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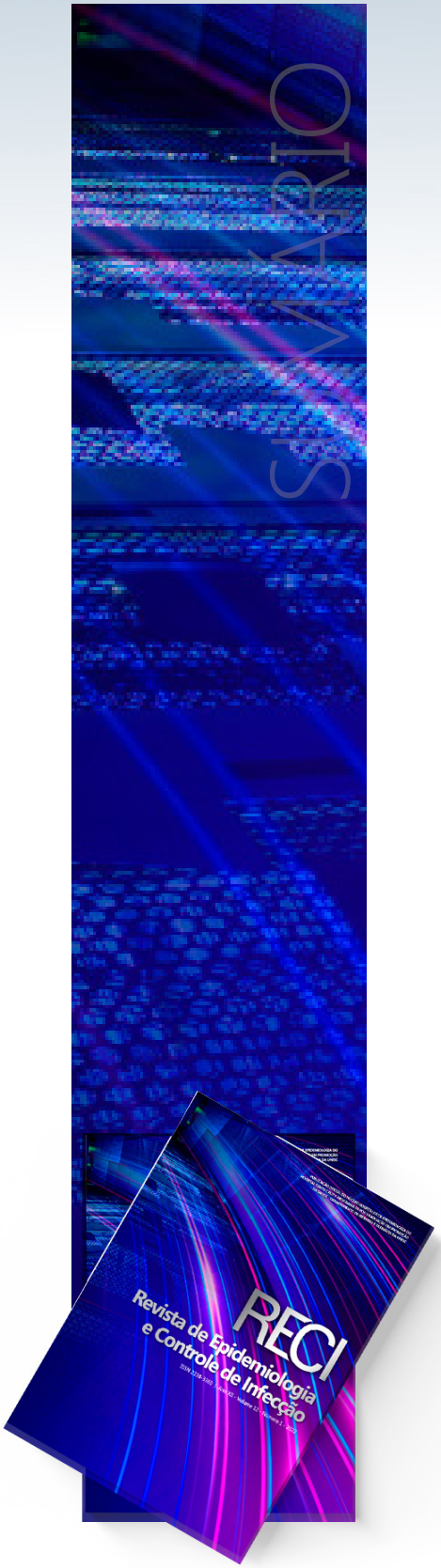

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COVID-19 infection rate and time spent at home: analysis of the beginning of the pandemic

Taxa de infecção por COVID-19 e tempo gasto em casa: análise do começo da pandemia

Tasa de infección por COVID-19 y tiempo en casa: análisis del inicio de la pandemia

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ABSTRACT

Background and Objectives: Evidence suggests that the failure of epidemiological control impedes the resumption of socioeconomic activities. Therefore, this study aimed to describe epidemiological aspects and the pattern of mobility on each continent and to verify the association between the COVID-19 infection rate and time spent at home. **Methods:** We analyzed reports from Global Positioning System of 97 countries and their epidemiological indicators until May 27, 2020. **Results:** Cases of COVID-19 ranged from 22 to 1,745,803, and deaths ranged from 0 to 102,107. The highest rates per 100,000 population were observed in Europe and America. Approximately 54% of COVID-19 cases occurred in America and 51% of deaths in Europe. Countries reduced mobility in retail and recreation (-43.45%±20.42%), grocery and pharmacy (-17.95%±20.82%), parks (-18.77%±37.34%), transit stations (-43.09%±20.31%), workplaces (-21.74%±19.92%), and increased time spent at home (13.00%±8.80%). Linear regression showed that European inhabitants stayed at home less when compared those on the American continent (β=-4.933, SE=0.976, p<.001). In addition, every unit increase in the infection rate per 100,000 population increased 0.005 points in the mean time spent at home (β=0.005, SE=0.001, p<.001). **Conclusions:** We provide evidence that increased infection rate of COVID-19 is associated with increased length of stay at home. As a main lesson, COVID-19 showed that in the absence of pharmacological resources, government authorities need to act quickly to contain the spread of infectious diseases.

Keywords: *Epidemics. Pandemics. Physical Distancing. Coronavirus Infections. Mortality.*

RESUMO

Justificativa e objetivos: Evidências sugerem que as dificuldades no controle epidemiológico impedem a retomada das atividades socioeconômicas. Diante disso, tivemos os objetivos de descrever aspectos epidemiológicos

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e o padrão de mobilidade em cada continente e verificar a associação entre a taxa de infecção por COVID-19 e o tempo de permanência em casa. **Métodos**: Analisamos relatórios de *Global Positioning System* de 97 países e seus indicadores epidemiológicos até 27 de maio de 2020. **Resultados:** Casos de COVID-19 variaram de 22 a 1.745.803, e as mortes variaram de 0 a 102.107. Maiores taxas por 100.000 habitantes foram observadas na Europa e América. Aproximadamente 54% dos casos de COVID-19 ocorreram na América e 51% dos óbitos na Europa. Os países reduziram a mobilidade no varejo e recreação (-43,45% ± 20,42%), mercearia e farmácia (-17,95%±20,82%), parques (-18,77%±37,34%), estações de trânsito (-43,09%±20,31%), locais de trabalho (-21,74%±19,92%), e aumentaram o tempo em casa (13,00% ± 8,80%). A regressão linear mostrou que os habitantes europeus ficaram menos tempo em casa do que os habitantes do continente americano (β=-4,933, EP=0,976, p<0,001). Além disso, cada unidade de aumento na taxa de infecção por 100.000 habitantes aumentou 0,005 pontos no tempo médio de permanência em casa (β=0,005, EP=0,001, p<0,001). **Conclusões:** Fornecemos evidências de que o aumento da taxa de infecção por COVID-19 está associado ao aumento do tempo de permanência em casa. Como lição principal, a COVID-19 mostrou que, na ausência de recursos farmacológicos, as autoridades governamentais precisam agir rapidamente para conter a propagação de doenças infecciosas.

Descritores: *Epidemia. Pandemia. Distanciamento Físico. Infecções por coronavírus. Mortalidade.*

RESUMEN

Justificación y Objetivos: Dificultades en el control epidemiológico dificultan la reactivación de actividades socioeconómicas. Nuestros objetivos fueron describir aspectos epidemiológicos y el patrón de movilidad en cada continente y verificar la asociación entre tasa de infección por COVID-19 y duración de estancia en casa. **Métodos:** Examinamos informes del *Global Positioning System* de 97 países y sus indicadores epidemiológicos hasta 27 de mayo de 2020. **Resultados:** Casos de COVID-19 oscilaron entre 22 y 1.745.803, y muertes entre 0 y 102.107. Tasas más altas por 100.000 habitantes ocurrieron en Europa y América. Aproximadamente 54% de los casos de COVID-19 ocurrieron en América y 51% de las muertes en Europa. Los países redujeron la movilidad en comercio y recreación (-43,45%±20,42%), tienda de comestibles y farmacia (-17,95%±20,82%), parques (-18,77%±37,34%), estaciones de tránsito (-43,09%±20,31%), lugares de trabajo (-21,74%±19,92%), y aumentaron la duración de la estancia en casa (13,00%±8,80%). La regresión lineal (R^2=0,906) mostró que los europeos permanecían menos tiempo en casa en comparación con los del continente americano (β=-4,933, EE=0,976, p<0,001). Además, cada unidad de aumento de la tasa de infección por 100.000 habitantes aumentó la duración media de la estancia en casa en 0,005 puntos (β=0,005, EE=0,001, p<0,001). **Conclusiones:** Mostramos que el aumento de la tasa de infección de COVID-19 se asocia con una mayor duración de la estancia en casa. Como lección clave, COVID-19 demostró que, en ausencia de recursos farmacológicos, las autoridades gubernamentales deben actuar rápidamente para contener la propagación de enfermedades infecciosas.

Palabras Clave: *Epidemia. Pandemia. Distanciamiento Físico. Infecciones por coronavirus. Mortalidad.*

INTRODUCTION

The rapid spread of SARS-CoV-2 promoted the World Health Organization (WHO) to declare a public health emergency at the end January 2020. Due to the substantial number of cases and deaths in a short period, collective efforts were needed to interrupt the SARS-CoV-2 transmission chains.[1] Despite the lower mortality rate compared to diseases caused by other coronaviruses such as SARS-CoV and MERS-CoV, the high transmissibility of SARS-CoV-2 resulted in more deaths than the sum of SARS-CoV and MERS-CoV.[2] In the initial months of the pandemic, when no vaccines were available, physical distancing has become the main strategy to contain the transmission of SARS-CoV-2.[3]

Despite recommendations from scientific community, social distancing has never been consensual in countries like Brazil and the United States. Specifically in Brazil, the reason for this resistance is that confinement would cause negative economic consequences such as bankruptcy and unemployment.[4] However, in the State of São Paulo, the Brazilian region most affected by COVID-19, municipalities with the highest rates of social distancing did not have the worst unemployment rates or tax revenues.[5] Historical records from 1918 reveal that cities in the United States that adopted faster and more rigid non-pharmacological measures were able to control infection and mortality curves more rapidly, with milder consequences in relation to economic crisis[6]. In contrast, regions that acted late had more difficulty in containing the health crisis, which impeded, for a long period, the resumption of economic activities.[6] In this context, we hypothesize that countries most successful in controlling the SARS-CoV-2 transmission chains came out of confinement quickly, while residents of countries with worse epidemiological indicators had to stay at home longer.

Investigating this hypothesis is important for understanding pandemic dynamics, especially in the absence of pharmacological resources. Currently, large-scale immunization faces difficulties due to factors such as mistrust of some social groups, centralized production of immunizers, slow governmental negotiations, and logistical problems. Furthermore, observations of reinfection and

the uncertainty about the efficacy of vaccines against new coronavirus lineages[8] indicates that there is still a long way to go.

Time spent at home is provided by smartphones, more specifically through Global Positioning System (GPS) technology. Because of the pandemic, Google started to periodically publish mobility reports about the occupation of different categories of places.[9] These reports offer information regarding the mobility of residents of 132 countries in categories such as retail and recreation, grocery and pharmacy, parks, transit stations, workplaces, and residential. From these reports and considering the context presented, this study aimed to describe epidemiological aspects and the pattern of mobility on each continent and to verify the association between the COVID-19 infection rate and time spent at home.

METHODS

We analyzed the COVID-19 mobility, infection, and mortality reports recorded through May 27, 2020. The inclusion criterion was the availability of information, excluding those countries that did not make public the variables of interest in the databases accessed. We also excluded countries whose first case of COVID-19 occurred after March 14, 2020, and which had a population of less than 1 million or more than 1 billion inhabitants. Reports from 132 countries were identified, of which 97 met our study criteria. The distribution of countries by continent was as follows: 34 countries from Europe, 28 from Asia, 13 from Africa, 20 from America (Central=6, North=4 and South=10) and 2 from Oceania.

Procedures

Two independent researchers accessed the Worldometer,[10] Our World in Data,[11] International Monetary Fund (IMF),[12] and Knoema[13] databases to obtain information about epidemiological and sociodemographic aspects. Independent researchers also accessed Google databases[9] to gather information about mobility and time spent at home. All information was cross-checked and revised to remove divergences.

Infection and mortality

Worldometer[10] statistics are based on official reports obtained from health departments or other government institutions. In this database, we recorded information about infections and deaths in each country considering the first case until May 27, 2020. Our World in Data[11] is an open-access database that allowed access to daily epidemiological indicators by COVID-19.

Potential confounders

Duration of epidemic: this was determined by subtracting the dates of the last and first case of COVID-19.[10] The duration of epidemic was used as a counting variable.

Human Development Index (HDI): countries of different continents have discrepant social, demographic, and health conditions, which can be sized by the HDI. The HDI is a coefficient calculated based on literacy rates, schooling, life expectancy at birth, and per capita income. The HDI and total population were obtained from the IMF.[12] The HDI was used as a continuous variable.

GINI index: The GINI index evaluates the income concentration, discriminating the magnitude of difference between the richest and the poorest. This index varies from 0 to 1, where the highest numbers indicate income disparity in the country. The GINI index was obtained from the Knoema database[13]. The Gini index was used as a continuous variable.

Mobility in different categories of places

Google provides mobility reports[9] based on user records of its applications, such as Google Maps. Users have to accept the application's privacy statement and enable the location history of the mobile device. Reports do not allow personal information to be identified, providing only a global estimate of the displacement pattern of the inhabitants of each country. Variation of mobility was based on the comparison of the baseline (i.e., the median between January 3 and February 6, 2020) with the records up to May 16, 2020. Reports issued by Google provided variation in frequency of occupancy of five categories of places: *Retail and recreation*, establishments such as restaurants, bars, shopping centers, museums, and libraries. *Grocery and pharmacy,* markets of food, agricultural products, drugstores, and pharmacies. *Parks,* squares, gardens, public parks, and beaches. *Transit stations,* mobility in public transportation such as buses, trains, and subways.

Outcome

Google's mobility reports also provided the variation in time spent at home, which was based on the comparison of the baseline (i.e., the median between January 3 and February 6, 2020) with the records up to May 16, 2020. The variation in time spent at home was used as a continuous variable.

Statistical analysis

Descriptive statistics were used to characterize the variables. The Shapiro-Wilk test was used to verify if continuous variables had a normal distribution. The Kruskall-Wallis test was used to compare mobility in different categories according to the continent, and the Steel Dwaas test for paired comparisons. We performed a correlation matrix between the different mobility categories and observed that "Retail and Recreation," "Grocery and Pharmacy," "Parks," "Transit Stations," and "Workplaces" categories were strongly correlated (supplementary file 1). Given this, we created a factor named "out-of-home mobility" through the Principal Components method, followed by the sphericity and KMO tests (supplementary file 1). We also observed that the variables "HDI," "Gini Index," and "Continents" were associated (supplementary file 2). Considering these aspects, we performed a Linear

Regression to test the following model:

$$Y\text{Time spent at home} = \beta_0 + \beta_1 \text{Out-of-home mobility} + \beta_2 \text{Continent} + \beta_3 \text{Duration of the pandemic in each country} + \beta_4 \text{Cases per 100,000 population} + \varepsilon$$

As pre-requisites, we analyzed the R^2, multicollinearity between independent variables, autocorrelation and the distribution of residuals through Durbin-Watson and Q-Q Plot tests, respectively (supplementary file 2). A statistical significance level of 5% was adopted in all analyses.

RESULTS

COVID-19 cases ranged from 22 to 1,745,803, and deaths ranged from 0 to 102,107. Table 1 describes the epidemiological situation in each continent until May 27, 2020. The highest rates per 100,000 population were observed in Europe and the American continent. Approximately 54% of COVID-19 cases occurred in America and 51% of deaths occurred in Europe.

Figure 1 superimposes the number of daily infections and deaths in each country. Africa presented low infection and mortality rates, but it is possible to observe ascending curves, indicating a tendency to worsen the epidemiological situation. In the American continent, there were three well-defined shades. The clearest indicates a pronounced rate of infection and mortality in the United States. In early April, the United States reduced transmission and mortality, but the Brazilian epidemiological situation worsened, giving rise to the ascending curve of intermediate tonality. Other countries presented with relative low numbers, giving rise to darker tonality. Asia and Europe were the first continents affected by COVID-19. In Asia, there was an initial outbreak in South Korea, but it was quickly controlled. In mid-March, there was an upward curve indicating an increase of cases or large-scale testing, while daily mortality remained stable. Europe showed a peak of infection and mortality at the end of March with an abrupt reduction in the following weeks. On May 27, infection and mortality rates were low on this continent.

Regarding mobility in the different categories of places, world mean (± standard deviation) showed a reduction in retail and recreation (-43.45% ± 20.42%), grocery and pharmacy (-17.95% ± 20.82%), parks (-18.77% ± 37.34%), transit stations (-43.09% ± 20.31%), workplaces (-21.74% ± 19.92%), and increased the time spent at home (13.00% ± 8.80%). Table 2 shows the variation of mobility according to continent. The largest reductions were observed in America, while Europe increased mobility in parks and spent less time at home.

Figure 2 describes the pattern of mobility in different categories of places according to continents. In all out-of-home categories, European countries were predominant in the upper region of the scatter plots, which was most pronounced in the category "parks." This result shows that inhabitants of 24 European countries frequented natural parks more than before the pandemic. Another observable pattern is the reduction of mobility in the countries of the American continent, concentrating at the base of the mobility categories and at the top of the residential category.

The statistical model (Table 3) was able to explain approximately 91% (R^2=0.906) of the variance of time spent at home in the initial months of the pandemic. There was good adherence to the pre-requisites, as described in the supplementary file 2. As expected, out-of-home mobility was the most explanatory factor in the model. We found a statistically significant difference for continent, in which the mean time spent at home in Europe was lower compared to America. We also observed that for every unit increase in the infection rate per 100,000 population, there is an increase of 0.005 points in the mean time spent at home.

Table 1. COVID-19 Epidemiological reports until May 27, 2020.

Region	N	Infections (per 100,000 population)			Deaths (per 100,000 population)		
		Median	IQR	Total	Median	IQR	Total
Africa	13	10.20	19.48	78,282	0.16	0.57	2,035
America	20	54.07	212.97	2,664,415	2.18	10.67	153,49
Central	6	21.25	56.22	25,742	0.47	2.34	752
North	4	259.28	366.51	1,919,610	12.93	21.18	117,321
South	10	55.61	253.49	719,063	2.01	11.79	35,417
Asia	28	19.38	190.65	458,628	0.43	0.85	7,187
Europe	34	159.79	255.00	1,707,376	5.53	22.49	170,112
Oceania	2	29.43	N/A	8,643	0.42	N/A	124
World	97	50.58	197.80	4,917,344	1.12	5.21	332,948

Abbreviations: N, number of countries; IQR, Interquartile range; N/A, not applicable.

