42% (n=21) used antidepressants, with an average of 1.2 (±0.5) medications (minimum 1 and maximum 3). The most prescribed medication was escitalopram, 33% (n=7), which belongs to the class of selective serotonin reuptake inhibitors (SSRIs). Table 2 describes the classes of antidepressants prescribed for the patients.

In the drug interactions analysis, 90% (n=45) of the patients presented some kind of potential interaction – which occurred between antidepressants, chemotherapy, or any other prescribed medications. Among the patients who used these medications (n=21), 62% (n=13) had contraindicated interactions and 100% (n=21) had larger interactions. Table 3 shows the drug interactions contraindicated between antidepressants that were presented by the patients.

Table 2. Description of the classes of antidepressants used by the patients in the study treated in a hospital in Southern Brazil. Passo Fundo, 2019. (n=21)

Class of antidepressant	n	%
Selective Serotonin Reuptake Inhibitors (SSRI) E.g.: Escitalopram, sertraline, and fluoxetine	16	76.0
Serotonin and norepinephrine reuptake inhibitor (SNRI) E.g.: Duloxetine	6	28.5
Tricyclic Antidepressants (TCA) E.g.: Amitriptyline	2	9.5
Selective Dopamine Reuptake Inhibitors (SDRI) E.g.: Bupropion	1	4.8
Melatonin agonists E.g.: Agomelatine	1	4.8

*Some patients used more than one antidepressant.

Table 3. Sociodemographic characteristics of the patients in the study, treated in a hospital in the Southern Brazil. Passo Fundo, 2019. (n=50)

Drugs involved in interactions*	n	Interaction mechanism**	Possible conduct
Sertraline × Dipyrrone	4	Increased risk of antiplatelet effect. Decrease in the therapeutic effect of selective serotonin reuptake inhibitor.	Replacement of dipyrrone with paracetamol
Escitalopram × Metoclopramide	3	Increased risk of extrapyramidal reactions and malignant neuroleptic syndrome	Replacement of metoclopramide with ondansetron or dimenidrinat
Escitalopram × Dipyrrone	3	Increased risk of antiplatelet effect and decreased therapeutic effect of selective serotonin reuptake inhibitor.	Replacement of dipyrrone with paracetamol
Sertraline × Metoclopramide	2	Increased risk of extrapyramidal reactions and malignant neuroleptic syndrome	Replacement of metoclopramide with ondansetron or dimenidrinat
Fluoxetine × Dipyrrone	1	Increased risk of antiplatelet effect. Decrease in the therapeutic effect of selective serotonin reuptake inhibitor.	Replacement of dipyrrone with paracetamol
Bupropion × Linezolid	1	Increased risk of hypertensive reactions	Monitoring the patient's blood pressure or replacing with another antibiotic

*Information taken from the Micromedex® database.

**One patient had two contraindicated interactions.

DISCUSSION

Although the epidemiological profile of cancer in Brazil indicates that most patients are male, in this study most cases involved women, as also shown by another study conducted in the Southern Brazil. Note that, although the disease is more prevalent in men, women seek health services more frequently, which increases the chances of early diagnosis and timely treatment. Men usually resort to care services when the disease is in a more advanced state and often do not follow the treatment.^{7,15}

According to the INCA, the most prevalent neoplasms in the population are breast, prostate, intestine, lung, and stomach. However, this study showed a higher frequency of AML and LBCNHL. Patients with hematological diseases (leukemias and lymphomas) require more complex chemotherapy regimens, which have greater myelosuppressive effects and, consequently, prolonged and more frequent periods of hospitalizations. On the other hand, patients with solid neoplasms usually do not require hospitalization to perform the treatment, which may justify the higher frequency of leukemias and lymphomas in the patients in this study.⁷

Cancer patients are particularly prone to polypharmacy, which may be related to the use of medications to handle the adverse effects of cancer therapy or the comorbidities presented by them. In addition to the higher risk of DI, more than one interaction can occur in the same patient, increasing the possibility of unwanted effects that worsen its prognosis. The frequency of drug interactions found in this study is high (90%) and similar to that found in a study carried out in a reference hospital in Murcia, Spain (95%), corroborating the significance of this theme for clinical practice in oncology.^{16,17}

The stigma of the death associated with the diagnosis of cancer, in addition to changes in the routine and quality of life of patients, resulting from cancer treatments, can trigger depressive symptoms. These symptoms may differ according to the type of cancer, stage of the disease, and demographic profile of the population. Depression not only compromises the patients' quality of life, but also increases their mortality.^{5,10}

Physicians often resort to the use of antidepressant medications to address this clinical situation, as observed in this study, which happened in 42% of cases. In other articles with the same approach, the use of antidepressants in cancer patients was relatively lower (23.2% and 16%) than found in this study.^{10,18}

However, choosing the appropriate antidepressant requires observing its use to avoid an interaction. The most prescribed class of antidepressants was selective serotonin reuptake inhibitors (SSRI), the first choice for cancer patients due to their tolerability. Among the representatives of SSRI, the most prescribed antidepressant was escitalopram. The Canadian international guideline for the treatment of depression in cancer patients recommends SSRI and, among them, citalopram and escitalopram as first-choice medications because of the lower potential for DI. The preference for these two antidepressants is due to the fact that both have low

CYP450 inhibition potential, configuring a better safety profile in cancer patients.^{18,20}

However, prescribing drugs with drug interaction potential does not necessarily imply damage to the patient. The drug interaction risk increases when the medications are classified as contraindicated, so replacing the prescribed medicine is recommended, unlike higher severity interactions, which do not necessarily require such change. These potential interactions become even more relevant in cancer patients due to their unfavorable clinical conditions and the physiological changes resulting from the disease.¹⁷

The drugs prescribed in this study that presented significant contraindicated drug interaction potentials were metoclopramide and dipyrone. Metoclopramide showed contraindicated interactions when used simultaneously with SSRI-class antidepressants (escitalopram and sertraline). The antiemetic action of metoclopramide is due to dopamine antagonism in D2 receptors. The association with antidepressants (class of TCAs, SNRI, and SSRI) can trigger or facilitate extrapyramidal effects, which generate a blockage of dopaminergic neurons, causing stiffness and tremors at rest. In extreme cases, it can cause malignant neuroleptic syndrome characterized by hyperthermia, autonomic dysfunction, altered consciousness, severe stiffness, and elevated serum creatine levels.^{21,22}

Metoclopramide is widely used in oncology to minimize the effects of nausea and vomiting presented by patients. However, as observed in this study, this drug has a high potential for DI contraindicated with antidepressants. To treat these symptoms, therapeutic options that do not generate contraindicated drug interaction are dimenhydrinate and ondansetron, belonging to the class of antihistamines and antagonists of 5-hydroxytryptamine receptors (5-HT₃), respectively.

The concomitant use of dipyrone with sertraline, escitalopram, or fluoxetine was frequently observed in the study. These SSRI, when used in conjunction with dipyrone, can increase the antiplatelet effect, potentiating the occurrence of hemorrhage, mainly gastrointestinal and intracranial hemorrhage. Cancer patients are spontaneously more likely to the risk of hemorrhage because of changes related to the disease and therapy to which they are submitted to treat cancer. Hemorrhage is more frequent in leukemias, but it may also occur in solid tumors, mainly due to tumor infiltration. Changes can happen in almost all stages of coagulation, such as quantitative (thrombocytopenia) and qualitative changes of platelets. Thus, it is noticed that drug interactions involving the use of dipyrone and SSRI antidepressants can cause damage to cancer patients. Concomitant use of these drugs should be evaluated, and the clinical status observed. If a possible effect of this interaction is evidenced, its use should be avoided.²³

Dipyrone is widely used in cancer patients, mainly for mild to moderate pain analgesia. A therapeutic alternative to replace it is paracetamol, a non-opioid analgesic with antipyretic property, effective in relieving pain with such intensity. In addition to being effective in relieving

pain, paracetamol does not have contraindicated drug interactions with the antidepressants sertraline, escitalopram, and fluoxetine. However, dipyron is often chosen because its injectable option is available in Brazil, which does not occur with paracetamol.²⁴

The use of linezolid in concomitance with bupropion – antidepressant of the SDR1 class – is classified as a contraindicated interaction, observed in one patient in this study. The combination of these two drugs is not indicated, as it may increase the risk of hypertension. As linezolid is an effective antibiotic to treat infections with Gram-positive microorganisms, and because its use is not continuous, it is suggested to monitor the blood pressure of patients during concomitant use of the two medications and, if necessary, adjust the dose or include an antihypertensive. If the hypertensive condition remains or progresses, an alternative is the replacement of linezolid with daptomycin, or suspension of the use of bupropion – during treatment with linezolid – which can be reintroduced 24 hours after the last dose of linezolid.

The high frequency of drug interaction potentials in cancer patients demonstrated in this study – with emphasis on contraindicated ones – reinforces the significance of evaluation in the process of medication use. Recognizing potential interactions and the main combinations of medications allows avoiding situations of therapeutic failure or minimizing the onset of drug toxicity. Studies like ours can help to establish computerized alert systems to guide the multidisciplinary team in oncology, reducing the exposure of patients to drug interactions, especially contraindicated ones. The data of this study also points to the need for the pharmacist to monitor the patient in order to adequately evaluate the occurrence of potential drug interactions in the prescription, allowing to prevent and to reduce damage.^{22,25}

This study has some limitations: in it, the potential drug interactions found were not monitored and the use of antidepressants by the patients before hospitalization was not assessed, a question that was not included in the interview. It is noteworthy that the interactions described are potential, that is, they were classified based on the medical prescription and did not necessarily imply the occurrence of negative clinical outcomes. The detection of drug interaction, even those classified as contraindicated, should be contextualized with the patient's clinic and the risk-benefit of the conduct should always be considered. Further investigations should be carried out to evaluate clinical outcomes related to interactions involving antidepressants, especially correlating them to clinical parameters, hospitalization time, and mortality.

The results of this study demonstrate that many patients on cancer use antidepressants, and that most individuals were exposed to potential contraindicated drug interactions. Thus, the significance of the multidisciplinary team in the care and monitoring of the patient is emphasized, in addition to the extreme relevance of the pharmacist to monitor the pharmacotherapy of patients and evaluate potential drug interactions. The results show that drug interactions in cancer patients should be

identified and monitored in order to avoid undesirable events related to pharmacotherapy. The pharmacist may suggest to the health team safer therapeutic options for the prevention of drug-related damage.

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Kelly Helena Kühn contributed to the conception, design, analysis, and writing of the article;

Siomara Regina Hahn contributed to the planning, design, review, and final approval of the article;

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Karine Knob Pietrzacka contributed to this conception of this article.

All authors approved the final version of this manuscript and declared themselves responsible for all aspects of the article, assuring their accuracy and integrity.

Molecular epidemiology of carbapenem-resistant *Acinetobacter baumannii* from southern Brazil

Epidemiologia molecular de Acinetobacter baumannii resistente aos carbapenêmicos provenientes do sul do Brasil

Epidemiología molecular de Acinetobacter baumannii resistente a carbapenem del sur de Brasil

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ABSTRACT

Background and Objectives: carbapenem resistance in *Acinetobacter baumannii* has reached extremely high levels worldwide, and class D OXA-type carbapenemases are the main associated mechanism. This study aimed to assess the phenotypic and molecular profile of clinical carbapenem-resistant *A. baumannii* (CRAb) isolates from a southern Brazilian border region. **Methods:** *A. baumannii* species was identified by the presence of the *bla*_{OXA-51} gene, and the susceptibility profile was determined by broth microdilution. The main carbapenemases were investigated by PCR and the molecular typing was performed by PFGE. **Results:** during the study, a total of 36 CRAb were recovered, of which 85.7% were from respiratory tract samples from ICU patients. High level resistance to were found in contrast to 100% of susceptibility for polymyxin B. The *bla*_{OXA-23} gene was present in 34 isolates and was the only one detected other than *bla*_{OXA-51}. Molecular typing revealed the presence of four clonal strains, two of them endemic during the period of the study. **Conclusion:** to the best of our knowledge, our study brings the first data about resistance profile in *Acinetobacter* in the western border of southern Brazil and make aware of endemic clones of CRAb-producing-OXA-23 in this region of state, contributing for the construction of the national epidemiologic scenario of CRAb.

Keywords: *Acinetobacter baumannii*. Carbapenems. Drug resistance, microbial.

RESUMO

Justificativa e Objetivos: a resistência aos carbapenêmicos em *Acinetobacter baumannii* atingiu níveis extremamente altos em todo o mundo, e as carbapenemases do tipo OXA classe D são o principal mecanismo associado. O objetivo deste estudo foi avaliar o perfil fenotípico e molecular de isolados clínicos de *A. baumannii* resistentes aos

carbapenêmicos (CRAb) de uma região de fronteira do sul do Brasil. **Métodos:** a espécie *A. baumannii* foi identificada através da presença do gene *bla*_{OXA-51} e o perfil de sensibilidade foi determinado por microdiluição em caldo. As principais carbapenemasas foram investigadas por PCR, e a tipagem dos isolados de CRAb foi realizada por PFGE. **Resultados:** durante o período do estudo, 36 CRAb foram recuperados, dos quais 85,7% foram provenientes de amostras do trato respiratório de pacientes de UTI. Uma elevada resistência a aminoglicosídeos e fluoroquinolonas foi encontrada em contraste com 100% de sensibilidade a polimixina B. O gene *bla*_{OXA-23} foi encontrado em 34 isolados e foi o único detectado além do *bla*_{OXA-51}. A tipagem molecular revelou a presença de quatro linhagens clonais, duas delas endêmicas ao longo do período do estudo. **Conclusão:** nosso estudo traz os primeiros dados sobre o perfil de resistência em *Acinetobacter* na fronteira oeste do sul do Brasil e alerta para a presença de clones endêmicos de CRAb produtores de OXA-23 nessa região, contribuindo para a construção do cenário epidemiológico nacional de CRAb.

Descritores: *Acinetobacter baumannii*. Carbapenêmicos. Resistência microbiana a medicamentos.

RESUMEN

Justificación y Objetivos: la resistencia a carbapenémicos en *Acinetobacter baumannii* ha alcanzado niveles extremadamente altos en todo el mundo y las carbapenemasas OXA de clase D son el principal mecanismo asociado. El objetivo de este estudio fue evaluar el perfil fenotípico y molecular de los aislados clínicos de *A. baumannii* resistentes a carbapenémicos (CRAb) de una región fronteriza en el sur de Brasil. **Métodos:** la especie *A. baumannii* se identificó a través de la presencia del gen *bla*_{OXA-51} y el perfil de sensibilidad se determinó por microdilución en caldo. Las principales carbapenemasas fueron investigadas por PCR y la tipificación se hizo con PFGE. **Resultados:** durante el período de estudio, se recuperaron 36 CRAb, 85,7% de muestras del tracto respiratorio de pacientes de la UCI. Se encontró una alta resistencia a los aminoglucósidos y las fluoroquinolonas en contraste con 100% de sensibilidad a polimixina B. El gen *bla*_{OXA-23} se encontró en 34 aislamientos y fue el único detectado además de *bla*_{OXA-51}. La tipificación molecular reveló la presencia de cuatro cepas clonales, dos de ellas endémicas durante el período de estudio. **Conclusiones:** hasta donde sabemos, nuestro estudio trae los primeros datos sobre el perfil de resistencia en *Acinetobacter* en la frontera oeste del sur de Brasil y reconoce los clones endémicos de CRAb productores de OXA-23 en esta región del estado, contribuyendo para la construcción del escenario epidemiológico nacional de CRAb.

Palabras-Clave: *Acinetobacter baumannii*. Carbapenémicos. Farmacorresistencia Microbiana

INTRODUCTION

Acinetobacter baumannii is a well-established pathogen worldwide that is responsible for several outbreaks and nosocomial infections with high levels of morbidity and mortality worldwide.¹⁻³ The *Acinetobacter* genus quickly acquired resistance to several classes of antibiotics and the vast majority of beta-lactams, including broad-spectrum cephalosporins, and due to this, carbapenems have become the main choice for the treatment of *Acinetobacter* infections in the last three decades.¹ However, isolates with multi-drug resistance (MDR) phenotype have become highly prevalent, and the emergence of mechanisms that confer resistance to carbapenems make treating infections a worrying challenge.²

The major mechanism responsible for carbapenem resistance in *A. baumannii* is due to OXA-carbapenemasases and less frequently due to Class B carbapenemasases.¹ The OXA enzymes commonly described in *A. baumannii* are divided in 6 subfamilies, comprising the intrinsic OXA-51-like and the acquired OXA-23-like, OXA-24-like, OXA-58-like, OXA-143 and OXA-235, all of them already reported in Brazil, except OXA-235.^{4,5} The *bla*_{OXA-23-like} gene is the most frequently reported in clinical isolates of carbapenem-resistant *A. baumannii* (CRAb) worldwide.^{1,2} The first case reported in Brazil was in 2003, in Curitiba city, and since then, there was a nationwide spread.⁴⁻⁶ In Brazil, the carbapenem resistance rate in *Acinetobacter*

spp. reaches almost 80%, according to the Brazilian National Health Surveillance Agency⁷, and OXA-23 producing CRAb is associated with several outbreaks and high mortality rates in ICUs.^{8,9}

Considering that data about bacterial resistance are still rare in some regions of the country, this study aimed to assess the phenotypic and molecular profile of clinical carbapenem-resistant *A. baumannii* (CRAb) isolates from a southern Brazilian border region.

METHODS

Bacterial isolates

A total of 39 non-duplicated clinical isolates of *Acinetobacter* spp., resistant or with reduced susceptibility to carbapenems by disk-diffusion method were selected. They were recovered from a bank of clinical isolates constituted as part of a surveillance study on carbapenem resistance in the western border of Rio Grande do Sul State, from May 2014 to December 2018, including gram-negative bacilli from community and hospital. The 39 isolates, previously identified as *Acinetobacter* spp., had their identification confirmed by conventional techniques (*coccobacilli* in Gram staining, catalase and oxidase reactions and non-fermentation on TSI agar), then they were submitted to PCR for *bla*_{OXA-51-like} gene to identify *A. baumannii* isolates.¹⁰ This study was developed as part of a main project approved by Research Ethics Committee

from Universidade Federal do Pampa (UNIPAMPA) (CAAE 32723414.2.0000.5323).

Susceptibility profile

Broth microdilution was performed for *A. baumannii* isolates to confirm the susceptibility profile to carbapenems. The isolates resistant to IPM and/or MER, designated as CRAB, were also assessed against ceftriaxone, ceftazidime, cefepime (CFP), amikacin (AMI), gentamicin (GEN), ciprofloxacin (CIP), and polymyxin B (POL). MICs were interpreted according to *Clinical and Laboratory Standards Institute* breakpoints.¹¹ *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853 were used as quality control strains.

Carbapenemase detection

Carbapenemase-encoding genes, including the main OXA-types, were investigated by conventional PCR for CRAB, as previously described (Table 1). Primers are shown in table 1. The amplified PCR products were visualized by electrophoresis on 1.5% (w/v) agarose gels in a 0.5 X tris-borate-EDTA buffer, stained with SYBR safe, using the photo documentation Alphamager HP (ProteinSimple, USA) system. The *E. coli* ATCC strain 25922 was used as negative control.

Genotyping

The genetic relationship among CRAB isolates were performed using an enzymatic restriction with *Apal* (Thermo Scientific, USA) followed by pulse-field gel electrophoresis (PFGE), performed according to the Centers for Disease Control and Prevention (CDC) guidelines, with modifications.¹⁶ Fragments were separated on 1.0% (w/v) agarose gel in a 0.5 X tris-borate-EDTA buffer for 23 h at 14°C using a pulse ramp rate changing from 5s to 35 s, at 6 V/cm in the CHEF-DRIII System (Bio-Rad, USA) apparatus. The restriction patterns were analyzed by GelJ

software (version 2.0), with dice similarity coefficient and the unweighted-pair group method using average linkage (UPGMA) algorithm with 1.5 % band matching tolerance. Genetic and clonal relatedness were established for similarity values $\geq 85\%$ and $\geq 99\%$, respectively.¹⁷

RESULTS

All the 39 isolates tested presented the *bla*_{OXA-51} gene; however, only 36 were confirmed as CRAB by broth microdilution. The majority of CRAB isolates were from clinical samples from ICU patients ($n=21$) isolated from respiratory tract specimens ($n=18$) (Figure 1). The isolates susceptibility profile is show in Figure 1. In addition to carbapenems, CRAB isolates were also resistant to third generation cephalosporins, cefepime and quinolones. All isolates were classified as MDR (non-susceptible to ≥ 1 agent in ≥ 3 antimicrobial categories).¹⁸

Molecular analysis revealed the presence of *bla*_{OXA-23-like} gene in 34 CRAB. None of the other genes searched were detected among the isolates. *Apal*-PFGE dendrogram of CRAB evidenced the presence of two clusters (I and II) and three singletons. The main cluster (I) included 17 isolates distributed from 2014 to 2018 and one main clonal lineages strains, type A ($n=14$). Cluster II included 13 isolates and two clonal lineages, B and B1, that appeared more recently, in 2017. In cluster III ($n=3$) only isolates collected in 2016 were present. Two of the three singletons represented the isolates 1ST and 16A, both non-carriers of the *bla*_{OXA-23-like} gene (Figure 1).

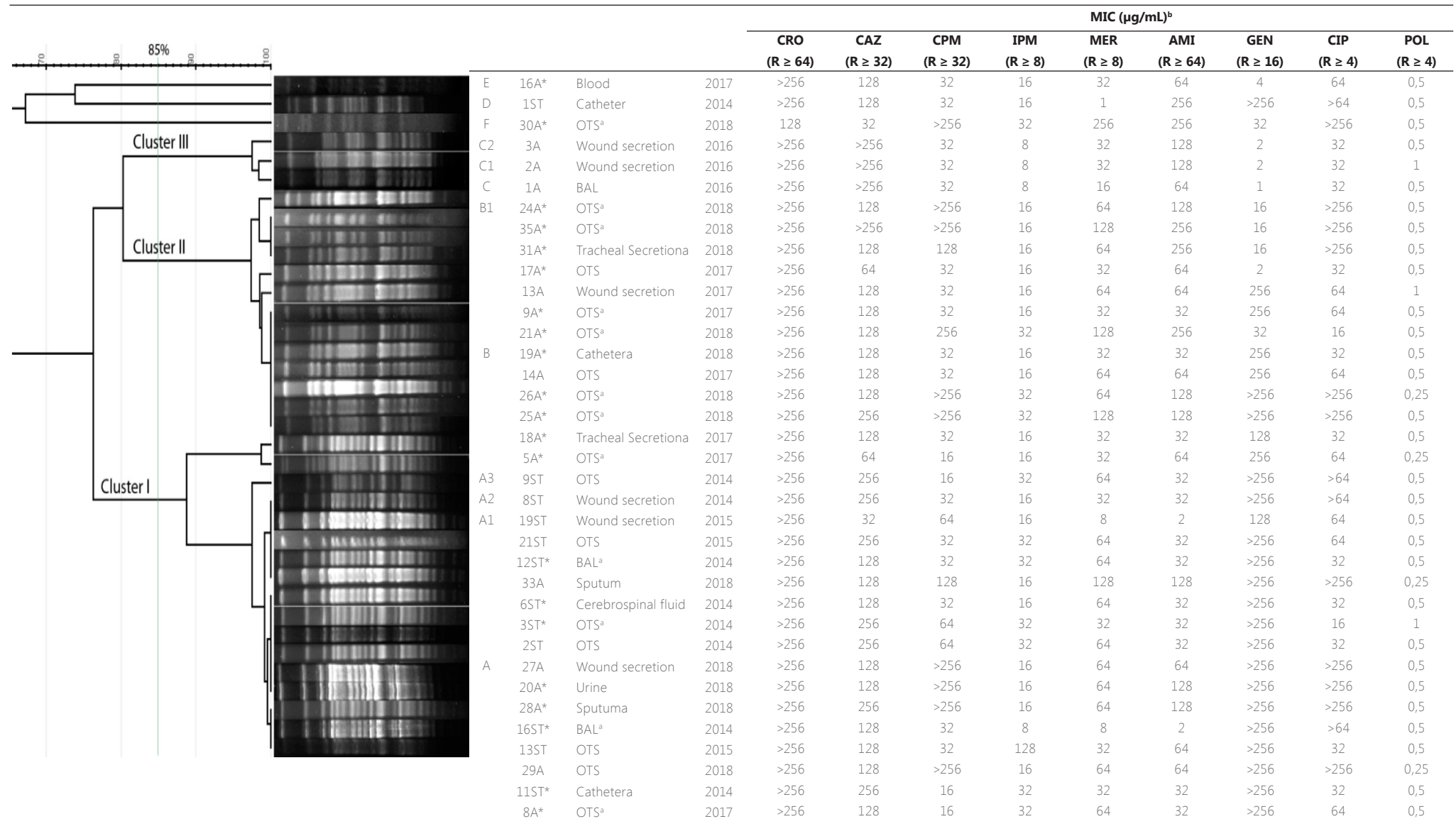
DISCUSSION

Ventilator-associated pneumonia (VAP) is the most frequently acquired infection in ICUs, with incidence rate

Table 1. Sequence of primers used to detect carbapenemase-encoding genes.

Target	Primer	Sequence (5' to 3') ¹	Amplicon size (bp)	Reference
<i>bla</i> _{OXA-51-like}	OXA-51f	TAA TGC TTT GAT CGG CCT TG	353	12
	OXA-51r	TGG ATT GCA CTT CAT CTT GG		
<i>bla</i> _{OXA-143}	OXA-143f	TGGCACTTTCAGCAGTTCCT	149	13
	OXA-143r	TAATCTTGAGGGGGCCAACC		
<i>bla</i> _{GES}	GESf	ATGCGCTTCATTCACGCAC	860	14
	GESr	CTATTGTCCGTGCTCAGG		
<i>bla</i> _{OXA-23-like}	OXA-23f	CCC CGA GTC AGA TTG TTC AAG G	330	
	OXA-23r	TAC GTC GCG CAA GTT CCT GA		
<i>bla</i> _{OXA-24-like}	OXA-24f	GCA GAA AGA AGT AAA RCG GGT	271	
	OXA-24r	CCA ACC WGT CAA CCA ACC TA		
<i>bla</i> _{KPC}	KPCf	TCG CCG TCT AGT TCT GCT GTC TTG	353	
	KPCr	ACA GCT CCG CCA CCG TCA T		
<i>bla</i> _{NDM}	NDMf	ACT TGG CCT TGC TGT CCT T	603	15
	NDMr	CAT TAG CCG CTG CAT TGA T		
<i>bla</i> _{IMP}	IMPf	ACA YGG YTT RGT DGT KCT TG	387	
	IMPf	GGT TTA AYA AAR CAA CCA CC		
<i>bla</i> _{VIM}	VIMf	TGT CCG TGA TGG TGA TGA GT	437	
	VIMr	ATT CAG CCA GAT CGG CAT C		
<i>bla</i> _{OXA-48}	OXA-48f	ATG CGT GTA TTA GCC TTA TCG	265	
	OXA-48r	CAT CCT TAA CCA CGC CCA AAT C		

Figure 1. Molecular typing and phenotype profile of CRAb isolates



Caption: Typing obtained by Apal-PFG digestion. Dendrogram displaying the genetic relatedness for all blaOXA-51-like gene producing isolate constructed using Dice coefficient with 1,5 % band matching tolerance and UPGMA for clustering.

^aICU patients. OTS: Orotracheal tube secretion; BAL: Bronchoalveolar lavage. a Respiratory tract sample provided from ICU patients.

ranging from 5% to 67%, and *A. baumannii* recovered from endotracheal aspirates and bronchoalveolar lavage is one of the most prevalent pathogens associated to VAP often involving MDR strains.¹⁹ In the present study, 85,7% (16/21) of ICU isolates were recovered from respiratory tract samples. Data of a national study involving isolates provided from endotracheal aspirates isolates from ICU patients also demonstrated a high prevalence (70.6%/n=29) of OXA-23-producing CRAB associated to VAP.²⁰

Although all of the CRAB isolates assessed in this study was MDR, all of them were susceptible to polymyxin B. Polymyxins play an important role in the treatment of CRAB infections due to the limited therapeutic options available.¹ Despite the low MIC values (≤ 1.0 $\mu\text{g}/\text{mL}$) found to POL in this study, it is quite likely that this profile may change in a next future as a consequence of its increased therapeutic use in recent years. Aminoglycosides have proved to be a great therapeutic option when susceptibility permits^{1,2}; however, high-level resistance to these drugs were also observed among CRAB, with only five isolates sensitive to gentamicin and two to amikacin. Indeed, but due to the toxicity in prolonged uses, they are commonly combined with other antimicrobials such as colistin and β -lactams to treat MDR *A. baumannii*.^{2,3} In recent years, different resistance mechanisms to these drugs have emerged leading to a considerable decrease in susceptibility in *A. baumannii* isolates worldwide.²¹

The susceptibility profile also revealed a considerable increase in MIC values over the years, mainly for β -lactams. It could be related to an overexpression of intrinsic genes like *bla*_{ADCr}, responsible for conferring natural resistance to narrow-spectrum cephalosporins.²² Although broad-spectrum cephalosporins are not hydrolyzed by class D carbapenemases, ceftazidime and cefotaxime resistance in OXA-23-producing *A. baumannii* isolates were assigned to AmpC overproduction. The association of other mechanisms, such as the overexpression of *adeABC* efflux systems should also be considered, as they can contribute for the increasing meropenem and ceftazidime MICs.²³

Thus, *bla*_{OXA-23-like} gene was responsible for resistance phenotype found in 94.4% of CRAB isolates. In 2014, a study performed in the capital of state, 600 km far from the western border, showed that OXA-23 was the main resistance mechanism associated to CRAB, remaining widespread five years after the first outbreak in the city.²⁴

In a recent study including CRAB clinical isolates from four Brazilian states, 87% (n=80) were positive for the presence of the *bla*_{OXA-23-like} gene.²⁵ Other studies confirm a high prevalence of OXA-23-producing CRAB associated with high mortality rates in ICUs in different Brazilian cities.^{8,9}

A and 1ST isolates were negative for the presence of all carbapenemase-encoding genes screened, except for *bla*_{OXA-51-like}. A study has shown that this gene, besides to be constitutive of the species, may be related to high MICs for carbapenems depending on the presence of the insertion elements, as IS*Aba*1.²²

Outbreaks due to CRAB in this hospital have oc-

curred since 2014, when we initiated the epidemiologic surveillance study of carbapenem resistant in gram-negative *bacilli*. Our data evidenced the prevalence of a major clonal lineages (type A) as well as the emergence of new ones (type B and C), since 2016. Several studies have described outbreaks caused by a single clone in a same institution although polyclonal outbreaks are not rare.²⁶ Until the moment, in 2018 was registered the highest number of cases of CRAB in the last five years. *A. baumannii* has the ability to survive on environmental surfaces for long periods, making transmission difficult to control. This feature is directly associated to hospital outbreaks.^{2,3} For a more dynamic and comprehensive epidemiological understanding, it would be interesting to carry out typing by MLST, in order to check whether the clones found are endemic in Brazil or even Latin America or whether represent a distinct and peculiar profile of the border region.

In conclusion, our results provide the first data on the local epidemiology of *Acinetobacter* resistance, evidencing the spread and permanence of OXA-23-producing *A. baumannii* with high level resistance to β -lactam, quinolones and aminoglycosides. The genetic typing revealed the permanence of two endemic lineages clonally related in the hospital, followed by the spread of polyclonal strains, highlighting that CRAB is a worrisome challenge not only restricted to large health centers. Thereby, the understanding of resistance mechanisms and local epidemiology provide important tool, in order to improve the appropriate treatment for serious infections, contributing for control and prevention of infections caused by CRAB.

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AUTHORS' CONTRIBUTION:

Gabriel de Paula Gollino, Bruna Machado Escobar, Ilson Dias da Silveira, Rosa Helena Robales Siqueira, Joseane Cristina Ferreira, Ana Lúcia da Costa Darini, Vanessa Bley Ribeiro contribuíram para a concepção, delineamento do artigo, metodologia e análise e redação do artigo;

Gabriel de Paula Gollino, Ana Lúcia da Costa Darini e Vanessa Bley Ribeiro contribuíram para o planejamento e delineamento do artigo, revisão e aprovação final do artigo;

Todos os autores aprovaram a versão final a ser publicada e são responsáveis por todos os aspectos do trabalho, incluindo a garantia de sua precisão e integridade.

Analysis of the spatio-temporal dynamics of incidence, mortality and test rates (rapid and RT-PCR) of COVID-19 in the state of Minas Gerais, Brazil

Análise da dinâmica espaço-temporal da incidência, mortalidade e taxas de testes (rápidos e moleculares) da COVID-19 no estado de Minas Gerais, Brasil

Análisis de la dinámica espacio-temporal de la incidencia, mortalidad y tasas de prueba (rápida e RT-PCR) de COVID-19 en el estado de Minas Gerais, Brasil

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ABSTRACT

Background and Objectives: A novel type of coronavirus, SARS-CoV-2, is responsible for an unprecedented pandemic with profound socioeconomic consequences. Owing to its recent discovery still represents a great unknown to researchers. Thus, this study aims to establish the spatio-temporal associations of the incidence, mortality, and the rate of both rapid and RT-PCR tests in Minas Gerais. **Methods:** This is a quantitative analysis of secondary data based on a cross-sectional research design. Incidence, mortality, date of the first notification of COVID-19 and number of rapid and RT-PCR tests were obtained from the sources: "GAL", "e-SUS VE" and "SES-MG". Pearson coefficient for correlation was calculated to establish the level of association between the relevant data. Descriptive statistical procedures were used to provide a comprehensive understanding of the distribution of incidence, mortality and test rates in the territory. **Results:** Positive correlations were found between the rate of rapid tests and incidence; rate of RT-PCR tests and incidence/mortality. At the municipal level, incidence, mortality, rate of rapid tests and RT-PCR revealed a negative correlation with days elapsed since the First Notified Case. The same effect occurs at the level of health macro-regions. **Conclusion:** The heterogeneity of the incidence and mortality of COVID-19 in the territory of Minas Gerais, as well as the rate of tests may be caused, in part, due to the different dates of introduction of the virus in the municipalities/macro-regions. It is speculated that this phenomenon occurs due to the dynamics of regional and inter-regional flows of people.

Keywords: SARS-CoV-2. Epidemiology. COVID-19. Immunologic Tests. Pandemics. Spatio-Temporal Analysis.

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RESUMO

Justificativa e Objetivos: Um novo tipo de coronavírus, SARS-CoV-2, é responsável por uma pandemia sem precedentes com profundas consequências socioeconômicas. Devido à sua recente descoberta, o vírus surgido na cidade chinesa de Wuhan, em dezembro de 2019, ainda lança grandes incógnitas. Este estudo objetiva estabelecer as associações espaço-temporais da incidência; mortalidade; e taxas de testes rápidos e RT-PCR em Minas Gerais.

Métodos: Trata-se de uma análise quantitativa de dados secundários a partir de um desenho de pesquisa transversal. Incidência, mortalidade, data da(s) primeira(s) notificações da doença, número de testes rápidos e de RT-PCR foram obtidos nas fontes: "Gerenciador de Ambiente Laboratorial", "e-sus VE" e SES-MG. O coeficiente de Pearson para correlação foi calculado para estabelecer o nível de associação entre os dados relevantes. Técnicas estatísticas descritivas foram empregadas para compreender a distribuição da incidência, mortalidade e taxas de testes no território. **Resultados:** Correlações positivas foram encontradas entre taxa de testes rápidos e incidência; taxa de testes RT-PCR e incidência/mortalidade. A nível municipal, incidência, mortalidade, taxa de testes rápidos e de RT-PCR têm correlação negativa com dias transcorridos desde o Primeiro Caso Notificado. O mesmo efeito ocorre, em diferentes intensidades, a nível das macrorregiões de saúde. **Conclusão:** A heterogeneidade da incidência e mortalidade da COVID-19 no território mineiro, assim como, das taxas de testes (rápidos e RT-PCR) pode ser causada, em parte, devido às diferentes datas de introdução do vírus nos municípios/macrorregiões de saúde. Especula-se que esse fenômeno se deve às dinâmicas dos fluxos regionais e inter-regionais de pessoas.

Descritores: COVID-19. Epidemiologia. SARS-CoV-2. Pandemias. Testes Imunológicos. Análise Espaço-Temporal.