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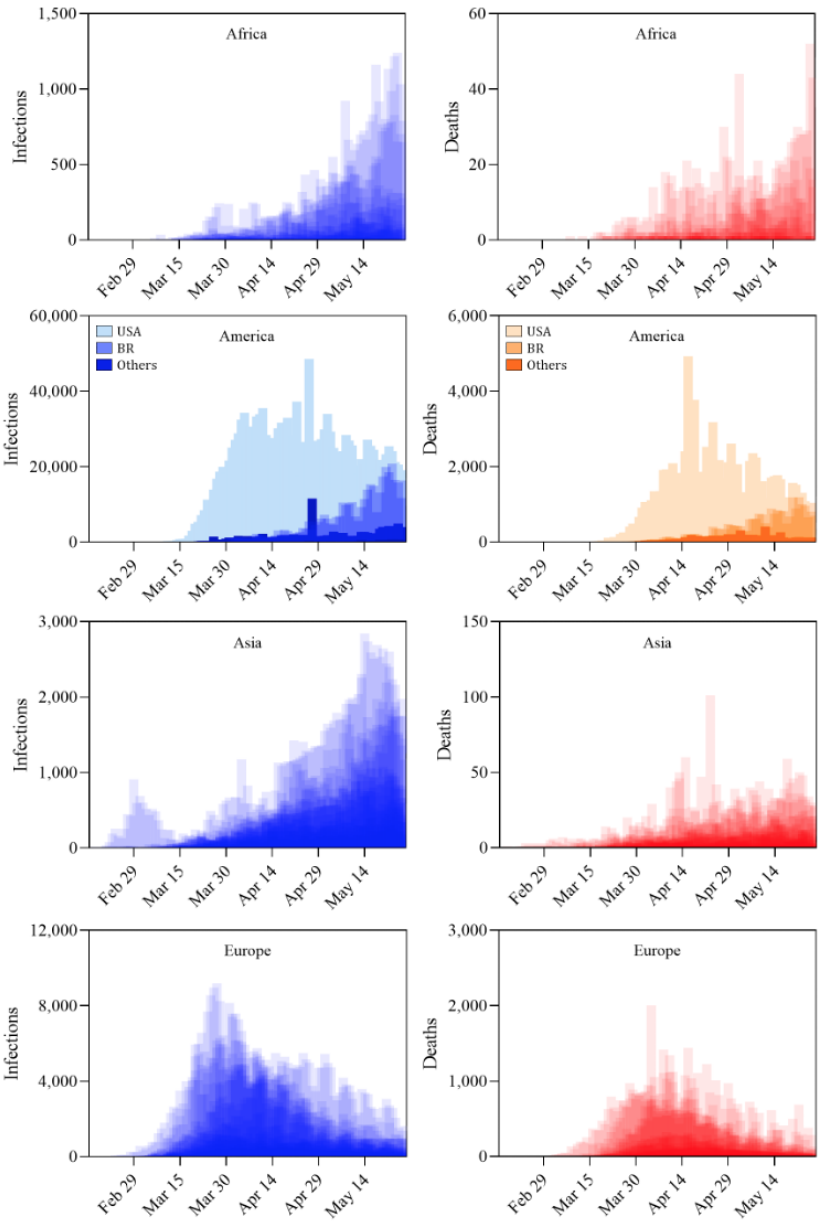

Figure 1. Infection and mortality by COVID-19 until 27 May, 2020. The superimposed bar charts contain the daily number of infections and deaths by COVID-19.

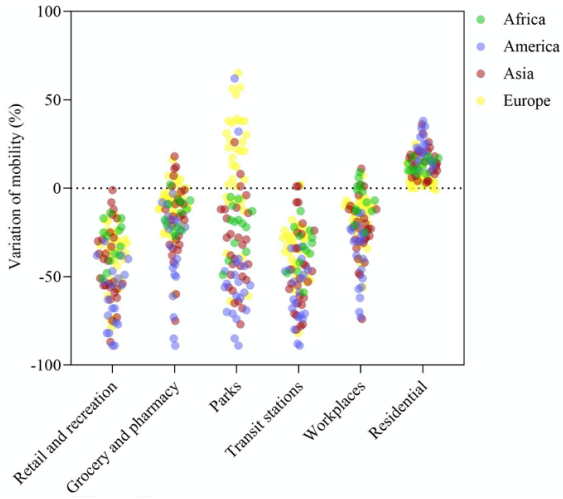

Figure 2. Scatter plots referring to variation of mobility in 97 countries according to the continent. Variation of mobility (%) was based on the comparison of the baseline (i.e., the median between January 3 and February 6, 2020) with the records up to May 16, 2020.

Table 2. Variations of mobility during COVID-19 pandemic in the continents.

Categories	Median	IQR	p	Paired comparisons
Retail and recreation				
Africa	-27.00	20.00	<.001	America < Africa (p<.001)
America	-59.00	29.25		America < Europe (p=0.002)
Asia	-46.00	28.50		
Europe	-35.00	25.25		
Oceania	-28.50	N/A		
Grocery and pharmacy				
Africa	-14.00	15.50	<.001	America < Europe (p=0.002)
America	-28.50	31.50		
Asia	-16.00	29.00		
Europe	-6.50	11.00		
Oceania	-2.50	N/A		
Parks				
Africa	-19.00	22.00	<.001	Europe > America (p<.001)
America	-55.50	25.00		Europe > Asia (p<.001)
Asia	-35.00	39.00		
Europe	19.00	43.50		
Oceania	-24.50	N/A		
Transit stations				
Africa	-33.00	19.00	<.001	América < Africa (p=0.004)
America	-61.00	26.50		América < Europe (p<.001)
Asia	-49.00	39.00		
Europe	-31.50	19.00		
Oceania	-36.00	N/A		
Workplaces				
Africa	-7.00	14.50	<.001	América < Africa (p<.001)
America	-30.00	30.50		América < Europe (p<.001) Asia
Asia	-23.00	18.50		< Africa (p=0.007)
Europe	-12.00	12.00		
Oceania	-17.00	N/A		
Residential				
Africa	12.00	6.00	<.001	Europe < America (p<.001)
America	20.50	13.00		Europe < Asia (p<.001)
Asia	14.50	12.25		
Europe	4.50	6.00		
Oceania	8.50	N/A		

Abbreviations: IQR, Interquartile range; N/A, not applicable. Variation of mobility (%) was based on the comparison of the baseline (i.e., the median between January 3 and February 6, 2020) with the records up to May 16, 2020. Data from Google's mobility report.

Table 3. Factors associated with time spent at home during the COVID-19 pandemic. Records up to May 16, 2020.

Predictor			95% Confidence Interval			
	β	SE	Lower	Upper	t	p
Intercept	13.291	3.195	6.942	19.639	4.160	< .001
Out-of-home mobility	-7.110	0.356	-7.818	-6.403	-19.970	< .001
Continents						
Asia – America	-0.486	0.964	-2.402	1.430	-0.504	0.615
Africa – America	2.073	1.114	-0.141	4.286	1.860	0.066
Europa – America	-4.933	0.976	-6.873	-2.993	-5.053	< .001
Oceania – America	-2.501	2.179	-6.829	1.828	-1.148	0.254
Duration of the pandemic (days)	0.007	0.037	-0.067	0.082	0.197	0.844
Cases per 100,000 population	0.005	0.001	0.002	0.007	3.459	< .001

Abbreviations: SE, Standard Error.

DISCUSSION

As main findings, the epidemiological course in Europe suggests that the rapid control of COVID-19 causes a population to leave confinement more quickly. Furthermore, lack of control of SARS-CoV-2 transmission chains was associated with increased time spent at home at the beginning of the pandemic, indicating that social engagement is crucial in situations where there are no proven effective pharmacological resources.

About the epidemiological moment of each continent, Europe had already gone through the most severe phase, while other regions were at the beginning of the epidemic. It was natural that Europe would show worse epidemiological indicators since it was affected by COVID-19 weeks before America and Africa. Epidemiological curves showed that Europe was quite effective in its public strategies. After control of COVID-19, people were able to gradually return to the community, unlike other continents (except Asia) that showed a clear tendency of worsening infection and mortality rates after may 2020.

Apparently, natural parks are the first place to be massively frequented after the acute phase of the local epidemic. If there is physical distance between people and the correct use of personal protective equipment, parks seem to be relatively safe, because there are lower risks of outdoor transmission as compared to indoor environments.[14] Although widely studied, infectivity by airborne particles still remains uncertain. Faridi et al.[15] did not find the presence of SARS-CoV-2 in air samples collected from rooms of critically ill patients in an Intensive Care Unit.[15] In contrast, different studies find viral RNA in air samples, indicating that aerosol infection is a plausible mechanism of transmission.[16,17] Despite this, it seems well established that the main route of transmission is via respiratory droplets (i.e. particles between 5 and 10 µm in diameter) and between the contact routes,[18] and that masks have a protective effect against the coronavirus, considerably reducing the risk of infection.[19]

Our results are important for understanding the dynamics of the pandemic in the absence of pharmacological resources and may support public health strategies in future pandemics. We show that lack of epidemiological control can be associated with longer confinement, indicating that reactivation of economic activities requires control of SARS-CoV-2. Our evidence suggests that countries that quickly reduced the SARS-CoV-2 transmission chains came out of lockdown faster,[20] corroborating reports of the 1918 influenza pandemic.[6] We emphasize that some Latin American countries have unfavorable sociodemographic conditions that make it difficult to adopt more rigid policies of social distancing. Therefore, we believe that communication and public assistance policies are critical for widespread popular acceptance. In Brazil, the denial of scientific evidence and the inaccuracy of the health surveillance systems may have favored the spread of the virus.[21]

In a broader perspective, we emphasize that failure to control a highly transmissible virus puts the world's public health at risk, as efforts must not only be regional, but coordinated globally. One example is the collapse of the health care system in Manaus,[22] the capital of the Brazilian State of Amazonas. In 2020, approximately 70% of the population had been exposed to SARS-CoV-2.[23] Between May and December 2020, COVID-19 infection and mortality rates remained low in Manaus,[22] suggesting collective immunity. However, a new unexpected outbreak began in January 2021 causing the health care system to collapse.[22] Genome samples identified that 42% of infections were caused by the P.1 lineage,[24] which can be resistant to immunity acquired by previous infection.[22] The lack of epidemiological control, besides being an ethical problem, increases the chances of co-infection of two variants of coronavirus,[25] which can generate even more dangerous lineages, putting the world's population at risk.

As limitations, results should be interpreted with parsimony due to short period of analysis, and also some confounding factors not considered, such as underreporting and seasons. Underreporting can be estimated by the crude mortality rate, which was predicted at 1% when the data was collected. This percentage can change according to age group, with higher values being associated with insufficient testing of the population. Crude mortality rate is available in the supplementary file 3 and reveals that underreporting occurred in most countries. Regarding seasons, rainy and cold periods are associated with longer stays at home, which was not considered in the statistical model. In addition, Asia and Africa had lower infection and mortality rates in the analyzed period, which may have underestimated our results.

Finally, examples from European countries suggest that rapid control of a highly transmissible virus is associated with low length of stay in the home. Current experience has shown that effectiveness of social distancing depends on multiple factors and its adherence appears to decrease over time. As a main lesson, COVID-19 showed that in the absence of pharmacological resources, government authorities need to act quickly to contain the spread of infectious diseases.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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AUTHOR CONTRIBUTIONS

Vinícius Nagy Soares conceptualized the study and performed the statistical analysis. **Hélio Mamoru Yoshida** contributed to conceptualizing the study. **Daniel Eduardo da Cunha Leme** contributed to interpretation of the results. **Ricardo Aurélio Carvalho Sampaio** contributed to interpretation of the results. **Gabriel de Oliveira Rufino** contributed to data collection. **Paula Teixeira Fernandes** guided the authors of the study. All authors contributed to drafting and critical review the manuscript.

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Hospital Santa Cruz

ORIGINAL ARTICLE

Inappropriate empirical antimicrobial treatment in bloodstream infections patients in the era of multidrug resistance

Terapia Empírica Inapropriada no Tratamento de Infecções de Corrente Sanguínea na Era da Multirresistência Antimicrobiana

Tratamiento antimicrobiano empírico inadecuado en pacientes con infecciones del torrente sanguíneo

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ABSTRACT

Background and objectives: Bloodstream infection (BSI) by multidrug-resistant *Pseudomonas aeruginosa* is a severe infection. This study aimed to evaluate and identify the predictors of mortality in patients who had bloodstream infection by carbapenem-resistant *P. aeruginosa*. **Methods:** This is a retrospective cohort study, approved by Committee of Ethics in Research with Human Participants, which included 87 consecutive patients hospitalized in a referral hospital in Brazil. Clinical and demographic information about each patient were obtained from hospital records. The Student's T-test was used to compare continuous variables and x^2 or Fisher's exact tests to compare categorical variables. To determine independent risk factors for 30-day mortality, a multiple logistic regression model was used. A survival curve was constructed using the Kaplan–Meier method. **Results:** Among the patients, 87.3% use antibiotics previously, 60.9% received inadequate empirical treatment, and the 30-day mortality rate was 57.5%. Inappropriate antibiotic empirical therapy was independently associated with a 30-days death and mortality rate. **Conclusion:** These findings can show some insights about the relationship between higher mortality and inappropriate empirical therapy for patients with BSI by *P. aeruginosa*. There is a need for better diagnostic tests and infection control programs should focus on de-escalation the antibiotic inappropriate therapy, mainly in BSI caused by carbapenem-resistant *P. aeruginosa*.

Keywords*: Pseudomonas aeruginosa, Carbapenem, bloodstream infection, mortality.*

RESUMO

Justificativa e objetivos: Infecção da corrente sanguínea (ICS) por *Pseudomonas aeruginosa* multirresistente é grave. Este estudo teve como objetivo avaliar e identificar os preditores de mortalidade em pacientes admitidos em uma Unidade de Terapia Intensiva que apresentaram infecção da corrente sanguínea por *P. aeruginosa* resistente aos carbapenêmicos. **Métodos:** Trata-se de um estudo de coorte retrospectivo, aprovado pelo Comitê de Ética em

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Pesquisa com Seres Humanos, que incluiu 87 pacientes consecutivos internados em um hospital de referência no Brasil. As informações clínicas e demográficas de cada paciente foram obtidas através de análise dos prontuários dos pacientes. O teste T de Student foi usado para comparar variáveis contínuas e o teste x2 ou exato de Fisher para comparar variáveis categóricas. Para determinar fatores de risco independentes para mortalidade em 30 dias, foi utilizado um modelo de regressão logística múltipla. Uma curva de sobrevida foi construída pelo método de Kaplan-Meier. **Resultados:** Do total de pacientes, 87,3% faziam uso prévio de antibióticos, 60,9% receberam tratamento empírico inadequado e a mortalidade em 30 dias foi de 57,5%. A terapia empírica inadequada foi fator de risco independente para mortalidade. **Conclusão:** Esses achados revelam alguns *insights* sobre a relação entre maior mortalidade e terapia empírica inadequada para pacientes com ICS por *P. aeruginosa*. Além disso, destacam a necessidade de melhores testes diagnósticos e os programas de controle de infecção devem se concentrar na redução da terapia inadequada com antibióticos, principalmente na ICS causada por *P. aeruginosa* resistente a carbapenêmicos.

Palavras-chave: *Pseudomonas aeruginosa. Carbapenêmicos. Infecção da corrente sanguínea. Mortalidade.*

RESUMEN

Justificación y objetivos: La infección del torrente sanguíneo por *Pseudomonas aeruginosa* multirresistente es grave. Este estudio tuvo como objetivo evaluar e identificar predictores de mortalidad en pacientes ingresados en una Unidad de Cuidados Intensivos que presentaban infección del torrente sanguíneo por *P. aeruginosa* resistente a carbapenémicos. **Métodos:** Se trata de un estudio de cohorte retrospectivo, aprobado por el Comité de Ética en Investigación con Participantes Humanos, que incluyó 87 pacientes consecutivos ingresados en un hospital de referencia en Brasil. La información clínica y demográfica de cada paciente se obtuvo mediante el análisis de las historias clínicas de los pacientes. Se utilizó la prueba t de Student para comparar variables continuas y x2 o prueba exacta de Fisher para comparar variables categóricas. Para determinar los factores de riesgo independientes para la mortalidad a los 30 días, se utilizó un modelo de regresión logística múltiple. Se construyó una curva de supervivencia utilizando el método de Kaplan-Meier. **Resultados:** Del total de pacientes, el 87,3% utilizaba antibióticos previamente, el 60,9% recibió tratamiento empírico inadecuado y la tasa de mortalidad a los 30 días fue del 57,5%. La terapia empírica inadecuada fue un factor de riesgo independiente de mortalidad. **Conclusión:** Estos hallazgos revelan algunos conocimientos sobre la relación entre el aumento de la mortalidad y la terapia empírica inadecuada para los pacientes con infección del torrente sanguíneo por *P. aeruginosa*. Además, destacan la necesidad de mejores pruebas de diagnóstico y los programas de control de infecciones deben centrarse en reducir la terapia con antibióticos inapropiados, particularmente en infección del torrente sanguíneo causados por *P. aeruginosa* resistente a carbapenémicos.

Palabras clave: *Pseudomonas aeruginosa, carbapenémicos, infección del torrente sanguíneo, mortalidad.*

INTRODUCTION

Pseudomonas aeruginosa is a ubiquitous opportunistic Gram-negative bacillus and is one of the main pathogens responsible for the occurrence of infections related to health care, contributing to the increase in morbidity and mortality rates, hospitalization time and patient costs.[1,2]

It mainly affects individuals with comorbidities, such as diabetes, cystic fibrosis and neoplasms; hospitalized and in prolonged use of invasive devices and antimicrobial therapy.[3,4] Among the most common infections are ventilator-associated pneumonia and bloodstream infection (BSI).[3,5,6]

Severe infections due to *P. aeruginosa*, such as BSI, results in higher morbidity and mortality, longer hospitalization, and high costs, especially among hospitalized patients in less developed countries, like Brazil. The problem is greater in large hospitals with many beds complex care levels.[5,6]

BSI in the resource-limited countries is largely caused by Gram-negative bacilli multidrug-resistant (MDR) strains that have been increasing in the last few decades[3,5,6,7] and, for this reason, empirical antibiotic treatment of patients with this infection has become a major challenge for physicians, considering that inappropriate empirical antibiotic treatment might be more frequent than desirable.[3,6,7,8,9]

Treatment of BSI in countries like Brazil is largely empirical and a challenge for patients with infections for multidrug-resistant (MDR) *P. aeruginosa*.[3] These patients had limited treatment options and are highly vulnerable to receiving inappropriate empiric therapy, which contributes to increased length of hospitalization and worst clinical outcomes.[5,6,8]

In the current study, we aimed to describe the rates of inappropriate antimicrobial therapy in a cohort of patients with bloodstream infection by carbapenem-resistant *P. aeruginosa* in the era of widespread antimicrobial resistance. Second, this study explored characteristics associated with the clinical outcomes of these patients in a large Brazilian tertiary-care hospital.

METHODS

Study design, Patients, and setting

A cohort study was employed to identify the predictors of mortality in the last ten years, and the impact of

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inappropriate therapy on the outcomes of patients with BSI by carbapenem-resistant *P. aeruginosa*. Clinical and demographic information about each patient was obtained from hospital records, such as age, gender, days in the hospital, admission to the Intensive Care Unit (ICU), surgery, invasive procedures, such as mechanical ventilation, central venous line, urinary catheter, tracheostomy, hemodialysis, catheter enteral or gastric nutrition, and use of surgical drain, underlying conditions such as diabetes mellitus, chronic renal failure, heart failure, and cancer.

Furthermore, the previous use of one or more of the following antibiotics was verified: piperacillin/tazobactam, gentamicin, amikacin, cefepime, ciprofloxacin, colistin, and carbapenems. These antibiotics exhibit antipseudomonal activity and are part of the local antibiotic policy.

This study was carried out at the Clinical Hospital of the Federal University of Uberlândia, Brazil, a tertiary-care hospital. The clinical microbiology laboratory database was reviewed, and 87 patients who had BSI by carbapenem-resistant *P. aeruginosa* were selected for the study. Only the first episode of infection was analyzed. Microbial identification and antimicrobial susceptibility test were performed on a Vitek 2 system (bioMérieux Vitek Systems, Hazelwood, MO, USA) for the following antimicrobials: piperacillin/tazobactam, gentamicin, amikacin, cefepime, ciprofloxacin, colistin, imipenem, and meropenem.

Antimicrobial therapy was considered inappropriate when the patient received antimicrobials that did not present "in vitro" activity and/or when treatment was started over 48 hours after the infection diagnosis.[10] Multidrug resistance (MDR) was defined as acquired non-susceptibility to at least one agent belonging to three or more antimicrobial categories.[11]

Statistical analysis

The Student's T-test was used to compare continuous variables and x^2 or Fisher's exact tests to compare categorical variables. To determine independent risk factors for 30-day mortality, a multiple logistic regression model was used to control the effects of confounding variables. A survival curve was constructed using the Kaplan–Meier method. *P* values of ≤0.05 were considered statistically significant.