RESUMEN

Justificación y Objetivos: El SARS-CoV-2 es responsable por una pandemia sin precedentes con profundas consecuencias socioeconómicas. Debido a su reciente descubrimiento, este virus representa una gran incógnita para los investigadores. Así, este estudio tiene como objetivo establecer las asociaciones espacio-temporales de la incidencia, la mortalidad y la tasa de pruebas rápidas y RT-PCR en Minas Gerais. **Métodos:** Trata-se de un análisis cuantitativo de datos secundarios basado en un diseño de investigación transversal. Incidencia, mortalidad, fecha de la primera notificación de COVID-19 y número de pruebas rápidas y RT-PCR se obtuvieron de las fuentes: "GAL", "e-SUS VE" y "SES-MG". Se calculó el coeficiente de correlación de Pearson para establecer el nivel de asociación entre los datos relevantes. Se utilizaron procedimientos estadísticos descriptivos para proporcionar una comprensión integral de la distribución de la incidencia, la mortalidad y las tasas de prueba en el territorio. **Resultados:** Se encontraron correlaciones positivas entre la tasa de pruebas rápidas y la incidencia; tasa de pruebas de RT-PCR y incidencia/mortalidad. A nivel municipal, la incidencia, mortalidad, tasa de pruebas rápidas y RT-PCR revelaron una correlación negativa con los días transcurridos desde el Primer Caso Notificado. El mismo efecto ocurre a nivel de macrorregiones de salud. **Conclusiones:** La heterogeneidad de la incidencia y mortalidad de COVID-19 en el territorio de Minas Gerais, así como la tasa de pruebas puede deberse, en parte, a las diferentes fechas de introducción de la virus en los territorios. Se especula que este fenómeno ocurre debido a la dinámica de los flujos regionales e interregionales de personas.

Palabras-clave: SARS-CoV-2. Epidemiología. COVID-19. Pruebas inmunológicas. Pandemias. Análisis Espacio-Temporal.

INTRODUCTION

For 50 years, different types of coronaviruses have been listed as a cause of respiratory infections.¹ However, in December 2019, several cases of pneumonia with unknown etiology were documented in the city of Wuhan, China. Afterwards, Chinese authorities isolated and identified a novel type of coronavirus, named SARS-CoV-2, which has a phylogenetic similarity with other beta-coronaviruses, including SARS-CoV, coronavirus of the severe acute respiratory syndrome, and MERS-CoV, responsible for the Middle East respiratory syndrome.² COVID-19 was declared a pandemic by the World Health Organization on March 11, 2020.¹⁻³

The virus is transmitted by inhalation through expelled droplets and aerosols, but also by fomites, through contaminated objects and surfaces that provide contact with an infected carrier with the hands and, later,

with the face, eyes and nose.^{1,3} In order to contain the rampant spread of the novel coronavirus, countries have adopted measures of social isolation.³ These measures, which include closing international borders, have caused devastating and long-lasting economic consequences around the world.^{2,3}

Up to 11 April, 2021, 134.957.021 cases were confirmed worldwide, and 2.918.752 thousand deaths.⁴ In most countries, the confirmation of cases increases exponentially, especially during the initial stages of the outbreak.³ Although it is difficult to compare fatal case rates between the countries, as they are at different stages of the outbreak, the variations are probably related to the scope of population tests, age structure, health status of population and health systems of each country.³ In Brazil, the first confirmed case was reported in the state of São Paulo on February 26, 2020.² To the current date, April 11, 2021, 13,449,940 cases and 351,591 deaths are attributed

to COVID-19 in the country.⁵

Minas Gerais (MG) has a pivotal role at the national level as it is the second largest Brazilian state in population size, estimated at 21 million people, located in a strategic region, close to states with high incidence rates, such as São Paulo and Rio de Janeiro, hence making it highly conducive to the transmittal of COVID-19.²

According to the Government of the State of Minas Gerais, in its last update of the human infection protocol for SARS-CoV-2 of July 20, both the reverse transcription assays followed by the polymerase chain reaction (RT-PCR) and the immunological techniques, which include rapid tests, can be used as a diagnostic criterion. It is noteworthy that negative results in rapid tests are not able to discard suspicious cases.⁶

In this sense, the importance of prevention, correct care and treatment of infection, as well as the need of establishing epidemiological correlations between tests and the temporal and geographical behavior of the disease in Minas Gerais is justified by the high rate of viral transmissibility, hospitalization and mortality,¹ which undoubtedly overburden the health system and harm the local economy.

Thus, this study aims to establish the spatio-temporal associations of the incidence, mortality, and the rate of both rapid and RT-PCR tests in Minas Gerais. The comprehension of these epidemiological phenomena according to the proposed prism can elucidate questions on which regions are most vulnerable and prepare health institutions to deal with the logistics of tests and health equipment, hence improving the management of the COVID-19 pandemic.

METHODS

Quantitative assessment of secondary data was performed from a cross-sectional epidemiological research design, and descriptive and inferential statistical methods were used for statistical analysis. In short, the descriptive statistical methods were aimed at detailing the relationship between two pandemic variables (i.e. the distribution of tests and the incidence of COVID-19) – in a given city and in a given health-macro-region (figure 1) – and core statistical estimators of the population demographic characteristics (e.g. population size); the statistical inferential method was aimed at trying to establish correlations between pandemic variables (e.g. incidence, mortality, rate of rapid and molecular tests and the date of the first notification).

The results were obtained through the use of the libraries Matplotlib (version 3.2.1), Pandas (version 1.0.5) and Statistics in the Python™ programming language (version 3.7.7). The programming environment used was Project Jupyter®.

The data obtained through the COVID-19 database available on the website of the Minas Gerais State Health Secretariat (SES-MG)⁷ are as follows: Incidence and Mortality for COVID-19 per 1000 inhabitants among March 4, 2020 and June 22, 2020; date of the first notification of

the disease in regard to the municipalities that reported cases of COVID-19 until the date of July 10, 2020.

Through the Datasus system, by accessing the e-SUS Epidemiological Surveillance platform (e-SUS VE), the number of rapid tests per 1000 inhabitants carried out between March 4 and June 22, 2020 was extracted. Similarly, by accessing the Laboratory Environment Manager (GAL) platform, the number of RT-PCR tests performed between March 4, 2020 and June 21, 2020 was extracted.

Initially, we merged the data according to the Brazilian Institute of Geography and Statistics (IBGE) code for the municipalities and prepared the descriptive statistical analyzes as follows: cities that exhibited more than two standard deviations from the mean in the distribution of rapid tests (>12.58) and RT-PCR tests (>4.84) were excluded due to the noise of these outliers in the general data, thus resulting in the exclusion of 23 cities for rapid tests and 28 for molecular tests. Then, mean, median and quartiles for city distributions according to the type of test were generated.

The quartiles for the two distributions obtained were assessed according to the macro-regions that were part of their composition. After, the number of tests, both rapid and molecular, was extracted according to the health macro-region.

The inferential analysis consisted of calculating Pearson's coefficients⁸ for correlation between the data obtained in the systems previously mentioned. The data used for this analysis refer to the period from March 4 to June 22, 2020. Only cities in which there was at least one notification of the disease until June 22 were considered. Therefore, it was necessary to exclude cities that did not present notifications of COVID-19 until that date, resulting in the exclusion of 215 cities. The variables incidence, mortality, rate of rapid and molecular tests and the date of the first notification were used to establish Pearson's coefficients, both at the municipal level and at the level of the health macro-regions.

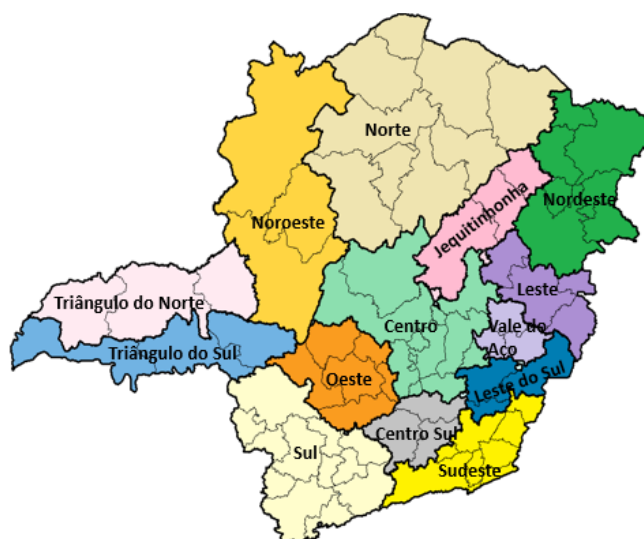


Figure 1. Health macro-regions of Minas Gerais State as of 2020 according to SES-MG.

Source: <https://www.saude.mg.gov.br/parceiro/regionalizacao-pdr2>

RESULTS

Until June 22, 2020, 638 cities had reported at least one positive case for COVID-19, while 215 cities had not reported any cases of the disease. Among the cities of the first group, 72 days (early May) have passed since the date of the first notification in the state - March 4 - for 319 cities (less than half of the 853 cities in Minas Gerais, all of which were included in the current study) to register at least one notification of the disease.

Notwithstanding that, the most populous municipalities have reported positive cases since at least mid-March 2020 (Figure 2). Remarkably, the two most populous cities in the state (Belo Horizonte and Uberlândia) totaled 7815 cases of COVID-19 (26.12% of the total cases) until the analyzed date (June 22), and revealed the first notifications of the disease in early March.

Cities in which there was no notification of COVID-19 until the date of analysis were less populous and exhibited lower rates of tests, both rapid and molecular (Table 1), in comparison to the cities in the other group. Accordingly, there was a notorious predominance of disease notifications in the health macro-regions (Figure 1) Central, Northern Triangle and Southeast. In turn, the macro-regions Northeast, Jequitinhonha and East concentrated more than 40% of the 215 cities without records of the disease until the date of analysis.

Table 1. Comparison between cities with reported cases and cities without reported cases. Mean and standard deviation for the variables population size, rate of rapid tests and rate of molecular tests. *Until June 22, 2020.

	Population Size (2019)		ABtests performed (per 1000)		RT-PCR tests performed (per 1000)	
	Mean	SD	Mean	SD	Mean	SD
Cities with reported cases* (n=638)	31175.97	115698.24	3.51	5.29	0.94	1.1
Cities with no reported cases* (n=215)	5946.6	3789.18	1.26	2.32	0.47	0.56

The cities of the health macro-regions Central, South Central, South and Northern Triangle accounted for 59% of the cities above the third quartile of the RT-PCR test rate (between 1.1 and 2.8). In turn, the analysis of the same quartile for rapid tests (between 3.4 and 12.58) showed a more homogeneous representation of other regions. However, the cities in the Central and Northern Triangle regions still represented the majority of cities in this category. In fact, the Central, Central South and Northern Triangle regions revealed the highest test rates (both rapid and molecular).

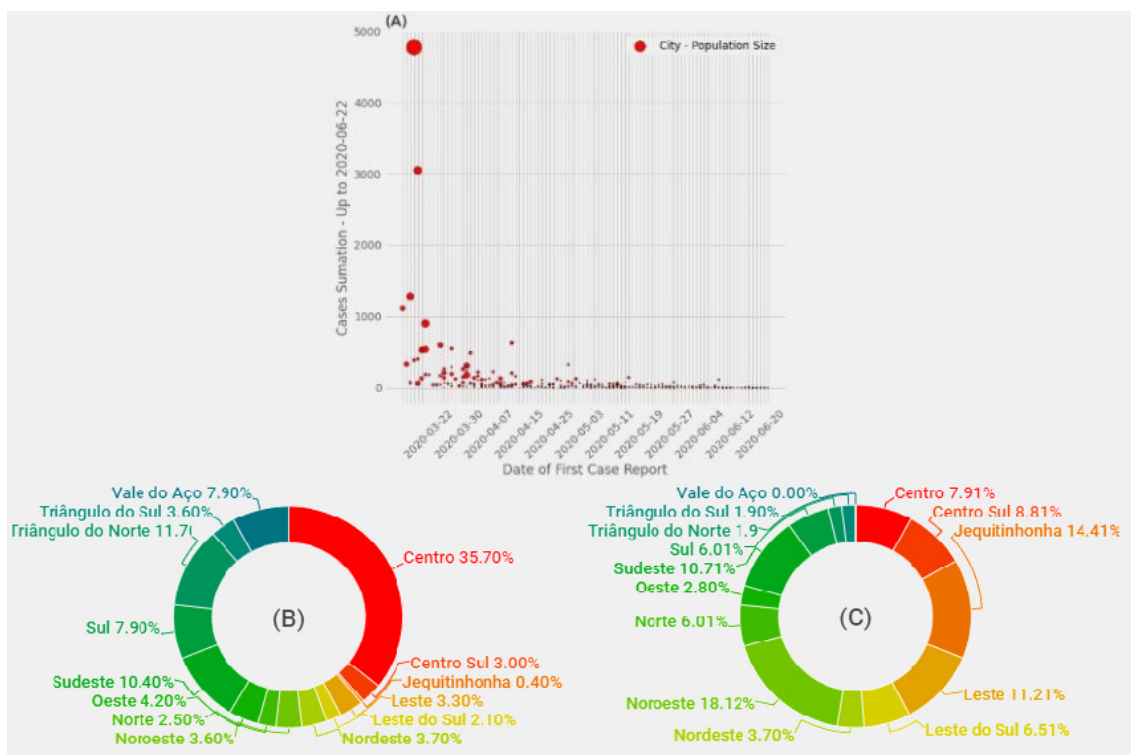


Figure 2. (A) Sum of notified cases in a specific city according to the date of the first notified case (March 4, 2020). (B) Cases notified according to the health macro-region by the date of June 22, 2020. (C) Health macro-regions to which cities belong without cases notified by the date of June 22, 2020.

Both rapid and RT-PCR tests performed for the detection of COVID-19 are in accordance with the incidence and mortality rates (Figure 3). The Pearson coefficients for correlation, at the municipal level, were: +0.39, between the rapid tests and the incidence rate; and +0.21 between the RT-PCR tests and the incidence rate. Regarding to the mortality rate, the same coefficients were 0 and +0.12 for rapid and RT-PCR tests, respectively.

Despite this, the temporal correlation was even more pronounced (Figure 4). At the municipal level, the analysis of the association between the elapsed time of the First Notified Case in the state of Minas Gerais and rapid tests produced a coefficient of -0.11; between the first notified case and RT-PCR tests, the coefficient was

-0.22; between the first notified case and incidence rate, it was -0.25; and between the first notified case and mortality rate, -0.19.

The same analysis used for the health macro-regions makes the association more evident. In fact, by aggregating cities in large regions, the outlier cities - whose tests per thousand exceed more than two standard deviations from the average and are small-sized - have their effect on the total overall reduced. Pearson's coefficient for correlation between the elapsed time of the first notified case in the state of Minas Gerais and rapid tests was -0.59; between the first notified case and RT-PCR tests, it was -0.25; between the first notified case and incidence rate, -0.70; and between the first notified case and mortality rate, -0.71.

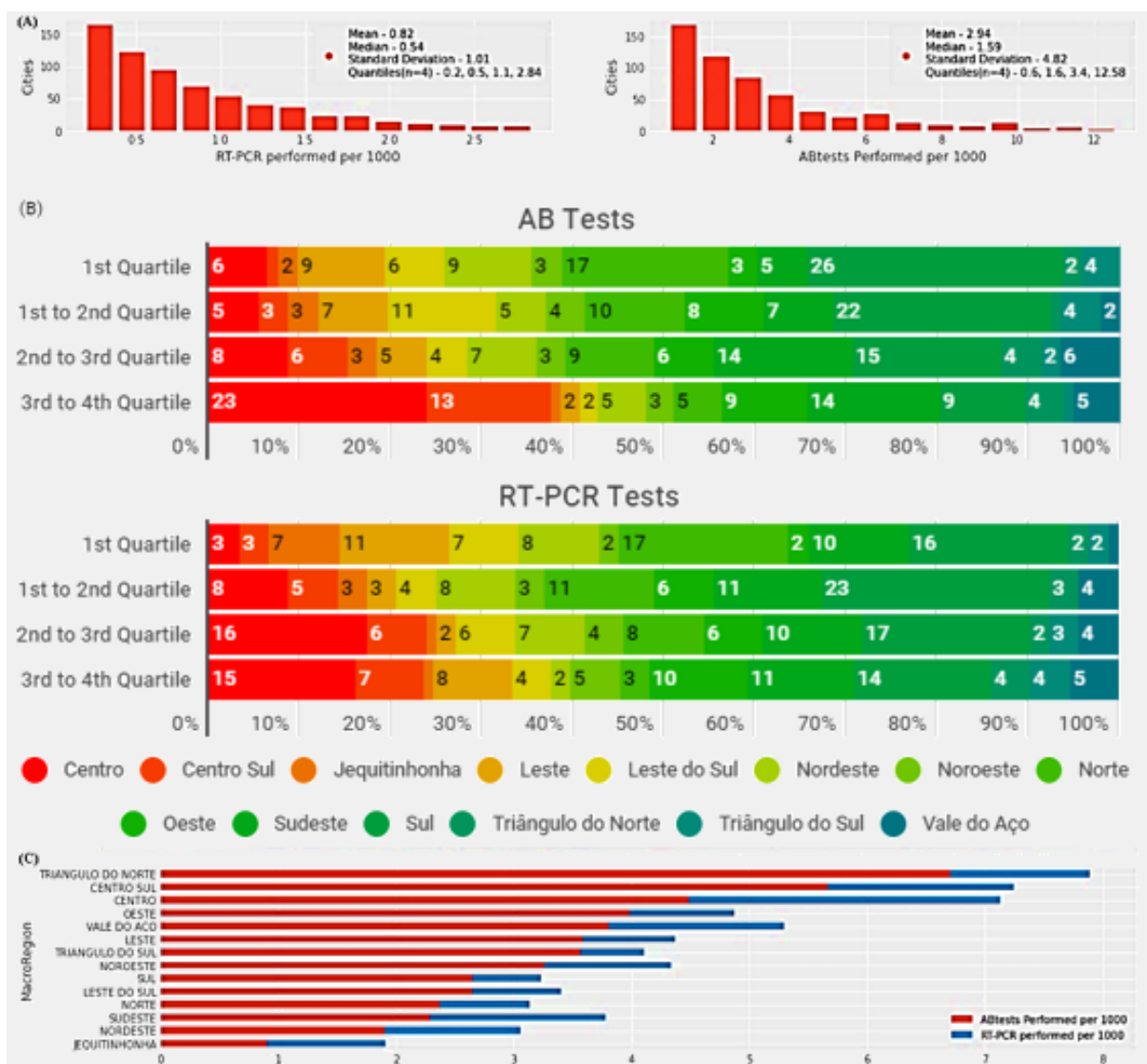


Figure 3. (A) Distribution of cities according to the tests performed; (left) rapid tests; (right) RT-PCR tests. (B) Composition of the quartiles of the distributions (A) according to the health macro-region; for rapid tests and RT-PCR tests, respectively. (C) Distribution of tests performed according to the health macro-region.