Ethical approval

The research was approved by the Federal University of Uberlandia Committee of Ethics in Research with Human Participants (Approval No. 2.527.621, CAAE: 77541517.9.0000.5152).

RESULTS

Among patients with BSI by carbapenem-resistant *P. aeruginosa* was observed a high ICU admission rate (63.2%). The previous use of antibiotics and central venous catheter use was common, with 87.3% and 88.5%, respectively. Of 87 eligible patients, 53 (61%) received inappropriate empirical antibiotic therapy of BSI onset, and 67.9% of these patients the infection was caused by *P. aeruginosa* MDR. The 30-day mortality rate was 57.5% for all patients. However, the 30-day mortality rates were 55% in patients with BSI by *P. aeruginosa* MDR (33/60). Table 1 summarizes the multivariate analysis of predictors for mortality in BSI by carbapenem-resistant *P. aeruginosa*.

The mean age among patients who died was 60.2 years (range 9 months to 89 years) and the majority of these patients had more comorbidities than the patients who survived (76% versus 37.8%). Also, a major frequency of invasive devices used was observed among patients with death outcomes within 30 days: CVC (92%), vesical catheter (78%), and mechanical ventilation (76%). The major of patients who died used previous antibiotic therapy (92%) and were submitted to inappropriate empirical antibiotic therapy (84%). Furthermore, inappropriate antibiotic empirical therapy was independently associated with death (*P*=0.0001).

The mean length of hospitalization was 87 days for survivors and 41.6 days for non-survivors. The Kaplan–Meier cumulative survival estimates (Figure 1) for patients with inappropriate versus appropriate therapy showed that the first group had a lower probability of survival (*P*=0.0001). The 30-day mortality rate of the first group was 79.2%, while the second group was 23.5%.

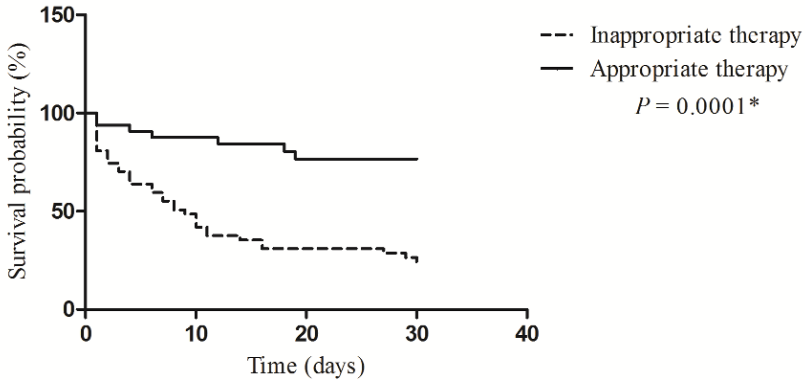

Figure 1. Survival curve (30 days) using the Kaplan–Meier method for patients who received antimicrobial appropriate therapy compared with those who received inappropriate therapy.

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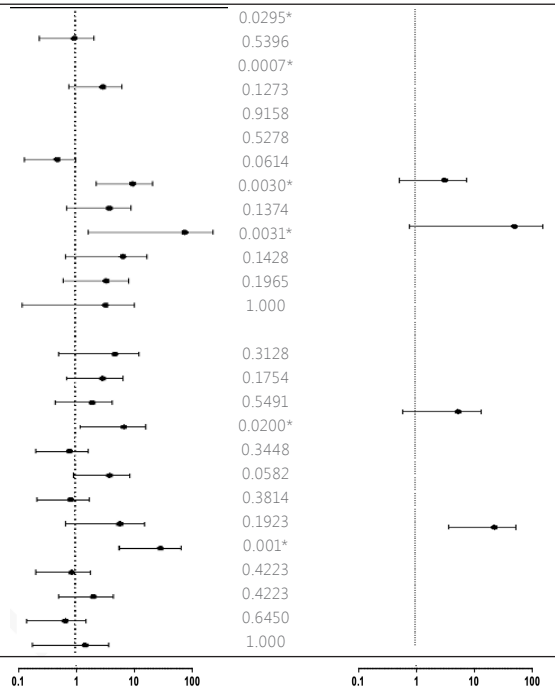
Table 1. Univariate and multivariate analysis of factors associated with the mortality of 87 patients with bloodstream infection caused by Carbapenem Resistant *P. aeruginosa*

		Outcome		Statistical analysis			
				Univariate		Multivariate	
Caracteristics	**Total N=87(%)**	**Death 30days N=50(%)**	**Discharge N=37(%)**	**OR[1] (IC[2] 95%)**	**P[3]**	**OR[1] (IC[2] 95%)**	**P[3]**
Mean age in years (DS)	57.12±20.5	60.2± 20.7	52.9±19.6		0.0295*		--
Male Sex	58 (66.7)	32 (64)	26 (70.3)		0.5396		--
Lenght of hospital stay-mean (days)	63.6±57.6	41.6±31.1	87±68.1		0.0007*		--
Intensive Care Unit	55 (63.2)	35 (70)	20 (54)		0.1273		--
Lenght of ICU stay-mean (days)	18.66±23.63	23.1±17.9	40.8±28.5		0.9158		--
Days at risk (time from admission to BSI)	38.71±37.36	34.4±28.9	44.7±46		0.5278		--
Hospitalization during summer months	37 (42.5)	17 (34)	20 (54)		0.0614		--
Comorbidity/ Underlying disease	52 (59.8)	38 (76)	14 (37.8)		0.0030*		0.3117
Heart Failure	21 (24.1)	15 (30)	6 (16.2)		0.1374		--
Cancer	14 (16.1)	13 (26)	1 (2.7)		0.0031*		0.7225
Diabetes Mellitus	13 (15)	10 (20)	3 (8.1)		0.1428		--
Chronic Renal Failure	20 (23)	14 (28)	6 (16.2)		0.1965		--
Lung disease	5 (5.7)	3 (6)	2 (5.4)		1.000		--
Invasive devices							
Central venous catheter	77 (88.5)	46 (92)	31 (83.8)		0.3128		--
Vesical cateter	63 (72.4)	39 (78)	24 (64.9)		0.1754		--
Mechanical ventilation	64 (73.6)	38 (76)	26 (70.3)		0.5491		--
Probes enteral or gastric nutrition	69 (79.3)	44 (88)	25 (67.6)		0.0200*		0.1819
Traqueostomy	49 (56.3)	26 (52)	23 (62.2)		0.3448		--
Hemodialysis	31 (35.6)	22 (44)	9 (24.3)		0.0582		-
Surgery	47 (54)	25 (50)	22 (59.4)		0.3814		--
Prior use of antibiotic	76 (87.3)	46 (92)	30 (81.1)		0.1923		--
Inappropriate antibiotic empirical therapy	53 (61)	42 (84)	11 (29.7)		0.001*		0.0001*
Primary bacteremia	57 (65.5)	31 (62)	26 (70.3)		0.4223		--
Secundary bacteremia	30 (34.5)	19 (37)	11 (29.7)		0.4223		--
MDR[4]	60 (69)	33 (66)	27 (73)		0.6450		--
Polymicrobial bloodstream infection	11 (12.6)	6(12)	5(13.5)		1.000		--



*Note: [1]Odds ratio; [2]Confidence interval; [3]P value; [4]Multidrug Resistance; *P statistically significant (≤ 0,05).*

DISCUSSION

The rapid emergence and spread of carbapenem-resistant *P. aeruginosa* are a worldwide public health problem, especially in less developed countries like Brazil, where there is a lack of efficient prevention and control actions.[5,12]

In Brazil, the mortality rate associated with infection by multidrug-resistant *P. aeruginosa* is close to 50%, with most patients evolving to death within 30 days after infection.[13] In countries of the world In the Middle East, mortality reaches 60%,[14] while in Asia this rate is 20%.[15]

The development of BSI contributes to the severity of the clinical condition during the hospitalization of the patients who have surgery, are immunocompromised, and use invasive devices. Currently, infection by carbapenem-resistant *P. aeruginosa* increases the risk of inappropriate empirical antibiotic therapy, frequent in hospitals worldwide, but more frequent in lower and middle-income countries.[5,6,16]

This study indicates that older patients, who remained hospitalized for a long period, with some comorbidity and that were in use of inappropriate empirical antibiotic therapy, were associated with worse outcomes. Moreover, our study confirms that a high number of patients with BSI by MDR *P. aeruginosa* receive inappropriate empirical treatment. According to the literature, the rates of escalation of antibiotic resistance

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and inadequate therapy considerably increase morbidity and mortality, days of hospitalization, and costs related to the treatment of the infection.[3,7,17]

We also identify some factors related to mortality (mean age in years, mean days of hospitalization, cancer, and use of probes for enteral or gastric nutrition) by univariate analysis that concords with previous research conducted mainly in patients with IRAS and BSI by *P. aeruginosa*.[16,17] Also, we identify that inadequate empirical therapy was associated with a 14-fold increase in mortality. This factor is important because it can be modified.[18]

According to the literature, BSI by resistant *P. aeruginosa* is complex and the impact of inappropriate empirical antibiotic therapy in the mortality of these patients has been a matter of great discussion by researchers and health professionals.[7,16,17] That's why protocols must be developed for each hospital, based on data from active epidemiological surveillance, which allows knowing the predominant species in each hospital unit, as well as the most frequently observed resistance mechanisms.

This study observed that *P. aeruginosa* causing BSI in this hospital were highly resistant to most antibiotics commonly used in our setting. This trend of resistance could be accounted for by the increasingly empirical, indiscriminate, and intense use of antibiotics. Countless papers showed empiric treatments often fail and increase mortality in these patients.[17,18]

In our study, a remarkable number of patients with BSI by carbapenem-resistance *P. aeruginosa* received inappropriate antibiotic therapy, and this percentage increased when considering MDR *P. aeruginosa* strains. In light of these results, novel ways of identifying patients with a high risk of MDR *P. aeruginosa* isolation is mandatory, as well as microbiological diagnosis might help to diminish inappropriate empirical antimicrobial therapy.

Our study had limitations. It was a single-centered, retrospective with small sample size. However, this study generated valuable data regarding infection control aspects, and how it impacts the outcomes of hospitalized patients who had BSI by carbapenem-resistant *P. aeruginosa* and were treated with inappropriate antibiotic therapy. Results should be validated in other centers and on larger populations.

This study concludes that the rate of inappropriate therapy among ICU patients who developed *P. aeruginosa* infection was high (61%), being higher among those who died (84%). In addition, the independent risk factors for 30-day mortality were: inappropriate antimicrobial therapy, use of gastric tube and presence of comorbidities, especially cancer.

Ultimately, these findings add some insights about the relationship between higher mortality and inappropriate empirical therapy for patients with BSI by *P. aeruginosa*. There is a need for better diagnostic tests and infection control programs should focus on de-escalation the antibiotic inappropriate therapy, mainly in BSI caused by carbapenem-resistant *P. aeruginosa*.

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CONFLICT OF INTEREST

None.

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AUTHORS' CONTRIBUTIONS

Jane Eire Urzedo*, Paulo P. Gontijo and Rosineide Marques Ribas contributed to the conception, design of the article, analysis and writing of the article;

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Melina Lorraine Ferreira contributed to the analysis, review and final approval of the article;

Cristiane Silveira de Brito and Raquel Cristina Cavalcanti Dantas contributed to the review and final approval of the article.

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Revista de Epidemiologia e Controle de Infecção

Hospital Santa Cruz

ORIGINAL ARTICLE

Impact of the COVID-19 pandemic on laboratory diagnosis of tuberculosis in southern Brazil

Impacto da pandemia de COVID-19 no diagnóstico laboratorial de tuberculose no sul do Brasil

Impacto de la pandemia COVID-19 en el diagnóstico de laboratorio de la tuberculosis en el sur de Brasil

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ABSTRACT

Background and objectives: to understand the impact of the COVID-19 pandemic on tuberculosis (TB) diagnosis in different settings is essential to guide the establishment of appropriate TB control strategies. This study aimed to assess the influence of COVID-19 pandemic in laboratory diagnosis of TB in patients tested and diagnosed for TB. **Methods:** a data survey was carried out in the database of laboratories that perform TB diagnosis for the public health system in Rio Grande city (Rio Grande do Sul, Brazil). **Results:** there was a decrease of 1,368 to 735 (reduction of 46.3%) in the number of patients tested for TB in public diagnostic services in 2019 and 2020, respectively, and a decrease of 197 to 119 (reduction of 39.6%) in the number of new TB cases diagnosed. In contrast, the positivity rate was 14.4% in 2019 and 16.2% in 2020. Moreover, it was observed that the laboratory that performs the diagnostic service for Primary Health Care was the most affected, when compared to Tertiary Health Care. **Conclusion:** as a consequence of measures to control the spread of SARS-CoV-2, there was a reduction in TB testing and in the detection of new cases, especially in Primary Health Care, where patients with less need for hospitalization are received.

Keywords: *COVID-19; Diagnosis; Health Services; Tuberculosis; SARS-CoV-2.*

RESUMO

Justificativa e objetivos: compreender o impacto da pandemia COVID-19 no diagnóstico da tuberculose (TB) em diferentes locais é essencial para orientar o estabelecimento de estratégias adequadas de controle da TB. O objetivo deste estudo foi avaliar a influência da pandemia de COVID-19 no diagnóstico laboratorial de TB, em pacientes testados e diagnosticados com TB. **Métodos:** foi realizado um levantamento de dados no banco de dados de laboratórios que realizam diagnóstico de TB para o sistema público de saúde na cidade de Rio Grande (Rio Grande do Sul, Brasil). **Resultados:** houve redução de 1.368 para 735 (redução de 46,3%) no número de pacientes testados para TB nos serviços públicos de diagnóstico em 2019 e 2020, respectivamente, e redução de 197 para 119 (redução

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de 39,6%) no número de novos casos de TB diagnosticados. Em contrapartida, a taxa de positividade foi de 14,4% em 2019 e 16,2% em 2020. Além disso, observou-se que o laboratório que realiza o serviço de diagnóstico para a Atenção Primária à Saúde foi o mais afetado, quando comparado com a Atenção Terciária à Saúde. **Conclusão:** como consequência das medidas de controle da disseminação do SARS-CoV-2, houve redução na testagem de TB e na detecção de novos casos, principalmente na atenção primária à saúde, onde são recebidos pacientes com menor necessidade de internação.

Descritores*: COVID-19; Diagnóstico; Serviços de saúde; Tuberculose; SARS-CoV-2.*

RESUMEN

Justificación y objetivos: comprender el impacto de la pandemia Covid-19 en el diagnóstico de tuberculosis (TB) en diferentes lugares es fundamental para orientar el establecimiento de estrategias adecuadas de control de la TB. El objetivo de este estudio fue evaluar la influencia de la pandemia de COVID-19 en el diagnóstico de laboratorio de TB, en términos de pacientes examinados y diagnosticados de TB. **Métodos**: los datos fueron recolectados de la base de datos de los laboratorios que realizan el diagnóstico de TB para el sistema público de salud en la ciudad de Rio Grande (Rio Grande do Sul, Brasil). **Resultados:** hubo una reducción de 1.368 a 735 (reducción del 46,3%) en el número de pacientes sometidos a pruebas de TB en los servicios públicos de diagnóstico en 2019 y 2020, respectivamente, y una reducción de 197 a 119 (reducción del 39,6%) en el número de nuevos casos de TB diagnosticados. Por otro lado, la tasa de positividad fue de 14,4% en 2019 y 16,2% en 2020. Además, se observó que el laboratorio que realiza el servicio de diagnóstico para la Atención Primaria de Salud fue el más afectado, en comparación con la Atención Terciaria de Salud. **Conclusiones**: como consecuencia de las medidas para el control de la propagación del SARS-CoV-2, hubo una reducción en las pruebas de TB y en la detección de nuevos casos, especialmente en la Atención Primaria de Salud, donde se encuentran los pacientes con menor necesidad de hospitalización.

Palabras clave*: COVID-19; Diagnóstico; Servicios de salud; Tuberculosis; SARS-CoV-2.*

INTRODUCTION

In January 2020, SARS-CoV-2 virus, the etiologic agent of COVID-19, was first described after being isolated from pneumonia patients in Wuhan, China.[1] Almost two years after, COVID-19 cases reported worldwide exceed 259 million, and more than 5.1 million deaths by the disease have been confirmed.[2] On the other hand, tuberculosis (TB), caused by the bacillus *Mycobacterium tuberculosis*, is an ancient infectious disease that remains as a public health concern worldwide. For several years, TB has been considered the leading cause of death from a single infectious agent, and it is estimated that in 2019 it affected about 10 million individuals and led to 1.4 million deaths.[3]

It is recognized that COVID-19 pandemic has been causing health, social and economic impacts since the beginning of 2020. Thus, authorities are engaged in controlling the spread of SARS-CoV-2, and for this, several measures were implemented at the beginning of the pandemic, such as physical distancing, limitation of movement of people, and reallocation of human and financial resources from other diseases to the COVID-19 response. In this context, some of these strategies adopted affected, in general, the routine of health services. In addition to supply and infrastructure reallocation for the COVID-19 response, there were changes in access and admission of patients to health services to support the demand of COVID-19.[3,4]

In Europe, diagnostic laboratories already reported a significant decrease in the number of samples received for TB diagnosis, when compared to the pre-pandemic years.[5] This reflect in the reduction of the number of patients tested for TB, and as result, there is an impact in the number of TB cases diagnosed and reported, as described in early 2020 in countries such as Nigeria,[6] Uganda,[7] South Korea,[8] China,[9] Sierra Leone,[10] and Brazil.[11] In a study carried out by Stop TB Partnership, an international agency that works in the fight against TB, it is estimated that the accumulation of undiagnosed and, consequently, not adequately treated TB cases during the COVID-19 pandemic generates a setback of years in the fight against TB, resulting, in the future, in an increase in disease incidence and mortality.[12]

Considering that undiagnosed TB cases contribute to the transmission chain of *M. tuberculosis*, and that monitoring TB cases is important for disease control programs,[3,12] it is emphasized the importance of understanding the impact of the COVID-19 pandemic on TB diagnosis in different settings, in order to guide the establishment of appropriate TB control strategies. In this regard, this study aimed to assess the influence of the COVID-19 pandemic in laboratory diagnosis of TB in a setting with high burden of TB and COVID-19 in patients tested and diagnosed for TB.

METHODS

Study design

A cross-sectional study was performed at TB diagnosis services in the public health care system of the city of Rio Grande, state of Rio Grande do Sul, Brazil. To understand the impact of COVID-19 on laboratory diagnosis of TB, the number of patients tested for TB, number of new TB cases diagnosed and positivity rate in 2019 and 2020 were compared.

Study setting

Rio Grande is a port city located in the extreme south of Brazil, with an estimated TB incidence of 77.6 new cases per 100,000 inhabitants in 2018. Rio Grande is one of the priority cities for TB control in Rio Grande do Sul, a state with TB incidence rate above the average of Brazil. In 2018, TB incidence for Rio Grande do Sul and for Brazil were 45.4 and 37.2 new cases per 100,000 inhabitants, respectively, and in 2020, incidences were lower (38.9 and 31.6 new cases per 100,000 inhabitants, respectively).[13,14] In relation to Brazil, the country ranks among the 30 countries with a high burden for TB and for TB-HIV co-infection, remaining a priority for disease control by the World Health Organization.[3]

COVID-19 cases were first reported in Rio Grande in March 2020, one month after the first confirmed case in Brazil. Throughout 2020, 7805 COVID-19 cases and 170 COVID-19 deaths were reported (Figure 1).[15] To contain the spread of the SARS-CoV-2 virus, social distancing measures were implemented in the municipality, including restriction of access to public places and non-essential commercial services, at the end of March 2020, after confirmation of the first SARS-CoV-2 cases in Rio Grande, and in early July, with the increase in the number of deaths from COVID-19. Moreover, as a way of limiting the movement of people and avoiding agglomerations, there was also a reduction in the number of public transport available and the suspension of routine medical care in health units.

Regarding laboratory diagnosis of TB, the study was conducted in laboratories that perform TB diagnosis for Primary and Tertiary Health Care of the public health care system of Rio Grande: the Municipal Laboratory of Clinical Analysis and the Mycobacteria Laboratory from the *Hospital Universitário Dr. Miguel Riet Corrêa Jr.*, respectively. These laboratories are responsible for diagnosing approximately 80% of TB cases reported in the city.[16] During the COVID-19 pandemic, there were no changes in the workflow of these laboratories and the availability of laboratory supplies and equipment, as they were not relocated for the COVID-19 response. However, the technicians who performed TB diagnoses reported a reduction in the demand for the services provided.

Data collection

The database of the laboratories included in the study were accessed, after authorization by the technicians in charge of TB diagnosis. Data referring to the number of patients tested for TB and new TB cases diagnosed were collected. These are secondary data recorded in the database of these laboratories during the TB diagnosis routine. In this study, patients with at least one sample sent for TB diagnosis, with positive results by microbiological methods (microscopy, culture and/or GeneXpert® MTB/RIF – Cepheid, USA), were considered new TB cases.

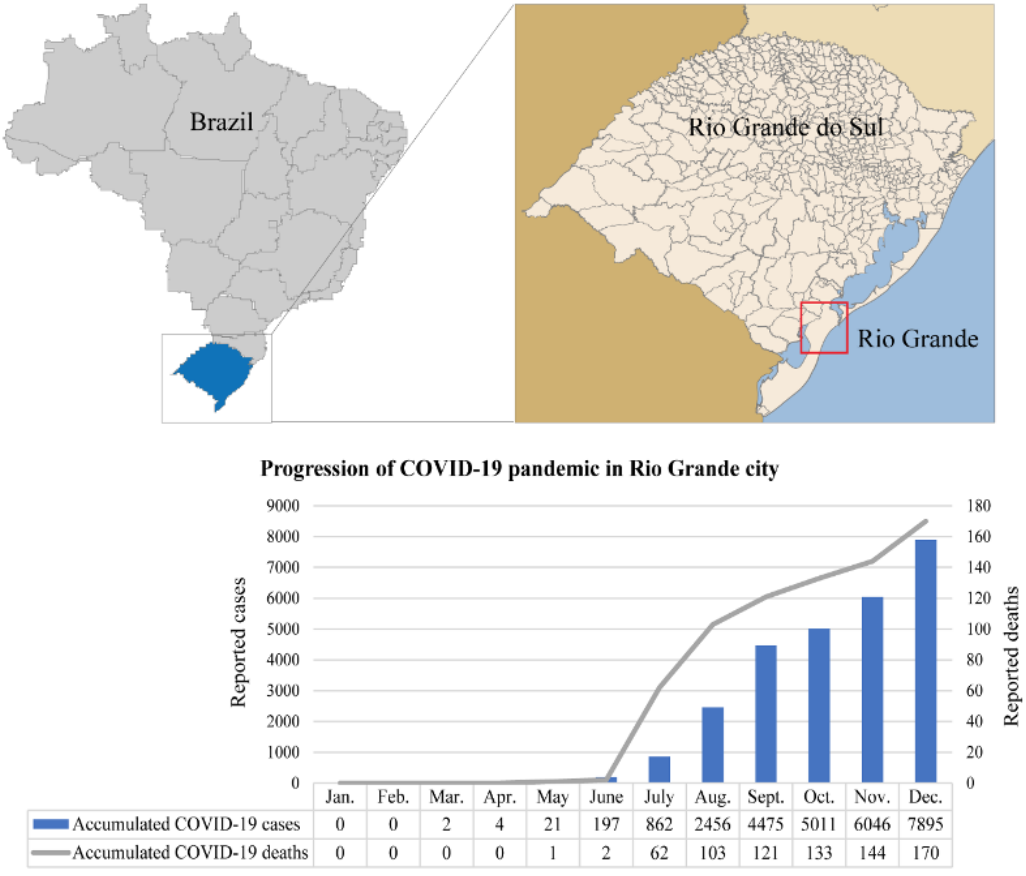

Figure 1. Rio Grande location, and number of COVID-19 cases and deaths in the city.[15]

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Statistical analysis

The collected data were tabulated in an Excel® spreadsheet (Microsoft, USA), and comparative analyzes between the 2019 and 2020 data were performed in the same software. The percent variation in the number of patients tested and positive for TB was estimated using the 2019 data as reference. The percent variation was calculated as follows: number of patients tested/positive in 2020 subtracted by the number of patients tested/positive in the reference year (i.e., 2019), divided by the number of patients tested/positive in the reference year. The resulting value was multiplied by 100. Furthermore, the positivity rate (percentage of TB positive patients among tested patients) of 2019 and 2020 was determined and compared.

Ethical aspects

The study was approved by the Municipal Nucleus of Education in Collective Health (NUMESC), from Rio Grande Municipal Health Department (acceptance number 004/2021). This study is a part of a larger research that was approved by the Research Ethics Committee of the *Universidade Federal do Rio Grande* (acceptance number 5.535.421).

RESULTS

The number of patients tested for TB, number of new TB cases diagnosed, diagnostic positivity rate in 2019 and 2020 and percent variation of patients tested and positives for TB in the municipal laboratory, hospital laboratory and both laboratories are represented in Tables 1, 2 and 3, respectively. The number of tested and positive patients for TB in association with COVID-19 cases and deaths progression in the municipality are represented in Figure 2.

Table 1. Number of patients tested for TB, number of new TB cases diagnosed, diagnostic positivity rate in 2019 and 2020 and percent variation of patients tested and positives for TB in the municipal laboratory.

Month	2019			2020			Variation of patients tested	Variation of new cases
	Patients tested	New cases	Positivity rate	Patients tested	New cases	Positivity rate		
Jan.	75	15	20.0%	62	5	8.1%	-17.3%	-66.7%
Feb.	64	9	14.1%	26	6	23.1%	-59.4%	-33.3%
Mar.	46	7	15.2%	71	5	7.0%	54.4%	-28.6%
Apr.	72	5	6.9%	45	4	8.9%	-37.5%	-20.0%
May	135	10	7.4%	36	3	8.3%	-73.3%	-70.0%
June	199	16	8.0%	26	6	23.1%	-86.9%	-62.5%
July	52	5	9.6%	49	3	6.1%	-5.8%	-40.0%
Aug.	59	11	18.6%	31	7	22.6%	-47.5%	-36.4%
Sept.	70	8	11.4%	45	7	15.6%	-35.7%	-12.5%
Oct.	66	10	15.2%	26	6	23.1%	-60.6%	-40.0%
Nov.	48	4	8.3%	36	5	13.9%	-25.0%	25.0%
Dec.	62	13	21.0%	20	4	20.0%	-67.7%	-69.2%
Total	948	113	11.9%	473	61	12.9%	-50.1%	-46.0%

Table 2. Number of patients tested for TB, number of new TB cases diagnosed, diagnostic positivity rate in 2019 and 2020 and percent variation of patients tested and positives for TB in the hospital laboratory.

Month	2019			2020			Variation of patients tested	Variation of new cases
	Patients tested	New cases	Positivity rate	Patients tested	New cases	Positivity rate		
Jan.	30	11	36.7%	28	12	42.9%	-6.7%	9.1%
Feb.	28	8	28.6%	22	8	36.4%	-21.4%	0.0%
Mar.	31	6	19.4%	39	10	25.6%	25.8%	66.7%
Apr.	28	3	10.7%	18	0	0.0%	-35.7%	-100.0%
May	33	8	24.2%	17	3	17.7%	-48.5%	-62.5%
June	35	6	17.1%	17	2	11.8%	-51.4%	-66.7%
July	46	4	8.7%	14	2	14.3%	-69.6%	-50.0%
Aug.	42	2	4.8%	17	5	29.4%	-59.5%	150.0%
Sept.	38	6	15.8%	30	4	13.3%	-21.1%	-33.3%
Oct.	45	10	22.2%	19	4	21.1%	-57.8%	-60.0%
Nov.	33	13	39.4%	18	4	22.2%	-45.5%	-69.2%
Dec.	31	7	22.6%	23	4	17.4%	-25.8%	-42.9%
Total	420	84	20.0%	262	58	22.1%	-37.6%	-31.0

Table 3. Number of patients tested for TB, number of new TB cases diagnosed, diagnostic positivity rate in 2019 and 2020 and percent variation of patients tested and positives for TB in both laboratories.

Month	2019			2020			Variation of patients tested	Variation of new cases
	Patients tested	New cases	Positivity rate	Patients tested	New cases	Positivity rate		
Jan.	105	26	24.8%	90	17	18.9%	-14.3%	-34.6%
Feb.	92	17	18.5%	48	14	29.2%	-47.8%	-17.7%
Mar.	77	13	16.9%	110	15	13.6%	42.9%	15.4%
Apr.	100	8	8.0%	63	4	6.4%	-37.0%	-50.0%
May	168	18	10.7%	53	6	11.3%	-68.5%	-66.7%
June	234	22	9.4%	43	8	18.6%	-81.6%	-63.6%
July	98	9	9.2%	63	5	7.9%	-35.7%	-44.4%
Aug.	101	13	12.9%	48	12	25.0%	-52.5%	-7.7%
Sept.	108	14	13.0%	75	11	14.7%	-30.6%	-21.4%
Oct.	111	20	18.0%	45	10	22.2%	-59.5%	-50.0%
Nov.	81	17	21.0%	54	9	16.7%	-33.3%	-47.1%
Dec.	93	20	21.5%	43	8	18.6%	-53.8%	-60.0%
Total	1368	197	14.4%	735	119	16.2%	-46.3%	-39.6%

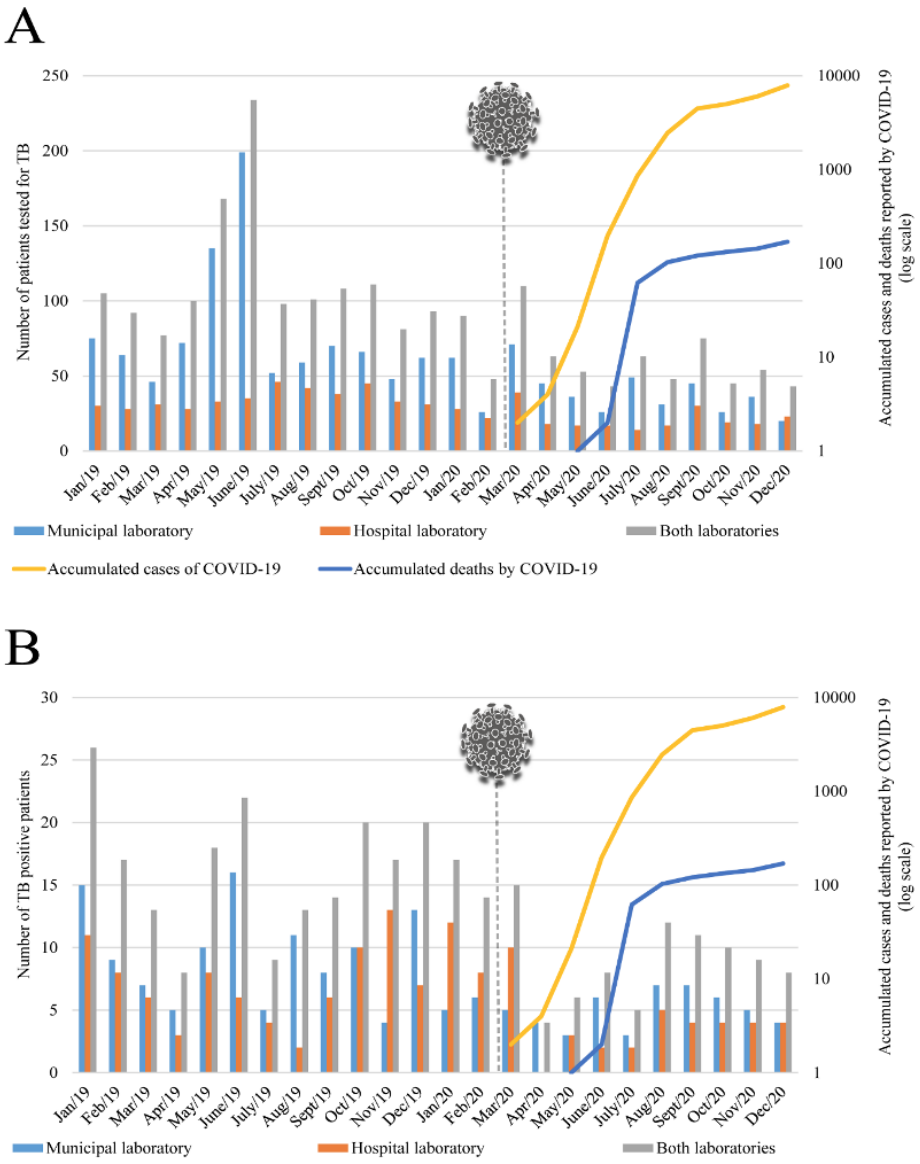

Figure 2. (A) Number of patients tested for TB in municipal and hospital laboratories and both laboratories, in 2019 and 2020, and accumulated reported cases and deaths by COVID-19. (B) Number of TB positive patients in municipal and hospital laboratories and both laboratories, in 2019 and 2020, and accumulated reported cases and deaths by COVID-19. Dashed grey line indicates the first reported COVID-19 case in Rio Grande.

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Patients tested for tuberculosis

In March 2020, the month when the first COVID-19 case was reported in Rio Grande, there was a 42.9% increase in the total number of patients tested for TB compared to 2019 (77 patients in 2019 to 110 patients in 2020). This increase was of 54.4% in the municipal laboratory (46 patients in 2019 to 71 patients in 2020) and 25.8% in the hospital laboratory (31 patients in 2019 to 39 patients in 2020). In the following months of COVID-19 pandemic, from April to December, there was a decrease in the number of patients tested in both laboratories, also compared to 2019. June and July had the highest reduction in the number of patients tested in the municipal laboratory (199 patients in 2019 to 26 patients in 2020, representing a decrease of 86.9%) and hospital laboratory (46 patients in 2019 to 14 patients in 2020, representing a decrease of 69.6%), respectively. In the municipal laboratory, the number of patients tested for TB in 2019 and 2020 was 948 and 473, respectively, representing a decrease of 50.1%. In the hospital laboratory, 420 and 262 patients were tested for TB in 2019 and 2020, respectively, representing a decrease of 37.6%. A total decrease of 46.3% in the number of patients tested for TB in 2020 compared to 2019 was observed in public TB diagnostic services (1,368 and 735 patients, respectively).

New tuberculosis cases

In March 2020, compared to March 2019, there was a 15.4% increase in the total number of new TB cases diagnosed. In the following months, there was a reduction in the number of new TB cases diagnosed, except August in the hospital laboratory (increase of 150%) and November in the municipal laboratory (increase of 25%). There was a total decrease of 197 to 119 (reduction of 39.6%) in the number of new TB cases diagnosed in public TB diagnostic services in 2019 and 2020, respectively. Also, 113 and 61 new TB cases were diagnosed by the municipal laboratory (reduction of 46%), and 84 and 58 new TB cases by hospital laboratory (reduction of 31%).

Positivity rate

In March, there was a reduction in the positivity rate in 2020 (13.6%) compared to 2019 (16.9%). In the months with the highest reduction in the number of patients tested, the positivity rate increased: in the municipal laboratory, the positivity rate was 8% in June 2019 and 23.1% in June 2020, while in the hospital laboratory, the positivity rate increased from 8.7% in July 2019 to 14.3% in July 2020. Furthermore, in the months in which there was an increase in the number of TB positive patients, the positivity rate also showed an increase: in the hospital laboratory, the positivity rate was 4.8% in August 2019 and 29.4% in August 2020, while in the municipal laboratory, the positivity rate increased from 8.3% in November 2019 to 13.9% in November 2020. In both laboratories the positivity rate was 14.4% in 2019 and 16.2% in 2020. In the municipal laboratory, it was 11.9% and 12.9%, while in the hospital laboratory, it was 20% and 22.1% in 2019 and 2020, respectively.

DISCUSSION

The first pillar of the END TB Global Strategy comprises "Integrated, people-centered care and prevention, aiming at early and universal access to diagnosis and treatment of all forms of TB"[3]. However, health system overload due to COVID-19, as well as restrictions needed to limit SARS-CoV-2 transmission, resulted in severe reductions in the availability and access to health services for detection and treatment of TB cases.[4,17]

Challenges in TB management during the pandemic have been observed especially in low- and middle-income countries, such as Brazil.[11] Brazil showed a reduction in the total number of TB reporting in the three levels of health care, with a sharp drop in tertiary care, in 2020 compared to 2019.[13] In addition to already being a country with a high burden of TB, Brazil was considered the epicenter of COVID-19 in 2020.[18]

Our results showed a significant reduction in the number of patients tested and positive for TB in 2020, during the COVID-19 pandemic, in comparison to 2019. In opposition to what was observed in Brazil,[13] we reported the highest reduction in the number of TB patients diagnosed in the municipal laboratory, which belongs to Primary Health Care, in relation to the hospital laboratory, which belongs to Tertiary Health Care. In Brazil, there is great heterogeneity among regions, including socioeconomic heterogeneity, which is reflected in the accessibility of regional health services.[19] Thus, the impact of the COVID-19 pandemic on the health system in each region has been different; therefore, the importance of epidemiological investigation to understand the health situation in different regions of the country stands out.

Regarding the number of patients tested monthly, it was observed that the months of 2020 with the largest variation of patients tested, compared to 2019, were June (-86.9%) and July (-69.6%), in municipal and hospital laboratories, respectively. It is important to emphasize that, during this period, there was an increase in reporting of COVID-19 cases and deaths in Rio Grande, resulting in the adoption of physical distancing strategies and limitation of the movement of people, which difficulted people's access to TB services of diagnosis and treatment. Furthermore, in the absence of severe symptoms, the population was discouraged from seeking health services, to avoid crowding and the social stigma given the similarity of some symptoms of COVID-19 and TB.[3,4]

We also observed that in March 2020, when the first COVID-19 case was reported in Rio Grande city, there was an increase of 42.9% and 15.4% in the total number of patients tested for TB and new TB cases diagnosed, respectively, in relation to March 2019. De Souza et al. (2020) reported a 17.8% increase in reporting of TB cases over the same period in the state of Bahia, Northeastern Brazil.[11] One month of increase in reported TB cases, coinciding with the first COVID-19 cases, followed by months of decrease, when compared to the same period in 2019, coinciding with the advance of the pandemic, was a pattern observed in all regions of Brazil.[20] We hypothesize that the increase in the number of patients tested for TB and

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new TB cases diagnosed has occurred due to lack of knowledge about the COVID-19 at the beginning of the pandemic and the similarity in symptoms with TB. It is known that suspected COVID-19 and TB cases have fever and/or similar respiratory symptoms, such as difficulty breathing, cough and chest pain.[21] Thus, patients who presented these symptoms may have been referred for TB diagnosis.