Figure 4. [Cities] Association between days elapsed since the first notified case and (A) Rapid tests per 1000 inhabitants; (B) RT-PCR tests per 1000 inhabitants; (C) Mortality per 1000 inhabitants; (D) Incidence per 1000 inhabitants. [Health macro-region] Association between days elapsed from the first notified case and (E) Rapid tests performed by 1000 inhabitants; (F) RT-PCR Tests per 1000 inhabitants; (G) Mortality per 1000 inhabitants; (H) Incidence per 1000 inhabitants.

DISCUSSION

The highest concentrations of COVID-19 cases accumulate in the hierarchically most influential regions of the state of Minas Gerais.^{9,10} The health macro-regions Central, Southeast, Northern Triangle, Vale do Aço and South were responsible for just over 73% of all cases of the infectious disease in the state until the date of analysis. All of these five regions contain at least one city of great relevance, being the metropolis or strong regional and sub-regional centers,⁹ with the exception of Vale do Aço, which is adjacent to the Central region and where it was notified the first case of COVID-19 in the state.

Case prevalence follows a pattern of regional distribution. The present study revealed that the Vale do Aço, Northern Triangle, Southeast and Central regions had the highest share of cases as shown in figure 2B. Based on the literature, it can be inferred that the causes of this pattern of territorial distribution are due to anthropogenic and

environmental factors that can contribute to the spread of the virus,¹¹⁻¹³ including climatic factors,¹⁴ transport flows,^{13, 15} economic activity^{13, 14} and air pollution.¹²

In a study,¹³ the author finds that the spread of influenza viruses in the twentieth century is accompanied with human flows, since there was a strong association between the spread of COVID-19 in the territory and different factors, such as economic activity and availability of transport, especially those from long distance. This phenomenon was corroborated in a study that confirmed a greater spread of the disease associated with the increase in distances traveled by air.¹⁶ Due to the similarity in transmission, it is expected that the spread of SARS-CoV-2 virus occurs in the same way. In fact, for the Chinese territory, the close association related to the flows of people between the territories and the disease incidence rates.¹⁵ Furthermore, the authors established a relationship between gross domestic product (GDP) and the population size, which loses

predictive value over time, hence suggesting migration of the virus to economically diverse and less affluent regions.

Therefore, the population size, economic activity and transport flow are essential factors to understand the spread of SARS-CoV-2 throughout the territory.^{12,17,18} The mortality rate, in turn, follows a similar pattern of territorial distribution in Brazil.¹⁹ Hence, there is multitude of parameters capable of explaining the distribution of tests, incidence and mortality.

In order to determine the effect size of each parameter on the phenomena at hand a multivariate analysis is imperative. But such an analysis has proved to be burdensome and complex due to the necessity to measure beforehand the relevant parameters (e.g. economic and political importance of a territory and human flow).

Therefore, we opted to investigate the relation between what we deemed probable parameters capable of explaining the tests (rapid and molecular) application throughout the Minas Gerais State territory. The reasoning behind this decision is as follows, the governmental officials would be motivated to test its population based on the perception of incidence and mortality of COVID-19, which would imply that more tests would be performed according to the rising of incidence and mortality of the disease.

The analysis has yielded a small correlation effect indicating that there is a significant relation between incidence and distribution of tests and mortality and distribution of tests. Which could indicate, but not prove, that the aforementioned reasoning is true, but, nonetheless, insufficient to explain all factors driving the tests distribution.

Another analysis of correlation has also proven to be of small, but significant, effect size. Time elapsed since first notification of COVID-19 in a given territory seems to play a role in the rates of the pandemic variables (e.g. incidence, mortality and tests performed). The effect size is greater at the health macro-regions level, which could be due to a filter effect, small cities play small roles on the aggregate of statistical data. Accordingly, the authors posit that territories in which the disease appeared early would perform more tests, and would be more prone to higher rates of incidence and mortality.

The negative correlations observed when analyzing the time elapsed between the first notified case in the city and the first notified case in the state may indicate that there is heterogeneity in the date of introduction of the virus in the territory, especially when considering the incidence and mortality rates that tend to be lower the later the first case is reported. In a study, the spatio-temporal flow of COVID-19 in the Brazilian territory was established and the authors described that the health macro-regions of the Northern Triangle, Central, Central South, South and Southeast are those in which the virus first entered the territory of Minas Gerais.¹⁶ This is in agreement with the findings of studies in Brazil¹⁹ and China,¹⁵ which demonstrated that the most affluent regions receive the virus before other regions.

The same negative correlation - with different coefficients and of greater intensity - was observed when the geographic level used was the health macro-region.

This more pronounced effect seems to indicate that SARS-CoV-2 tends to be concentrated for a longer time in the sub-region where it was first inserted, that is, interregional spread is subsequent to the spread in the locality itself. In fact, in Brazil, the virus seems to spread through the territory in two ways: spatial, when the virus leaves the metropolitan region for the rest of the territory; and hierarchical, located in sub-regions in which cities of regional importance allow the spread of COVID-19 to other locations at a lower hierarchical level.¹⁹

Across the state, at the municipal level, there was a positive correlation between the rate of rapid tests and incidence and the rate of RT-PCR tests and incidence. Also, the rates of RT-PCR tests and mortality remained positively correlated and more concentrated in three health macro-regions (Central, Central South and Northern Triangle). Besides that, there was a notable negative correlation between time and test rates, at the municipal and regional level.

The incidence rate, as a function of time, reflects biological factors, including the microorganism-host interaction, susceptible population size, contagiousness of the infection and the rate of tests. Moreover, the incidence rate reflects the organizational capacity and infrastructure of the health sector of a territory. Therefore, richer regions would have more available testing resources,²⁰ which was confirmed in this study.

Although the findings of the present research, this study has limitations. The methods applied, notably the Pearson coefficient for correlation, without other studies regarding the flow of people or even the flow of disease spread through the state of Minas Gerais are less sensitive tools to point the cause of the explored phenomena. The univariate analysis also limits our comprehension of the role that each variable has in the overall effect. Notwithstanding that, the procedures used, together with the literature, are capable of directing new paths to clarify the nature of the evidenced associations.

It is worthwhile noting that the test rate must influence the incidence and mortality rates, as the diagnostic criterion for the disease is based on diagnostic tests. In this context, it is expected that the higher the rate of tests in a given territory, the greater the reported number of incidence and mortality. Thus, territories that are not suitable for testing can suffer from severe under-reporting.²¹ The present methodological design would be more appropriate in a homogeneous situation of the rate of tests, which is not possible.

The heterogeneous distribution of COVID-19 across the territory overlaps the areas with the highest affluence in the state. This may indicate that the most interconnected regions are those with a greater increase in incidence and mortality in the first moments of the pandemic, which would cause the testing rate to increase in parallel, with privilege for rapid tests in all regions and RT-PCR tests where there is a higher mortality rate.

Undoubtedly, this study reported a phenomenon underlying the spatio-temporal dynamics of the rates of tests, incidence and mortality in Minas Gerais, notably the

influence of the hierarchy levels of urban centers and the demographic aspects of the territory. Thus, these findings contribute to a greater understanding of the association between parameters of territorial dynamics and epidemiological parameters of COVID-19, which may imply in the preparation of health systems and competent institutional authorities in order to develop potential strategies to combat the life-threatening disease based on prior knowledge of the demographic and hierarchical aspects of the territory.

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AUTHORS' CONTRIBUTION:

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Nutritional determinants as potential contributors to anemia in children and adolescents with malaria by *P. vivax*

Determinantes nutricionais como potenciais contribuintes para anemia em crianças e adolescentes com malária por P. vivax

Determinantes nutricionales como posibles contribuyentes para la anemia en niños y adolescentes con malaria por P. Vivax

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ABSTRACT

Background and Objectives: Nutrition, in addition to its physiological function, plays an important role in the recovery of individuals with malaria, a disease that still represents a serious public health problem in the world. The objective of this study was to assess nutritional determinants in the frequency of food intake and the occurrence of anemia in children and adolescents with *P. vivax* malaria. **Methods:** A cross-sectional analytical study was carried out between 2014 and 2015 in the Marajo Island. The hemoglobin level was measured by the colorimetric enzymatic reaction and a questionnaire of food intake frequency was used to assess the consumption of different types of food. **Results:** A total of 67 patients met the inclusion criteria, from which 62.7% were children and 37.3% were adolescents. There was a high consumption of ultra-processed foods in both age groups. Anemia occurred in 52.2% of patients, and in most of them it was moderate. There was no significant association between anemia and sex, age group or parasitemia at admission. However a significant association was found between anemia and the ingestion of ultra-processed foods. **Conclusion:** The ingestion of ultra-processed foods contributes to anemia in children and adolescent with malaria by *P. vivax*.

Keywords: *Plasmodium vivax*; Anemia; Nutritional Status; Food Consumption.

RESUMO

Justificativa e Objetivos: A nutrição, além de sua função fisiológica, desempenha um papel importante na recuperação de indivíduos com malária, uma doença que ainda representa um grave problema de saúde pública no mundo. O objetivo deste estudo é avaliar os determinantes nutricionais na frequência da ingestão alimentar e a

ocorrência de anemia em crianças e adolescentes com malária por *P. vivax*. **Métodos:** Estudo transversal analítico, realizado entre 2014 e 2015 na ilha do Marajó. O nível de hemoglobina foi medido pela reação enzimática colorimétrica e um questionário de frequência de ingestão alimentar foi utilizado para avaliar o consumo de alimentos. **Resultados:** Um total de 67 pacientes atendeu aos critérios de inclusão do estudo, dos quais 62,7% eram crianças e 37,3% adolescentes. Houve alto consumo de alimentos ultraprocessados em ambas as faixas etárias. A anemia foi detectada em 52,2% dos pacientes e, na maioria deles, foi moderada. Não houve associação significativa entre anemia e sexo, faixa etária ou parasitemia na admissão. No entanto, encontramos uma associação significativa entre presença de anemia e ingestão de alimentos ultraprocessados. **Conclusão:** A ingestão de alimentos ultraprocessados contribui para a anemia em crianças e adolescentes com malária por *P. vivax*.

Palavras-chave: *Plasmodium vivax*; Anemia; Estado nutricional; Consumo alimentar.

RESUMEN

Justificación y objetivos: La nutrición, además de su función fisiológica, juega un papel importante en la recuperación de las personas con malaria, una enfermedad que todavía representa un importante problema de salud pública en el mundo. El objetivo de este estudio es evaluar los determinantes nutricionales en la frecuencia del consumo de alimentos y la ocurrencia de anemia en niños y adolescentes con malaria por *P. vivax*. **Métodos:** se realizó un estudio analítico transversal entre 2014 y 2015, en la Isla de Marajó. El nivel de hemoglobina fue evaluado por ensayos enzimáticos colorimétricos y se utilizó un cuestionario de frecuencia de consumo de alimentos para evaluar el consumo. **Resultados:** Un total de 67 pacientes cumplió los criterios de inclusión en el estudio, de los cuales el 62,7% eran niños y el 37,3% adolescentes. Se registró un alto consumo de alimentos ultraprocessados en niños y adolescentes. La anemia se detectó en el 52,2% de los pacientes, de carácter moderada principalmente. No se encontró una asociación significativa entre anemia y sexo, grupo de edad o parasitemia al ingreso. Sin embargo, se encontró una asociación significativa entre la anemia y la ingestión de alimentos ultraprocessados. **Conclusión:** La ingesta de alimentos ultraprocessados se asocia con la presencia de anemia en niños y adolescentes con malaria por *P. vivax*.

Palabras clave: *Plasmodium vivax*; Anemia; Estado Nutricional; Consumo Alimentario.

INTRODUCTION

Malaria is still one of the major health public problems in the Brazilian Amazon with approximately 145,000 cases reported every year. *Plasmodium vivax* is the most prevalent species in the Region of the Americas, representing 82% of the cases notified to the health surveillance system in the Amazon Region.^{1,2} As a rule, the parasite density in *P. vivax* malaria is lower than in *P. falciparum*. However, it is worth mentioning that *P. vivax* infection can range from asymptomatic cases to serious complications that can lead to death. Groups at risk for severe disease are children, pregnant women, and primary infected patients.³⁻⁵

Anemia is common in vivax malaria, and the exact mechanisms are still unclear. Several host-related factors contribute to anemia in these patients. These include genetic and environmental factors as intestinal helminthes, comorbidities, and inadequate alimentary habits.⁶ The latter is relevant because it can lead to the deficiency of essential nutrients including vitamin A, zinc, iron, and folate, which contribute to the increase in the rate and intensity of anemia in patients with malaria. Moreover, the adequate intake of nutrients is important for an adequate immune response of the human host against infections.⁷ In malaria, the deficit of essential nutrients can be due to either the inadequate alimentary habits related to low levels of education and low economic status of most of the people who live in endemic areas or to the

anorexia, nausea, and vomiting caused by the disease, which lead to an inadequate food intake and contribute to the negative nitrogen balance.⁸

The objective of this study was to evaluate nutritional determinants in the frequency of food intake and the occurrence of anemia in children and adolescents with malaria by *P. vivax*.

METHODS

Study site and participants

This was a cross-sectional descriptive study of cases carried out from January 2014 to December 2015 in the municipality of Anajas in the Marajo Island (00° 59' 21"S e 49° 56' 24"W). The municipality has an area of about 6,913,068 km² and a population estimated at 24,759 inhabitants, most of them (61.6%) living in rural areas. Anajas has a very low human development index of 0.484. The municipality concentrates most of the cases of malaria in the State of Para, and 3,004 cases were notified in 2013. *Plasmodium vivax* accounted for 90% of the cases.^{9,10}

The criteria for inclusion were children and adolescents with slide-confirmed infection by *P. vivax* who spontaneously searched for assistance in the malaria health facility of the municipality and displayed signals and symptoms of the disease. The criteria for exclusion were children and adolescents with other infectious or chronic-degenerative diseases, signals and symptoms of

severe malaria (parasitemia above 5%, jaundice, pulmonary impairment, altered levels of consciousness), G6PD deficiency, congenital diseases and/or antimalarial use three to six months prior to the inclusion in the study.

Data collection

A semi-structured questionnaire was applied to the guardian of the children and adolescents included in the study. Data regarding sex, age range, history of malaria, parasitemia at admission, economic status of family, and education level of the mother were registered in an appropriated database.

Laboratory analysis

Blood samples were collected at enrollment from patients in the study for parasite count and hemoglobin measurement. Parasite count was performed according to the Walker technique. The number of parasites was recorded in 200 white blood cells, considering a total count of 8,000/mL of white blood cells.¹¹ The measurement of hemoglobin was based on photometric detection of cyanmethemoglobin which is a stable compound derived from hemoglobin, using Labtest diagnostic Kits, following good laboratory practices. The diagnosis of anemia and its severity followed the criteria of the World Health Organization, which consider anemia in children from 6 to 59 months when hemoglobin < 11 g/dl, for children from 5 to 11 years when hemoglobin < 12.5g/dl, for children from 12 to 14 years and non-pregnant adolescents when hemoglobin < 12g/dl and for adolescent males when hemoglobin < 13g/dl.¹²

Frequency of food intake

A food frequency questionnaire (FFQ) previously validated for the Brazilian population was used to estimate the frequency of foods intake. The questionnaire was applied to the guardians of the children and adolescents at their enrollment in the study. The instrument is composed of 100 different foods, which are classified in two categories: a) *in natura* or minimally processed, including fresh fruits, milk and eggs, beef, vegetables and cereals and flours; b) ultra-processed foods such as fast foods and savory snacks, canned foods, treats and sweets, and sweet drinks. The intake of these foods was considered regular if ingested 5 or more times in a week. The categories and the classification of weekly ingestion were based on the guidelines of adequate and healthy food intake for the Brazilian population.¹³

Data analysis

Data was presented as frequency of occurrence for categorical variables. The Chi-square test and the Fisher's exact test were performed for comparisons of these quantitative variables. Continuous variables are presented as median (interquartile range), and were compared using the Mann-Whitney test. Data was analyzed in WHO programs AnthroPlus and SPSS software v.21.0 (IBMinc, Chicago, IL, USA), and a p-value <0.05 was considered significant.

Ethical aspects

The present study was revised and approved by the ethical committee of Institute of Health Sciences of the Federal University of Pará, under the number 261.593/2013 and CAAE 207199612.0.0000.0018. The parents or guardians of the patients provided consent for their inclusion in the study.

RESULTS

A total of 67 patients met the criteria for the inclusion in the study. The mean age was 9.5 (8.0-12.8) years and children represented 62.7% of the casuistic ($p > 0.05$). In most cases, the mother was the guardian of the children and adolescents (91%), they have a low education level, live with a monthly stipend below \$100.00 and they were included in social programs of cash transfer (Table 1).

Table 1. Socioeconomic characteristics of the families of patients included in the study, Anajás-Pará, 2015.

Characteristic	n	%	IC _{95%}
Guardian			
Mother	61	91.0	81.5 – 96.6
Other	6	9.0	3.4 – 18.5
Education (years in school)			
0	15	22.4	13.1 – 34.2
1 - 4	24	35.8	24.5 – 48.5
5 - 8	13	19.4	10.8 – 30.9
≥ 9	11	16.4	8.5 – 27.5
Not reported	4	6.0	1.7 – 14.6
Employment situation of the person in charge of the house			
Self Employed	11	16.4	8.5 – 27.5
Unemployed	51	76.1	64.1 – 85.7
Employee / Retired	5	7.5	2.5 – 16.6
Family income			
<1 Minimum wage	55	82.1	70.8 – 90.4
≥ 1 Minimum wage	12	17.9	9.6 – 29.2
Cash transfer program			
Yes	59	88.1	77.8 – 94.7
No	8	11.9	5.3 – 22.2

The frequency of anemia was 52.2% and in most cases moderate (74.3%), with classification of microcytic (51.4%). The sex, age group, and parasitemia at admission were similar between patients with and without anemia (Table 2).

The frequency of ingestion of *in natura* or minimally processed foods was similar in both anemic and non-anemic patients, with a low ingestion of fresh fruits (64.2%), vegetables (53.7%), and a regular intake of beans (77.6%), beef (86.6%), milk and eggs (74.6%) and cassava root (89.5%). The frequency of processed foods ingestion was higher in anemic patients compared to non-anemic ones. Patients reported a low frequency of ingestion of canned foods (95.5%) and treats and sweet (74.6%), but a regular ingestion of fast food (52.2%) and sweet drinks (52.2%). Data is presented in table 3.