Another relevant fact evidenced in our study was the increase of 150% and 25% in the number of patients positive for TB in August at the hospital laboratory and in November at the municipal laboratory. During this same period, there was no increase in the number of patients tested, but a reduction. However, it is important to highlight that in these months, there was an increase in the positivity rate in the hospital (4.8% in August 2019 to 29.4% in August 2020) and the municipal (8.3% in November 2019 to 13.9% in November 2020) laboratories. When observing the total positivity rate in TB diagnostic services in 2019 and 2020 (14.4% and 16.2%, respectively), a similar phenomenon can also be observed. This was observed even with a reduction in the total number of patients tested and patients positive for TB in 2020 because the reduction in the number of patients tested was greater than the reduction in the number of new TB cases in that year. In the municipal laboratory, the positivity rate increased from 11.9% in 2019 to 12.9% in 2020. In the hospital laboratory, the positivity rate increased from 20% in 2019 to 22.1% in 2020.

The hospital laboratory, where the highest increase in the positivity rate occurred, only it diagnoses patients admitted to the hospital. Thus, it is possible that for both cases, especially in the hospital laboratory, there were an increase in the positivity rate due to referral only of patients who had prolonged and/or aggravated symptoms suggestive of TB or COVID-19, needing hospitalization. In addition to this, TB can be considered a risk factor for COVID-19, aggravating the morbidity and mortality of the disease.[21] Thus, increased positivity rate in the hospital laboratory, especially in August, due to the increase in TB cases detected, may be due to cases with TB/COVID-19 co-infection that required hospitalization. However, TB/COVID-19 coinfection was not investigated in the present study, as it was outside the scope of this study.

In our study, we did not assess the full scenario of how the COVID-19 pandemic affects TB response. This can be considered a study limitation. We do not take into account, for instance, possible treatment interruptions and co-infection of people with TB and COVID-19. However, a modelling study that performed a conservative estimate, considering TB detection only, suggested that if the COVID-19 pandemic led to an overall 25% reduction in expected TB detection in 3 months, we can expect an increase of 13% in deaths from TB.[12]

Between 2020 and 2025, health care service disruption worldwide as a consequence of the COVID-19 pandemic could lead to an additional 6.3 million cases and 1.4 million additional TB deaths.[12] Our results showed an overall alarming reduction of 46.2% in the number of patients tested in 2020 compared to 2019. TB cases not diagnosed by the laboratories included in the study due to a reduction in testing, as they do not receive adequate treatment, will negatively impact TB control in southern Brazil. In view of this, it will be possible to see that the adverse responses of restrictions in health systems to control SARS-CoV-2 transmission will last beyond the COVID-19 pandemic.

Thus, considering that the COVID-19 pandemic is still ongoing and its effects will be visualized in the long term, it is recommended that studies including a longer period of time and assessing different aspects of TB care be carried out. As a limitation, the present study includes an analysis of a relatively short period, as an analysis was carried out only one year before and during the pandemic. Despite this limitation, it is believed that the results obtained will provide immediate answers to guide the adoption of TB control strategies in the studied setting, as well as in other priority settings for TB control.

Finally, it is important highlight that in the laboratories included in the study, there was no interruptions in TB diagnostic services provided during the COVID-19 pandemic, as well as in acquisition of laboratory supplies. In the municipality, there was strategic planning for creating a diagnostic service for COVID-19, including the creation of a laboratory with an appropriate biosafety level focused on molecular diagnosis of this disease only. Thus, no reallocation of staff, supplies and equipment from TB to COVID-19 in terms of laboratory diagnosis. Therefore, it is assumed that the impact of the pandemic on laboratory diagnosis of TB is due to factors external to TB laboratories, such as absence of patients with suspected TB in health facilities.

In conclusion, as a consequence of measures to control the spread of SARS-CoV-2, there was a reduction in TB testing and in detecting of new cases, especially in Primary Health Care, where patients with less need for hospitalization are received. This study was carried out at a setting with high TB burden and high incidence of COVID-19, and showed the negative influence of COVID-19 pandemic in TB diagnosis. Thus, 2020 data, in addition to guiding the necessity of adoption of public policies for TB control, emphasizes the importance of maintaining and strengthening TB services during the pandemic and in the following years, so that missed diagnoses are recovered.

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AUTHORS' CONTRIBUTIONS

Mariana Quaresma de Souza contributed to the conceptualization, formal analysis, investigation, data curation and writing (original draft, review and editing).

Juliana Lemos Dal Pizzol contributed to the formal analysis, investigation and writing (original draft, review and editing).

Ana Bárbara Scholante Silva, Felipe Furtado Gomes Riet Vargas, Denise Silva Brião and Carolina Almeida Martinato contributed to the investigation, data curation and writing (review and editing).

Andrea von Groll and Pedro Eduardo Almeida da Silva contributed to the conceptualization and writing (review and editing).

Ivy Bastos Ramis contributed conceptualization, formal analysis, writing (original draft, review and editing), project supervision and administration.

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.

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DE PÓS GRADUAÇÃO EM PROMOÇÃO DA SAÚDE - DEPARTAMENTO DE BIOLOGIA E FARMÁCIA DA UNISC

Revista de Epidemiologia e Controle de Infecção

Hospital Santa Cruz

ORIGINAL ARTICLE

Evaluation of triatomines infestation occurrence in home environments in the city of Taua-Ce, 2012

Avaliação da ocorrência de infestação por triatomíneos em ambientes domiciliares no município de Tauá-Ce, 2012

Evaluación de la ocurrencia de infestación por triatominos en ambientes domiciliarios en el municipio de Tauá-Ce, 2012

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ABSTRACT

Background and Objectives: Triatomines are vectors of Trypanosoma cruzi, the etiologic agent of Chagas disease, a parasitic disease that affects mammals and humans. The destruction or transformation of natural ecotopes has intensified, resulting in the invasion of triatomines in households, bringing risks to the population. Thus, the objective of the study was to carry out a data survey on triatomine infestation in the countryside of the city of Taua-Ce, in 2012. **Methods:** This is a descriptive/exploratory study of a quantitative nature, where the Secondary data were obtained from the Municipal Health Department (Endemic Nucleus). **Results:** The percentage of infestation in the 15 locations studied was 26.1%, with the most affected locations being: Sítio Central do Incra 50%, Fazenda Brôco 18.2%, Jordão 16.7%, Fazenda Bom Lugar 0%, Fazenda Riacho do Mato 40%, Fazenda Cearauai 37.5%, Sítio Riacho do Mato 30%, Fazenda Cedro 17.4%, Cachoeirinha 27%, Fazenda Várzea do Feijão 24%, Cachoeira do Júlio 41.2%, Fazenda Mutuquinha 9,4%, Sítio Várzea Grande 33.3%, Iparana 9.1% and Cachoeira do Celso 16.7%. **Conclusion:** The study showed that there is a significant rate of triatomine infestation in the home environment, which represents a great risk to the health of the population of Taua. Therefore, a more frequent entomological control is suggested, going beyond the period of campaigns for a better monitoring of the occurrence of these insects in the area.

Descriptors: *Vector Insects. Infection. Chagas Desease. Entomological surveillance.*

RESUMO

Justificativa e Objetivos: Triatomíneos são vetores de *Trypanosoma cruzi,* agente etiológico da doença de Chagas, parasitose que atinge mamíferos e humanos. A destruição ou transformação dos ecótopos naturais tem se intensificado, resultando na invasão de triatomíneos em domicílios trazendo riscos a população. Diante do exposto,

o objetivo do estudo foi realizar um levantamento de dados sobre a infestação de triatomíneos em localidades do interior do município de Tauá-Ce, em 2012. **Métodos:** Trata-se de um estudo descritivo/exploratório de natureza quantitativa, onde os dados secundários foram obtidos junto à Secretaria de Saúde (Núcleo de Endemias) do município. **Resultados:** O percentual de infestação nas 15 localidades estudadas foi de 26,1%, sendo as localidades mais afetadas: Sítio Central do Incra 50%, Fazenda Brôco 18,2%, Jordão 16,7%, Fazenda Bom Lugar 0%, Fazenda Riacho do Mato 40%, Fazenda Cearauai 37,5%, Sítio Riacho do Mato 30%, Fazenda Cedro 17,4%, Cachoeirinha 27%, Fazenda Várzea do Feijão 24%, Cachoeira do Júlio 41,2%, Fazenda Mutuquinha 9,4%, Sítio Várzea Grande 33,3%, Iparana 9,1% e Cachoeira do Celso 16,7%. **Conclusão:** O estudo mostrou que há um expressivo índice de infestação triatomínica em ambiente domiciliar, o que representa um grande risco a saúde da população tauaense. Sendo assim, sugere-se um controle entomológico mais frequente, ultrapassando o período de campanhas para um melhor acompanhamento da ocorrência desses insetos na região.

***Descritores*:** *Insetos Vetores. Infecção. Doença de Chagas. Vigilância entomológica.*

RESUMEN

Justificación y Objetivos: Los triatomíneos son vectores de *Trypanosoma cruzi*, agente etiológico de la enfermedad de Chagas, parasitosis que afecta a mamíferos y humanos. La destrucción o transformación de los ecótopos naturales se ha intensificado, resultando en la invasión de triatomíneos en domicilios trayendo riesgos a la población. Ante lo expuesto, el objetivo del estudio fue realizar un levantamiento de datos sobre la infestación de triatomíneos en localidades del interior del municipio de Tauá-Ce, en 2012. **Métodos:** Se trata de un estudio descriptivo/exploratorio de naturaleza cuantitativa, donde los datos secundarios fueron obtenidos junto a la Secretaría de Salud (Núcleo de Endemias) del municipio. **Resultados:** El porcentaje de infestación en las 15 localidades estudiadas fue de 26,1%, siendo las localidades más afectadas: Sítio Central do Incra 50%, Fazenda Brôco 18,2%, Jordão 16,7%, Fazenda Bom Lugar 0%, Fazenda Riacho do Mato 40%, Fazenda Cearauai 37,5%, Sítio Riacho do Mato 30%, Fazenda Cedro 17,4%, Cachoeirinha 27%, Fazenda Várzea do Feijão 24%, Cachoeira do Júlio 41,2%, Fazenda Mutuquinha 9,4%, Sítio Várzea Grande 33,3%, Iparana 9,1% e Cachoeira do Celso 16,7%. **Conclusión:** El estudio mostró que hay un expresivo índice de infestación triatomínica en ambiente domiciliar, lo que representa un gran riesgo para la salud de la población tauaense. Siendo así, se sugiere un control entomológico más frecuente, superando el período de campañas para un mejor seguimiento de la ocurrencia de esos insectos en la región.

***Palabras clave*:** *Vectores de insectos. Infección. La enfermedad de Chagas. Vigilancia entomológica.*

INTRODUCTION

A total of 156 species of triatomines, vectors of Chagas disease, are known.[1,2] In Brazil, triatomines are known by the most different names: *bicudo, chupa-pinto, bicho-de-parede preto, fincão, chupão, barbeiro, chupança, percevejão, percevejo-do-sertão, procotó, baratão, piolho-de-piaçava, bruxa, quiche do sertão, prorocotó, rondão vunvun, cascudo, percevejo gaudeiro, percevejo francês and percevejo grande*.[3,4,5]

The northeast caatinga is a region where there are a large number of these insects. They are insects of the Hemiptera, hematophagous order and the main transmitter of Chagas disease. Triatomines must feed on blood, they inhabit both wild environments and peridomiciles and homes.[6] They are found in cracks in the walls, in stables, pigsties, chicken coops, dovecotes, tree hollows and boulders.

The domiciliation process occurs when these insects leave their natural habitat due to destruction or modification and end up migrating to homes where domestic animals are raised, in the peridomicile, with precarious structures providing a source of shelter for the insect. Thus, this process directly influences the occurrence and transmission of Trypanosoma cruzi, the etiological agent of Chagas disease.[7,8]

Chagas disease has been known for over 100 years, as it was described by Carlos Chagas in 1909. Even so, it is still considered a neglected disease, which victimizes millions of Brazilians.[6]

Studies on triatomine infestation at home have been conducted, including the assessment of the occurrence in household environments in the city of Aurora, Ceara, between 2012 and 2015;[9] geographic distribution, household infestation and natural infection of triatomines in the state of Piaui, Brazil, 2008;[10] home infestation by triatoma infestans and some epidemiological aspects of American trypanosomiasis in an area of the state of Sao Paulo, Brazil;[11] triatoma infestans in an area under entomological surveillance for Chagas disease, state of Sao Paulo, Brazil;[12] occurrence of triatomines in intra and peridomiciliary environments in the city of Campos Sales, Ceara,[13] among other studies.

In the state of Ceara, between 2015 and 2019, about 28% (51) of the cities had triatomine infestation greater than 5%. This percentage of triatomine infestation is considered high. What draws attention is the dispersion of these cities throughout the state, showing the wide distribution of triatomines in the state, which in the same period, recorded 557 positive triatomines for T. cruzi in an

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indoor environment and about 3.4% of natural infection (557/16365), distributed in 66 (36%) of the cities.[14]

In 2013, a total of 1218 cases of CD were cataloged in people over 15 years old in the state of Ceara, and 22 cases (~1.7%) of this record were confirmed in the city of Taua.[6] The city has numerous locations with the presence of triatomines, which justifies the study. There is still insufficient information on the processes of triatomine domiciliation. Therefore, this study aimed to carry out an analysis of the infestation of triatomines in the countryside of Taua-Ce, in 2012.

METHODS

The survey was carried out in the city of Taua-Ce, in 2020. It is a descriptive/exploratory study of a quantitative nature, where secondary data were obtained from the Health Department (Endemic Nucleus) of the city, having as object of study the occurrence of triatomines in households in the city.

The city of Taua is located in the State of Ceara, northeast of Brazil, located in the Inhamuns Region. The city is located at a distance of approximately 357 km from the capital Fortaleza, with the geographical coordinates: latitude: 06°00'11"S, longitude: 40°17'34"W, altitude 402.7m, with an area of 4011 km^2, with a total of 59062 inhabitants. It has a hot, semi-arid tropical climate, with rains from February to April, with open shrubby caatinga vegetation and thorny deciduous forest with an average rainfall of 416.9 mm.[15,16]

Since 1995, the city has been made up of 8 districts, including the district of Taua (Headquarters), Barra Nova, Carrapateiras, Inhamuns, Marrecas, Marruas, Santa Teresa and Trici.[15]

The city borders on the north with Pedra Branca and Independencia, on the south with Parambu and Arneiroz, on the east with Mombasa and Pedra Branca and on the west with Quiterianopolis and Parambu.[16] (Figure 1)

Secondary data were obtained in January 2020 from the Health Department (Endemic Nucleus). The endemics nucleus is responsible for the surveillance of triatomines of the Chagas Disease Control Program (CDCPh).

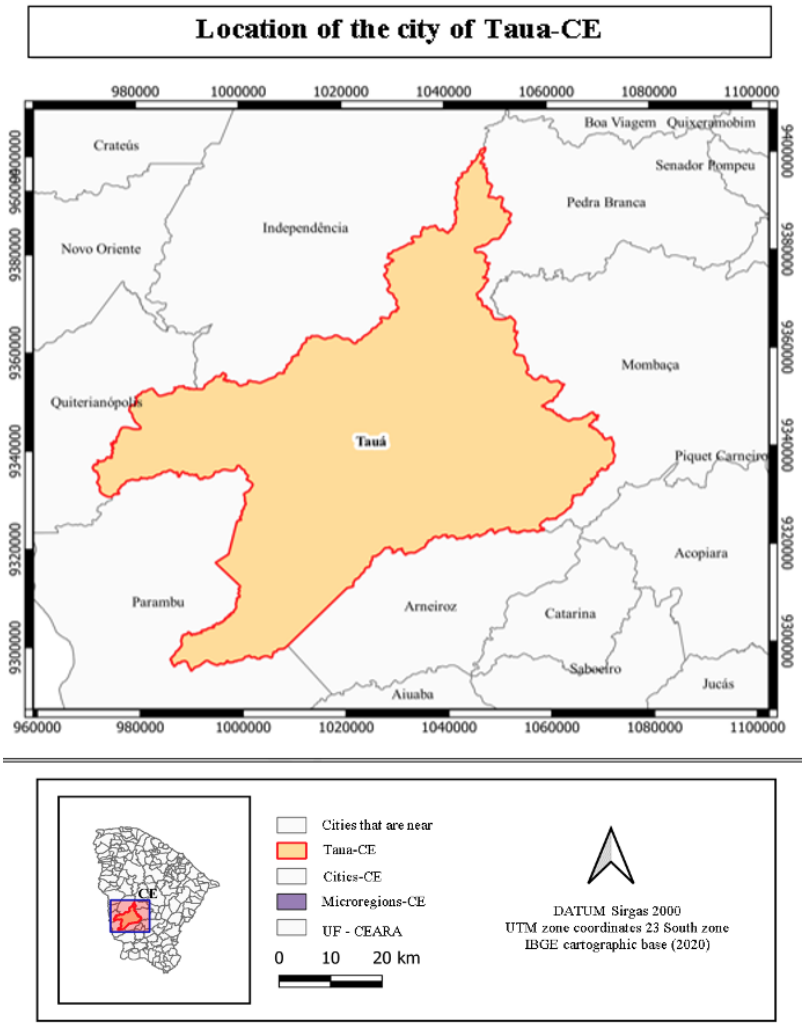

Figure 1. Geographical catalog of the location of the city of Taua-CE.

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As an inclusion criterion in the study, data collected from 06/05/2012 to 09/26/2012 in fifteen areas of the countryside of the city were selected and, as an exclusion criterion, the houses in which there was nobody at the time of the visit of the Endemic Combat Agents (ECAs).

The triatomines are captured in visits programmed during the PCDCh, by the ECAs of the center of endemic diseases of the city. A field visit was carried out along with the ECAs to capture the insects (triatomines).

The captured insects are placed in a container (five insects in each jar), with a label identifying the type of indoor environment (inside the house) or peridomiciliary environment (yard) and later taken to the Entomology Laboratory of Taua (LEM), where insect identification and parasitological analysis are carried out.[17]

The procedures for capturing and conserving live specimens follow the norms of the Manual of technical norms of the Chagas disease control campaign.[17]

In order to carry out intra and peridomiciliary capture, the following field materials were needed: bag, flashlight, large tweezers, batteries, containers to store the samples, GPS device, gloves, labels, manual sprayer, dislodging product for triatomines and a field sheet according to the Manual of technical standards.[17,18]

Data were analyzed by descriptive statistical techniques using Excel Office 2013® software and presented in the form of absolute numbers, relative frequency (infestation index) and average percentage.

The number of houses in the localities (N_1), the number of inhabitants (N_2), the number of houses surveyed (N_3), the number of positive houses (N_4), the number of pack-loads (N_5) containing Alfacypermethrin (Alfatek Insecticide 200 SC) used in spraying to control the insect.

The relative frequency (%) was calculated by the following formula: $Fr = \left(\frac{Fi}{n}\right) \times 100$, where (Fr) is the relative frequency; (Fi) the Absolute Frequency and (n) represents the amount of data. The average percentage $M_e(\%)$ was calculated by the formula: $M_e(\%) = \frac{L1+L2_{L3}\ldots L15}{NL}$, where the variable L_1, L_2, L_3..., L_{15} represents the percentage of locations and NL the number of locations. The number of houses not surveyed, that is, that had no inhabitants during the PCDCh campaign, was calculated using the formula: $NCNP = N_1\text{-}N_3$, where N1 is the number of houses in the localities and N3 is the number of houses surveyed.

This study complies with the ethical principles of Resolution 466/12 of the National Health Council. The data used in this study do not address nominal data of the residents or any other that establish their identification. Thus, submission to the Research Ethics Committee (REC) was not necessary, according to Resolution No. 510 of the National Health Council, of April 7, 2016.[19]

RESULTS

Figure 2 shows the triatomine infestation rate in the locations: Sítio Central do Incra 50%, Fazenda Brôco 18.2%, Jordão 16.7%, Fazenda Bom Lugar 0%, Fazenda Riacho do Mato 40%, Fazenda Cearauai 37, 5%, Sítio Riacho do Mato 30%, Fazenda Cedro 17.4%, Cachoeirinha 27%, Fazenda Várzea do Feijão 24%, Cachoeira do Júlio 41.2%, Fazenda Mutuquinha 9.4%, Sítio Várzea Grande 33.3%, Iparana 9.1% and Cachoeira do Celso 16.7%. The average percentage of triatomine infestation was ≅ 24.7%.

In the analyzed period, a total of 15 locations with 732 residents were surveyed. Of these, only one home was not found to have triatomines. Of the 386 houses visited, 333 (86.3%) were evaluated, with 87 (26.1%) houses being positive for triatomines and 53 (13.7%) houses were not surveyed, as there was nobody in the house in the moment of the PCDCh campaign. (Table 1).

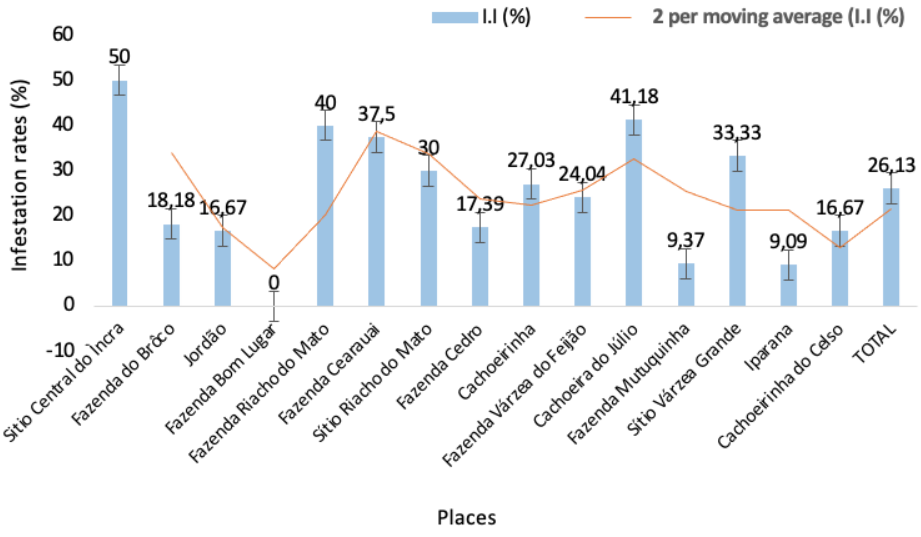

Figure 2. Triatomine infestation rates in the countryside of Taua-CE, 2012.

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Table 1. Occurrence of Triatomines in a home environment in Taua, CE.

PLACES	N_1	N_2	N_3	N_4	N_5
Sítio Central do Incra	33	46	18	9	7
Fazenda do Brôco	22	36	22	4	9
Jordão	6	5	6	1	3
Fazenda Bom Lugar	7	15	3	0	0
Fazenda Riacho do Mato	16	26	15	6	14
Fazenda Cearauai	8	9	8	3	8
Sítio Riacho do Mato	10	20	10	3	7
Fazenda Cedro	30	40	23	4	11
Cachoeirinha	38	92	37	10	19
Fazenda Várzea do Feijão	105	252	104	25	58
Cachoeira do Júlio	18	25	17	7	18
Fazenda Mutuquinha	35	79	32	3	7
Sítio Várzea Grande	8	5	3	1	3
Iparana	11	26	11	1	3
Cachoeirinha do Celso	6	10	6	1	3
TOTAL	386	732	333	87	170

Legend: N_1= number of houses in the place; N_2= number of inhabitants in the places; N_3= number of houses surveyed; N_4 = Number of positive houses; N_5 = pack-loads containing Alfacypermethrin (Alfatek Insecticide 200 SC) used in spraying for insect control.

A total of 21 triatomines (Triatoma infestans) were captured during the field research carried out along with the ECAs and sent to the LEM for identification and parasitological analysis of the insects. Spraying was performed in all homes where the insects were found using the alpha-cypermethrin-based insecticide (ALFATEK 200 SC).

DISCUSSION

The triatomine infestation rate analyzed in this study was 26.1%. The value is compatible with that found by Candido and Collaborators in Campos Sales (CE), which was 20.4%. However, it differs greatly from the results found by Pinto and Collaborators in Aurora (CE), which was 80.97%.[13-9] Therefore, despite the low infestation rate found in Taua (CE), it can be observed in this work that there are areas of up to 50% infestation in the city, forming colonies of triatomines may occur in households and annexes, indicating considerable rates of infection by Trypanosoma cruzi.[18]

The invasion by triatomines inside homes and annexes is worrying, since these insects are potential sources of natural infection. In addition, it expresses the housing conditions that the populations live, in which the domicile of these insects took place.[13,9,18]

It is also believed that this invasion of triatomines in homes is linked to the occurrence and transmission of the parasite, in addition to connecting the wild and domestic cycles of Chagas disease.[8,13, 18,20-22]

It is concluded that there is home colonization by triatomines in the city of Taua. Therefore, improvements are necessary in the epidemiological surveillance of the city and the adoption of prophylactic measures by the residents, such as: always keeping the house and surroundings clean, as well as the use of mosquito nets, protection screens on doors and windows, as well as educational work by authorities focused on the prevention of Chagas disease, aiming to raise awareness of the vector of the disease and its main shelters as a way of minimizing the risks to which they are exposed. In addition, a more frequent entomological control is suggested, going beyond the period of the campaigns for a better monitoring of the occurrence of these insects.

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AUTHOR CONTRIBUTIONS

Elivan Custodio Araujo contributed to the conception, article design, analysis, article writing, article planning and design, review and final approval of the article;

The author approves the final version to be published and is responsible for all aspects of the work, including ensuring its accuracy and integrity.

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Revista de Epidemiologia e Controle de Infecção

Hospital Santa Cruz

ORIGINAL ARTICLE

Toxoplasma gondii Prevalence in Pregnant Women in Jataí - GO: a 10-year profile

Prevalência do Toxoplasma gondii em Gestantes no Município de Jataí – GO: um recorte de 10 anos

Prevalencia de Toxoplasma gondii en mujeres embarazadas de la Ciudad de Jataí - GO: un período de 10 años

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ABSTRACT

Background and Objectives: Toxoplasmosis is a cosmopolitan zoonosis caused by the *Toxoplasma gondii* protozoan, transmitted mainly through contaminated water or food, beyond vertical transmission. In the State of Goiás, there is a lack of data on the prevalence of the disease, hence the relevance of this cross-sectional study to determine the prevalence of toxoplasmosis in pregnant women in the municipality of Jataí. **Methods:** Data were collected from pregnant women attended by the public health network in the municipality from January 2005 to December 2015. **Results:** During the analyzed period, 11,350 pregnant women were attended; 75% with IgG antibodies and 0,60% IgM antibodies reactive for *T. gondii*, with a reduction in the number of cases since 2010. **Conclusion:** The high seroprevalence found shows that pregnant women are in close contact with factors that trigger the infection and a reduction in the number of cases indicates the efficacy of epidemiological surveillance actions developed for this population group.

Keywords: *Toxoplasmosis. Toxoplasma gondii. Pregnant women. Seroprevalence.*

RESUMO

Justificativa e Objetivos: Toxoplasmose é uma zoonose cosmopolita causada pelo protozoário *Toxoplasma gondii,* transmitido principalmente através de água e alimentos contaminados e pela transmissão vertical. No estado de Goiás existe uma escassez de dados referentes à prevalência da toxoplasmose. Diante dessa realidade, tornou-se relevante esse estudo transversal que determinasse a prevalência da toxoplasmose nas gestantes no município de Jataí. **Métodos:** Foram coletados dados de grávidas atendidas pela rede pública de saúde no município no período de janeiro de 2005 a dezembro de 2015. **Resultados:** No período analisado, foram atendidas 11.350 gestantes, sendo 75% delas com anticorpos IgG e 0,60% anticorpos IgM reagentes para *T. gondii,* com redução no número de casos a

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partir de 2010. **Conclusão**: A alta soroprevalência encontrada demonstra que as grávidas estão em íntimo contato com os fatores que desencadeiam a infecção. É necessário investigar os fatores que contribuem para a elevada taxa de infecção.

Descritores: *Toxoplasmose. Toxoplasma gondii. Gestantes. Soroprevalência.*

RESUMEN

Justificacíon y Objetivos: La toxoplasmosis es uma zoonosis cosmopolita causada por el protozoo *Toxoplasma gondii*, que se transmite principalmente através del agua o alimentos contaminados, además de la transmisión vertical. Em el estado de Goiás, se carece de dados sobre la prevalência de la enfermedad y ante esta realidade, es relevante este estudio transversal para determinar la prevalência de toxoplasmosis em gestantes del município de Jataí. **Métodos:** Se recolectaron dados de gestantes atendidas por la red de salud pública del município de Enero de 2005 a Diciembre de 2015. **Resultados:** Entre el período analizado se trató a 11.350 gestantes, 75% de ellas com anticuerpos IgG y 0,60% anticuerpos IgM reactivos para *T. gondii*, com uma reducción em el número de casos a partir de 2010. **Conclusión:** La alta soroprevalência encontrada muestra que las mujeres embarazadas están em estrecho contacto com los fatores desencadenantes de la infección y uma reducción em el número de casos apunta a uma eficácia em las acciones de vigilância epidemiológica desarrolladas para este grupo de problación.

Palabras-clave: *Toxoplasmosis. Toxoplasma gondii. Gestantes. Seroprevalencia.*

INTRODUCTION

Toxoplasmosis is an infection caused by the *Toxoplasma gondii* protozoan distributed worldwide and with high prevalence, especially in Brazil, where it has high genetic diversity.[1,2] There are several forms of transmission of this disease, the main ones are the ingestion of oocyst-contaminated food and water and vertical transmission, when there is the passage of tachyzoites from the placenta to the fetus during the three trimesters of pregnancy.[3, 4]

Given the high risk of *T. gondii* vertical transmission to the fetus associated with the severity of signs and symptoms of congenital toxoplasmosis, since 2015, the Ministry of Health has assigned the Health Surveillance Secretariat to monitor and supervise gestational and congenital toxoplasmosis in the country in order to standardize the care provided to pregnant women and their children after proven infection.[5] For this reason, the disease in these conditions was considered an important public health problem and its inclusion in the Compulsory Disease Notification List is an important strategy of this body to monitor the disease. From the investigation of risk cases or proof of gestational transmission, it is possible to identify the origin of the infection and the closure of outbreaks, and create prevention, control and treatment strategies for individuals affected by the disease.[5-6]

Symptoms of congenital toxoplasmosis can manifest during fetal development, childhood and even puberty, or the disease can remain subclinical. After infection, the main signs presented by the fetus are chorioretinitis, microcephaly, macrocephaly, hydrocephalus, mental retardation, brain calcifications and even hearing loss.[4,7] Gestational age and primary infection during pregnancy are the main factors responsible for *T. gondii* transmission to the fetus. The acute phase determines the pathogenicity of the parasite in the host, as well as the transmission rate and the severity of the baby's involvement, especially if the mother's infection occurs during the first gestational weeks, as it leads to abortion and several complications.[8-9] Gestational age, in turn, determines the degree of transmission. The frequency of infection of the conceptus during the first trimester of pregnancy is 4.5%, in the second it is 17.3% and in the third trimester it is 75%.[4,9,10] On the other hand, *T. gondii* vertical transmission is considered low in immunocompetent pregnant women who developed seroconversion to the parasite before pregnancy.[10]

The prevalence of seropositivity in pregnant women varies according to geographic region, cultural factors, climatic characteristics of the environment, educational level, self-reported color and age.[7,10-13] The worldwide prevalence of toxoplasmosis is 1.1%[7], ranging from 10.9% in Norway,[14] 28.88% in Morocco[15] and 30% in Germany,[16] with an average of 56.2% in South American countries[7]. In Brazil, it ranges between 32.7% in São Paulo and 92% in Mato Grosso do Sul.[10]

In the state of Goiás, data on the prevalence of toxoplasmosis is lacking. Given this reality, this cross-sectional study to determine the prevalence of toxoplasmosis in pregnant women in the city of Jataí became relevant. The lack of this information makes it impossible to recognize the situation of the disease in the place, and to create and adopt strategies to manage the disease in this group and the population.

METHODS

In this descriptive cross-sectional study, the results of IgG and IgM serological tests for *Toxoplasma gondii* performed in pregnant women attended by the public health network in the municipality of Jataí, state of Goiás, between January 2005 and December 2015 were analyzed.

The test results were provided by the Institute for Diagnosis and Prevention (IDP) of the Association of Exceptional Parents and Friends (APAE), accredited by the state to perform all serological tests of pregnant women

assisted by the National Health Service (Brazilian SUS).

The present study was approved by the Research Ethics Committee of the Universidade Federal de Goiás under number 1.882.407 and Certificate of Presentation of Ethical Appreciation 60106616.0.0000.5083.

RESULTS

During the selected period, 11,350 pregnant women were assisted. Of these, 8,514 (75%) had IgG anti-*T. gondii* antibodies (Table 1). The average annual number of cases was 774. A reduction and stabilization in the number of cases was observed after 2010. Pregnant women were significantly associated with seropisitivity of anti-*T. gondii*.

Table 1. Distribution of the number of services and pregnant women with positive IgG and IgM antibodies to *T. gondii* served at the Rede Cegonha (antenatal care service) in the municipality of Jataí, state of Goiás, between 2005 and 2015.

Year	Nº	IgG⁺ (%)	IgM (%)
2005	1,090	851 (78.07)	5 (0.46)
2006	961	768 (79.92)	5 (0.52)
2007	1,028	882 (85.80)	9 (0.87)
2008	944	680 (72.03)	12 (1.27)
2009	1,011	843 (83.38)	2 (0.20)
2010	1,043	945 (90.60)	1 (0.09)
2011	1,031	702 (68.09)	6 (0.58)
2012	1,043	707 (67.79)	5 (0.48)
2013	1,065	703 (66.01)	5 (0.47)
2014	1,047	721 (68.86)	12 (1.15)
2015	1,087	712 (65.50)	6 (0.55)
Total	11,350	8,514 (75.01)	68 (0.60)

Among pregnant women assisted at the *Rede Cegonha* during the study period, 68 showed reactivity for IgM anti-*T. gondii* antibodies (Table 2).

In this study, 68 IgM-reactive pregnant women (0.60%) did this test and there was a predominance of cases with avidity >60% (79.41%), suggesting the occurrence of the infection more than 12 weeks before the test was performed, and the IgM found was considered as residual antibody. The opposite of 7.35% and 13.23% of mothers who presented results of avidity < 30% and between 30 - 60%, respectively, suggests maternal infection for less than 12 weeks, with a high possibility of transmitting the parasite to the fetus.[9]

DISCUSSION

The percentage of reactivity for *T. gondii* found in the city shows that most pregnant women attended had previous contact with the parasite before conception, reducing the chances of transmission of the disease to the fetus during pregnancy. The prevalence found was higher than that observed in Fortaleza, 68.6%,[17] Aracaju, 69%,[18] in Jaguapitã (city in the state of Paraná) 66%,[19] and in São Luiz (state of Maranhão) 66.38%.[20] Seroprevalence in pregnant women remained high throughout the analyzed period, especially between 2005 and 2010, with a reduction and stabilization of infection in the number of cases after that year, demonstrating that this population is in close contact with factors that promote the infection, and the general population of the municipality may be in the same situation. Faced with this reality, the investigation of factors contributing to the high rate of infection in the population is essential, as well as the creation and implementation of primary measures for protection of the uninfected population, in addition to secondary and tertiary prevention measures for those who present symptoms and even sequelae of the disease.

The low prevalence of IgM observed (0.60%) was close to that found in studies conducted in Mato Grosso do Sul (0.42%)[21] and Sergipe (0.40%),[22] and lower than rates observed in a reference hospital in Rio de Janeiro (48.8%).[23] The period from 2008 to 2014 showed a significant increase in the number of cases, with greater evidence in the number of women who tested positive for the IgM anti-*T. gondii* antibody. This situation may indicate an outbreak of toxoplasmosis in the municipality, despite the lack of information to prove such suspicion, since clinical signs of acute toxoplasmosis can be easily confused with other infections and are mostly self-resolving.[24] For this reason, the diagnosis for the disease is often unconfirmed or confused with other infections.

For women who have not had previous contact with *T. gondii*, (24.99%) it is recommended to increase care to avoid contamination by the protozoan, considering the severity of signs and symptoms that fetuses and neonates present when infected in utero.

It is possible to conclude that the municipality of Jataí has a high number of pregnant women who had previous contact with *T. gondii*. The high prevalence of anti-*T. gondii* antibodies in pregnant women points to an important public health problem, because in certain situations, such as the fall of immunological mechanisms of affected individuals, toxoplasmosis can generate serious physiological changes.[25]

Knowing the real situation of the disease in the population of the municipality as well as the factors responsible for maintaining the cases is of paramount importance, since even asymptomatic in most cases, toxoplasmosis is an opportunistic infection with serious sequelae when carriers have some type of immunosuppression. Therefore, its monitoring is essential for effective health surveillance actions.