Table 2. Baseline characteristics of patients. Anajas-Pará, 2015.

Characteristic	Total (n= 67)	Anemic (n= 35)	Non-Anemic (n= 32)	P
Sex (%)				
Male	37 (55.2)	16 (45.7)	21 (65.6)	0.164*
Female	30 (44.8)	19 (54.3)	11 (34.4)	
Age group (%)				
Child (2-10 years)	42 (62.7)	19 (54.3)	23 (71.9)	0.217*
Adolescent (<10-16 years)	25 (37.3)	16 (45.7)	9 (28.1)	
Anemia level (%)				
Light	-	26 (74.3)	-	-
Moderate	-	9 (25.7)	-	-
Mean Corpuscular Volume (MCV) – Classification (%)				
Microcytic	-	18 (51.4)	-	-
Normocytic	-	10 (28.6)	-	-
Macrocytic	-	7 (20.0)	-	-
Parasitemia at admission**	2,500 (500-7,000)	2000 (750-5,750)	3000 (500-10,000)	0.482+
Red blood cells, millions, M/μL**	3.9 (3.4-4.3)	3.5 (3.2-4.1)	4.1 (3.8-4.5)	0.002+
Hemoglobin, g/dl **	11.1 (10.1-12.2)	10.2 (9.8-10.9)	12.3 (11.8-13.0)	<0.0001+
Hematocrit, % **	30.3 (27.7-33.7)	29.2 (26.2-32.1)	32.0 (29.9-34.0)	0.024+

* Chi-square test; ** median (interquartile range); +Mann-Whitney test.

Table 3. Distribution of food consumption of patients and the presence of anemia. Anajas-Pará, 2015.

Variables	Total n (%)	Anemic n (%)	Non-anemic n (%)	P
In natura or minimally processed				
Fresh fruits				
< 5 times	43 (64.2)	22 (62.9)	21 (65.6)	>0.99*
\geq 5 times	24 (35.8)	13 (37.1)	11 (34.4)	
Vegetables				
< 5 times	36 (53.7)	21 (60.0)	15 (46.9)	0.405*
\geq 5 times	31 (46.3)	14 (40.0)	17 (53.1)	
Beans				
< 5 times	52 (77.6)	28 (80.0)	24 (75.0)	0.770*
\geq 5 times	15 (22.4)	7 (20.0)	8 (25.0)	
Cereals and flours				
< 5 times	7 (10.5)	4 (11.4)	3 (9.4)	>0.99**
\geq 5 times	60 (89.5)	31 (88.6)	29 (90.6)	
Beef				
< 5 times	9 (13.4)	4 (11.4)	5 (15.6)	0.885**
\geq 5 times	58 (86.6)	31 (88.6)	27 (84.4)	
Milk and eggs				
< 5 times	17 (25.4)	11 (31.4)	6 (18.8)	0.362*
\geq 5 times	50 (74.6)	24 (68.6)	26 (81.2)	
Ultra-processed				
Fast Foods and savory snacks				
< 5 times	32 (47.8)	11 (31.4)	21 (65.6)	0.010*
\geq 5 times	35 (52.2)	24 (68.6)	11 (34.4)	
Canned foods				
< 5 times	64 (95.5)	33 (94.3)	31 (96.9)	>0.99**
\geq 5 times	3 (4.5)	2 (5.7)	1 (3.1)	
Treats and sweets				
< 5 times	50 (74.6)	26 (74.3)	24 (75.0)	>0.99*
\geq 5 times	17 (25.4)	9 (25.7)	8 (25.5)	
Sweet drinks				
< 5 times	32 (47.8)	18 (51.4)	14 (43.8)	0.701*
\geq 5 times	35 (52.2)	17 (48.6)	18 (56.2)	

*Chi-square test; ** Fisher's Exact test

DISCUSSION

The study was designed to assess the frequency of ingestion of different types of foods and the occurrence of anemia in children and adolescents with vivax malaria from the Brazilian Amazon. The evaluation of the alimentary habits of the population that lives in endemic areas could provide relevant information about determining factors of anemia in subjects with malaria. In the area of the study, most of the inhabitants live below the poverty line and have a low level of education, and this could contribute to an inadequate intake of essential nutrients. In fact, the social and economic profile of children and adolescents enrolled in the study are in agreement with other reports about the epidemiology of malaria in the Brazilian Amazon. Moreover, the repeated episodes of the disease in children and adolescents with a low parasite count when compared to *P. falciparum* cases is common in this endemic area.

The analysis of the food frequency questionnaire showed an ingestion of fruits and vegetables below that recommended by the WHO.¹⁴ A similar result was found by a study that included children and adolescents from an endemic area in the state of Amazonas.¹⁵ Moreover, there is a high ingestion of ultra-processed foods by both children and adolescents. This scenario reflects a potential change in the nutritional standard of Brazilian population, which might promote negative consequences for the health of those individuals, especially in areas of food insecurity, as *in natura* foods are important sources of essential macronutrients and micronutrients that are required to an adequate immune response to environmental stressors. In addition, the intake of fruits and vegetables by the native population of the Amazon is lower than in other regions of the country.¹⁶⁻¹⁸

Anemia is an important complication of vivax malaria and the exact mechanism underlying is still unclear. In the present study, around half of the patients experienced moderate anemia which is in accordance with previous studies of the same endemic scenario that reported a high prevalence of anemia.¹⁹

In children from the Brazilian Amazon, anemia has been associated with the deficiency of iron and of other micronutrients, including folate, vitamin A, and vitamin B12. This is a result from genetic or environmental factors such as intestinal and other parasitic infections as well as chronic infection or non-infectious diseases, and the inadequate ingestion of essential nutrients.^{13,20-22} In the present study, we could not find association between anemia and sex, age, or parasite count at admission. However, the presence of anemia was associated with high frequency of weekly intake of ultra-processed foods, which have high levels of free sugars and total, saturated, and trans-fat, and low levels of proteins, dietary fibers and, especially micronutrients (vitamins and minerals),²³ demonstrating the low nutritional quality of the population studied.

Overall, population groups with low socioeconomic status and low educational levels have a lower prevalence of healthy food consumption. Therefore with a low content of essential nutrients, they are more vulnerable to

micronutrient deficiencies,^{23,24} such as iron, which is an important cause of anemia. The association between iron deficiency and malaria incidence by *P. vivax* was observed in a study carried out with children in the Amazon Region. Thus, the deficiency of this micronutrient, besides being a marker of a serious socioeconomic problem, represents a greater risk for malaria.²⁵

On the other hand, there was no significant association between the frequency of ingestion of *in natura* foods with the occurrence of anemia in children and adolescents included in the study. These results could be due to the low ingestion of foods from this group by the patients included in the study.

The results of the current study are relevant to understand the factors underlying anemia in patients with malaria by *P. vivax* from the Brazilian Amazon. Surprisingly, people living in this forest area have a low ingestion of fruits, vegetables and usually have meals with a high content of ultra-processed foods. Finally, there is a significant association between anemia and the consumption of foods with low content of essential nutrients.

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AUTHORS' CONTRIBUTIONS:

Bianca da Conceição Cabral contributed to the conception, design, analysis and data collection and writing of the article;

Fernanda Maria Lima Moura contributed to the design, analysis and data collection;

Rosa Maria Dias, José Luiz Fernandes Vieira and Marcieni Ataíde de Andrade contributed to the planning and design of the article, review and final approval of the article;

All authors approved the final version to be published and are responsible for all aspects of the work, including ensuring its accuracy and integrity.

Febrile neutropenia management in pediatric onco-hematologic patients: a systematic review

Manejo da neutropenia febril em pacientes pediátricos onco-hematológicos: uma revisão sistemática

Manejo de la neutropenia febril en pacientes pediátricos oncohematológicos: una revisión sistemática

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ABSTRACT

Background and Objectives: cancer cases are gradually increasing, and most treatments still cause several adverse reactions, such as myelosuppression. When neutrophils decline, febrile neutropenia (FN) can be triggered, considered an oncological emergency, leaving patients susceptible to infections. Therefore, it is necessary to determine the best treatment, seeking to reduce the risk of complications. The purpose of this review is to identify, in literature, randomized clinical studies that compare different treatments for FN in pediatric onco-hematological patients. **Content:** a systematic search was carried out on the PubMed database, for randomized clinical studies, from 2009 to 2019, in English, using "Febrile Neutropenia", "Pediatric", and "Therapeutics" as descriptors. A total of 233 articles were found, seven of which were selected for review. The most described antimicrobial for FN treatment was Piperacillin/Tazobactam (PIP/TAZ) and its use is justified by its spectrum of action to cover the most frequent microorganisms in patients with FN. The possibility of using oral antimicrobials may be an alternative and should be analyzed. The description of the risk classification criteria is essential to guide the therapy, and new tools, such as the stewardship, add safety to patient care. **Conclusion:** the most used antimicrobial to treat FN was PIP/TAZ, and the establishment of standardized risk classification scores in pediatric onco-hematological patients is essential to guide clinical management in FN treatment.

Keywords: Febrile Neutropenia; Pediatrics; Therapy.

RESUMO

Justificativa e objetivos: os casos de câncer estão aumentando gradativamente, e a maioria dos tratamentos

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ainda causa várias reações adversas, como a mielossupressão. Com o declínio dos neutrófilos, pode-se desencadear a neutropenia febril (NF), considerada uma emergência oncológica, deixando o paciente suscetível a infecções. Portanto, é necessário determinar o melhor tratamento, visando reduzir o risco de complicações. O objetivo desta revisão é identificar, na literatura, estudos clínicos randomizados que comparem diferentes tratamentos para NF em pacientes onco-hematológicos pediátricos. **Conteúdo:** foi realizada busca sistemática na base de dados PubMed, de estudos clínicos randomizados, no período de 2009 a 2019, na língua inglesa, utilizando como descritores "Febrile Neutropenia", "Pediatric" e "Therapeutics". Foram encontrados 233 artigos, dos quais sete foram selecionados para revisão. O antimicrobiano mais descrito para o tratamento com FN foi Piperacilina / Tazobactam (PIP / TAZ) e seu uso justifica-se por seu espectro de ação para cobrir os microrganismos mais frequentes em pacientes com FN. A possibilidade de uso de antimicrobianos orais pode ser uma alternativa e deve ser analisada. A descrição dos critérios de classificação de risco é essencial para orientar a terapia, e novas ferramentas, como o stewardship, agregam segurança ao atendimento ao paciente. **Conclusão:** o antimicrobiano mais utilizado para tratar FN foi o PIP / TAZ, e o estabelecimento de escores de classificação de risco padronizados em pacientes onco-hematológicos pediátricos é essencial para orientar o manejo clínico no tratamento de FN.

Palavras-chave: Neutropenia febril; Pediatria; Terapia.

RESUMEN

Antecedentes y objetivos: los casos de cáncer están aumentando gradualmente y la mayoría de los tratamientos aún causan varias reacciones adversas, como la mielosupresión. Cuando los neutrófilos disminuyen, se puede desencadenar la neutropenia febril (FN), considerada una emergencia oncológica, dejando a los pacientes susceptibles a infecciones. Por tanto, es necesario determinar el mejor tratamiento, buscando reducir el riesgo de complicaciones. El propósito de esta revisión es identificar, en la literatura, estudios clínicos aleatorizados que comparen diferentes tratamientos para la FN en pacientes pediátricos oncohematológicos. **Contenido:** se realizó una búsqueda sistemática en la base de datos PubMed, de estudios clínicos aleatorizados, de 2009 a 2019, en inglés, utilizando como descriptores "Febrile Neutropenia", "Pediatric" y "Therapeutics". Se encontraron un total de 233 artículos, siete de los cuales fueron seleccionados para revisión. El antimicrobiano más descrito para el tratamiento de FN fue Piperacilina / Tazobactam (PIP / TAZ) y su uso se justifica por su espectro de acción para cubrir los microorganismos más frecuentes en pacientes con FN. La posibilidad de utilizar antimicrobianos orales puede ser una alternativa y debe analizarse. La descripción de los criterios de clasificación de riesgo es fundamental para orientar la terapia, y nuevas herramientas, como la rectoría, añaden seguridad a la atención al paciente. **Conclusión:** el antimicrobiano más utilizado para tratar la FN fue la PIP / TAZ, y el establecimiento de puntuaciones estandarizadas de clasificación de riesgo en pacientes pediátricos oncohematológicos es fundamental para orientar el manejo clínico en el tratamiento de la FN.

Palabras llave: Neutropenia febril; Pediatría; Terapia.

INTRODUCTION

It is estimated that 420 thousand new cases of cancer will occur in Brazil for the 2018-2019 biennium, excluding non-melanoma skin cancer from this number. Considering that the median percentage of childhood and juvenile tumors observed is 3%, it is expected that 12,500 new cases of cancer will occur in children and adolescents (up to 19 years old). The Southeast and Northeast regions are those with the highest numbers, 5,300 and 2,900, respectively, followed by the Center-West (1,800), South (1,300) and North (1,200).¹

Despite advances in cancer treatment, the main drugs used to treat neoplasms, hematology and solid tumors still cause numerous adverse reactions. One of the main ones that competes at great risk to patients is myelosuppression, characterized by a decrease in the elements of the immune system, leaving patients exposed to various infections. When there is a decline in neutrophils, the first line of defense against some pathogens,

it can trigger febrile neutropenia (FN), considered an oncological emergency.²

The severity of FN can vary due to the type and cycle of therapy, type of cancer, sex and clinical conditions of patients. The incidence of FN in the United States is estimated at 60,294 cases per year, 7.83 cases per 1,000 cancer patients, and 43.3 cases per 1,000 hematological tumor patients. The epidemiology of FN is related to some factors, which may be responsible for 50% of deaths in patients receiving chemotherapy for solid tumors and 75% for leukemias. In relation to Brazil, there are no general data; however, we can use as a basis the results of a study carried out in a hospital in northeastern Brazil with onco-hematological children and adolescents, which out of 180 occurrences, 87 were FN, giving rise to the 74 cases of infection reported in the study.²⁻⁴ According to the guideline published by the European Society for Medical Oncology (ESMO) in 2016, FN is defined as oral temperature > 38.3°C or two consecutive measurements > 38.0°C for 2h and absolute neutrophil count (ANC) of

500 cells/mm³, or an expectation that it will decrease to below 500 cells/mm³.⁵ When FN is detected, the rapid onset of broad-spectrum empirical antibiotics is necessary, as the permanence of patients with FN can lead to delay in treatment, which directly or indirectly affects morbidity and mortality.⁶

Cancer patients have a higher risk of infection, not only due to chemotherapy treatment that induces immunosuppression and neutropenia, but also due to hypogammaglobulinemia and loss of normal physiological barriers. This increases the risk of infections by bacteria, viruses, fungi and parasites, as well as complications or spread of common pathogens from normal flora and latent viral infections.⁷

The clinical identification of infections can contribute to the diagnosis in more than 30% of the cases of FN and thus guide the treatment. However, a relevant portion (10-60%) of FN in patients is treated due to fever of unknown origin, without elucidating the pathogen.⁸

The purpose of this review is to identify, in the literature, randomized clinical trials that compare different treatments for FN in pediatric onco-hematological patients.

METHODS

The question used to guide the research was: what is the most used therapy to treat FN in pediatric onco-hematological patients?

This is a literature review based on PICO strategy. The population consisted of pediatric patients with solid or hematological tumors who developed FN and who needed treatment with antimicrobial or antifungal agents. They were randomized to studies that aimed to compare the effectiveness of each treatment and, with that, to define the best conduct for this population.

The search was carried out in literature through combination of "Febrile Neutropenia", "Pediatric" and "Therapeutics" descriptors using the Boolean operators (OR and AND) and limited to the English language. These criteria were defined after a search for articles was carried out in other databases, such as Scielo and LILACS, in Brazilian Portuguese, English and Spanish, not finding studies that fit the defined criteria, so it was decided to include only the articles found on PubMed.

Articles published from 2009 to 2019, a randomized clinical trial comparing treatments for FN in pediatric onco-hematological patients (maximum age up to 18 years) were included. Review articles, guidelines, case reports, non-pediatric population (over 18 years old), duplicate articles, which addressed FN prophylaxis or which did not address the comparison of treatments for FN were excluded. The search was limited to pediatric onco-hematological patients, as information on treatment and management of FN in this population is scarce when compared with adult patients, with no standard risk classification score.

After selecting the articles by two reviewers screened using the keywords, the titles and abstracts were read, focusing on their methodology. The data of the

selected articles were compiled and presented in a table, according to the objectives of this review.

RESULTS AND DISCUSSION

The search in the database resulted in a total of 233 articles that met the descriptors used. Of these, 217 were excluded after reading the summary. A total of 16 articles were selected for detailed analysis. Nine articles were excluded because they did not address the comparison between treatments for FN in randomized controlled trials. Thus, seven articles presented information relevant to the research objective for this review, as described in figure 1.

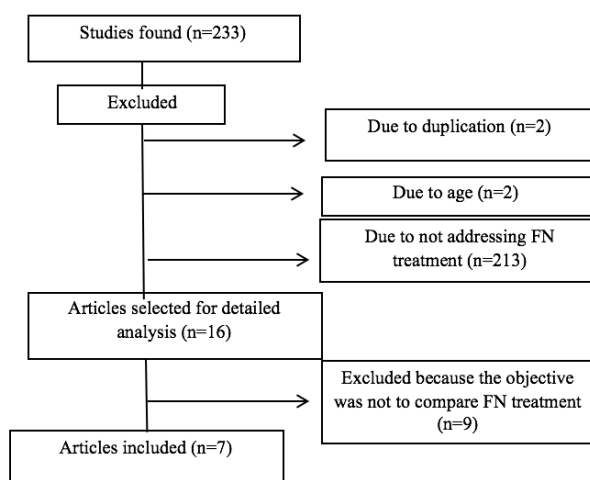


Figure 1. Flowchart of articles selected for review.

Of the seven articles selected, five sought to compare antimicrobial regimens, an antifungal regimen and a treatment for viral infections.⁹⁻¹⁵ In clinical practice, most infections that affect patients with FN are caused by bacteria and because of this, studies mainly seek to define the best antimicrobial scheme (ATB) to be used in this clinical situation. Only one article used a different definition for FN, characterized by ANC of ≤ 1000 cells/mm³, the others used the ESMO criterion.¹⁰ The most frequent ATB in the regimens was piperacillin/tazobactam (PIP/TAZ) and amoxicillin/clavulanate (AMOX/CLAV).⁹⁻¹³ Only two articles described the chemotherapeutic drugs used in the treatment of pediatric onco-hematological patients.^{9,13} The most frequent neoplasm in the cases of FN in the articles assessed was acute lymphoid leukemia, with a high prevalence of other hematological neoplasms compared to solid tumors. Three articles described the FN classification criteria, but they were not the same criteria.^{10,13-14} There was evidence of infection in the seven articles.⁹⁻¹⁵

FN is a clinical condition originated by chemotherapy, which can make an individual susceptible to infections.