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PUBLICAÇÃO OFICIAL DO NÚCLEO HOSPITALAR DE EPIDEMIOLOGIA DO HOSPITAL SANTA CRUZ E PROGRAMA DE PÓS GRADUAÇÃO EM PROMOÇÃO DA SAÚDE - DEPARTAMENTO DE BIOLOGIA E FARMÁCIA DA UNISC

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ORIGINAL ARTICLE

An epidemiologic analysis of Candida spp. urinary infections in intensive care unit

Uma análise epidemiológica das infecções urinárias por Candida spp. em unidade de terapia intensiva

Un análisis epidemiológico de las infecciones urinarias por Candida spp. en la unidad de cuidados intensivos

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ABSTRACT

Background and objectives: The finding of *Candida* species in urine is an usual finding and is called candiduria. There is an increase in the frequency of urinary tract infections (UTI) caused by *Candida* especially in critically ill patients. This study aimed to determine the epidemiological, clinical, and mycological characteristics of *Candida* urinary infections in intensive care unit (ICU) and antifungal susceptibilities. **Methods:** Urine cultures of 394 ICU patients with clinical suspicion of UTI were evaluated. After 24-48 hours of incubation, colonies appeared to grow as yeast, were morphologically examined by Gram staining. *Candida* strains that grew $10^4 \geq$ CFU/mL in urine cultures were accepted as candiduria. The susceptibilities of the *Candida* strains to amphotericin B, itraconazole, fluconazole, voriconazole, flucytosine, and caspofungin were investigated with broth microdilution method. **Results:** The distribution of the isolated 100 urinary *Candida* strains were as, 54 *Candida albicans*, 34 *C. glabrata*, 7 *C. tropicalis*, 2 *C. kefyr*, 2 *C. lusitaniae*, and 1 as *C. parapsilosis*. Among 100 *Candida* species isolated in our study susceptibility rates of amphotericin B, flucytosine, caspofungin, fluconazole, itraconazole, and voriconazole were 100%, 100%, 91%, 23%, 13%, 25.8%, respectively. **Conclusion:** Accurate identification of *Candida* spp., as well as the investigating the antifungal susceptibility, will be beneficial in terms of the effectiveness of the treatment and the prevention of resistance development.

Keywords: *Candida. Urinary tract infection. Fluconazole. Amphotericin B.*

RESUMO

Justificativa e objetivos: O achado de espécies de *Candida* na urina é um achado comum e é chamado de candidúria. Há um aumento na frequência de infecções do trato urinário (ITU) causadas por *Candida*, principalmente em pacientes críticos. Este estudo teve como objetivo determinar as características epidemiológicas, clínicas

e micológicas das infecções urinárias por *Candida* em unidade de terapia intensiva (UTI) e a susceptibilidade aos antifúngicos. **Métodos:** Foram avaliadas culturas de urina de 394 pacientes de UTI com suspeita clínica de ITU. Após 24-48 horas de incubação, as colônias pareceram crescer como leveduras, foram morfologicamente examinadas por coloração de Gram. As cepas de *Candida* que cresceram ≥10^4 UFC/mL em culturas de urina foram aceitas como candidúria. As suscetibilidades das cepas de *Candida* à anfotericina B, itraconazol, fluconazol, voriconazol, flucitosina e caspofungina foram investigadas com o método de microdiluição em caldo. **Resultados:** A distribuição das cepas 100 isoladas de *Candida* urinária foi de 54 *Candida albicans*, 34 *C. glabrata*, 7 *C. tropicalis*, 2 *C. kefyr*, 2 *C. lusitaniae* e 1 como *C. parapsilosis*. Entre 100 espécies de *Candida* isoladas em nosso estudo, as taxas de susceptibilidade de anfotericina B, flucitosina, caspofungina, fluconazol, itraconazol e voriconazol foram de 100%, 100%, 91%, 23%, 13%, 25,8%, respectivamente. **Conclusão:** A identificação precisa de *Candida* spp., bem como a investigação da susceptibilidade aos antifúngicos, será benéfica em termos de eficácia do tratamento e prevenção do desenvolvimento de resistência.

Palavras chave: *Candida. Infecções urinárias. Fluconazol. Anfotericina B*

RESUMEN

Justificación y objetivos: El hallazgo de especies de *Candida* en la orina es un hallazgo habitual y se denomina candiduria. Hay un aumento en la frecuencia de infecciones del tracto urinario (ITU) causadas por *Candida*, especialmente en pacientes críticamente enfermos. Este estudio tuvo como objetivo determinar las características epidemiológicas, clínicas y micológicas de las infecciones urinarias por *Candida* en la unidad de cuidados intensivos (UCI) y la susceptibilidad antifúngica. **Métodos:** Se evaluaron urocultivos de 394 pacientes de UCI con sospecha clínica de ITU. Después de 24-48 horas de incubación, las colonias parecían crecer como levadura, se examinaron morfológicamente mediante tinción de Gram. Las cepas de *Candida* que crecieron 104 ≥ UFC / ml en urocultivos se aceptaron como candiduria. Las susceptibilidades de las cepas de Candida a la anfotericina B, itraconazol, fluconazol, voriconazol, flucitosina y caspofungina se investigaron con el método de microdilución en caldo. **Resultados:** La distribución de las cepas 100 urinarias aisladas de *Candida* fue de, 54 *C. albicans*, 34 *C. glabrata*, 7 *C. tropicalis*, 2 *C. kefyr*, 2 *C. lusitaniae* y 1 como *C. parapsilosis*. Entre las 100 especies de *Candida* aisladas en nuestro estudio, las tasas de susceptibilidad de anfotericina B, flucitosina, caspofungina, fluconazol, itraconazol y voriconazol fueron 100%, 100%, 91%, 23%, 13%, 25,8%, respectivamente. **Conclusión:** La identificación precisa de *Candida* spp., así como la investigación de la susceptibilidad antifúngica, será beneficiosa en términos de la eficacia del tratamiento y la prevención del desarrollo de resistencias.

Palabras clave: *Candida. Infecciones urinarias. Fluconazol. Anfotericina B*

INTRODUCTION

Candida species are members of microbioata at various sites in the human body.[1] However, they are capable of colonizing mucocutaneous tissues via attaching to the superficial mucosal cells and are accepted as opportunistic pathogens.[2] The finding of *Candida* species in urine is a usual clinical situation and is called candiduria.[3] In urine cultures, *Candida albicans* and non-*albicans* species are predominantly isolated among fungi, and in the last two decades, there was a remarkable increase in urinary tract infections (UTIs) caused by opportunistic fungi, especially among hospitalized patients which create considerable public health predicaments.[1,4] Also, there is an increase in the frequency of UTIs caused by fungi, especially *Candida* species in critically ill patients.[5]

Candida species may cause UTIs via both antegrade pathway by entering the upper urinary tract from the systemic circulation and retrograde pathway by ascending the urinary tract from a colonization site around the urethra.[6] Several reports indicate that *Candida* species are responsible for at least 10-15% of nosocomial UTIs.[3,7] UTIs caused by *Candida* is an emergent problematic issue for immunocompromised and critically ill patients, among the hospitalized patients, candiduria is a frequent finding particularly in intensive care units (ICUs) and in adult surgical ICUs candiduria more frequently go along with UTIs.[3,7-10]

There are well defined independent risk factors for candiduria and *Candida* UTIs including; age >65 years, female sex, prolonged hospitalization, ICU admission, diabetes mellitus, disturbance in microbiome caused by broad-spectrum antimicrobials, female sex, total parenteral nutrition, bladder dysfunction, congenital abnormalities of the urinary tract, renal transplantation, urinary stasis, nephrolithiasis, concomitant bacteriuria, genitourinary tuberculosis, neutropenia, urinary tract instrumentation, chronic renal failure, mechanical ventilation and immunosuppressive therapy.[2,3,5,8,9-11]

Even though *C. albicans* is often reported as the predominant species responsible for UTIs, all common *Candida* species can cause UTIs, and non-*albicans* species emerge with better adaptation to the urinary tract system because many studies worldwide stating that half of the candiduria isolates are non-albicans.[7-9,12] Frequent use of antifungal prophylaxis and treatment results in infections with non-*albicans* species showing resistance to antifungals.[13] An increase in non-*albicans* species appears

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as a significant problem due to decreased susceptibility of non-albicans species to antifungals, which may result in complexities or failures in the management of UTIs.[14] This study aimed to determine the epidemiological, clinical, and mycological characteristics of *Candida* urinary infections in intensive care unit (ICU) patients and antifungal susceptibilities of *Candida* species.

METHODS

In our study, urine cultures of ICU patients were investigated duplicate samples and patients who were taking prior antifungal therapy were excluded. A total of 394 nonrepetitive patients with clinical suspicion of UTIs from anesthesiology and reanimation ICU (50.7%) and internal diseases ICU (49.3%) were evaluated. Since urinary catheterization is a standard practice in ICUs, all patients included in the study had an indwelling urinary catheter. The demographic information and laboratory findings of the patients including age, sex, length of stay, existence of concomitant bacteriuria, existence of concurrent candidemia and average days for detection of candiduria after admittance to th ICU were recorded. Urine samples were transferred with sterile urine containers and inoculated onto Sabouraud Dextrose Agar (SDA; Salubris, Turkey) medium. After 24-48 hours of incubation at 25 °C and 37 °C, colonies appeared to grow as yeast, were morphologically examined by Gram staining. *Candida* strains that grew $10^4 \geq$ CFU/mL in urine cultures were accepted as candiduria and included in our study.[15,16]

For the identification of *Candida* species an automated identification system Phoenix (Becton Dickinson, Germany) and chromogenic agar (Chromagar; Salubris, Turkey), as well as classical methods like germ-tube formation was used. Color change of colonies at chromogenic agar was observed after 48 hours of incubation; *C. albicans* was observed as green, *C. tropicalis* as blue, *C. glabrata,* and *C. kefyr* as pink-purple

The susceptibilities of the *Candida* strains to amphotericin B, itraconazole, fluconazole, voriconazole, flucytosine, and caspofungin were investigated using the reference broth microdilution method in the Clinical and Laboratory Standards Institute (CLSI) M27-A3, M27-S3, and M27-S4.[17-19] For broth microdilution susceptibility experiments, caspofungin (Sigma, China), amphotericin B (Sigma, Israel), fluconazole (Sigma, USA), flucytosine (Sigma, UK), voriconazole (Sigma, USA), and itraconazole (Sigma, USA) were used as antifungals. Distilled water was used for fluconazole and flucytosine, DMSO (dimethyl sulfoxide) (Merck, USA) was used for water-insoluble caspofungin, amphotericin B, voriconazole, and itraconazole as a solvent. Stock solutions were prepared at 1280 µg / mL for fluconazole, 1600 µg / mL for amphotericin B, 1600 µg / mL for voriconazole, 1600 µg / mL for itraconazole, 1600 µg / mL for flucytosine, and 640 µg / mL for caspofungin. Prepared antifungal stock solutions were passed through a membrane filter, divided into 1 mL volumes, placed in sterile Eppendorf tubes, and stored at -80 ° C until use. Amphotericin B was coated, protected from light.

An inoculum concentration adjusted to $1.5\times10^3\pm1.0\times10^3$ cells/ml with using RPMI 1640 medium (Sigma, USA), were tested with two-folds increasing antifungal concentrations of amphotericin B (0.0313-16 µg/mL), flucytosine (0.125-64 µg/mL), itraconazole (0.0313-16 µg/mL), fluconazole (0.125-64 µg/mL), voriconazole (0.0313 - 16 µg/mL), caspofungin (0.015-8 µg/mL) by broth microdilution method. After incubation at 35 °C for 48 h (24 hours for caspofungin), minimum inhibitory concentrations (MICs) were defined as the lowest concentration that inhibited visual fungal growth compared with the drug-free controls. *C. parapsilosis* ATCC 22019 and *C. krusei* ATCC 6258 strains were used for control.

Breakpoints for antifungal susceptibility were evaluated according to CLSI guidelines but, CLSI has not determined breakpoints for amphotericin.[19] The isolates inhibited by amphotericin B at ≤1 µg /ml were considered susceptible, resistant isolates were defined as isolates with MIC >1 µg/ml. Also, since there is no new update in M27-S4 for *C. kefyr*, the values in M27-S3 were taken into consideration while evaluating the MIC breakpoints. [18, 19] Also for *C. lusitaniae*, since there is no update for M27-S4 fluconazole and voriconazole, the MIC breakpoints specified in M27-S3 were taken into consideration.

SPSS 16.0 (Statistical Package for Social Sciences) Package program was used for the analysis of the data obtained from the study. Mean, standard deviation, and percentage distributions were given as descriptive statistics. In addition, the Chi-Square test was used for the comparison of non-numerical variables. Mann Whitney-U test was used to compare binary variables with numerical data. The results obtained were evaluated at the 95% ($P < 0.05$) significance level. In order to carry out this study, ethics committee approval was obtained from Gaziantep University Clinical Research Ethics Committee (Code:2016/298).

RESULTS

Urine samples from 394 ICU patients were examined; there was candiduria in 54 (13.7%) patients, candiduria and concomitant bacteriuria in 46 (11.6%) patients, bacteriuria in 69 (17.5%) patients, and 235 (59.6%) patients had negative urine cultures. A total of 100 *Candida* strains were evaluated. The distribution of the isolated urinary *Candida* strains were as, 54 *C. albicans*, 34 *C. glabrata*, 7 *C. tropicalis*, 2 *C. kefyr*, 2 *C. lusitaniae*, and 1 as *C. parapsilosis*. Concurrent candidemia was detected in 14 of patients with candiduria. The distribution of *Candida* species isolated from blood cultures was 10 (71.4%) *C. albicans*, 2 (14.2%) *C. parapsilosis*, 1 (7.1%) *C. glabrata*, and 1 (7.1%) *C. lusitaniae*.

Determined by broth microdilution; 91 *Candida* species were susceptible to caspofungin, 8 were moderately susceptible, and 1 was resistant, 23 *Candida* species were susceptible to fluconazole, 37 were dose-related susceptible, and 40 were resistant, 13 *Candida* species were susceptible to itraconazole, 18 were dose-dependent susceptible, and 69 were resistant. There were 17

(25.8%) voriconazole susceptible strains, 13 dose-dependent susceptible (19.7%) strains, and 36 (54.5%) resistant *Candida* strains (*C. glabrata* not included due to CLSI statement: current data are insufficient to demonstrate a correlation between *in vitro* susceptibility testing and clinical outcome). Among the 100 *Candida* strains examined, resistant strains against amphotericin B (≥2 µg/mL) and flucytosine (≥32 µg/mL) were not detected. MIC range, $MIC_{50,}$ and MIC_{90} values of antifungal drugs for *Candida* species are given in Table 1. Also, detailed antifungal susceptibility results of different *Candida* species were given in Table 2.

Table 1. MIC ranges, MIC_{50} and MIC_{90} values of antifungals for different *Candida* species.

Species (n)	Antifungal	MIC range (µg/mL)	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)
C. albicans	Amphotericin B	0.125-1	0.5	1
(54)	Itraconazole	0.06-16	2	16
	Voriconazole	0.03-16	2	16
	Caspofungin	0.015-0.5	0.03	0.25
	Fluconazole	0.125-64	4	64
	Flucytosine	0.125-2	0.125	0.5
C. glabrata	Amphotericin B	0.125-1	1	1
(34)	Itraconazole	0.03-16	8	16
	Voriconazole	0.03-16	1	16
	Caspofungin	0.015-0.5	0.03	0.25
	Fluconazole	0.125-64	4	64
	Flucytosine	0.125-0.5	0.125	0.25
C. tropicalis	Amphotericin B	0.5-1	0.5	1
(7)	Itraconazole	0.06-16	0.125	16
	Voriconazole	0.03-16	0.125	1
	Caspofungin	0.03-0.125	0.06	0.06
	Fluconazole	1-32	8	32
	Flucytosine	0.125-0.5	0.125	0.5
C. kefyr	Amphotericin B	0.5-1	0.5	1
(2)	Itraconazole	1-16	1	16
	Voriconazole	1	1	1
	Caspofungin	0.03-0.125	0.03	0.125
	Fluconazole	0.25-64	0.25	64
	Flucytosine	0.125	0.125	0.125
C. lusitaniae	Amphotericin B	0.25-1	0.25	1
(2)	Itraconazole	0.06-1	0.06	1
	Voriconazole	0.5-16	0.5	16
	Caspofungin	0.06	0.06	0.06
	Fluconazole	8-16	8	16
	Flucytosine	0.125	0.125	0.125
C. parapsilosis	Amphotericin B	0.5	0.5	0.5
(1)	Itraconazole	0.06	0.06	0.06
	Voriconazole	0.06	0.06	0.06
	Caspofungin	0.25	0.25	0.25
	Fluconazole	8	8	8
	Flucytosine	0.5	0.5	0.5

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Table 2. Antifungal susceptibility results of different *Candida* species.

Antifungal		*C. albicans*	*C. glabrata*	*C. tropicalis*	*C. lusitaniae*	*C. kefyr*	*C. parapsilosis*
Caspofungin†	S	50(92.6%)	29(85.3%)	7(100%)	2 (100%)	2(100%)	1 (100%)
	I	4 (7.4%)	4 (11.8%)	-	-	-	-
	R	-	1 (2.9%)	-	-	-	-
Fluconazole†	S	18(33.3%)	-	3(42.9%)	1 (50%)	1 (50%)	-
	I	11(20.4%)	25(73.5%)	-	1 (50%)	-	-
	R	25(46.3%)	9 (26.5%)	4(57.1%)	-	1 (50%)	1 (100%)
Voriconazole†,‡	S	9 (16.7%)	17(97.6%)	4(57.1%)	1 (50%)	2(100%)	1 (100%)
	I	12(22.2%)	1	1(14.3%)	-	-	-
	R	33(61.1%)	16 (2.4%)	2(28.6%)	1 (50%)	-	-
Itraconazole	S	4(7.4%)	4 (11.8%)	3(42.9%)	1 (50%)	-	1 (100%)
	I	12(22.2%)	5 (14.7%)	1(14.2%)	-	-	-
	R	38(70.4%)	25(73.5%)	3(42.9%)	1 (50%)	2(100%)	-
Flucytosine	S	54 (100%)	34 (100%)	7 (100%)	2 (100%)	2(100%)	1 (100%)
	I	-	-	-	-	-	-
	R	-	-	-	-	-	-
Amphotericin B	S	54 (100%)	34 (100%)	7 (100%)	2 (100%)	2(100%)	1 (100%)
	I	-	-	-	-	-	-
	R	-	-	-	-	-	-
Total		54 (54%)	34 (37%)	7 (7%)	2 (2%)	2 (2%)	1 (1%)

Abbreviations: S,susceptible; I,intermediate/susceptible-dose dependent; R,resistant.
†There is no CLSI defined breakpoints for C. kefyr and C. lusitaniae, breakpoints for C. tropicalis was applied
‡There is no CLSI defined voriconazole breakpoints for C.glabrata, breakpoints for C. krusei was applied

In our study, 60 (60%) of the patients with candiduria were female and 40 (40%) were male. A significant difference was found between the two groups in terms of sex distribution (p=0.046). When *Candida* species were analyzed according to sex, *C. albicans* was higher (53.7%) among males and non-*albicans* species were higher (58.3%) among females. Non-albicans species were isolated more frequently in females and a statistically significant difference was found (p=0.002). Of the 100 patients whose *Candida* strains were isolated, 9 were in the age range of 20-40, 16 were 41-60, and 75 were 61 and over. The length of stay of the patients in the ICUs was varying between 6 and 120 days (mean 33.8 days). After admittance to ICU, candiduria was detected (mean 9.7 days) within 1-9 days in 64 patients, 10-19 days in 23 patients, 20-29 days in 8 patients and >30 days in 22 patients. While the mortality rate was 41.1% among patients included in our study (n:349), the overall mortality rate among patients with candiduria was 69%, and among patients with both candiduria and candidemia was 92.8%. There was a significant difference in mortality rate between patients with candiduria and without candiduria (p <0.001). No significant difference was found between the causative agent of candiduria and the mortality rate.