Patients' characteristics (age, neoplasia, treatment, type of infection, performance status) need to be considered when choosing the best therapy.

Bacterial infections are generally associated with FN in onco-hematological patients, and the identification of the pathogen causing the infection is important for choosing the appropriate ATB. The use of empirical PIP/TAZ in the management of patients with FN is explained by its spectrum of action, which includes the microorganisms most associated with FN in pediatric patients (*Enterobacteriaceae* (30%) and Coagulase-negative *staphylococci* (24%), and *Pseudomonas aeruginosa* (5%)).^{16,17}

No statistically significant differences were found in clinical outcomes when compared to therapy with PIP/TAZ versus cefepime, drugs routinely used in bacterial infections in neutropenic patients. However, an increase in mortality was observed in the PIP/TAZ group, when patients have a previous history of treatment with etoposide, a chemotherapy used in several protocols for childhood and juvenile neoplasms. This reinforces the importance of knowing patients' history and assessing the medications they use so that the choice of ATB is adequate, as this information may interfere with patients' clinical evolution.^{9,18}

The combination of PIP/TAZ with other ATBs can help to improve the clinical condition of patients with FN, however, it is essential to define the best association. One study found that sulbactam/ampicillin associated with aztreonam (62.5%) is equivalent to or higher than PIP/TAZ associated with ceftazidime, (57.1%), with fewer cases of new infections and deaths.¹¹ However, another study that assessed the association of cefoperazone/sulbactam and amikacin, found no statistical difference between the groups (47.5% versus 52.6%, respectively). The search for different combinations of ATB is essential, especially in cases of microbial resistance or non-response to PIP/TAZ, requiring the use of other effective alternatives, such as schemes with broad-spectrum ATB that are not routinely used.¹²

In practice, the concern with the rapid evolution of the infection, makes the use of ATB often occur empirically. In this context, the use of PIP/TAZ for the empirical treatment of FN is of great value, as demonstrated in a study, in which the results found showed that the decrease in body temperature in patients occurred in 62.5% on the fourth day, 57.1% on the seventh day and 75.0% at the end of treatment, suggesting that the applicability of the empirical form of PIP/TAZ is satisfactory for the resolution of FN.¹⁹

Comparing the use of oral ATB with intravenous ATB in patients with FN can be an effective alternative, especially for those who have a low risk of infection and with the opportunity to perform treatment at home. The use of oral ATB can facilitate treatment in pediatrics, allowing greater autonomy for family members and patients, decreasing the number of punctures, in addition to being also considered the alternative of hospital discharge, reducing the possibility of exposure to nosocomial infection and providing reduction of hospitalization costs.^{13,17,20-22}

However, it is important to classify the severity of the risk of infection for this patient, considering several factors that directly affect the conduct to be taken. There is no internationally accepted risk stratification, requiring each hospital to choose a validated stratification and adapt to its reality. Risk score for children with FN was validated in a hospital in India and compared with other models already published. The authors concluded that this model demonstrated applicability, however, a multicenter study is needed to verify the possibility of employment in practice in developed countries, in which health conditions differ from those in development, such as malnutrition.²³⁻²⁵

Despite the fact that most infections in FN patients are of microbial origin, other etiologic agents such as fungi and mycobacteria can also be the cause, especially in more severe and prolonged episodes of neutropenia, in a period longer than 10 days of hospitalization.²⁶

Fungi can be considered responsible for 30-40% of infections after the fifth day of neutropenia, the most common being *Candida albicans* and *Aspergillus*, but there is an increase in documentation related to *Non-albicans candida*. A study compared the effectiveness of two antifungals, caspofungin and amphotericin B liposomal in patients divided into low and high-risk groups. The results found, demonstrated that both treatments are effective for management of fungal infections in patients with FN. However, it is important to develop studies that compare broad-spectrum antifungals with those of minors, most used in routine.^{14,27}

In addition to bacterial or fungal infections, viral infections, especially respiratory infections, appear as potential pathogens in this specific population. Viral respiratory infections can induce morbidity and mortality, being detected in more than 57% of FN episodes in children with cancer.^{28,29}

It is essential to determine the type of pathogen that causes the infection for the appropriate choice of therapy, since ATBs are ineffective in viral infections and their indiscriminate use can induce antimicrobial resistance. The suspension of ATB after confirming the results of negative cultures, does not interfere in the final outcome, with the resolution rates in both groups without significant difference (97% in the group with ATB and 95% in the group without ATB).¹⁵

The use of adjuvant therapies to decrease patients' neutropenia time can be considered a useful tool, such as the use of granulocyte growth stimulating factors (G-CSF), adopted in the onco-hematological routine. Its use contributes to the increase of ANC and, with that, it decreases the time that patients would be susceptible to opportunistic infections, also reducing the time of use of ATB.^{30,31}

The guidelines for initial management of FN in children and adolescents with cancer, published by the Brazilian Society of Pediatrics, indicate the initial empirical use of monotherapy with B-lactam antipseudomonal, fourth-generation cephalosporin or carbapenem.³² These indications corroborate the studies included in this review, in which most studies used PIP/TAZ and/or

Chart 1. Distribution of articles included in this literature review, according to the reference, type of study, study description, neoplasia, chemotherapy, therapy used, results and limitations, PubMed, 2009-2019.

Reference	Type of study	Description of study	Neoplasm	Chemotherapy	Therapy used	Result	Limitations
Amir, M., et al, 2015, India. ⁹	Randomized, prospective, open-label clinical study (n=40)	Patients aged ≤18 years, receiving CT, who did not receive ATBs in 1 week.	ALL (n=18), osteosarcoma (n=10), Ewing's sarcoma (n=4), NHL (n=4), AML (n=4)	Antibiotics (36), vinca alkaloids (26), folic acid analogs (22), steroids (18), alkylating agents (18), enzymes (18), epipodophyllotoxins (12), platinum complexes (10), analogues of pyrimidines (8).	Group 1: PIP/TAZ 100mg/Kg/dose 8h/8h IV; Group 2: CEF 50mg/Kg/dose 8h/8h IV	Success rate: Group 1: 75%; Group 2: 80% There was no significant difference between the two groups (P=0.705). Mortality rate doubled in the PIP/TAZ group when patients used Etoposide.	Small sample, schematics should be assessed in a larger sample.
Caselli, D. et al, 2012, England. ¹⁴	Clinical, randomized, prospective, multicenter study (n=110).	Patients aged ≤18 years, with CT-induced neutropenia or HSCT, persistent fever after 96h even after ATB use. Patients were divided into low or high-risk groups, according to criteria.	ALL (n=29), AML (n=32). CML (n=1), lymphoma (n=13), brain tumor (n=15), other solid tumors (n=19), severe aplastic anemia (n=1).	Not described.	Arm A: control group (low-risk patients without receiving antifungal); Arm B: 3mg/Kg/day IV; Arm C 50mg/m ² /day, with an attack dose of 70mg/m ² /day. IV;	Patients classified as high risk: Arm B: 88%; Arm C: 83% (P=0.72). Patients classified as low risk: Arm A: 87.5%, Arm B: 80%, Arm C: 94.1% (P=0.41). The three experimental arms provided complete response (i.e., survival), disappearance of fever and no evidence of fungal infection.	There was evidence of fungal infection in only 9 of the 110 patients. It would be important to have isolation of the fungus greater sample. One of the arms could be composed of antifungal slower spectrum of action, such as fluconazole, routinely used.
Gupta, A. et al, 2009, India. ¹³	Prospective, randomized, open study (n=88).	Patients aged between 2 and 15 years, with low-risk FN, who did not need hospitalization.	ALL (n=41)*, primitive neuroectodermic tumor (n=26)*, rhabdomyosarcoma (n=25)*, osteosarcoma (n=17)*, Others (n=14)*. Number of episodes*	Cis/adria: cisplatin, adriamycin (n=8); EC1: ifosfamide, carboplatin, etoposide (n=4); Ifos/adria: ifosfamide, adriamycin (n=4); Ifos/etop: ifosfamide, etoposide (n=21), VAC: vincristine, actinomycin D, cyclophosphamide (n=25), VadrC: vincristine, adriamycin, cyclophosphamide (n=14), others (n=6), indicated for ALL (n=41).	Group 1: OFL OR 7.5 mg/Kg 12/12h and AMOX/CLAV OR 12.5 mg/Kg 8h/8h; Group 2: CEF EV 75mg/Kg and AMK IV 15mg/Kg IV 1 time daily.	Success rate: Group 1: 90.32%; Group 2: 93.44%. No statistical difference (P=0.56).	Parents checked the temperature. Although there is no statistical difference between the groups, due to convenience and fewer invasive procedures, the use of oral therapy could be highlighted.
Santolaya, M.E. et al, 2017, Chile. ¹⁵	Prospective, randomized, multicenter study (n=176).	Patients aged 18 ≤ and FN were treated with 4th generation cephalosporins. After 48 hours, patients with a positive sample for respiratory virus and negative culture for bacteria were randomized for the study.	Leukemia/lymphoma (n=104), leukemia recurrence (n=11), solid tumor (n=61).	Not described.	Group 1: Permanence of AtB until the end of the febrile episode; Group 2: ATB withdrawal.	The median duration of ATBs was 7 days (group 1) versus 3 days (group 2) (P=<0.0001), with similar frequency of uncomplicated resolution (97% versus 95%, respectively) (P=0.41) and a similar number of fever days (2 versus 1), hospitalization days (6 versus 6) and bacterial infections throughout the episode (2% versus 1%). There were no deaths.	It does not clearly demonstrate the outcome between the groups. They use as conclusion the incorporation of techniques to determine viral infections in the routine, not highlighting the result. This study could have highlighted the result that the withdrawal of ATB when it is not necessary, does not decrease the success of solving the problem, and may contribute to the reduction of microbial resistance.

Cagol, A.R., et al, 2009, Brazil. ¹⁰	Prospective, randomized, double-blind, placebo-controlled study (n=58).	Patients aged 18 ≤, with neutropenia episode, classified as low risk for bacterial invasion, treated with CT.	Osteosarcoma (n=10), primitive neuroectodermic tumor of the central nervous system (n=7), T=Willm's tumor (n=7), rhabdomyosarcoma (n=6), soft tissue sarcoma (n=7), leukemia (n=7), hepatoblastoma (n=2), neuroblastoma (n=6), lymphoma (n=1), gonadal tumor (n=1), Ewing's sarcoma (n=2), retinoblastoma (n=2).	Not described.	Group A: Ciprofloxacin 30mg/Kg/day 12h/12h OR + AMOX/CLAV 30mg/Kg/day 8h/8h OR + placebo IV. Group B: Cefepime 150mg/Kg/day 8h/8h IV and placebo OR.	Group A: ineffectiveness rate was 51.2%, with an average length of hospitalization of 8 days. Group B: ineffectiveness rate was 45.8%, with an average length of hospitalization of 7 days. No statistical difference (P=0.77). Number of episodes in which patients remained with fever after 72h: Group A: 7 episodes; Group B: 14 episodes.	The way of classification of patients with FN was different from the other studies. It could have been highlighted the fact that there was no significant difference between the groups, saying that if patients had the OR preserved, it would be the preferred route for treatment, avoiding unnecessary punctures.
Kobayashi, R. et al, 2009, Japan. ¹¹	Prospective, randomized study (n=53).	Pediatric patients aged 17 ≤ 17 years, with FN in CT or who received HSCT.	ALL (n=46)*, AML (n=44)*, other leukemias (n=6)*, neuroblastoma (n=17)*, retinoblastoma (n=5)*, hepatoblastoma (n=4)*, calf sac tumor (n=3)*, Ewing's sarcoma (n=2)*, LH (n=2)*, NHL (n=2)*, rhabdomyosarcoma (n=2)*, Wilms' tumor (n=1)*. Number of episodes*	Not described.	Group 1: PIP/TAZ 125mg/Kg/day 6h/6h IV + CAZ 100mg/Kg/day 6h/6h IV; Group 2: SBT/ABPC 150mg/Kg/day IV + AZT 150mg/Kg/day 6h/6h IV.5	Success rate Group 1: 57,1%; Group 2: 62,5%. Success rate considered equivalent (P>0.05). Length of neutropenia, treatment, and days of fever were similar in both groups, but there were fewer new infections and deaths due to infection in Group 2.	In the "Patients and Methods" topic, it is described that the sample is composed of 54 patients, but in the description of the results, it is changed to 53. Neoplasms are not mentioned by number of patients, but by episodes of FN. There was evidence of infection in only 14 episodes in group 1 and 8 episodes in group 2, out of a total of 134 episodes.
Demirkaya, M. et al, 2013, Turkey. ¹²	Prospective, randomized, open study (n=46).	Patients from 0-18 years with FN, diagnosed with lymphoma or other solid tumor, without antibiotic prophylaxis.	NHL (n=10), LH (n=1), neuroblastoma (n=4), medulloblastoma (n=4), astrocytoma (n=1), ependymoma (n=1), germinoma (n=1), tumor atypical teratoid rhabdoid (n=1), Ewing's sarcoma (n=4), osteosarcoma (n=3), fibrosarcoma (n=2), rhabdomyosarcoma (n=1), Wilms' tumor (n=1), rhabdoid tumor of the kidney (n=1), clear cell sarcoma of the kidney (n=1), retinosarcoma (n=1), nasopharyngeal carcinoma (n=2), hepatocarcinoma (n=2).	Not described.	Group 1: PIP/TAZ 360mg/Kg/day 6h/6h plus AMK 15mg/Kg/day 8h/8h; Group 2: CS 100mg/Kg/day 8h/8h plus AMK 15mg/Kg/day 8h/8h.	Success rate: Group 1: 47,5%; Group 2: 52,7%. No statistical difference in length of neutropenia, fever and hospitalization (P=>0.05)	From a total of 116 episodes of NDF, they needed treatment modification (adding other ATBs and/or antifungals) in 31 episodes in group 1 and 27 in group 2, characterizing half of episodes, which can interfere in the success rate, generating an unreliable result.

Caption: PIP/TAZ: Piperacillin-Tazobactam; CEF: Cefepime; ALL: Acute Lymphoid Leukemia; AML: Acute Myeloid Leukemia; CML: Chronic Myeloid Leukemia; NHL: Non-Hodking Lymphoma; HL: Hodking lymphoma; Arm A: without antifungal treatment; Arm B: Liposomal Amphotericin B; Arm C: Caspofungin; CT: Chemotherapy; G-CSF: Granulocyte Colony-Stimulating Factor; FN: Febrile Neutropenia; OR: Oral route; IV: Intravenous; HSCT: Hematopoietic Stem Cell Transplantation; CAZ: Ceftazidime; SBT/ABPC: Sulbactam/Ampicillin; AZT: Aztreonam; AMK: Amikacin; CS: Cefoprazone + Sulbactam; OFL: Ofloxacin; AMOX/CLAV: Amoxicillin + Clavulanate; CEF: Ceftriaxone; GEM: Gentamicin

cefepime as ATB compared to other ATB.

Although the empirical use of PIP/TAZ is widespread in the treatment of FN in pediatric onco-hematological patients, it is necessary to consider the infectious focus and modify the therapy as necessary. For this, it can be considered that the stewardship program, a term used to describe an integrated strategy that seeks to reduce the irrational use of ATB, helps in choosing the best treatment. This program has acquired some objectives over the years, including cost reduction, optimization of therapeutic results and reduction of antimicrobial resistance, associated with tools that are characterized by the restrictions of ATB classes, rotation in the use of ATB, support in clinical decisions, education of the team of prescribers.^{33,34}

Recent systematic reviews and meta-analysis on stewardship differ in some points, however they converge in the fact that the application of this tool reduces the occurrence of nosocomial infections caused by drug-resistant bacteria. Moreover, it increases control and reduces the time of using ATB, without increasing the mortality rate, reducing hospital length of stay.^{35,36}

Establishing protocols of the stewardship program in pediatric onco-hematological patients with FN, can be a useful resource for decreasing microbial resistance and the unnecessary use of broad-spectrum ATB. As they are patients who often use protocols that cause severe myelosuppression, when they have neutropenia, they seek to protect themselves from serious infections, but that can often be treated simply, and in some cases, on an outpatient basis.

CONCLUSION

Treatment with ATB was the most used, with PIP/TAZ being the most frequent in the regimens, followed by AMOX/CLAV. There was no statistically significant difference between treatment outcomes. However, length of stay, ANC, presence of fever and other clinical conditions must be taken into account when choosing the most appropriate ATB. Viral and fungal infections need to be considered to determine treatment with the correct class of drugs, and to avoid the irrational use of ATB. The establishment of standardized risk classification scores in pediatric onco-hematological patients is essential to guide clinical management in FN treatment.

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AUTHORS' CONTRIBUTIONS

Tatiane Bertella contributed to the conception, design, analysis and writing of the article;

Siomara Regina Hahn contributed to the planning, design, review and final approval of the article.

All authors have approved the final version to be published and are responsible for all aspects of the work, including ensuring its accuracy and integrity.

Systematic review of temporal trends of congenital syphilis in Brazil

Revisão sistemática das tendências temporais de sífilis congênita no Brasil

Revisión sistemática de las tendencias temporales de sífilis congénita em Brasil

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ABSTRACT

Justificativa e objetivos: Em vista do aumento do número de casos de Sífilis Congênita (SC) no Brasil, o presente estudo buscou identificar e sumarizar os dados de tendências temporais de SC em estudos conduzidos no país, bem como listar seus principais fatores associados. **Conteúdo:** Em agosto de 2019, uma revisão sistemática foi desenvolvida em quatro bases de dados eletrônicas (*Lilacs, Pubmed, Scielo e Web of Science*) e em pesquisas manuais em listas de referências. Foram procurados estudos ecológicos que apresentassem tendências temporais da SC no território brasileiro, independentemente das características e representatividade das amostras. Estabeleceu-se que a prevalência de SC do primeiro e do último ano de cada série temporal seria apresentada na síntese descritiva. Dos 2.157 estudos iniciais, 14 foram incluídos. Doze (85,7%) desses estudos mostraram aumentos nas tendências temporais, com ênfase especial nos dois estudos de porte nacional, que mostraram tendências positivas entre 2003–2008 (0,4) e 2010–2015 (3,7). Foram encontradas associações entre CS e fatores socioeconômicos e étnicos, especialmente nos grupos de mulheres com baixa renda, baixa escolaridade, cor da pele marrom/preta e que tinham parceiros não tratados. **Conclusões:** Foi verificado aumento nas tendências temporais da SC no país, destacando que esses dados foram observados nos níveis nacional, estadual e municipal. Como fatores socioeconômicos e étnicos das mães estão associados às frequências mais elevadas de CS, são necessários esforços para aumentar a cobertura das ações do Sistema Único de Saúde nestes grupos.

Descritores: Sífilis Congênita. Estudos de Séries Temporais. Revisão. Brasil.

ABSTRACT

Background and objectives: In view of the increase in the number of cases of Congenital Syphilis (CS) in Brazil, the present study sought to identify and summarize the CS temporal trends in studies conducted in the country, as well as to list its main associated factors. **Contents:** In August 2019, a systematic review was carried out in four

electronic databases (Lilacs, Pubmed, Scielo and Web of Science) and by manual searches on reference lists. Ecological studies that presented temporal trends of CS in Brazilian territory were included, regardless of the sample's characteristics and its representativeness. It was established that the prevalence of CS in the first and last years of each time series would be presented in the descriptive synthesis. Of the 2,157 initial studies, 14 were included. Twelve (85.7%) of these studies showed increases in temporal trends, with special emphasis on the two national studies, which showed positive trends between 2003–2008 (0.4) and 2010–2015 (3.7). Associations between CS and socioeconomic and ethnic factors were found, especially in groups of women with low income, low education, brown/black skin color and who had untreated partners. **Conclusions:** There was an increase in the temporal trends of CS in the country, highlighting that these data were observed at the national, state and municipal levels. As mothers' socioeconomic and ethnic factors are associated with higher frequencies of CS, efforts are needed to increase the coverage of the actions of the Brazilian Health System in these groups.

Keywords: *Syphilis, Congenital. Time Series Studies. Review. Brazil.*

RESUMEN

Justificación y objetivos: en vista del aumento en el número de casos de Sífilis Congénita (SC) en Brasil, el presente estudio buscó identificar y resumir los datos sobre tendencias temporales de SC en estudios realizados en el país, así como enumerar sus principales factores asociados. **Contenido:** en agosto de 2019, se desarrolló una revisión sistemática en cuatro bases de datos electrónicas (Lilacs, Pubmed, Scielo y Web of Science) y en búsquedas manuales en listas de referencias. Se buscaron estudios ecológicos que mostraran tendencias temporales de SC en el territorio brasileño, independientemente de las características y representatividad de las muestras. Se estableció que la prevalencia de SC en el primer y último año de cada serie temporal se presentaría en la síntesis descriptiva. De los 2,157 estudios iniciales, 14 fueron incluidos. Doce (85.7%) de estos mostraron aumentos en las tendencias temporales, con especial énfasis en dos estudios nacionales, que mostraron tendencias positivas entre 2003–2008 (0.4) y 2010–2015 (3.7). Se encontraron asociaciones entre SC y factores socioeconómicos y étnicos, especialmente en grupos de mujeres con bajos ingresos, baja educación, color de piel marrón/negro y que tenían parejas no tratadas. **Conclusiones:** Hubo un aumento en las tendencias temporales de SC en el país, destacando que estos datos se observaron a nivel nacional, estatal y municipal. Como los factores socioeconómicos y étnicos de las madres están asociados con frecuencias más altas de SC, se necesitan esfuerzos para aumentar la cobertura de las acciones del Sistema Público de Salud en estos grupos.

Descriptores: *Sífilis congénita. Estudios de series de tiempo. Revisión. Brasil.*

INTRODUCTION

Congenital syphilis (CS), characterized by the vertical transmission of the bacterium *Treponema Pallidum* to the foetus through the placenta, is considered as one of the most serious preventable adverse outcomes of pregnancy, since its evolution can lead to more drastic consequences, such as premature birth, abortion spontaneous and neonatal death.^{1,2}

Even with the existence of simple and low-cost resources for its diagnosis and prevention, as well as the continuous institutional efforts aimed at the care of pregnant women², which involve, for example, the formulation and implementation of preventive policies, strategies and actions, with particular focus on prenatal care in Brazil, an increase in the prevalence of CS is observed³, which makes a more comprehensive analysis of these changes useful.⁴

Ecological time series studies represent a good estimate for investigating the behaviour of a given disease during a specific period, since they offer a sequence of data collected at regular time intervals, which allow the identification of time trends⁵. Complementarily, still considering the punctuality of the problem in the country,

the importance of recognizing the factors associated with it is also highlighted, so that this survey can support preventive actions in the specific contexts.

In this sense, considering these aspects, the present study sought to identify and summarize the CS temporal trends in studies conducted in the country, as well as to list its main associated factors.

METHODS

This work is configured as a systematic review of the literature, grounded, developed and reported from the items of MOOSE (Meta-analyses of Observational Studies in Epidemiology)⁶ and PRISMA checklists (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).⁷ Its protocol was registered in the PROSPERO database (CRD42020149244).

It was previously established that the synthesis of this review would consist of ecological studies of CS time series in Brazilian territory, regardless of the characteristics of the populations (e.g., ethnicity, socioeconomic level) and the representativeness of the data (e.g. local, regional or national). More specifically,

it was also established that the prevalence of CS in the first and last year of the time series would be presented in the descriptive synthesis. Original studies reported in, English, Italian, Portuguese and Spanish were assessed, without restrictions regarding the year of publication.

On September 1, 2019, potential articles were searched in four electronic databases: Lilacs (I: Syphilis AND Brazil; II: Sífilis AND Brasil), Pubmed (Syphilis[Text Word] AND brazil[Text Word]), Scielo (I: Syphilis AND Brazil; II: Sífilis AND Brasil) and Web of Science (TS=Syphilis AND Brazil). To avoid possible losses, additional manual searches were carried out on Google Scholar and on the full texts of the assessed studies.

Two independent researchers (CJ and MM) conducted the assessment by titles and abstracts, full texts and data extraction, with the support of a senior researcher (PG). The extraction of the original data was performed in an electronic spreadsheet, divided into descriptive data of the studies (e.g., place of research, data source, information about the time series) and results (prevalence data, gross number of CS cases registered at the over the years and additional data, such as, for example, associated and related factors of CS).

RESULTS AND DISCUSSION

At all, searches resulted in 2,157 studies, 280 of which were identified and removed as duplicate records

(Figure 1). Thus, of the 1,877 titles and abstracts evaluated, 29 were sent for full text assessment, and 15 of these were identified as CS time series studies, composing the descriptive synthesis.^{3,8-21}

A great distinction was observed between the objectives of the included studies. In any case, it is worth highlighting the concern with analyzing important aspects of CS, such as, for example, data on prevalence, incidence, the identification of factors that may be associated with it and its relationship with the Brazilian Health System (in Portuguese: Sistema Único de Saúde).

Regarding data coverage (Table 1), were found eight studies of state coverage, five studies of local coverage (municipalities) and two of national coverage. In 13 studies were showed an increase in the CS time trends (86.7%).

In order to offer a better presentation of the results, the studies were organized in three strata, based on the duration of the time series (≤ 4 years; 5–9 years and ≥ 10 years). In the stratum of time series of up to four years, the only two studies that point to decreases in the CS temporal trends, found both in Amazonas state (-0.1, comparing the prevalences of 2007 and 2009)¹⁸ and Rio Grande do Norte state (-1.8, comparing the prevalences of 2007 and 2010).⁹ On the other hand, in this same stratum, the second largest increase in the temporal trend of CS identified in the synthesis can be observed, from a study conducted in the city of Rio de Janeiro (22.8, comparing the prevalences of 2012 and 2014)¹¹ (Table 1).

In the stratum of time series between five and nine

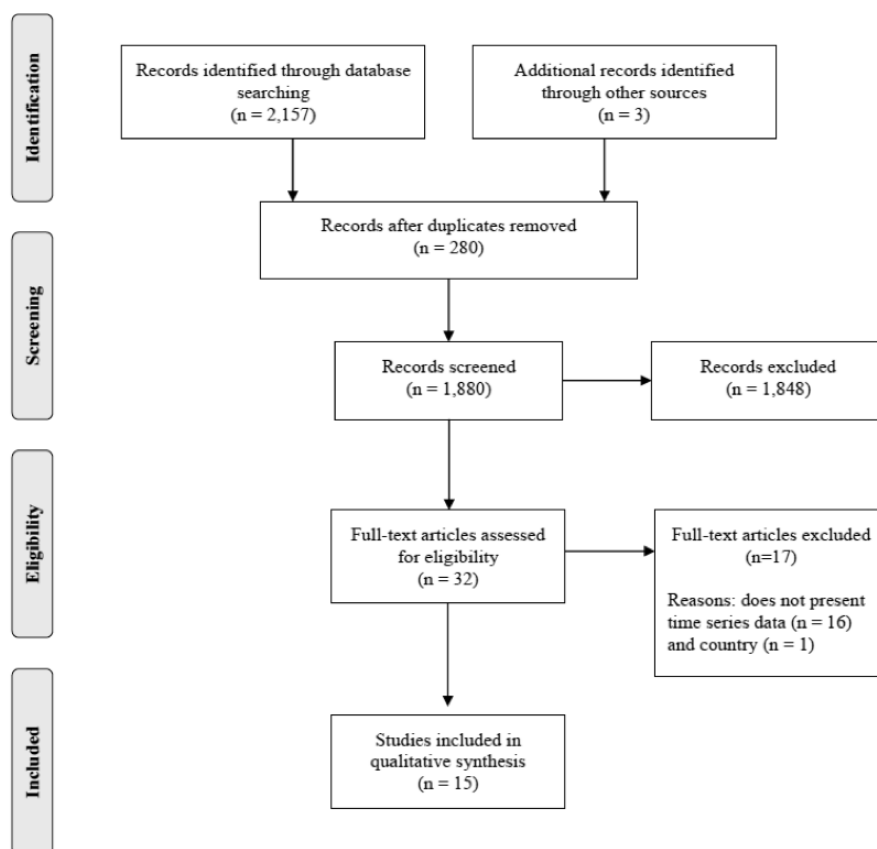


Figure 1. Flowchart of Systematic Review.

Table 1. Data coverage, period and prevalence of the time series and number of cases of Congenital Syphilis in the period (n=14).

Reference	Data coverage	Time series	Time series distal points*	CS cases
Soeiro et al., 2018 ⁸	Amazonas state	2007–2009	2.1–2.0	486
Carvalho; Brito, 2014 ⁹	Rio Grande do Norte state	2007–2010	2.7–0.9	598
Tiago et al., 2017 ²⁰	Mato Grosso do Sul state	2011–2014	8.6–8.8	69
Cerqueira et al., 2017 ¹¹	Rio de Janeiro (RJ)	2012–2014	22.0–44.8	nd
Lima et al., 2013 ¹²	Belo Horizonte (MG)	2001–2008	0.9–1.6	296
Araujo et al., 2012 ⁸	Brazil (country wide)	2003–2008	1.7–2.1	nd
Nunes et al., 2018 ¹⁴	Goiás state	2007–2014	0.3–2.5	663
Cavalcante; Pereira; Castro, 2017 ¹⁰	Palmas (TO)	2007–2014	2.9–8.1	204
Silva Neto; Silva; Sartori, 2018 ¹⁷	Itapeva (SP)	2010–2014	15.1–22.3	101
Bezerra et al., 2019 ³	Brazil (country wide)	2010–2015	2.2–5.9	77,414
Martinez et al., 2019 ¹³	São Paulo state	2010–2015	26.6–77.7	nd
Costa Neto et al., 2018 ²¹	Palmas (TO)	2011–2015	3.8–7.0	176
Oliveira et al., 2014 ¹⁵	Mato Grosso state	2001–2011	0.4–1.7	525
Teixeira et al., 2018 ¹⁹	Rio Grande do Sul state	2001–2012	1.0–5.1	3,613
Sellera et al., 2019 ¹⁶	Distrito Federal state	2005–2017	2.6–4.7	nd

Legends: *: expressed by/1,000 live births; CS: Congenital syphilis; MG: Minas Gerais; nd: not described; RJ: Rio de Janeiro; SP: São Paulo; TO: Tocantins.

years in duration, national studies are located, which showed positive trends between 2003–2008 (0.4)⁸ and 2010–2015 (3.7).³ We also find the study with the greatest increase in the temporal trend, carried out in the state of São Paulo (51.1, comparing the prevalences of 2010 and

2015)¹³. Of the three studies that made up the time series stratum over ten years, the increases of 1.3 (2001–2011),¹⁵ 4.1 (2001–2012)¹⁹ and 2.1 (2005–2017)¹⁶ can be highlighted, in the states of Mato Grosso¹⁵ Rio Grande do Sul¹⁹ and in the Federal District,¹⁶ respectively.

Table 2. Additional results from included studies (n=12)*

Reference	Additional results
Araújo et al., 2012 ⁸	Negative association between the incidence of CS in municipalities with high coverage of Brazilian Health Family Strategy, but, after controlling for covariates, this effect may be attributable to prenatal coverage and the demographic characteristics of the municipalities in which this Strategy was implemented primarily.
Bezerra et al., 2019 ³	Higher rates in the Northeast, Southeast and South and infant mortality rates due to CS were higher in the Northeast and Southeast. Correlations observed between rates of CS and infant death, spontaneous abortion and rates of stillbirths and correlations between rates of stillbirths caused by syphilis and inadequate prenatal care.
Carvalho; Brito, 2014 ⁹	Higher number of cases in urban regions (83.4%). Most of the notifications were of live births whose mothers had up to 8 years of study (65.0%), had performed prenatal care (72.2%) and diagnosed with syphilis at the time of delivery/curettage (41.0%).
Cavalcante; Pereira; Castro, 2017 ¹⁰	Predominance of brown women (90.2%), aged 20–34 years (73.5%), with incomplete or complete high school education (48.0%). Of the total number of CS cases, 81.4% of mothers performed prenatal care during pregnancy and 48.0% were diagnosed during prenatal care. Of the mothers who received prenatal care, 83.0% did not have their partners treated.
Cerqueira et al., 2017 ¹¹	CS underreporting in the period was 6.7%.
Costa Neto et al., 2018 ²¹	Higher occurrence of gestational syphilis in the 20 to 34-year-old age group.
Lima et al., 2013 ¹²	Indicators of low maternal socioeconomic status, as well as the lack of prenatal care during pregnancy were independently associated with the diagnosis of CS. The chance of a child being diagnosed as a case of CS was 2.1 (95%CI:1.5–2.8) times greater in children born to mothers of brown or black color, 1.3 (1.2–1.4) times higher in children whose mothers had less than eight years of study and 11.4 (8.5–15.4) times higher in children born to mothers who did not undergo prenatal care.
Martinez et al., 2019 ¹³	In 2016, it was estimated that between 79.4% and 95.3% of CS cases among women who did not have prenatal care could have been avoided.
Nunes et al., 2018 ¹⁴	There was a significant increase in CS cases in the municipalities that had Brazilian Health Family Strategy coverage percentages below 75%
Oliveira et al., 2014 ¹⁵	In the period, 77.6% of women received inadequate treatment for syphilis; in addition, 75.8% of its partners were not treated. There was a statistically significant reduction in prenatal consultations (p=0.004) and an increase in the proportion of mothers reactive to non-treponemal tests at birth (p=0.031) between the two periods.
Silva Neto; Silva; Sartori, 2018 ¹⁷	Higher frequency of CS in children of smokers, mothers who attended <6 prenatal consultations and mothers with late diagnosis of syphilis.
Teixeira et al., 2018 ¹⁹	59.6% of mothers had white skin color, 55.9% had incomplete primary education or were illiterate; 50.8% comprised the age group between 20–29 years and 93.5% lived in the urban area. Regarding prenatal care, 77.4% of pregnant women were followed up, and in 51.9% the test for syphilis was performed during this period.

Legends: *: Sellera et al., 2019¹⁵; Soeiro et al., 2018¹⁷ and Tiago et al., 2017¹⁹ did not evaluate risk associations; 95%CI: 95% Confidence Interval; CS: Congenital Syphilis.

As additional results (Table 2), many studies included point out that CS is associated with socioeconomic factors, highlighting its occurrence in urban regions, in women of low socioeconomic status, low education, of brown/black skin color and who had untreated partners.

In order to identify the evidence from studies of CS time series in Brazil, in 13 of the 15 studies included, increases in time trends were observed. It was also identified that a good portion of the studies included points out that CS is associated by socioeconomic and ethnic factors, with emphasis on the groups of women with low income, low education, brown/black skin color and who had untreated partners.

Of the 13 studies that showed increases in temporal trends of CS, there are two analyses of national coverage,^{3,8} with particular emphasis on the increases in temporal trends observed since the last decade. In one of these,³ specifically, it was observed that in the five Brazilian regions there was a continuous increase in cases of congenital syphilis, between 2010 and 2015. During this period, rates were doubled and even tripled, elucidating the importance of time series studies.

These findings corroborate other international studies, which showed an increase in CS rates in the Americas in the past decade, which may reinforce the epidemic status at the continental level.²²⁻²⁴ It is worth mentioning that, in the global context, only Eastern Europe also shows increasing rates of CS.²²

In the included studies, some factors that are associated with vertical transmission of syphilis can be highlighted, such as absence of health coverage, not having consultations and also low quality of prenatal care.^{3,9,12} More specifically, a study,¹⁴ suggests an increase in CS cases in municipalities that had health coverage rates below 75% and, in other study,¹⁷ it is pointed out that although most pregnant women start prenatal care in the first trimester of pregnancy, with regular visits to the health unit, the percentage of vertical transmission of CS is high.

The descriptive synthesis also shows that, in 2016 it was estimated that 80% to 95% of CS cases among women who did not have prenatal care, could be avoided, demonstrating the country's need to invest in care and quality of care for pregnant women with syphilis.^{3,13,25} In addition, it can be observed in two studies^{10,12} limitations that go beyond the provision of health services, highlighting educational, social and cultural fragility of populations at risk.

Another highlighted point is the lack of treatment of pregnant women's partners.¹⁰ Specifically, one study¹⁵ suggests that this may be a causal factor for reinfection in pregnant women and also for the expansion of the disease due to non-adherence to treatment or even due to lack of information and/or negligence on the part of the partner. Since other studies have also identified the same problem, especially in contexts of vulnerability,²⁶⁻²⁸ it is important to reinforce strategies that also focus on the treatment of partners infected with syphilis²⁸ (and/or other sexually transmitted diseases).