DISCUSSION

The detection of candiduria manifests as a diagnostic and therapeutic challenge for all levels of health care settings and may be frustrating for physicians from primary care or infectious diseases, along with intensive medicine and surgery.[6] Urinary *Candida* may be related to a number of conditions ranging from sample contamination to UTIs, including invasive candidiasis, therefore, require detailed analysis.[1,6] Obtaining new urine samples and confirming whether candiduria persists, can usually help for differentiation of contamination from colonization or UTI.[2] If there is growth in the second culture repeated, but the patient is asymptomatic, predisposing factors should be reviewed, the urinary catheter should be removed, and antibiotic therapy should be terminated.[5] Urinary tract imaging is recommended in patients with diabetes mellitus and patients with known urinary tract abnormalities, it may be guiding for appropriate treatment.[5]

In our study, female sex and advanced age were detected as risk factors for the development of candiduria. Although females are twice as likely to develop nosocomial candiduria when compared to males, possibly due to the anatomical differences of their genitals and vaginal colonization, females with candiduria was linked to a reduced risk of candidemia when compared to males.[20] *Candida* species are more common in the urine of the elderly, especially after broad-spectrum antibiotic treatments, advanced age, normal physical changes, and/or various metabolic disorders or neoplastic diseases that cause disruption of the mucosal and cutaneous barriers and make the person vulnerable to *Candida* infections.[21] Interestingly we did not find a correlation between long-stay in ICU and candiduria while 64% of our patients develop candiduria in 9 days after admittance to ICU, in a similar study from France, the time between admission to the ICU and the development of candiduria was reported as 17.2±1.1 days.[4]

There are no defined standard diagnostic criteria for diagnosis of *Candida* UTIs and their differention of

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from asymptomatic candiduria, and differentiation of upper from lower UTIs.[22] Also, there is no consensus in diagnostic evaluation colony counts(CFU/ml) and urine collection technique for neonatal candiduria unlike in bacteriuria.[11] Although the clinical significance of candiduria is still contradictory, various researchers suggest that colony counts greater than 10^3–10^4CFU/mL are more likely related to primary or disseminated candidiasis, rather than sample contamination or colonization.[16]

Candiduria frequency among ICU patients increased in recent years, especially among patients requiring urinary instrumentation or receiving broad-spectrum antibiotics and risk of occurence is as high as 22.89% in ICU patients.[23] The finding of *Candida* in the urinary samples is associated with higher mortality, particularly in ICU patients with accompanying comorbidities. However, higher mortality rates in patients with candiduria are not often directly attributable to invasive candidiasis. Nevertheless, candiduria may be an indicator of severe underlying diseases.[7] In a clinical study in-hospital mortality was 48.8% in patients with candiduria compared to 36.6% in those without candiduria (p <0.001), they also found significant differences for ICU mortality (38.% vs. 28.1%, p <0.001).8 Researchers found, candiduria detected at any time in the surgical ICU was independently associated with mortality.[24] Our study also revealed candiduria as an independent risk factor for mortality (p <0.001). The incidence of concurrent candidemia is infrequent and has been encountered in 1-8% of patients with candiduria, even so, ICU patients constitute the high-risk group.[10] Our results showing 14% candiduria with concurrent candidemia in ICU patients also indicate physicians should be more alarmed about invasive candidiasis in critically ill patients with candiduria. Long hospital-stay and malignancy are predictors for developing candidemia in patients with candiduria; however, the patient characteristics linked to concomitant candidemia in the presence of candiduria remain unknown.[20]

Management of candiduria is still contradictory because the finding of *Candida* spp. in urinary specimens may indicate asymptomatic infection, lower UTI, upper UTI with a potential for ascending pyelonephritis, renal candidiasis leading to invasive and disseminated candidiasis, which not only results in considerable morbidity and mortality but also prolonged hospitalization and growing cost.[2] Candiduria may be an indicator of disseminated candidiasis in neutropenic, low birth weight infants, patients undergoing urological procedures, and renal transplant recipients patient groups.[5] Candiduria in critically ill patients whether symptomatic or not should initially be considered as a clue of disseminated candidiasis and antifungal drug prophylaxis appears to be warranted since the kidney is affected by disseminated candidiasis in 80% of patients.[2] Detection of candiduria may be the only evidence that the patient has a serious infection. In these patients, systemic therapy with fluconazole or another azole derivative is recommended. An echinocandin, such as caspofungin, is selected if the patient has had recent exposure to fluconazole, which is the drug of choice.[5] In the treatment of cystitis and pyelonephritis, oral fluconazole is used in susceptible strains, and flucytosine and amphotericin B are used in those with fluconazole resistance. Bladder irrigation with amphotericin B may be beneficial in cystitis caused by fluconazole-resistant strains such as *C. glabrata* and *C. krusei*.[5] Voriconazole is stated as an effective antifungal that can be used in isolates resistant to fluconazole. However, a significant portion of fluconazole-resistant *Candida* isolates become resistant to voriconazole as well as itraconazole as a result of cross-resistance.[17] The most important features of caspofungin are that it is effective against azole and amphotericin B resistant *Candida* strains. Since there is no cross-resistance between azole antifungals, caspofungin can be a good option for *Candida* species resistant to azole antifungals.[1]

Although *C. albicans* is the most prevalent species reported in urine culture, other species such as *C. glabrata, C. parapsilosis, C. tropicalis, C. kefyr, C. lusitanae, C. guilhermondi,* and *C. dubliniensis* can also be isolated.[1] The distribution of causative agents of *Candida* UTIs is shifting, non-albicans species are detected in more than half of the urinary samples, which also bring along antifungal resistance issues. [7] These non-albicans *Candida* may not only show better adaptation to the kidney and collecting system but also more challenging to eradicate than *C. albicans*.[9] The detection of candiduria in an ICU patient should be regarded as an indicator of poor prognosis and the accurate identification of *Candida* spp., as well as the investigating the antifungal susceptibility, will be beneficial in terms of the effectiveness of the treatment and the prevention of resistance development.

DECLARATIONS OF INTEREST

None.

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AUTHOR'S CONTRIBUTION

Fahriye Ekşi and **Süleyman Ganidağlı** was responsible for the organization and coordination and was the chief investigator. **Ban Ali Hassan, Mehmet Erinmez, Berna Kaya Uğur**, and **Hamit Yıldız** performed the data analysis and developed the trial design. **Mehmet Erinmez** and **Fahriye Ekşi** critically revised the manuscript for important intellectual content. All authors contributed to the writing of the final manuscript.

PUBLICAÇÃO OFICIAL DO NÚCLEO HOSPITALAR DE EPIDEMIOLOGIA DO HOSPITAL SANTA CRUZ E PROGRAMA
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Revista de Epidemiologia e Controle de Infecção

Hospital Santa Cruz

SHORT COMMUNICATION

Chikungunya, Zika and Dengue seroprevalence rates among pregnant women in a hospital of southeastern Brazil

Soroprevalência de chikungunya, zika e dengue em gestantes de um hospital do sudeste do Brasil

Seroprevalencia de chikungunya, zika y dengue en mujeres embarazadas en un hospital del sureste de Brasil

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ABSTRACT

Background and objectives: For decades, dengue outbreaks have been affecting vast territories of the Americas. In 2010's decade, Chikungunya and Zika virus (CHIKV and ZIKV) emerged as new arboviruses in the region. While several seroprevalence rates have been reported for dengue virus (DENV) infection in Brazil, serological surveys for the latest are scarce. We aimed to evaluate the seroprevalence of CHIKV, ZIKV, and DENV infections in pregnant women at admission to a public maternity hospital of Nova Iguaçu, state of Rio de Janeiro. **Methods**: A simple questionnaire was applied, containing limited demographic, obstetric, and clinical data, alongside with blood collection. Different commercial test kits, based on enzyme-linked immunosorbent assay (ELISA), were used. **Results**: Among 349 pregnant women enrolled from July to December 2017, there was a 28.4% seroreactivity for CHIKV, 47.2% for ZIKV, and 88.8% for DENV. **Conclusion**: These findings reflect the high dengue endemicity scenario and suggest a significant reach of the recent outbreaks of ZIKV and CHIKV infections in the region.

Keywords*: Chikungunya Fever. Zika Virus Infection: Dengue. Seroepidemiologic Studies. Pregnant women.*

RESUMO

Justificativas e objetivos: Há décadas, surtos de dengue afetam vastos territórios das Américas. Na década de 2010, os vírus Chikungunya e Zika (CHIKV e ZIKV) surgiram como arbovírus emergentes na região. Embora diversas taxas de soroprevalência tenham sido relatadas para a infecção pelo vírus da dengue (DENV) no Brasil, pesquisas sorológicas para chikungunya e zika são escassas. Objetivou-se avaliar a soroprevalência das infecções por CHIKV, ZIKV e DENV em gestantes admitidas em uma maternidade pública de Nova Iguaçu, estado do Rio de Janeiro. **Métodos**: Foi aplicado um questionário simples, contendo dados demográficos, obstétricos e clínicos limitados, sendo realizada

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coleta de sangue na mesma visita. Diferentes kits de teste comerciais, baseados em ensaio imunoenzimático (ELISA), foram utilizados. **Resultados**: De 349 gestantes recrutadas de julho a dezembro de 2017, houve sororreatividade de 28,4% para CHIKV, 47,2% para ZIKV e 88,8% para DENV. **Conclusão**: Esses achados refletem o cenário de alta endemicidade da dengue e sugerem um alcance significativo dos surtos recentes causados por ZIKV e CHIKV na região.

***Descritores**: Febre de Chikungunya. Infecção pelo vírus Zika. Dengue. Estudos Soroepidemiológicos. Gestantes.*

RESUMEN

Justificación y objetivos: Durante décadas, los brotes de dengue han afectado a vastos territorios de las Américas. En la década de 2010, los virus Chikungunya y Zika (CHIKV y ZIKV) surgieron como arbovirus emergentes en la región. Aunque se han reportadas varias tasas de seroprevalencia para la infección por el virus del dengue (DENV) en Brasil, la investigación serológica para el chikungunya y el Zika es escasa. Este estudio tuvo como objetivo evaluar la seroprevalencia de infecciones por CHIKV, ZIKV y DENV en mujeres embarazadas ingresadas en una maternidad pública en Nova Iguaçu, estado de Rio de Janeiro. **Métodos**: Se aplicó un sencillo cuestionario, que contenía datos demográficos, obstétricos y clínicos limitados, y se extrajo sangre en la misma visita. Se utilizaron diferentes kits de prueba comerciales basados en el ensayo inmunoabsorbente ligado a enzimas (ELISA). **Resultados**: De 349 mujeres embarazadas reclutadas de julio a diciembre de 2017, hubo serorreactividad de 28,4% para CHIKV, 47,2% para ZIKV y 88,8% para DENV. **Conclusión**: Estos hallazgos reflejan el escenario de alta endemicidad para el dengue y sugieren una variedad significativa de brotes recientes causados por ZIKV y CHIKV en la región.

***Palabras clave**: Fiebre Chikungunya. Infección por el virus del Zika. Dengue. Estudios seroepidemiológicos. Mujeres Embarazadas.*

During the early 2010s, Chikungunya and Zika virus (CHIKV and ZIKV) were introduced and spread throughout the Americas, leading to large outbreaks.[1] Like Dengue virus (DENV) besides several other arboviruses, ZIKV and CHIKV are transmitted to humans by *Aedes* spp. mosquitoes, superimposing public health challenges toward historically dengue endemic regions. These arboviral infections are known to cause health complications to newborns of infected mothers, even in asymptomatic maternal infection involving preterm delivery, fetal anomalies, low birth weight, and miscarriage.[2, 3]

While several seroprevalence rates have been reported for dengue in Brazil, serological surveys for chikungunya and zika infections are still scarce. This study aimed to evaluate the serological prevalence of CHIKV, ZIKV, and DENV among pregnant women in a public maternity hospital in the state of Rio de Janeiro, Brazil.

We conducted a cross-sectional study at the Hospital Municipal Mariana Bulhões, located in the municipality of Nova Iguaçu. The city is part of the Baixada Fluminense region, northwest of the state capital, and had approximately 800,000 inhabitants in 2017, with a low-to-middle socioeconomic index. While being the only public maternity hospital in Nova Iguaçu, it provides maternal-infant care to the neighboring municipalities and performs around 5,000 deliveries per year.

As eligibility criteria, we defined any pregnant women, above 18 years old, who were admitted to the emergency/pre-delivery room. We excluded women presenting severe/unstable clinical conditions at admission. Sample size calculation was based on the average of deliveries for the recruitment period, which occurred from July to December 2017, through a convenience sampling. A simple questionnaire was applied, containing limited demographic, obstetric, and clinical data. Self-reported previous history of dengue, zika, and chikungunya infections, as well as yellow fever vaccination, were probed. Acute arboviral suspect cases were defined on a clinical basis. Blood samples were collected at the same visit. Samples were assayed in duplicate with ELISA commercial kits for dengue, zika, and chikungunya, performed according to manufacturer instructions. "Borderline" results were considered as negative for this analysis. These included: Anti-DENV IgM (Serion Elisa Classic - Virion\Serion, Germany); Anti-DENV IgG (Euroimmun, Germany); DENV NS1 antigen (Panbio Dengue Early ELISA, South Korea); Anti-ZIKV IgM capture (Novagnost, Germany); Anti-ZIKV IgG (Euroimmun, Germany); Anti-CHIKV IgM and Anti-CHIKV IgG (Euroimmun, Germany).

This study was approved by the Instituto Oswaldo Cruz Ethics Committee (protocol number: 66996217.7.2002.5254). All participants signed an informed consent form.

A total of 349 pregnant women were enrolled, with no exclusions or refusals to participate. The average age was 26.9 years (Table 1). The average gestational age was 38.8 weeks. Participants came from different parts of the city, especially from the central and populous zones. Approximately 36% came from neighboring municipalities. Most pregnant women were admitted in labor (81%). No participants presented clinical manifestations of acute arboviral infections. When asked about the history of dengue, zika, and chikungunya, there were affirmative answers in, respectively, 6%, 12%, and 9% of the cases. Out of 168 participants who were asked about previous vaccination against yellow fever, only one answered affirmatively.

From the 349 specimens submitted to the different commercial ELISA tests, there were 163 IgG positive and 6 IgM positive specimens for ZIKV, corresponding to 47.2% (95% CI: 42.0 to 52.5) of seroreactivity. The positivity for DENV occurred in 310, corresponding to 88.8% (95% CI: 85.5 to 92.1). All specimens were negative for DENV NS1

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Table 1. Demographic and obstetric data of pregnant women in a public maternity hospital in Nova Iguaçu (RJ), from July to December 2017 (n = 349).

Variable	Category	n (%)
Age (years)	18-24	141 (40.4)
	25-29	100 (28.7)
	29-47	108 (30.9)
Municipality of origin	Nova Iguaçu	222 (64)
	Belford Roxo	36 (10)
	Mesquita	12 (3)
	Queimados	38 (11)
	Japeri	17 (5)
	Other municipalities	19 (6)
	No data	5 (1)
Gestation trimester	First trimester	2 (<1)
	Second trimester	2 (<1)
	Third trimester	332 (95)
	Indeterminate / no data	13 (4)
Prenatal care	Yes	310 (89)
	No	12 (3)
	No data	27 (8)
Reason for hospital admission	Labor	282 (81)
	Suspected arboviral infection	0 (0)
	Other reasons	58 (17)
	No data	9 (2)

antigen. As for CHIKV, 99 of the specimens had positive IgG, and none had positive IgM; thus, it corresponded to 28.4% (95% CI: 23.6 to 33.1) (Table 2).

Despite being a convenience sampling, serological surveys involving pregnant women recruited from health services are a good tool, since may offer a glimpse of the general population's actual seroprevalence. Moreover, most of the Baixada Fluminense population is assisted by the public health system, like the participants in our study.

In comparison with two other chikungunya serological surveys carried out during 2017 in Brazil, our finding is superior to that of Netto et al.[4] in Salvador (7.4%), and that of Cunha et al.[5] in Riachão do Jacuípe (20%), both cities in the state of Bahia. Concerning zika, Netto et al.[4] found even higher seroprevalence in Salvador (63.3%), highlighting a subgroup of 273 pregnant women with 69.3%, recruited between 2015-2016. In another study involving blood donors in São Paulo state, Slavov et al.[6] demonstrated ZIKV seroreactivity obtained in 2015, 2016, and 2017 of 5.3%, 12.8% and 13.2%, respectively. Another study has found 61.3% of ZIKV IgG positive among mothers who gave birth between 2015 and 2016, during the peak of zika fever and microcephaly outbreak in Recife, Pernambuco state.[7] As for dengue, we have found a seroprevalence rate that approximates those most remarkable from population-based studies conducted in Brazil (4.0-91.1%).

Among the limitations of this study, there are the possible cross-reactions involving antibodies against DENV and ZIKV. This phenomenon typically occurs among flaviviruses and has long been known, leading to false positives in serological tests.[8] Neutralizing antibody tests, not used in this study, have been used in serological surveys, increasing specificity, and reducing this problem. The commercial test for ZIKV used herein is based on the non-structural protein NS1, generally considered more specific than certain targets of the envelop glycoprotein E.[9] Some studies reported satisfactory accuracy for this test,[10, 11] while one did not.[12]

Finally, these results reflect a scenario of dengue high endemicity in Baixada Fluminense, pointing out to the deficiency of vector control policies in recent decades. This context favored the emergence of *Ae. aegypti*-related new arboviruses, like chikungunya and zika, with high impact on public health. While showing significant seroprevalence, it also suggests the possibility of new and imminent epidemic waves, taking into account the observed proportion of susceptibility in our sample.

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Table 2. Results of ELISA tests for DENV, ZIKV and CHIKV among 349 pregnant women in a public maternity hospital in Nova Iguaçu (RJ), from July to December 2017.

Virus	Serology	Commercial test	Positive n (%)	Borderline n (%)	Negative n (%)	Seroprevalence n (%)	CI (95%)
DENV	IgM	Virion\Serion	32 (9.2)	39 (11.1)	278 (79,7)	310/349 (88.8)	85.5% - 92.1%
	IgG	Euroimmun	308 (88.3)	4 (1.1)	37 (10.6)		
	NS1	Panbio	0 (0.0)	-	349 (100.0)		
ZIKV	IgM	Novagnost	6 (1.7)	8 (2.3)	335 (96.0)	165/349 (47.2)	42.0% - 52.5%
	IgG	Euroimmun	163 (46.7)	39 (11.2)	147 (42.1)		
CHIKV	IgM	Euroimmun	0 (0.0)	3 (0.9)	346 (99.1)	99/349 (28.4)	23.6% - 33.1%
	IgG	Euroimmun	99 (28.4)	4 (1.1)	246 (70.5)		

DENV - dengue virus; ZIKV- zika virus; CHIKV - chikungunya virus

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Bernardo Bastos Wittlin and José Henrique Pilotto contributed to the design;

Bernardo Bastos Wittlin, Dalziza Victalina de Almeida and Carolina Cipriano Monteiro contributed to the formal analysis;

José Henrique Pilotto and Sheila Maria Barbosa de Lima contributed to the acquisition of the financing;

Bernardo Bastos Wittlin and Luiz Felipe Moreira contributed to the investigation; Bernardo Bastos Wittlin, Bianca Cristina Leires Marques, José Henrique Rezende Linhares, Sheila Maria Barbosa de Lima and Rosalina Jorge Koifman contributed to the methodology;

José Henrique Pilotto and Dalziza Victalina de Almeida contributed supervision and review.

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.