Underreporting of the data is another topic which

deserves attention as it does not allow the recognition of correct estimates of CS in the country.¹¹ For example, was identified that underreporting cases in information systems hides the magnitude of the disease among indigenous people in Mato Grosso do Sul.²⁰ It is worth mentioning that this problem also affects other infectious diseases in Brazil,^{29,30} which makes further studies necessary to identify the factors associated with underreporting of CS.

In this work, some critical points regarding CS in Brazil could be mentioned, however, it is worth highlighting, as informed in previous paragraphs, the magnitude of CS in the Americas.²¹ In a study developed in United States,³¹ most of the increase in CS cases occurred in newborns of black mothers, with an association with chemical dependency and sex work as its occupation. Was reported an CS increase from 26.6 per 100,000 live births in 2005 to 34.6 in 2008. Black, Latin and Asian mothers were the most vulnerable groups.³¹

In the same way as highlighted in the present synthesis, the study conducted in the United States³¹ also showed flaws in the prenatal care system, where in some cases the treponemal tests for Syphilis were not performed. Comparatively, it was identified in this study that a significant percentage of women were diagnosed for the disease late and even after the child-birth.

As it involves ecological studies, our systematic review is limited to the presentation of the temporal rates of CS, as well as a more comprehensive look to its associated factors, without inferring about incidence and/or causality. In this sense, caution is recommended in the interpretation and extrapolation of the data. On the other hand, since this is one of the first reviews to appraise the temporal trends of CS in Brazil, it is worth suggesting the implementation of new research designs, longitudinal and intervention, which can, in addition to strengthening the causal inference, to develop techniques that can increase the number of women who are prevented or even being treated for syphilis.

CONCLUSION

In conclusion, most of the available research has shown an increase in CS temporal trends in Brazil, highlighting that these data were observed at the national, state and municipal levels. Since mothers' socioeconomic and ethnic factors are associated with higher CS rates, efforts are needed to increase the coverage of the Brazilian Health System to women in vulnerable situations.

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Covid-19 and prisons: a reflection on public health and human rights

Covid-19 e prisões: Reflexões sobre saúde pública e direitos humanos

Covid-19 y las cárceles: Reflexión sobre la salud pública y los derechos humanos

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ABSTRACT

Background and Objectives: The 2019 coronavirus pandemic (Covid-19) is a public health challenge. Identifying risk groups is essential for establishing prevention, screening, containment, and treatment strategies. In Brazil, prisons overcrowding and unhygienic conditions have been a historical problem that enables infectious diseases. This study sought to reflect upon incarcerated population vulnerability and present strategies to face the pandemic. **Methods:** This is a theoretical-reflective study based on the review of scientific publications and Covid-19 coping guidelines. **Results:** Prison populations are highly vulnerable to Sars-Cov-2 infections. Such vulnerability is aggravated by prisons' structural conditions, which accelerates diseases spread, especially respiratory illnesses, and hinders the adoption of preventive measures. Healthcare strategies aimed at this population are still scarce. **Conclusion:** Covid-19 outbreaks in prisons affect prisoners, staff, and family members, possibly leading the health system to an unprecedented collapse. Considering that, strategies to reduce coronavirus impact in prisons and on public health are urgent. Preventive measures of virus spread among this population must be supported by priority health measures, contingency protocols, and coordinated actions between the health and justice sectors.

Keywords: Prisons. Coronavirus Infections. Communicable Diseases. Pandemics. Public health

RESUMO

Justificativa e Objetivos: A pandemia do coronavírus 2019 (Covid-19) é um problema de saúde pública desafiador. A identificação de grupos de risco é fundamental para o estabelecimento de estratégias de prevenção,

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rastreamento, contenção e tratamento. No Brasil, a superlotação e as condições insalubres das prisões são um problema histórico que facilita a disseminação de doenças. O objetivo deste estudo é refletir sobre a vulnerabilidade da população penitenciária e apresentar estratégias de enfrentamento à pandemia. **Métodos:** Estudo teórico-reflexivo construído a partir da revisão de publicações científicas e diretrizes de enfrentamento da Covid-19. **Resultados:** A PPL apresenta alta vulnerabilidade clínica para contaminação pelo Sars-Cov-2, o qual é agravado pelas condições estruturais das prisões que potencializam a disseminação de doenças, sobretudo respiratórias e dificultando o estabelecimento de medidas de prevenção. Surtos de Covid-19 em prisões afetam presos, funcionários e familiares e podem levar o sistema de saúde a um colapso sem precedentes. As estratégias de atenção a saúde desta população ainda são insuficientes. **Conclusão:** O estabelecimento de estratégias para reduzir o impacto do Covid-19 nas prisões e o seu reflexo na saúde pública é uma urgência. A prevenção da propagação do vírus nesta população deve ser apoiada por medidas prioritárias de saúde, implementação de protocolos de contingência e estabelecimento de ações coordenadas entre os setores de saúde e justiça.

Descritores: Prisões. Infecções por Coronavirus. Doenças Transmissíveis. Pandemias. Saúde Pública.

RESUMEN

Justificación y Objetivos: La pandemia de la enfermedad por coronavirus 2019 (Covid-19) es un problema de salud pública desafiante. La identificación de los grupos de riesgo es esencial para establecer estrategias de prevención, detección, contención y tratamiento. En Brasil, el hacinamiento y las condiciones insalubres en las cárceles son un problema histórico que facilita la propagación de enfermedades. El objetivo de este estudio es reflexionar sobre la vulnerabilidad de la población carcelaria al Covid-19 y presentar estrategias de afrontamiento a la pandemia. **Métodos:** Estudio teórico-reflexivo con base en la revisión de publicaciones científicas y guías de afrontamiento del Covid-19. **Resultados:** La población penitenciaria presenta una alta vulnerabilidad clínica a la contaminación por Sars-Cov-2 agravado por las condiciones estructurales de las cárceles, lo que aumenta la propagación de enfermedades, especialmente respiratorias, y dificulta el establecimiento de medidas preventivas. Los brotes del Covid-19 en las cárceles afectan a los presos, al personal y a los miembros de la familia, y podrían llevar al sistema de salud a un colapso sin precedentes. Las estrategias sanitarias de esta población aún son insuficientes. **Conclusión:** Las estrategias para reducir el impacto del Covid-19 en las cárceles y su impacto en la salud pública son urgentes. La prevención de la propagación del virus en esta población debe apoyarse en medidas prioritarias de salud, la implementación de protocolos de contingencia y el establecimiento de acciones coordinadas entre los sectores de salud y justicia.

Palabras clave: Cárceles. Infecciones por Coronavirus. Enfermedades Transmisibles. Pandemias. Salud Pública.

The novel coronavirus 2019 (SARS-CoV-2) has infected millions of people worldwide¹ and Brazil is one of the main outbreak epicenters.² The disease contamination rates are still increasing³, and vulnerable groups such as persons deprived of liberty are at greatest risk of infection.³⁻⁵

Large-scale studies have shown that the prevalence of infectious diseases such as human immunodeficiency virus (HIV), hepatitis C virus (HCV), hepatitis B virus (HBV), and tuberculosis is higher among prisoners than in the general population.⁶ This can be explained by the fact that detainees are predominantly from vulnerable communities with limited access to health services.⁷ Moreover, vulnerability to these conditions is exacerbated during incarceration due to unhygienic and poorly ventilated prison facilities and may be aggravated by other risk factors such as drug use and shared consumption devices (cigarettes, pipes), inadequate nutrition, high-risk sexual behavior, poor hygiene habits, psychological stress of isolation⁸, and overcrowding.

Implementing social distancing in prisons is a laborious task, exposing the imprisoned population to infectious diseases⁹ and making them a potential source of infection.¹⁰ In February 2020, Brazil's inmate population

was 710,000 individuals, 31% of which were provisional (without trial). Considering that the estimated system capacity is 423,000 vacancies, such incarceration rate generates an overcrowding of 287,000 people.¹¹ Given that previous evidence showed that Covid-19 transmission rate is higher among individuals living in the same household than among individuals who have contact but do not live in the same environment,¹² this is a disturbing data that raise awareness to the possibility of high transmissibility among prisoners who share the same cell. More than 40 of the 50 largest Covid-19 clusters in the USA occurred within prisons.³ The number of cases is 55 times higher among incarcerated individuals when compared to the general population.¹³⁻¹⁵ We should also consider the transmission potential to staff, law enforcement officers, family members,¹⁰ and visitors, who can spread the virus within prisons and in their communities. According to the Brazilian National Justice Council, by August 2020, over 17,000 prisoners were infected (2.3% of the total) and about 100 died from Covid-19. However, these data may be underreported given that only 7.8% of detainees were tested and that 7,000 of the 110,000 prison officers were infected and 75 died in this period, demonstrating the vulnerability of the prison system.

Implementing measures to contain the spread of Covid-19 has been challenging in all social spheres worldwide. Such challenges are even potentiated regarding the Brazilian prison system, since the implementation of preventive measures within this environment imply ethical, social, economic, and legal particularities.

For analyzing these issues, we must consider that Brazil is a continental country with the world's third largest prison population, posing barriers for preventive and treatment strategies. Despite recent progress, investments for implementing health services within the prison context are still insufficient and historically weak.⁹ The National Policy for Comprehensive Health Care in the Prison System (PNAISP) was developed in response to this population adverse conditions to healthcare access within the scope of the Brazilian Unified Health System (such as increased spread of diseases, scarcity of health services and lack of health professionals, limited infrastructure, and low-quality healthcare). The PNAISP aims to effectively ensure prisoners' constitutional right to health based on the principles of integrality and intersectorality¹⁶ through primary health care and human rights strategies that implement preventive measures and provide hospital support. Logistical processes may represent a challenge for referring prisoners to medium and high-complexity hospitals, possibly delaying the diagnosis and treatment of infected patients due to security protocols and consequently increasing death risk.¹⁰ The health system may also not be able to provide enough assistance to these patients in view of their clinical aggravations.

Ensuring prisoners' access to health is a matter of concrete human rights responses, health protection, and citizenship defense through a set of actions addressing health promotion and environmental health surveillance. Considering that, the World Health Organization (WHO) issued a series of guidelines¹⁷ concerning the Prevention and Control of Covid-19 in Prisons and other Places of Detention, among which the main are:

1. To perform screening and risk assessment for all individuals entering the prison environment (prisoners, visitors, employees), as well as for those released from prison;
2. To provide special attention for risk groups, especially older adults and individuals with chronic lung diseases;
3. To implement strict daily hygiene and disinfection protocols;
4. To provide the necessary materials (for all people involved) for individual hygiene and hand washing;
5. To develop psychoeducational measures on respiratory hygiene;
6. To establish a contingency plan for individuals suspected of Covid-19; perform medical observation until further evaluations and, if necessary, conduct tests and refer individuals to hospitals in severe cases of Covid-19; and
7. To unify and disseminate protocols to all those involved in contingency planning.

Corroborating these international measures, the Brazilian Justice Council published the Recommendation No. 62/2020¹³, establishing provisional measures to prevent contagion from the novel coronavirus within the scope of the criminal and socio-educational justice system. They also encouraged campaigns promotion to raise awareness concerning risks and hygiene procedures to avoid virus spread, besides recommending restrictive measures for holding hearings, re-evaluating prisons, interrupting visits, and attention to staff. These guidelines are in line with the Inter-American Commission on Human Rights (IACHR).¹⁸

As a result, governments must monitor Covid-19 restrictions considering other public policies and programs compatible with prisoners' right to personal integrity and health, extending outdoors hours or optimizing spaces and leisure times. Considering this population high vulnerability and penitentiary policy fragility, authorities must develop and monitor control- and containment-focused actions to avoid worsening this scenario.

These strategies must be supported by priority health measures, contingency protocols, and coordinated actions between the health and justice sectors, as well as different sectors of society (social services, civil society organizations, non-governmental organizations) to promote an integrated and articulated response that guarantees access to health and human right.

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Epidemiological investigation reveals local transmission of SARS-CoV-2 lineage P.1 in Southern Brazil

Investigação epidemiológica revela transmissão local da variante P.1 do SARS-CoV-2 no Sul do Brasil

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ABSTRACT

Since its detection in December of 2020, the SARS-CoV2 lineage P.1, descendent of B.1.1.28 lineage, has been identified in several places in Brazil and abroad. This Variant of Concern was considered highly prevalent in Northern Brazil and now is rapidly widening its geographical range. Here, we present epidemiological and genomic information of the first case of P1 lineage in Rio Grande do Sul state, in a patient without reported travel history and a tracked transmission chain. These findings occurred in a tourist destination representing an important hub receiving tourists from diverse places.

Keywords: SARS-CoV-2. COVID-19. transmission. B.1.1.28.

RESUMO

Desde a sua detecção em dezembro de 2020, a linhagem P.1 do SARS-CoV2, descendente da linhagem B.1.1.28, foi identificada em diversos locais no Brasil e no mundo. Essa variante de preocupação era considerada altamente frequente no Norte do Brasil e agora está ampliando rapidamente sua distribuição geográfica. Aqui, apresentamos informações epidemiológicas e genômicas do primeiro caso da linhagem P.1 no Rio Grande do Sul em um paciente sem histórico de viagens relatado e com cadeia de transmissão identificada. Esses achados ocorreram em um destino turístico que representa um importante pólo de recepção de turistas de diversas localidades.

Descritores: SARS-CoV-2. COVID-19. transmissão. B.1.1.28.

RESUMEN

Desde su detección en diciembre de 2020, del linaje P.1 del SARS-CoV2, derivada de la B.1.1.28, hay sido ampliamente identificada en Brasil y en todo el mundo. Esta variante preocupante es muy frecuente en el norte de Brasil y ahora está ampliando rápidamente su distribución geográfica. Aquí, presentamos información epidemiológica y genómica del primer caso de P.1 en Rio Grande do Sul en un paciente sin antecedentes de viaje y con una cadena de transmisión identificada. Estos datos se han obtenido en un destino turístico que representa un importante centro de acogida de turistas de diferentes lugares.

Palabras clave: SARS-CoV-2. COVID-19. transmisión. B.1.1.28.

Recently, a new variant first detected in Manaus/ Amazonas in the North Region of Brazil has become a concern worldwide. The named P.1 lineage is descendent of B.1.1.28 lineage and carries a set of mutations with important biological significance, mainly at region encoding spike protein (E484K, K417T and N501Y) (N.R. Faria, et al., unpub. data, <https://virological.org/t/genomic-characterisation-of-an-emergent-sars-cov-2-lineage-in-manaus-preliminary-findings/586>).

The P.1 lineage emerged with high frequency in a short period of time, spreading fast in North of Brazil, and in the recent weeks in other cities from Southeastern Brazil (F. Naveca et al., unpub. data, <https://virological.org/t/sars-cov-2-reinfection-by-the-new-variant-of-concern-voc-p-1-in-amazonas-brazil/596>). Here we described the first detected case of SARS-CoV-2 P.1 lineage in Rio Grande do Sul, the southernmost state in Brazil. The case occurred in Gramado city, a mountain town with German colonization that receives 6.5 million tourists every year. Gramado belongs to the 5th Regional Health Coordination (an administrative division) that comprises 49 municipalities with a 1,240,319 estimated population, also known as Caxias do Sul Region (<https://cidades.ibge.gov.br/brasil/panorama>).

An 88-years-old male patient (A) presented acute

respiratory symptoms on Jan 29th, 2021 and was hospitalized on Feb 3rd after medical examination. At the same day, the patient was admitted at the intensive care unit with fever of 39°C, no leg movements, chest pain, besides flu-like symptoms/Acute Respiratory Syndrome. Respiratory secretion was collected on Feb 1st and RT-qPCR for SARS-CoV-2 detection was performed at Central Laboratory of Public Health from Rio Grande do Sul (LACEN-RS). The RNA was extracted from respiratory clinical sample through MagMAX Viral/Pathogen II Isolation kit on KingFischer Flex extractor (Thermo Fisher Scientific, Waltham, USA). The multiple detection of 3 target genes (E gene, RdRP gene and N gene) from pathogen was performed on Applied Biosystems 7500 Real-Time PCR System (Thermo Fisher Scientific, Waltham, USA), using Allplex SARS-CoV-2 Assay (Seegene Inc, Seoul, Republic of Korea). The SARS-CoV-2 RT-qPCR was positive (Ct 22) and the result released on Feb 2nd, the patient died on Feb 10th, nine days after hospitalization.

As part of SARS-CoV-2 genomic surveillance in Rio Grande do Sul State, the collected sample, along with samples from different cities, were sequenced aiming to obtain the current scenario of SARS-CoV-2 genomic diversity in this region. Whole genome library preparation of SARS-CoV-2 was performed using QIAseq SARS-CoV-2

and permanent tool to identify the underlying events as in the present case, where, due to genomic surveillance, it was possible to detect an unsuspected variant of concern P.1 on a case of COVID-19 death in a patient practicing self-isolation, living in a remote area.

Our analysis highlights monitoring protocols for new variants must consider key social mobilization sites in the state. From all cities of Rio Grande do Sul state, Gramado and Canela are by far the most important from the point of view of social mobility, as they receive tourists from Brazil and abroad. The Capital and the border/port regions must also be constantly monitored in order to guarantee success in monitoring new circulating strains. The joint observation of epidemiological and laboratory surveillance findings can assist the community in COVID-19 control measures.

DATA AVAILABILITY

Whole genome sequence from SARS-CoV-2 genome sequenced in this work it is available on GISAID database under accession ID EPI_ISL_983865.

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AUTHORS' CONTRIBUTIONS

Richard Steiner Salvato and **Tatiana Schäffer Gregianini** conceived the study and its design;

Richard Steiner Salvato and **Aline Alves Scarpellini Campos** conducted phylogenetic analysis;

Lara Villanova Crescente, **Marcelo Jostmeier Vallandro**, **Tani Maria Schilling Ranieri**, **Sabrina Vizeu**, **Letícia Garay Martins** and **Eduardo Viegas da Silva** analyzed epidemiological data;

Ellen Regina Pedroso and **Andreia Burille** conducted epidemiological investigation; **Ludmila Fiorenzano Baethgen** performed laboratorial experiments, contributed to data analysis and manuscript writing;

Sun Hee Schiefelbein, **Taís Raquel Marcon Machado**, **Irina Marieta Becker**, **Raquel Ramos**, **Cláudia Fasolo Piazza** and **Zenaida Marion Alves Nunes** were in charge for clinical sample and laboratorial experiments;

Cynthia Goulart Molina Bastos read the manuscript and revised it critically. All authors read and approved the manuscript. The authors declare no conflict of interests.